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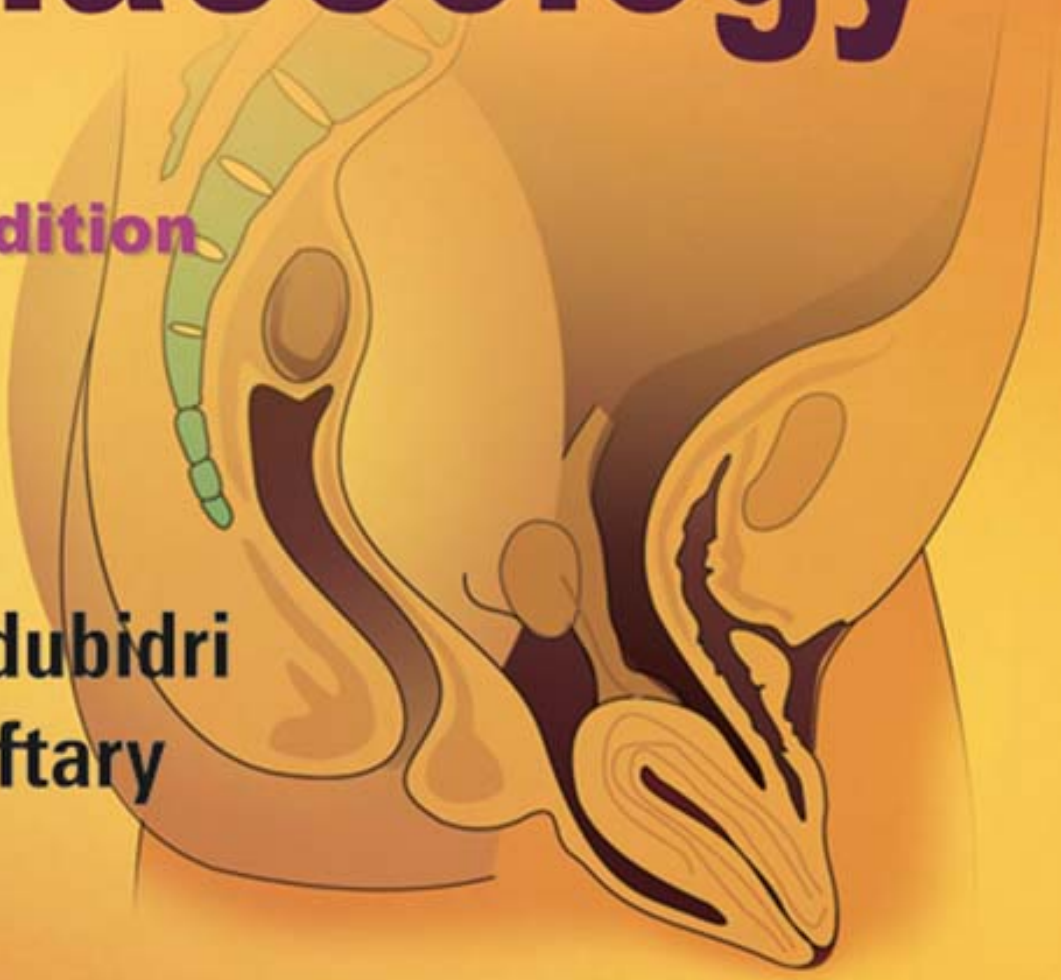
Shaw's Textbook of Gynaecology

16th Edition



VG Padubidri
SN Daftary

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16TH EDITION

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Shaw's Textbook of Gynaecology, 16/e
Padubidri and Daftary

Previous editions, 1936, 1938, 1941, 1945, 1948, 1952, 1956, 1962, 1971, 1989, 1994, 1999, 2004, 2008, 2011

ISBN: 978-81-312-3672-7
e-book ISBN: 978-81-312-3872-1

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The Publisher

Published by Reed Elsevier India Private Limited
Registered Office: 305, Rohit House, 3 Tolstoy Marg, New Delhi-110001
Corporate Office: 14th Floor, Building No. 10B, DLF Cyber City, Phase II, Gurgaon-122002, Haryana, India

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Typeset by GW India

Printed and bound at Thomson Press India Ltd., Faridabad, Haryana

Dedicated to
the medical students
who have always been the source of inspiration
and the patients
who have provided valuable clinical knowledge

Preface
to the 16th edition

We, the editors of *Howkins and Bourne Shaw's Textbook of Gynaecology,* are pleased to acknowledge that this book has continued to provide basic foundation of this speciality since 1936. Keeping in view of the popularity of the book, the first Indian edition (10th edition) was published in 1989. Since then, the book has been updated from time to time in the light of the advances made in this speciality. The 15th edition was revised in 2010. Our commitment to the students to improve and update the quality of the book, and provide them with the advanced knowledge prompted us to bring out the 16th edition.

In this edition, not only we have added the latest knowledge on the subject, but also inserted more illustrations, flowcharts and tables to make the reading easier and understandable. We have added more MRI, CT, and many other illustrations wherever required.

Considering the high associated morbidity and mortality of gynaecological malignancies, we have approached the topic of genital tract cancers more exhaustively in this edition. Emphasis has also been laid on the gynaecological problems amongst adolescents and menopausal women. Minimal invasive surgery for the benign conditions is now being replaced by non-surgical therapy such as MRI-guided ablative therapy without the need for hospitalization. Hopefully these procedures will turn safe and effective in near future.

A website of the book has been created for more information on the subject in the form of video clips, online testing and MCQs for entrance tests and the latest updates on the subject.

We owe our special thanks to the entire staff of Elsevier for their wholehearted support and encouragement. We will fail in our duty if we did not make a special reference to Shabina Nasim with whom we interact on a daily basis and also Renu Rawat. We appreciate their professional attitude and their knowledge towards the project, their efficiency and enormous patience to bring out the best for this project.

Our very special thanks and gratitude go to Mr YR Chadha, Publishing Consultant, BI Churchill Livingstone, New Delhi, who initiated and guided us in the First Indian Edition in 1989, without whose persuasion and encouragement this book would not have seen the day. There are many others who have worked behind the scene, we acknowledge our thanks to them.

Last, but not the least, we thank our readers and the student community for their unstinted support over the last 25 years.

VG Padubidri
Shirish N Daftary

Preface
to the 10th edition

Ever since *Shaw's Textbook of Gynaecology* appeared in the United Kingdom in 1936, it has maintained its popularity with teachers, examiners and the student community. It has gone through several editions. The ninth edition, edited by Dr John Howkins and Dr Gordon Bourne, was brought out in 1971, and its popularity in India has remained undiminished. It is therefore timely and opportune that this standard textbook should be revised by Indian teachers of gynaecology to meet the requirements of our undergraduate students. We consider ourselves fortunate for having been assigned this challenging task by the publishers.

In revising the book we have endeavoured to update the contents to include new methods of investigations and treatment. In particular, recent advances in the physiology of menstruation and its hormonal control, carcinoma of the cervix and related preventive measures, endometriosis, and the management of tuberculosis of the genital tract have been incorporated. In addition, the latest methods of birth control and a separate chapter on Medical Termination of Pregnancy have been added to equip our students with the knowledge required to promote India's family welfare programme.

We have also tried to make the text more concise by deleting information that we felt was unnecessary for the Indian undergraduate student, without substantially changing the original style.

We are indebted to Mr YR Chadha, Publishing Director of BI Churchill Livingstone, New Delhi for his constant encouragement and invaluable suggestions in the preparation of this edition. Sincere thanks are extended to Churchill Livingstone, Edinburgh, for their assistance in making this edition possible.

VG Padubidri
Shirish N Daftary

Contents

Chapter 1 Anatomy

CHAPTER OUTLINE

The anatomical knowledge of the female genital organs (Figure 1.1) and their relation to the neighbouring structures help in the diagnosis of various gynaecological diseases and in interpreting the findings of ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) scanning. During gynaecological surgery, distortions of the pelvic organs are better appreciated and dealt with and a grave injury to the structures such as bladder, ureter and rectum is avoided. The understanding of the lymphatic drainage of the pelvic organs is necessary in staging various genital tract malignancies and in their surgical dissection.

The Vulva

The vulva is an ill-defined area which in gynaecological practice comprises the whole of the external genitalia and conveniently includes the perineum. It is, therefore, bounded anteriorly by the mons veneris (pubis), laterally by the labia majora and posteriorly by the perineum.

Labia Majora

The labia majora pass from the mons veneris to end posteriorly in the skin over the perineal body. They consist of folds of skin which enclose a variable amount of fat and are best developed in the childbearing period of life. In children before the age of puberty and in postmenopausal women, the amount of subcutaneous fat in the labia majora is relatively scanty, and the cleft between the labia is therefore conspicuous. At puberty, pudendal hair appear on the mons veneris, the outer surface of the labia majora and in some cases on the skin of the perineum as well. The inner surfaces of the labia majora are hairless and the skin of this area is softer, moister and pinker than over the outer surfaces (Figure 1.2). The labia majora are covered with squamous epithelium and contain sebaceous glands, sweat glands and hair follicles. There are also certain specialized sweat glands called apocrine glands, which produce a characteristic aroma and from which the rare tumour of hidradenoma of the vulva is derived. The secretion increases during sexual excitement.

The presence of all these structures in the labia majora renders them liable to common skin lesions such as folliculitis, boils and sebaceous cysts (Figure 1.3). Its masculine counterpart is the scrotum.

Bartholin's Gland

Bartholin's gland lies posterolaterally in relation to the vaginal orifice, deep to the bulbospongiosus muscle and superficial to the outer layer of the triangular ligament. It is embedded in the erectile tissue of the vestibular bulb at its posterior extremity. It is normally impalpable when healthy, but can be readily palpated between the finger and the

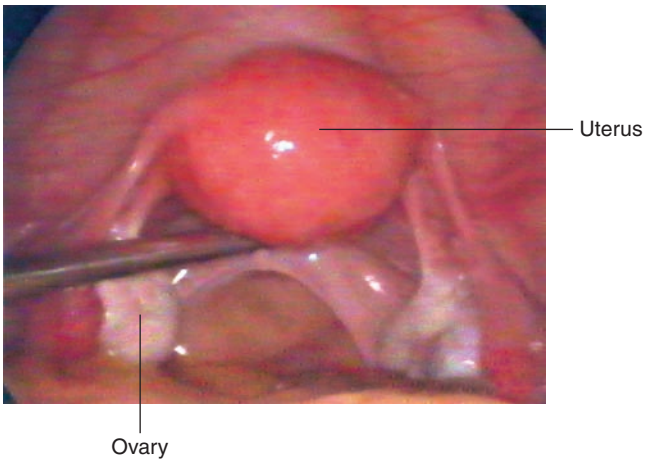


Figure 1.1 General view of internal genital organs showing the normal uterus and ovaries.

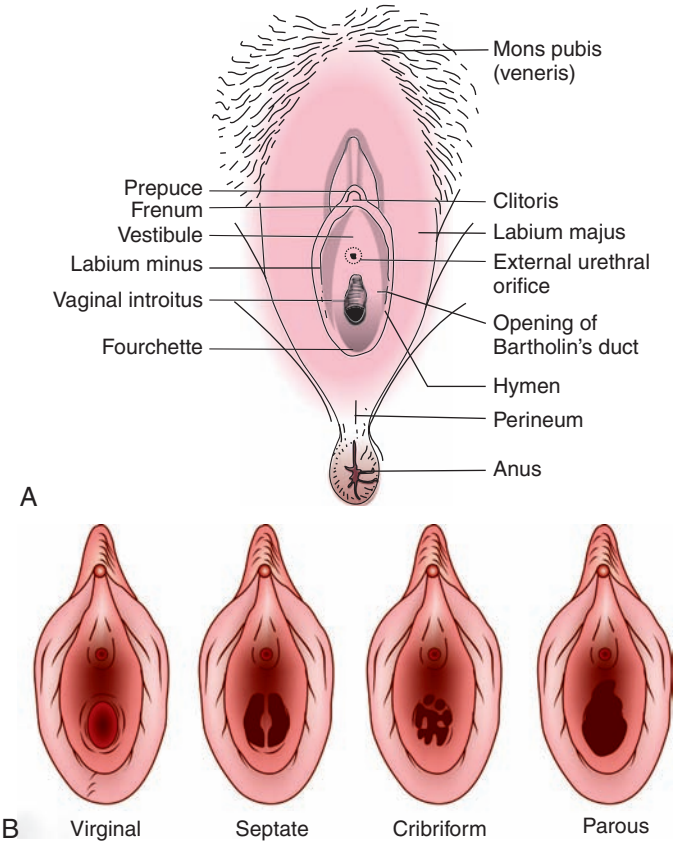


Figure 1.2 **(A)** Anatomy of the vulva. **(B)** Variations of the hymen.

thumb when enlarged by inflammation. Its vascular bed accounts for the brisk bleeding, which always accompanies its removal. Its duct passes forwards and inwards to open, external to the hymen, on the inner side of the labium minus. The gland measures about 10 mm in diameter and lies near the junction of the middle and posterior thirds of the labium majus. The duct of the gland is about 25 mm long and a thin mucous secretion can be expressed from it by pressure upon the gland. Bartholin's gland and its duct are infected in acute gonorrhoea, when the reddened mouth of

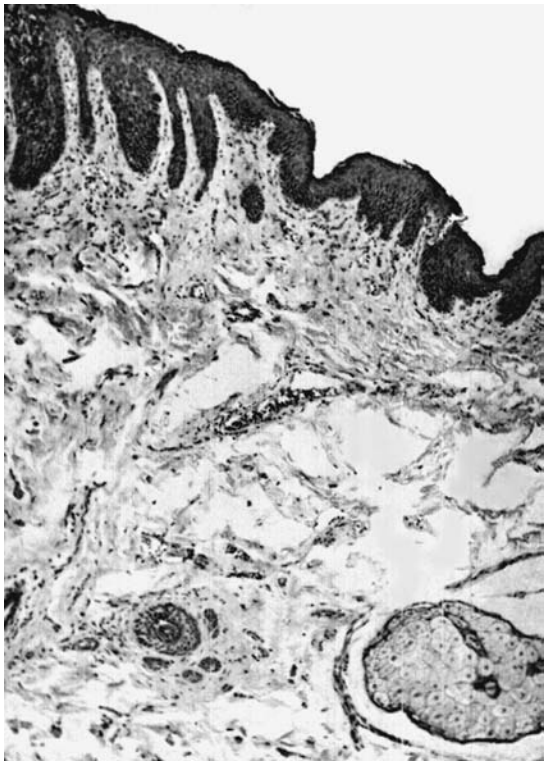


Figure 1.3 Histological section of the labium majus showing squamous epithelium with hair follicle and sebaceous gland (×55).

the duct can easily be distinguished on the inner surface of the labium minus to one side of the vaginal orifice below the level of the hymen. Bartholin's gland is a compound racemose gland and its acini are lined by low columnar epithelium (Figure 1.4). The epithelium of the duct is cubical near the acini, but becomes transitional and finally squamous near the mouth of the duct. The function of the gland is to secrete lubricating mucous during coitus. The labia majora join at the posterior commissure and merge imperceptibly into the perineum.

Labia Minora

The labia minora are thin folds of skin which enclose veins and elastic tissue and lie on the inner aspect of the labia majora. The vascular labia minora are erectile during sexual activity; they do not contain any sebaceous glands or hair follicles (Figure 1.5). Anteriorly, they enclose the clitoris to form the prepuce on the upper surface and the frenulum on its undersurface. Posteriorly, they join to form the fourchette. The fourchette is a thin fold of skin, identified when the labia are separated, and it is often torn during parturition. The fossa navicularis is the small hollow between the hymen and the fourchette. Labia minora is homologous with the ventral aspect of the penis.

The **clitoris** is an erectile organ and consists of a glans, covered by the frenulum and prepuce, and a body which is subcutaneous; it corresponds to the penis and is attached to the undersurface of the symphysis pubis by the suspensory ligament. Normally, the clitoris is 1–1½ cm long and 5 mm

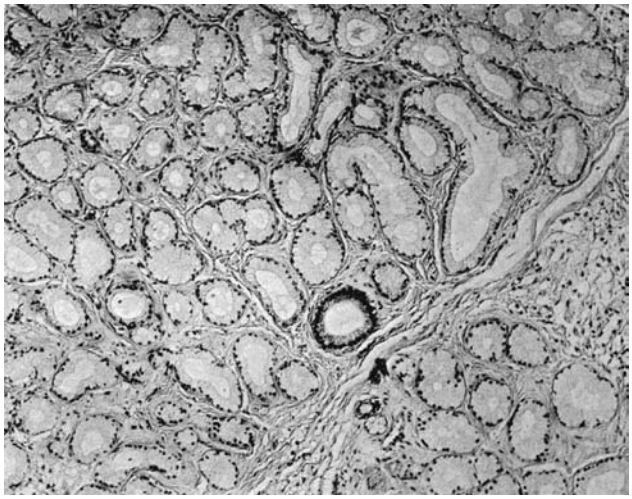


Figure 1.4 Bartholin's gland. Low-power view showing the structure of a compound racemose gland with acini lined by low columnar epithelium (×92).

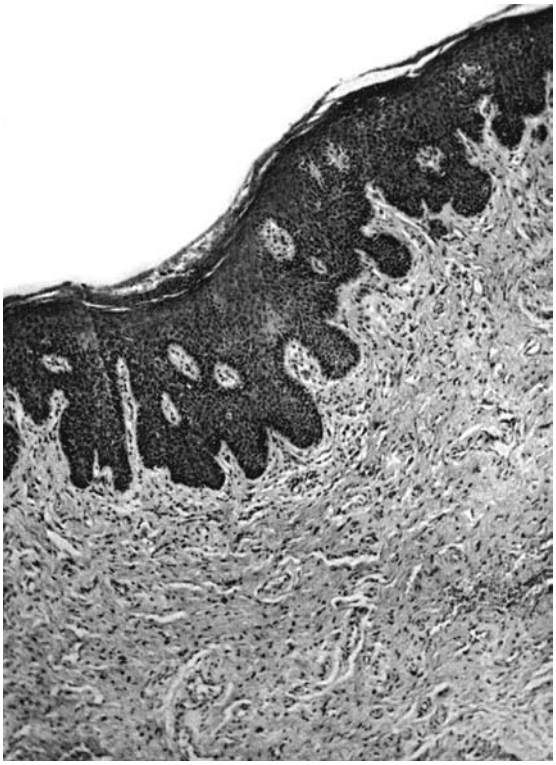


Figure 1.5 Histological section of the labium minus showing squamous epithelium. Note complete absence of hair follicles and sebaceous and sweat glands.

in width. Clitoris of more than 3.5 cm in length and 1 cm in width is called clitoromegaly, and occurs in virilism due to excess of androgen hormone. The clitoris is well supplied with nerve endings and is extremely sensitive. During coitus it becomes erect and plays a considerable part in inducing orgasm in the female. The clitoris is highly vascular. An injury to the clitoris causes profuse bleeding and can be very painful.

The **vestibule** is the space lying between the anterior and the inner aspects of the labia minora and is bounded posteriorly by the vaginal introitus. The *external urinary meatus lies* immediately posterior to the clitoris. The vaginal orifice lies posterior to the meatus and is surrounded by the hymen. In virgins, the hymen is represented by a thin membrane covered on each surface by squamous epithelium. It generally has a small eccentric opening, which is usually not wide enough to admit the fingertip. Coitus results in the rupture of the hymen; the resulting lacerations are radially arranged and are multiple. Occasionally, coital rupture can cause a brisk haemorrhage. During childbirth, further lacerations occur: the hymen is widely stretched and subsequently is represented by the tags of skin known as the carunculae myrtiformes. With the popularity of the use of internal sanitary tampons, the loss of integrity of the hymen is no longer an evidence of loss of virginity.

The vulval tissues respond to hormones, especially oestrogen, during the childbearing years. After menopause, atrophy due to oestrogen deficiency makes the vulval skin thinner and drier, and this may lead to atrophic vulvitis and itching. *Mons pubis* is an area which overlaps the symphysis pubis and contains fat. At puberty, abundant hair grow over it.

The Vagina

The vagina is a fibromuscular passage that connects the uterus to the introitus. The lower end of the vagina lies at the level of the hymen and of the introitus vaginae. It is surrounded at this point by the erectile tissue of the *bulb*, which corresponds to the corpus spongiosum of the male. The direction of the vagina is approximately parallel to the plane of the brim of the true pelvis; the vagina is slightly curved forwards from above downwards, and its anterior and posterior walls lie in close contact. It is not of uniform calibre, being nearly twice as capacious in its upper part and somewhat flask shaped. The vaginal portion of the cervix projects into its upper end and leads to the formation of the anterior, posterior and lateral fornices. The depth of the fornices depends upon the development of the portio vaginalis of the cervix. In girls before puberty and in elderly women in whom the uterus has undergone postmenopausal atrophy, the fornices are shallow while in women with congenital elongation of the portio vaginalis of the cervix, the fornices are deep. The vagina is attached to the cervix at a higher level posteriorly than elsewhere, and this makes the posterior fornix the deepest of the fornices and the posterior vaginal wall longer than the anterior. The posterior wall is 4.5 inch (11.5 cm) long, whereas the anterior wall measures 3.5 inch (9 cm). Transverse folds which are present in the vaginal walls of nulliparae allow the vagina to stretch and dilate during coitus and parturition. These folds are partly obliterated in women who have borne many children. In the anterior vaginal wall, three sulci can be distinguished. One lies immediately above the meatus and is called *submeatal sulcus* (Figure 1.6). About 35 mm above this sulcus in the anterior vaginal wall is a second sulcus, known as the *transverse vaginal sulcus,* which corresponds approximately

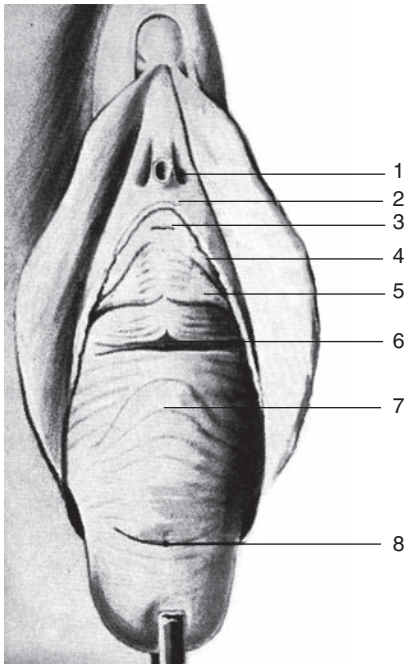
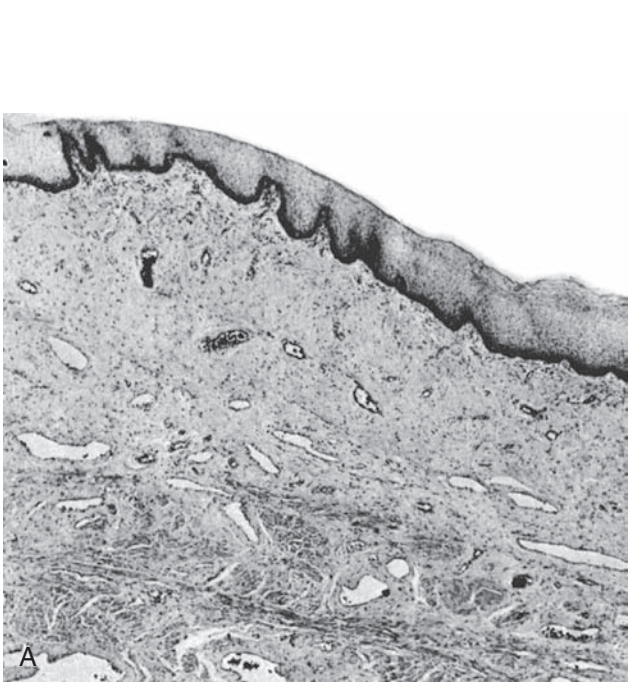


Figure 1.6 A case of prolapse in which the cervix has been drawn down. (1) Parameatal recess, (2) hymen, (3) submeatal sulcus, (4) paraurethral recess, (5) oblique vaginal fold, (6) transverse sulcus of the anterior vaginal wall, (7) arched rugae of the vaginal wall and (8) bladder sulcus.

to the junction of the urethra and the bladder. Further upwards is the *bladder sulcus*, indicating the junction of the bladder to the anterior vaginal wall.

The vaginal mucosa is lined by nonkeratized squamous epithelium which consists of a basal layer of cuboidal cells, a middle layer of prickle cells and a superficial layer of cornified cells (Figure 1.7). In the newborn, the epithelium is almost transitional in type and cornified cells are scanty until puberty is reached. No glands open into the vagina, and the vaginal secretion is derived partly from the mucous discharge of the cervix and partly from transudation through the vaginal epithelium. The subepithelial layer is vascular and contains much erectile tissue. A muscle layer consisting of a complex interlacing lattice of plain muscle lies external to the subepithelial layer while the large vessels lie in the connective tissues surrounding the vagina. If the female fetus is exposed to diethylstilboestrol (DES) taken by the mother during pregnancy, columnar epithelium appears in the upper two-thirds of vaginal mucosa, which can develop vaginal adenosis and vaginal cancer during adolescence. The keratinization of vaginal mucosa occurs in prolapse due to the exposure of vagina to the outside and ulcer may form over the vaginal mucosa (decubitus ulcer). The keratized mucosa appears skin-like and brown. Menopause causes atrophy of the vagina.

The *vaginal secretion* is small in amount in healthy women and consists of white coagulated material. When it is examined under the microscope, squamous cells which have been shed from the vaginal epithelium and Döderlein's bacilli alone are found. *Döderlein's bacillus* is a large Gram-positive rod-shaped organism, which grows anaerobically on acid media. The vaginal secretion is acidic due to the presence of lactic acid, and this acidity inhibits the growth of pathogenic organisms. The pH of the vagina averages about 4.5 during reproductive life. The acidity, which is undoubtedly oestrogen dependent, falls after menopause to neutral or even alkaline. Before puberty, the pH is about 7. This high pH before puberty and after menopause explains



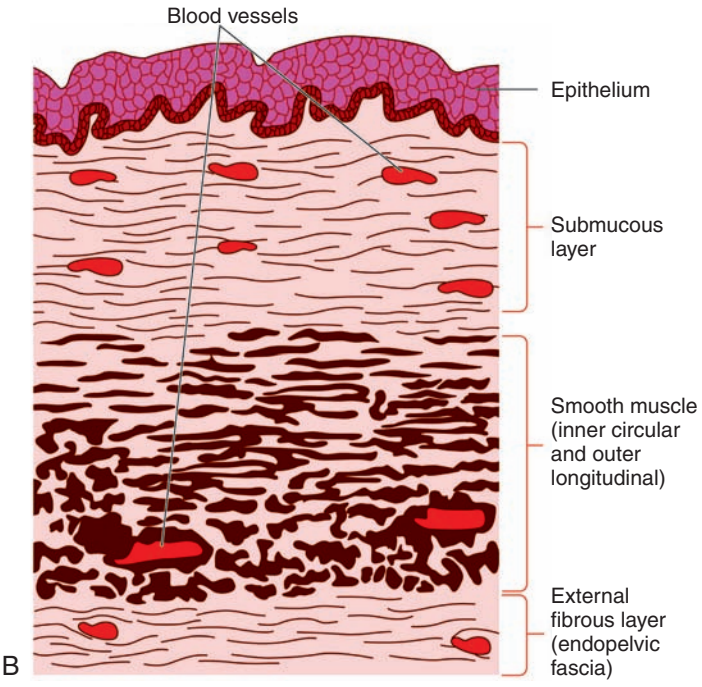


Figure 1.7 **(A)** Low-power (×36) microscopic appearance of the vaginal wall showing the corrugated squamous epithelium and bundles of plain muscle cells subjacent to the vascular subepithelial layer. **(B)** Structure of the vaginal wall.

the tendency for the development of mixed organism infections in these age groups.

The synthesis of lactic acid is probably influenced by either enzyme or bacterial activity (Döderlein's) on the glycogen of the epithelial cells, which itself is dependent on the presence of oestrogen, so that its deficient activity can be boosted by the administration of oral or local oestrogen. During the puerperium and also in cases of leucorrhoea, the acidity of the vagina is reduced and pathogenic organisms are then able to survive. The squamous cells of the vagina and cervix stain a deep brown colour after being painted with iodine solution, owing to the presence of glycogen in healthy cells (positive Schiller's test). In a postmenopausal woman, because of the absence of or low glycogen-containing superficial cells, Schiller's test becomes negative.

The vaginal epithelium is under the ovarian hormonal influences of oestrogen and progesterone. Oestrogen proliferates the glycogen-containing superficial cells and progesterone causes proliferation of intermediate cells. Lack of these hormones in a menopausal woman leaves only the basal cells with a thin vaginal mucosa.

The abnormal and malignant cells also do not contain glycogen and do not take up the stain. Similarly, these abnormal cells turn white with acetic acid due to coagulation of protein. These areas are selected for biopsy in the detection of cancer.

Relations of Vagina

Anterior Relation

In its lower half the vagina is closely related to the urethra and the paraurethral glands (Skene's tubules), so closely in fact that the urethrovaginal fascia is a fused structure and only separable by a sharp dissection. In its upper half the vagina is related to the bladder in the region of the trigone, and here the vesical and vaginal fasciae are easily separable by blunt dissection via the vesicovaginal space. There is a considerable vascular and lymphatic intercommunication between the vesical and the vaginal vessels, a sinister relationship having a bearing on the surgery of malignant disease of this area.

Posterior Relations

The lower third of the vagina is related to the perineal body, the middle third to the ampulla of the rectum and the upper third to the anterior wall of the pouch of Douglas, which contains large and small bowel loops. This partition dividing the vagina from the peritoneal cavity is the thinnest area in the whole peritoneal surface and, therefore, a site of election for pointing and opening of pelvic abscess or the production of a hernia or enterocele. This is also an ideal site for colpocentesis in the diagnosis of ectopic pregnancy.

Pouch of Douglas (Figure 1.8) is a peritoneal cul-de-sac in the rectovaginal space in the pelvis. It is bounded anteriorly by the peritoneum covering the posterior vaginal wall and posteriorly by the peritoneum covering the sigmoid colon and the rectum. Laterally, the uterosacral ligaments limit its boundary whereas the floor is the reflection of the peritoneum of the peritoneal cavity.

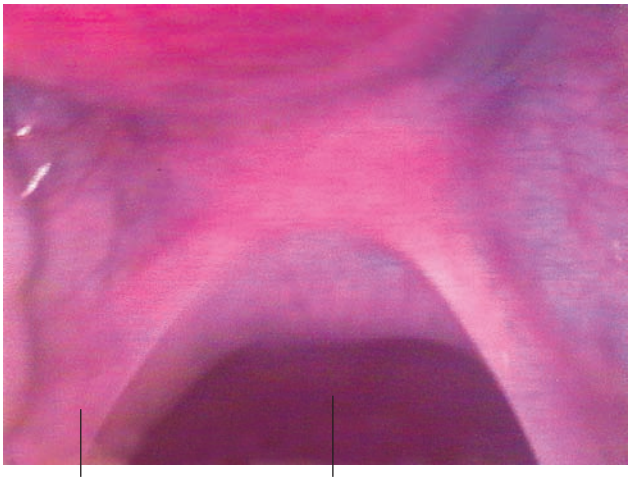


Figure 1.8 Pouch of Douglas showing uterosacral ligaments as upper border.

The endometriotic nodules and metastatic growth of an ovarian cancer are felt in the pouch of Douglas, so also pelvic inflammatory mass. The uterosacral ligaments are thickened and become nodular in advanced cancer cervix.

Lateral Relations

The lateral relations from below upwards are the cavernous tissue of the vestibule; the superficial muscles of the perineum; the triangular ligament and at about 2.5 cm from the introitus the levator ani, lateral to which is the ischiorectal fossa. Above the levator lies the endopelvic cellular tissue, and its condensation, called Mackenrodt's ligament, on either side. The ureter traverses this tissue in the ureteric canal and is about 12 mm anterolateral to the lateral fornix.

Superior Relations

The cervix with its four fornices—anterior, posterior and two lateral—are related to the uterine vessels, Mackenrodt's ligament and the ureter. Posteriorly, surrounding the pouch of Douglas lie the uterosacral ligaments which can be identified on vaginal examination, especially if thickened by disease such as endometriosis and cancer cervix.

Squamocolumnar junction, also known as transitional zone, is clinically a very important junction where the squamous epithelium lining the vagina merges with the columnar epithelium of the endocervix and is 1–10 mm (Figure 1.9). Here, the constant cellular activity of the cells takes place, and the cells are highly sensitive to irritants, mutagens and viral agents such as papilloma virus 16, 18. These cause nuclear changes that can eventually lead to dysplasia and carcinoma cervix, which is the most common malignancy of the female genital tract in India. Squamocolumnar junction is of two types: first one is embryonic when columnar epithelium spreads over the external os. After

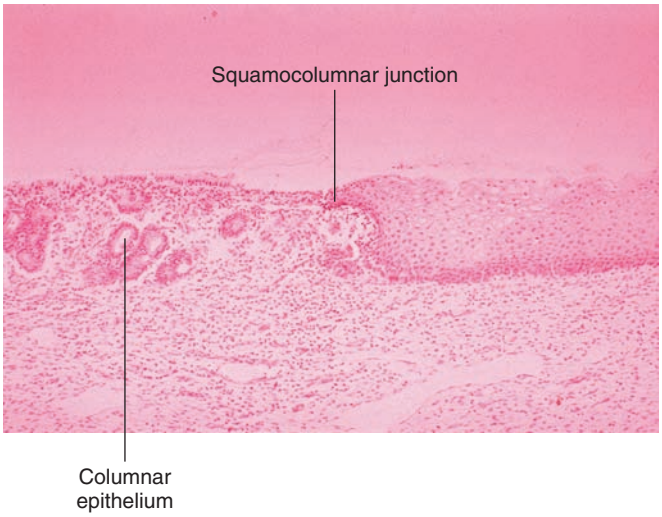


Figure 1.9 Squamocolumnar junction. In the 'ideal' cervix, the original squamous epithelium abuts the columnar epithelium. (Source: Hacker NF, Gambone JC, Hobel CJ, Hacker and Moore's Essentials of Obstetrics and Gynecology, 5th ed. Philadelphia: Elsevier, 2010.)

puberty, metaplasia of columnar epithelium under the influence of oestrogen brings squamous epithelium close to the external os, thus creating transitional zone between the two junctions. In women exposed to DES in utero, this zone is well outside the os, spreading over the vaginal vault. In a menopausal woman, it gets indrawn inside the os. During pregnancy and with oral contraceptives, it pouts out of os.

The squamocolumnar junction is well outside the external os during the reproductive period, and in Pap smear this area is scraped and the cytology of its cells studied for the nuclear changes, in the screening programme for cancer cervix.

During pregnancy, the external os becomes patulous and the squamocolumnar junction is well exposed all round. Pap smear yields the most accurate cytological findings.

In menopausal women, the cervix shrinks and the squamocolumnar junction gets indrawn into the cervical canal. It is therefore not easily accessible, and ill exposed to the vagina, for visual inspection. This explains high false-negative findings in Pap smear in older women. Giving oestrogen locally or orally or prostaglandin E (misoprostol) pessary allows this junction to pout out and improves the efficacy of the Pap smear cytology.

The squamocolumnar junction is studied colposcopically when the Pap smear shows abnormal cells, and the abnormal areas are biopsied for cancer detection.

The Uterus

The uterus is pyriform in shape and measures approximately 9 cm in length, 6.5 cm in width and 3.5 cm in thickness. It is divided anatomically and functionally into body and cervix. It weighs 1 ounce (60 g). The line of division corresponds to the level of the internal os, and here the

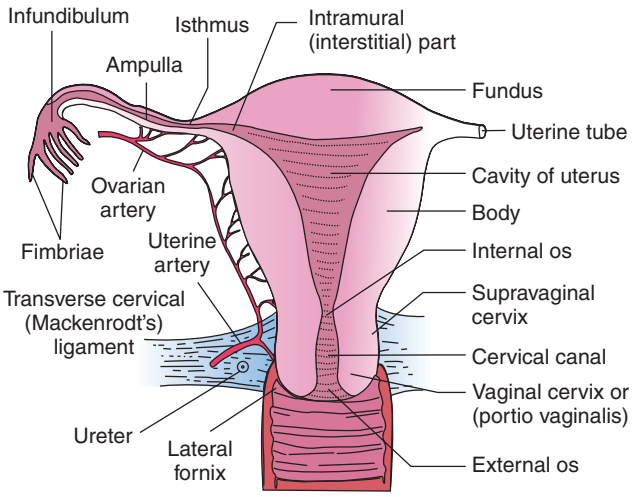


Figure 1.10 A nulliparous uterus showing the anatomical structures.

mucous membrane lining the cavity of the uterus becomes continuous with that of the cervical canal (Figure 1.10). At this level the peritoneum of the front of the uterus is reflected on to the bladder, and the uterine artery, after passing almost transversely across the pelvis, reaches the uterus, turns at right angle and passes vertically upwards along the lateral wall of the uterus. The cervix is divided into vaginal and supravaginal portions. The fundus of the uterus is that part of the corpus uteri which lies above the insertion of the fallopian tubes. The cavity of the uterus communicates above with the openings of the fallopian tubes, and by way of their abdominal ostia is in direct continuity with the peritoneal cavity. The uterine cavity is triangular in shape with a capacity of 3 mL. The lower angle is formed by the internal os. The lateral angle connecting to the fallopian tube is called the cornual end. The wall of the uterus consists of three layers, the peritoneal covering called perimetrium, the muscle layer or myometrium and the mucous membrane or endometrium.

The uterus is capable of distension during pregnancy, as well as with distended media during hysteroscopic examination. Otherwise the two walls are in opposition.

Perimetrium

The peritoneal covering of the uterus is incomplete. Anteriorly, the whole of the body of the uterus is covered with peritoneum. The peritoneum is reflected on to the bladder at the level of the internal os. The cervix of the uterus has therefore no peritoneal covering anteriorly. Posteriorly, the whole of the body of the uterus is covered by peritoneum, as is the supravaginal portion of the cervix. The peritoneum is reflected from the supravaginal portion of the cervix on to the posterior vaginal wall in the region of the posterior fornix. The peritoneal layer is incomplete laterally because of the insertion of the fallopian tubes, the round and ovarian ligaments into the uterus, and below this level the two sheets of peritoneum, which constitute the broad ligament, leave a thin bare area laterally on each side.

Myometrium

The myometrium is the thickest of the three layers of the wall of the uterus. In the cervix the myometrium consists of plain muscle tissue together with a large amount of fibrous tissue, which gives it a hard consistency. The muscle fibres and fibrous tissues are mixed together without orderly arrangement. In the body of the uterus the myometrium measures about 10–20 mm in thickness, and three layers can be distinguished which are best marked in the pregnant and puerperal uterus. The external layer lies immediately beneath the peritoneum and is longitudinal, the fibres passing from the cervix anteriorly over the fundus to reach the posterior surface of the cervix. This layer is thin and cannot easily be identified in the nulliparous uterus. The main function of this layer is a detrusor action during the expulsion of the fetus. The middle layer is the thickest of the three and consists of bundles of muscle separated by connective tissue, the exact amount of which varies with age; plain muscle tissue is best marked in the childbearing period, especially during pregnancy while before puberty and after menopause it is much less plentiful. There is a tendency for the muscle bundles to interlace, and as the blood vessels which supply the uterus are distributed in the connective tissues, the calibre of the vessels is in part controlled by the contraction of the muscle cells. The purpose of this layer is therefore in part haemostatic, though its expulsive role is equally important. This layer is described as *living ligatures of the uterus*, and is responsible for control of bleeding in the third stage of labour. Inefficient contraction and retraction of these muscle fibres cause prolonged labour and atonic postpartum haemorrhage (PPH).

The inner muscle layer consists of circular fibres. The layer is never well marked and is best represented by the circular muscle fibres around the internal os and the openings of the fallopian tubes. It can be regarded as sphincteric in action. The myometrium is thickest at the fundus (1–2 cm) and thinnest at the cornual end (3–4 mm), one should therefore be careful during curettage and endometrial ablation not to perforate the cornual end.

Endometrium

The endometrium or mucous membrane lining the cavity of the uterus has a different structure from that of the endocervix. It is described in Chapter 2, 'Normal Histology'.

The cervix is spindle shaped and measures 2.5 cm or a little more. It is bounded above by the internal os and below by the external os (Figure 1.10). The mucosal lining of the cervix differs from that of the body of the uterus by the absence of a submucosa. The endocervix is lined by a single layer of high columnar ciliated epithelium with spindle-shaped nuclei lying adjacent to the basement membrane with abundant cytoplasm and mucin. The direction of the cilia is downwards towards the external os. The glands are racemose in type (Figure 1.11A and B) and secrete mucus with a high content of fructose glycoprotein, mucopolysaccharide and sodium chloride. The secretion is alkaline and has a pH of 7.8 and its fructose content renders it attractive to ascending spermatozoa. This secretion collects as a plug in the cervical canal and possibly hinders ascending infections. In gonococcal and chlamydial infections of the cervix, the organisms collect amongst the crypts of the cervical glands. In nulliparous women, the external os is circular but vaginal delivery results in the transverse slit which characterizes the parous cervix. The cervix contains more of fibrous tissue and collagen than the muscle fibres, which are dispersed scarcely amongst the fibrous tissue. Cervix contains mainly collagen and only 10% of muscle fibres. Light microscopic examination reveals 29% muscle fibres in its upper one-third, 18% in the middle one-third and only 6% in the lower one-third, whereas the body of the uterus contains 70% muscle fibres. The change from fibrous tissue of cervix to the muscle tissue of the body is quite abrupt. In late pregnancy and at term, under the influence of

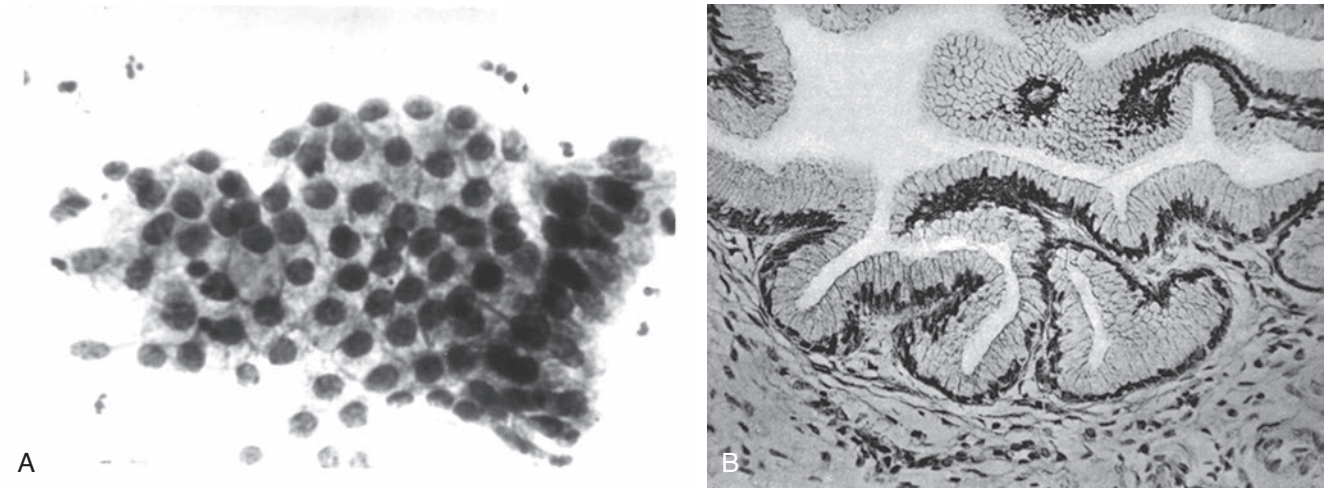


Figure 1.11 (**A**) Normal endocervical cells. (**B**) Normal cervical glands. These are of the racemose type and are lined by high columnar epithelium which secretes mucous (×250).

prostaglandin, collagenase dissolves collagen into fluid form and renders the cervix soft and stretchable during labour.

Functions of the endocervical cell lining are as follows:

- The cilia are directed downwards and prevent ascending infection.
- The cells sieve out abnormal sperms and allow healthy sperms to enter the uterus.
- It provides nutrition to the sperms.
- It allows capacitation of sperms.

Structurally and functionally, the body of the uterus and that of the cervix are in marked contrast. The cervical epithelium shows no periodic alteration during the menstrual cycle, and the decidual reaction of pregnancy is seen only rarely in the cervix. Similarly, the malignant disease of the uterus is an adenocarcinoma of the endometrium while carcinoma of the cervix is usually a squamous cell growth of high malignancy.

An intermediate zone, *the isthmus,* 6 mm in length, lies between the endometrium of the body and the mucous membrane of the cervical canal. Its epithelial lining resembles and behaves like the endometrium of the body. The isthmic portion stretches during pregnancy and forms the lower uterine segment in late pregnancy. This isthmic portion is less contractile during pregnancy and labour but further stretches under uterine contractions. It is identified during caesarean delivery by the loose fold of peritoneal lining covering its anterior surface.

The relationship between the length of the cervix and that of the body of the uterus varies with age. Before puberty, the cervix to corpus ratio is 2:1. At puberty, this ratio is reversed to 1:2, and during the reproductive years, cervix to corpus ratio may be 1:3 or even 1:4. After menopause, the whole organ atrophies and the portio vaginalis may eventually disappear.

Whereas the endometrial secretion is scanty and fluid in nature, the cervical secretion is abundant and its quality and quantity change in the different phases of the menstrual cycle, under different hormonal effects. The cervical mucous is rich in fructose, glycoprotein and mucopolysaccharides. Fructose is nutritive to sperms during their passage in the cervical canal. Under oestrogenic influence in the preovulatory phase, the glycoprotein network is arranged parallel to each other and facilitates sperm penetration, whereas under the progesterone secretion, the network forms interlacing bridges and prevents their entry into the cervical canal. This property of progesterone is used in contraceptive pill and progesterone-impregnated intrauterine contraceptive device. Sodium chloride content in the mucous increases at ovulation and forms a fern-like pattern when a drop of mucous is dried on a slide and studied under microscope.

Position of the Uterus

The uterus normally lies in a position of anteversion and anteflexion. The body of the uterus is bent forwards on the cervix approximately at the level of the internal os, and this forward inclination of the body of the uterus on the cervix constitutes anteflexion. The direction of the axis of the cervix depends upon the position of the uterus. In anteversion (Figure 1.12B), the external os is directed downwards and backwards so that on vaginal examination the examining fingers find that the lowest part of the cervix is the anterior lip. When the uterus is retroverted the cervix is directed downwards and forwards, and the lowest part of the cervix is either the external os or the posterior lip. As a result of its normal position of anteflexion, the body of the uterus lies against the bladder. The pouch of peritoneum that separates the bladder from the uterus is the uterovesical pouch. The peritoneum is reflected from the front of the uterus on to the bladder at the level of the internal os.

Posteriorly, a large peritoneal pouch lies between the uterus and the rectosigmoid colon. If the uterus is pulled forwards, two folds of peritoneum can be seen to pass backwards from the uterus to reach the parietal peritoneum lateral to the rectum. These folds, the uterosacral folds, lie at the level of the internal os and pass backwards and upwards. The uterosacral ligaments are condensation of the pelvic cellular tissues and lie at a lower level and within the uterosacral folds. The pouch of peritoneum below the level of the uterosacral folds, which is bounded in front by the peritoneum covering the upper part of the posterior vaginal wall and posteriorly by the peritoneum covering the sigmoid colon and the upper end of the rectum, is the pouch of Douglas. The posterior fornix of the vagina is in close relation to the peritoneal cavity, as only the posterior vaginal wall and a single layer of peritoneum separate the vagina from the peritoneal cavity. Collection of pus in the pouch of Douglas can therefore be evacuated without difficulty by incising the vagina in the region of the posterior fornix. On the other hand, the uterovesical pouch is approached with difficulty from the vagina; first the vagina must be incised and then the bladder separated from the cervix and the vesicocervical space traversed before the uterovesical fold of the peritoneum is reached (Figure 1.12A).

The Uterine Appendages

The uterus projects upwards from the pelvic floor into the peritoneal cavity and carries on each side of it two folds of peritoneum, which pass laterally to the pelvic wall and form the *broad ligaments.* The fallopian tubes pass outwards from the uterine cornua and lie in the upper border of the broad ligaments. The ovarian ligaments posteriorly, and the round ligaments anteriorly, also pass into the uterine cornua, but at a slightly lower level than the fallopian tubes. Both these ligaments and the fallopian tubes are covered with peritoneum.

The *round ligament* passes from the uterine cornua beneath the anterior peritoneal fold of the broad ligament to reach the internal abdominal ring. In this part of its course it is curved and lies immediately beneath the peritoneum, and is easily distinguished. The round ligament passes down the inguinal canal and finally ends by becoming adherent to the skin of the labia majora. The ligaments consist

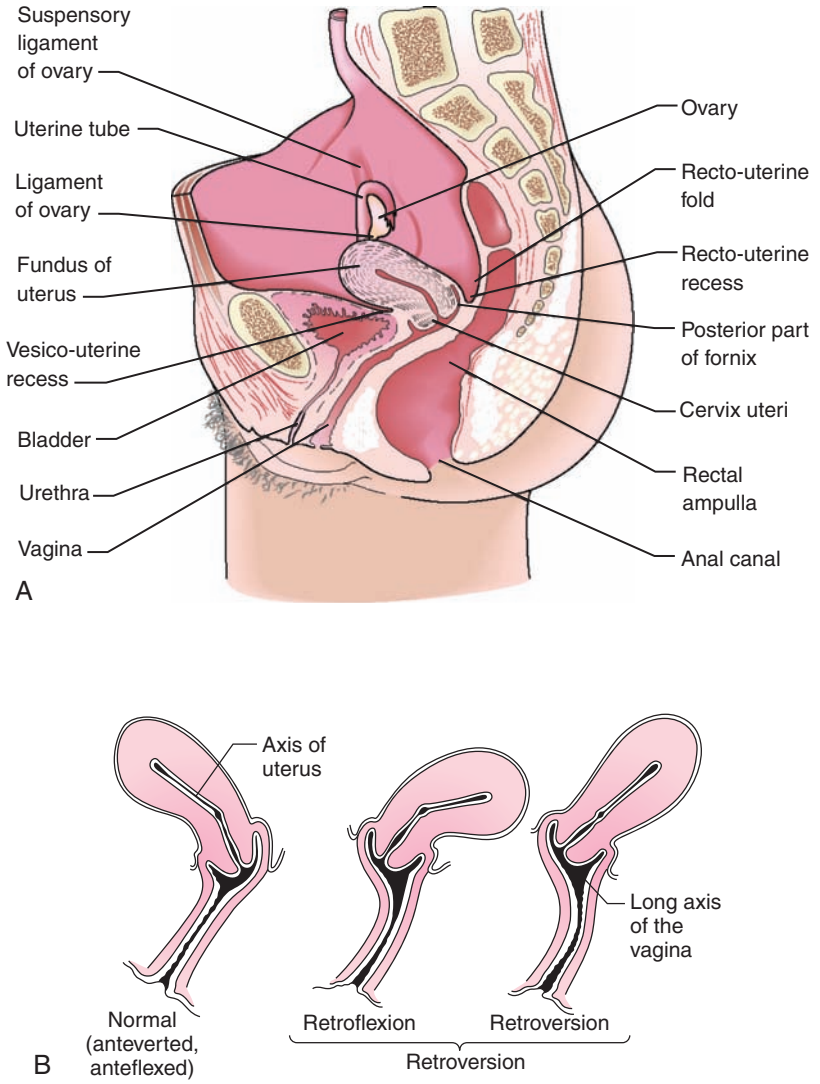


Figure 1.12 **(A)** The relationship of the female reproductive organs: sagittal section. (From Figure 7-1. Chris Brooker: Alexander's Nursing Practice, 4th Ed. Churchill Livingstone: Elsevier, 2011.) **(B)** Anteverted, anteflexed and retroverted uterus.

of plain muscle and connective tissue and vary considerably in thickness. They hypertrophy during pregnancy. The round ligaments are much better developed in multiparae than in nulliparae. They are most remarkably hypertrophied in the presence of large fibroids when they may attain a diameter of 1 cm. They correspond developmentally to the gubernaculum testis and are morphologically continuous with the ovarian ligaments, as during intrauterine life the ovarian and round ligaments are continuous and connect the lower pole of the primitive ovary to the inguinal canal. The round ligaments are lax and, except during labour, are free of tension. There is no evidence that the normal position of anteflexion and anteversion of the uterus is produced by contraction of the round ligaments. The ligaments, however, may be shortened by operation or they may be attached to the anterior abdominal wall, both procedures being used to cause anteversion in a uterus which is pathologically retroverted. The round ligaments are supplied by a branch of the ovarian artery derived from its anastomosis with the uterine artery, hence the necessity for ligation of the round ligament during hysterectomy. Along it lymphatic vessels pass from the fundus, which connect with those draining the labium majus into the inguinal glands. This explains the possibility of metastases in these glands in late cases of cancer of the endometrium of the fundus.

The *ovarian ligaments* pass upwards and inwards from the inner poles of the ovaries to reach the cornua of the uterus (Figure 1.13) below the level of the attachment of the fallopian tubes. They lie beneath the posterior peritoneal fold of the broad ligament and measure about 2.5 cm in length. Like the round ligaments, they consist of plain muscle fibres and connective tissue, but they are not so prominent because they contain less plain muscle tissue. They are morphologically a continuation of the round ligament (contents of broad ligaments are listed in Table 1.1).

Infundibulopelvic ligament is that portion of the broad ligament that extends from the infundibulum of the fallopian tube to the lateral pelvic wall. It encloses the ovarian vessels, lymphatics and nerves of the ovary. The ureter

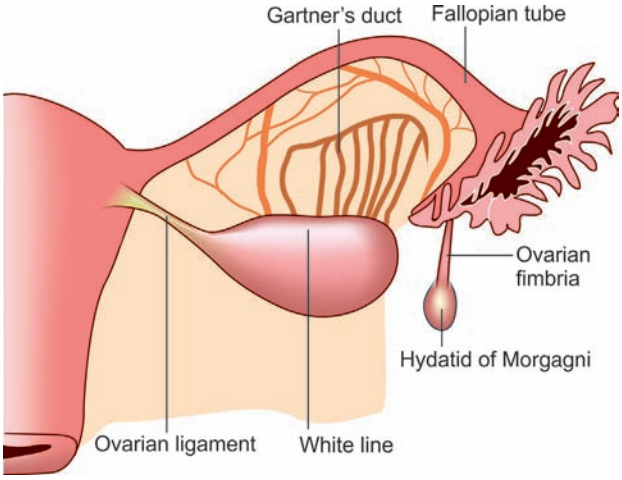


Figure 1.13 The right uterine appendages viewed from behind.

TABLE 1.1 Contents of broad ligament

- Fallopian tube—upper portion
- Round ligament—anteriorly
- Ovarian ligament—posterior fold
- Vestigial structures of Wolffian body—epoophoron and paroophoron
- Vestigial structure of Wolffian duct—Gartner's duct
- Ureter
- Uterine vessels
- Pelvic nerves
- Parametrial lymph node
- Pelvic cellular tissue condensed to form Mackenrodt's ligament
- Infundibulopelvic ligament

is also in close contact and can be damaged during clamping of this ligament.

Mesovarium attaches the ovary to the posterior fold of peritoneum of the broad ligament and contains vessels, lymphatics and nerves of the ovary. Mesosalpinx lies between the fallopian tube and the ovary and contains the anastomotic vessels between the ovary and uterus and the vestigial structures of the Wolffian body and the duct (see section on The Ovaries).

Fallopian Tubes

Each fallopian tube (Figures 1.13 and 1.14) is attached to the uterine cornu and passes outwards and backwards in the upper part of the broad ligament. The fallopian tube measures 4 inch (10 cm) or more in length and approximately 8 mm in diameter, but the diameter diminishes near the cornu of the uterus to 1 mm. The fallopian tube is divided anatomically into four parts:

1. **The interstitial portion** is the innermost part of the tube which traverses the myometrium to open into the endometrial cavity. It is the shortest part of the tube, its length being the thickness of the uterine muscle, about 18 mm. It is also the narrowest part, its internal diameter being 1 mm or less so that only the finest cannula can be passed into it during falloscopy examination. There are no longitudinal muscle fibres here but the circular fibres are well developed (Figure 1.15).
2. **The isthmus** comprises the next and inner part of the tube and represents about one-third of the total length, i.e. 35 mm. It is narrow but a little wider than the interstitial part and its lumen has a diameter of 2 mm. Its muscle wall contains both longitudinal and circular fibres, and it is covered by peritoneum except for a small inferior bare area related to the broad ligament. It is relatively straight.
3. **The ampulla** is the lateral, widest and longest part of the tube and comprises roughly two-thirds of the tube, measuring 2.5–3 inch (60–75 mm) in length. Here the mucosa is arborescent with many complex folds (Figure 1.16). Fertilization occurs in the ampullary portion of the fallopian tube.
4. **The fimbriated extremity or infundibulum** is where the abdominal ostium opens into the peritoneal cavity. The fimbriae are motile and almost prehensile, and enjoy a considerable range of movement and action. One fimbria—the ovarian fimbria—is larger and longer than

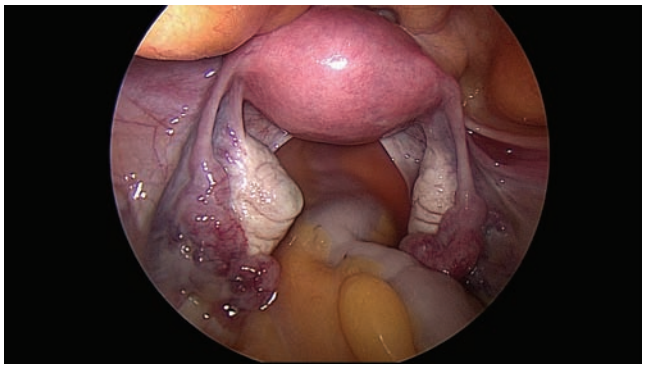


Figure 1.14 Laparoscopic view of the pelvis showing normal uterus and bilateral adnexa. (Courtesy: Dr Marwah.)

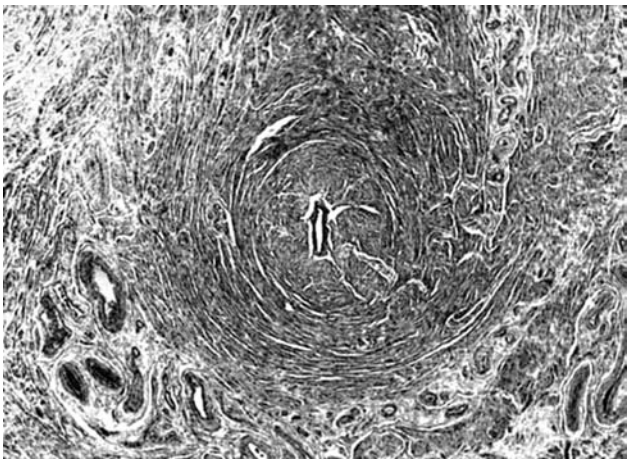


Figure 1.15 Interstitial part of fallopian tube. Note complete absence of plicae and the narrow calibre of the canal (×22).

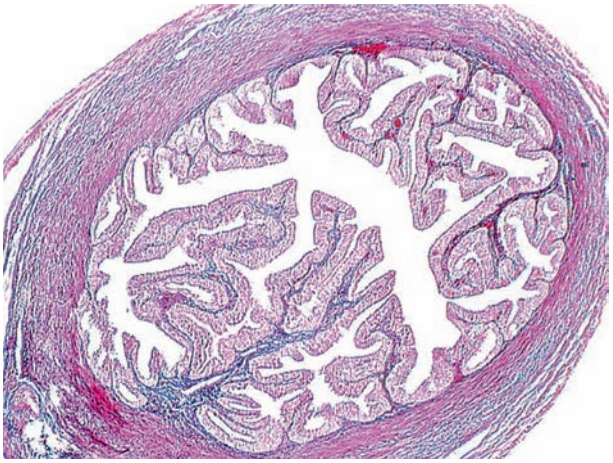


Figure 1.16 Ampullary portion of fallopian tube to show arrangement of plicae (×18). (Source: Gwen V Childs, PhD, Professor and Chair, Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Little Rock.)

the others and is attached to the region of the ovary. This fimbria embraces the ovary at ovulation, picks up the ovum and carries it to the ampullary portion.

The fallopian tube represents the cranial end of the Müllerian duct, and its lumen is continuous with the cavity of the uterus. Consequently, spermatozoa and the fertilized ovum can pass along the tube. Fluids such as dyes and gases such as carbon dioxide may be injected through the uterus and by way of the fallopian tubes into the peritoneal cavity, and by these means the patency of the fallopian tubes can be investigated clinically by dye test (Figure 1.17). The fallopian tubes lie in the upper part of the broad ligaments and are covered with peritoneum except along a thin area inferiorly, which is left bare by the reflection of the peritoneum to form the two layers of the broad ligament. The blood supply of the fallopian tube is mainly derived from the tubal branches of the ovarian artery, but the anastomosing branch of the uterine artery supplies its inner part. Unlike the vermiform appendix, the fallopian tube does not become gangrenous when acutely inflamed, as it has two sources of blood supply which reach it at opposite ends. The lymphatics of the fallopian tube communicate with the lymphatics of the fundus of the uterus and with those of the ovary, and they drain along the infundibulopelvic ligament to the para-aortic glands near the origin of the ovarian artery from the aorta. Some drain into the pelvic glands.

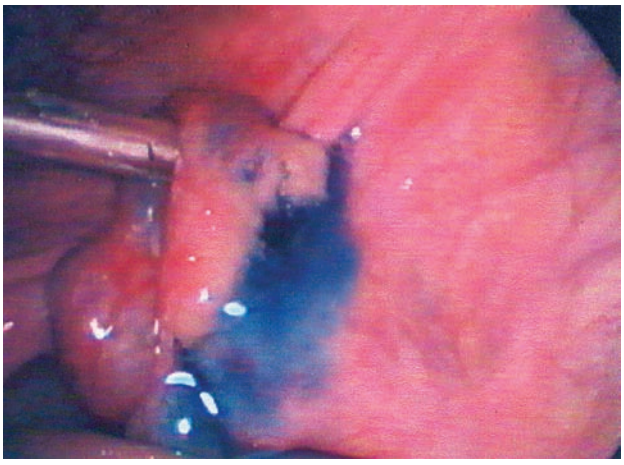


Figure 1.17 Fimbrial end of a patent fallopian tube. Dye test shows spill.

The fallopian tubes have three layers: serous, muscular and mucous. The serous layer consists of the mesothelium of the peritoneum. Intervening between the mesothelium and the muscle layer is a well-defined subserous layer in which numerous small blood vessels and lymphatics can be demonstrated. The muscular layer consists of outer longitudinal and inner circular fibres. The circular fibres are best developed in the isthmus and are thinned out near the fimbriated extremity. The mucous membrane is thrown into folds or plicae. Near the isthmus three folds can be recognized, but when traced laterally they divide and subdivide so that in the ampullary region they become highly complex. Each plica consists of stroma which is covered by epithelium. The stroma is cellular and its cells are in some ways similar to those of the endometrium. The blood vessels of the stroma are plentiful and are particularly well marked in the ampullary region. The epithelium of the mucous membrane consists of three types of cells: the most common is ciliated, and is either columnar or cubical in type. Its function is to propel a fluid current towards the uterus and plays some part in the transport of the inert ovum which, unlike the sperm, has no motile power of its own. Next in order of frequency is a goblet-shaped cell, not ciliated, which does not give the histochemical reactions for mucin. Its function is lubricant and possibly nutritive to the ovum. A cell intermediate in type to the two already mentioned can be distinguished, and small rod-shaped cells are also present. These are the so-called peg cells whose purpose is not known. It has been possible to demonstrate differences in the histological appearances of the epithelium of the fallopian tubes during the menstrual cycle. *The hysterosalpingogram, sonosalpingogram and laparoscopic chromotubation are the clinical methods of testing the patency of the fallopian tubes*. Laparoscopy also identifies external tubal adhesions.

The Ovaries

Each ovary weighs 4–8 g and measures about 35 mm in length, 25 mm in width and 18 mm in thickness. The ovary (Figures 1.14 and 1.18) is almond shaped, pearly grey due to a compact tunica albuginea, and the surface is slightly corrugated. Before puberty, the ovaries are small and located near the pelvic brim. After menopause they atrophy and become shrunken and the grooves and furrows on the surface become well marked. The menopausal ovary measures 20 mm × 10 mm × 15 mm with a volume of 8 mL or less. An ovary larger than this as measured ultrasonically

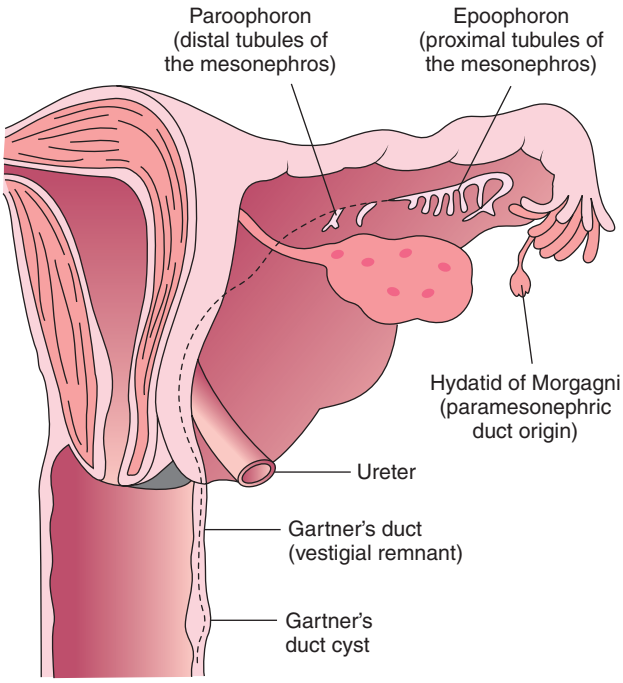


Figure 1.18 Remnants of the mesonephric (Wolffian) ducts that may persist in the anterolateral vagina or adjacent to the uterus within the broad ligament or mesosalpinx.

is of great concern in menopausal women. The ovary is attached to the back of the broad ligament by a thin mesentery, the *mesovarium*. Laterally, the ovary is related to the fossa below the bifurcation of the common iliac artery and the ureter. Medially, it is close to the fimbria of the fallopian tube, which stretches over it around ovulation. It is attached to the cornu of the uterus by the ovarian ligament. The infundibulopelvic ligament is the outer border of the broad ligament and contains the ovarian vessels, nerves and lymphatics. The ovaries are not normally palpable during bimanual examination, but cause pain on touch. The *epoophoron,* also known as the organ of Rosenmüller, represents the cranial end of the Wolffian body. It consists of a series of vertical tubules in the mesovarium and mesosalpinx between the fallopian tube above and the ovary below. Each tubule is surrounded by plain muscle and is lined by cubical cells.

The paroophoron represents the caudal end of the Wolffian body and similarly contains vertical tubules. It sometimes forms paraovarian cyst.

The Wolffian duct (Gartner's duct) is an imperfect duct which runs parallel to, but below, the fallopian tube in the mesosalpinx. The duct passes downwards by the side of the uterus to the level of the internal os where it passes into the tissues of the cervix. It then runs forwards to reach the anterolateral aspect of the vaginal wall and may reach as far down as the hymen. The duct sometimes forms a cyst, called Gartner's cyst, in the broad ligament or in the vagina, and may need surgical enucleation (Figure 1.18). Histology of the ovary is described in Chapter 2.

The Urethra

The urethra measures 35 mm in length and 5–6 mm in diameter. It passes downwards and forwards from the base of the bladder behind the symphysis pubis to end in the external meatus. Its epithelial lining consists of squamous epithelium at the external meatus, but becomes transitional in the canal. Deep to the epithelium is a layer rich in small vessels and connective tissue. The urethral wall comprises inner longitudinal and outer circular involuntary muscle fibres, which are arranged as crisscross spirals. The longitudinal fibres contract and shorten the urethra during micturition. The outer circular fibres keep the internal sphincter closed.

The neck of the bladder (internal urethral sphincter) lies above the levator ani muscles and thus maintains the continence of urine by receiving the same abdominal pressure as the bladder. The bladder base forms an angle of 100° with the posterior urethral wall (posterior urethrovesical angle), which is also responsible for maintaining urinary continence.

Relations

Posteriorly, upper portion of the urethra is loosely connected to the vagina by vesicovaginal fascia and can be dissected easily. In its lower one-third, it is firmly attached to the vagina by pubourethral ligament and requires a sharp dissection. Laterally, it is surrounded by the areolar tissue, the compressor urethra and the superficial perineal muscles. Pubourethral ligament fixes the mid-urethra to the pubic bone and the lateral pelvic wall and maintains continence of urine. Anteriorly, the urethra is separated from the pubic bone by the areolar tissue.

The external urinary meatus lies in the vestibule, 2 cm below the clitoris and is partly concealed by the upper end of the labia minora. Numerous periurethral glands surround the urethra and open by tiny ducts into its lumen. These are analogues of the prostate in males. The paraurethral glands of Skene are important paired glands which lie alongside the floor of the urethra and open by tiny ducts close to the external meatus. The glands when infected form periurethral abscess and cysts.

The proximal urethra derives blood supply from the inferior vesical artery and distal urethra from internal pudendal artery. The veins drain into the vesical plexus and internal pudendal vein. The urethra is innervated by the internal pudendal nerve. The urethra is developed from the cloaca.

The proximity of the urethra to the vagina makes it susceptible to infection spreading from the lower genital tract. The commonest infective organisms are gonorrhoea, chlamydia and trichomonads. The urethral swab, culture and urine culture can identify the organisms.

The Bladder

The bladder is a smooth muscle organ with a body and a trigone. It lies between the symphysis pubis in front and the uterus behind, being separated from the uterus by the

uterovesical peritoneum. It is a pelvic organ with a capacity to hold 500–600 mL of urine. The bladder distends upwards with a fixed base at the trigone, and then becomes palpable abdominally.

The bladder has an apex, a base, a superior and two inferolateral surfaces. The neck of the bladder (internal urinary sphincter) lies above the levator ani muscles, so that the raised abdominal pressure transmits the pressure equally to the bladder and its neck, hence maintaining urinary continence during coughing and sneezing. Anteriorly, lies the cave of Retzius (retropubic space). Posteriorly, it is in proximity to the uterus and supravaginal portion of the cervix, separated from them by the uterovesical pouch of peritoneum.

The ureters enter the bladder obliquely, and the area between the ureteric openings and the internal urinary sphincter forms a fixed triangular area called trigone. The apex is continuous with the urachus.

The bladder receives blood supply from the superior and inferior vesical arteries, and the pubic branch of the inferior epigastric artery. The venous plexus drains into internal iliac vein. The lymphatics drain into internal and external iliac glands.

Nerve Supply

The sympathetic outflow is from first and second lumbar segments of the spinal cord which inhibits contractions of the detrusor (bladder) muscle and maintains internal sphincteric contraction. The parasympathetic outflow from S2, S3 and S4 stimulates the detrusor muscle and relaxes the internal sphincter, thus initiating micturition. The sensory nerve fibres reach the central nervous system via the splanchnic nerves (parasympathetic S2–S4). The somatic afferent fibres travel with sympathetic nerves via hypogastric plexus and enter the first and second lumbar segments of the spinal cord. The bladder wall is lined by transitional epithelium, which gets folded when empty but allows bladder distension. The lining membrane of the trigone is fixed to the muscle wall. The muscular coat of the bladder is composed of smooth muscle known as detrusor. The neck of the bladder (internal urinary sphincter) is surrounded by circular muscle fibres.

The Ureter

Every gynaecologist should be familiar with the anatomy of the pelvic portion of the ureter, as injury can occur during pelvic surgery. The ureter needs to be dissected during Wertheim's hysterectomy for cancer of the cervix. The ureter may run in close relation to the broad ligament cyst and myoma.

The pelvic portion of the ureter is 13 cm long and 5 mm in diameter. It passes over the bifurcation of the common iliac artery and runs downwards and forwards in the ovarian fossa deep to the peritoneum. Where it enters the true pelvis at the brim it is crossed by the ovarian vessels, and on the left side the mesosigmoid is an anterior relation. In this situation, the obturator vessels and nerve lie laterally, and the hypogastric lymph nodes are closely related. The course of the ureter is then downwards and forwards immediately beneath the peritoneum to which it is always closely attached.

On the pelvic floor, the ureter pierces Mackenrodt's ligament where a canal, the ureteric canal, is developed. It is necessary that the ureter must have room for normal peristalsis without any pressure from the surrounding structures, and the ureteric canal protects the ureter from the outside pressure. In its passage through the ureteric canal, the ureter is crossed by the uterine artery above and the uterine plexus of veins below, thus being forked between the uterine vessels. After leaving the ureteric canal, the ureter passes forwards and medially to reach the bladder, being separated from the cervix by a distance of 1–2 cm (Figure 1.19). The course of the ureter through the pelvis is

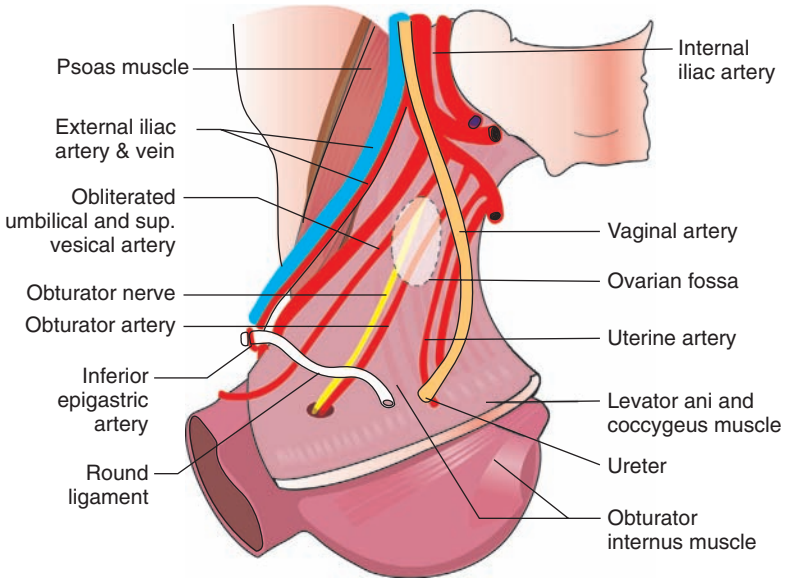


Figure 1.19 Relation of the ureter to the pelvic vessels in the ovarian fossa.

not always constant. At operation, the ureter is recognized by its pale glistening appearance and by a fine longitudinal plexus of vessels on its surface, but more particularly by its peristaltic movements. It can also be recognized by palpation between the finger and the thumb as a firm cord, which, as it escapes, gives a characteristic snap. The ureter is rarely duplicated. In advanced stage of cancer of the cervix with extensive involvement of the parametrium, stricture of the ureter causes hydronephrosis and uraemia.

The ureter derives its blood supply from the common, external and internal iliac arteries in addition to a constant vessel from the uterine and inferior vesical artery. The vessels form a longitudinal anastomosis up and down the ureter which protects the ureter from ischaemia if one vessel is ligated or injured. However, damage of several small vessels can cause avascular necrosis and ureteric fistula. The small branches of the renal artery also supply blood to the ureter above the pelvic brim.

The blood supply to the pelvic ureter is principally from the lateral side, and the ureteric dissection should be done along its medial side.

The injury to the ureter occurs at the infundibulopelvic ligament on the lateral pelvic wall, in the ureteric canal when the uterine vessels are ligated, near the internal cervical os and near the uterosacral ligament. It is important to identify the ureter during Wertheim hysterectomy, broad ligament tumour dissection and while ligating the internal iliac artery.

The lymphatics drain into internal and external iliac glands. The sympathetic nerve supply comes from hypogastric and pelvic plexus; para sympathetic from sacral plexus.

The Rectum and Anal Canal

The rectum is the continuation of the pelvic colon and lies in the pelvis at the level of third sacral vertebrae. It measures 12–15 cm and continues as anal canal. It is covered anteriorly and laterally by pelvic peritoneum which forms the posterior surface of the pouch of Douglas. Lower down, it is in close contact with the posterior vaginal wall, separated by rectovaginal septum. The anal canal is separated from the lower one-third of posterior vaginal wall by the perineal body. Posteriorly, it lies close to the sacrum and coccyx with loose articular tissue, middle sacral artery and pelvic nerve plexus. Laterally lie the two uterosacral ligaments above and levator ani muscles below and ischiorectal fossa. The rectum is surrounded by rectal fascia. The anal canal measures 2.5 cm. Anteriorly, it is related to the perineal body and posteriorly to the anococcygeal body. It has two sphincters: (i) involuntary internal sphincter in the upper two-thirds and (ii) voluntary external sphincter surrounded by puborectalis muscle of the levator ani muscle below.

The rectum and anal canal receive the blood supply from (i) superior rectal branch of interior mesenteric artery and (ii) middle and inferior rectal branches of internal iliac artery. The rectum and upper one-third of anal canal drain via superior rectal veins into portal circulation. Lower one-third portion of anal canal drains into inferior rectal vein (systemic circulation).

The Lymphatics

The rectum and upper one-third of anus drain into internal iliac and preaortic lymphatic nodes. Lower one-third drains into superficial inguinal lymph nodes.

Autonomic pelvic plexus innervate the rectum and upper portion of the anal canal. The lower portion of the anal canal is innervated by the inferior haemorrhoidal nerve. The rectum and upper two-thirds of the anal canal develop from the dorsal portion of the cloaca. The lower anal canal is derived from ectoderm.

Breasts

The breasts are bilateral modified sweat glands extending from second to sixth intercostal spaces in the midclavicular line (Figure 1.20). Each breast contains 15–20 lobes and each lobe is made up of acini, ducts and fat. All the ducts open into the nipple. Each breast receives blood supply from lateral thoracic branches of axillary artery and intercostal arteries. The veins accompany the arteries. The lymphatics drain into axillary, transpectoral and internal mammary nodes, hence the need to remove them in breast cancer. The nerves come from fourth, fifth and sixth intercostal nerves.

During pregnancy, the oestrogen and progesterone hormones cause increased vascularity and size in the breasts, and also skin pigmentation. The raised prolactin level starts watery and milk secretion from early weeks onwards. The parenchyma of the breast develops from ectoderm, but stroma is derived from mesoderm.

The Pelvic Musculature

The pelvic muscles of importance in gynaecology are those of the pelvic floor. These muscles are grouped into three layers: (i) those of the pelvic diaphragm; (ii) those of the

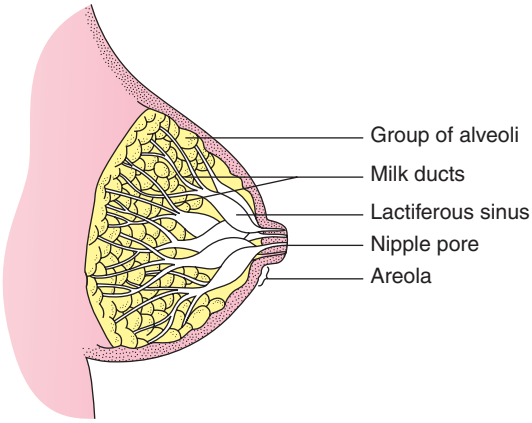


Figure 1.20 Anatomy of the female breast.

urogenital diaphragm and (iii) the superficial muscles of the pelvic floor.

Pelvic Diaphragm

The pelvic diaphragm consists of two levator ani muscles. Each levator ani muscle consists of three main divisions: the pubococcygeus, the iliococcygeus and the ischiococcygeus. The pubococcygeus muscle arises from the posterior surface of the body of the pubic bone and passes backwards, lateral to the vagina and the rectum, to be inserted into the anococcygeal raphe and into the coccyx. The inner fibres which come together posterior to the rectum are known as the puborectalis portion of the muscle: they sling up and support the rectum. Some of the inner fibres of the puborectalis fuse with the outer wall of the vagina as they pass lateral to it. Other fibres decussate between the vagina and the rectum in the situation of the perineal body. These decussating fibres divide the space between the two levator ani muscles into an anterior portion, the hiatus urogenitalis, through which passes the urethra and vagina, and a posterior portion, the hiatus rectalis, through which passes the rectum. The dimensions of the hiatus urogenitalis depend upon two main factors: the tone of the levator muscles and the existence of the decussating fibres of the puborectalis muscle.

Perineal tears occurring during parturition divide these decussating fibres, causing the hiatus urogenitalis to become patulous and lead to prolapse. In visceroptosis and asthenic states, the levator muscles become lax, the dimensions of the hiatus urogenitalis are increased and there is a tendency for the pelvic viscera to prolapse. The iliococcygeus is a fan-shaped muscle arising from a broad origin along the white line of the pelvic fascia and passing backwards and inwards to be inserted into the coccyx. The ischiococcygeus or coccygeus muscle has a narrow origin from the ischial spine and spreads out posteriorly to be inserted into the front of the coccyx (Figures 1.21 and 1.22).

The levator muscles together constitute the pelvic diaphragm and support the pelvic viscera: contraction of the levator muscle pulls the rectum and vagina towards the symphysis pubis; the rectum is thereby kinked and closed, and the vagina narrowed anteroposteriorly. The origin of the levator muscle is fixed because the muscle arises anteriorly either from bone or from fascia which is attached to the bone; posteriorly the insertion is either into the anococcygeal raphe or into the coccyx, both of which are moveable. It follows that the contraction of the levator muscles leads to the posterior attachments being pulled towards the symphysis pubis. The movement of the internal rotation of the presenting part during parturition is assisted by this property of the levator muscles. Uterine contractions push the presenting part down upon the levator ani (pelvic floor) and cause the muscles to contract as a result of the direct pressure of the presenting part. The lowest part of the fetus is carried forwards during the contractions of the levator muscles, and as the anterior fibres of the muscles are directed inwards as well as forwards, the presenting part rotates forwards and inwards.

The superior and inferior surfaces of the levator muscles are covered by the pelvic fascia, which separates the muscles from the cellular tissues of the parametrium above and from the fibrous and fatty tissues of the ischiorectal fossa below.

Urogenital Diaphragm

The urogenital diaphragm is also called the triangular ligament. It is not so well developed in the female as in the male. It extends from the pubic arch anteriorly to the central point of the perineum posteriorly and consists of two layers of fascia through which pass the vagina and the urethra. The central point of the female perineum lies between the vagina and the rectum. Within the two fascial layers of the urogenital diaphragm lies the deep transverse perineal muscle, which extends laterally on each side to reach the

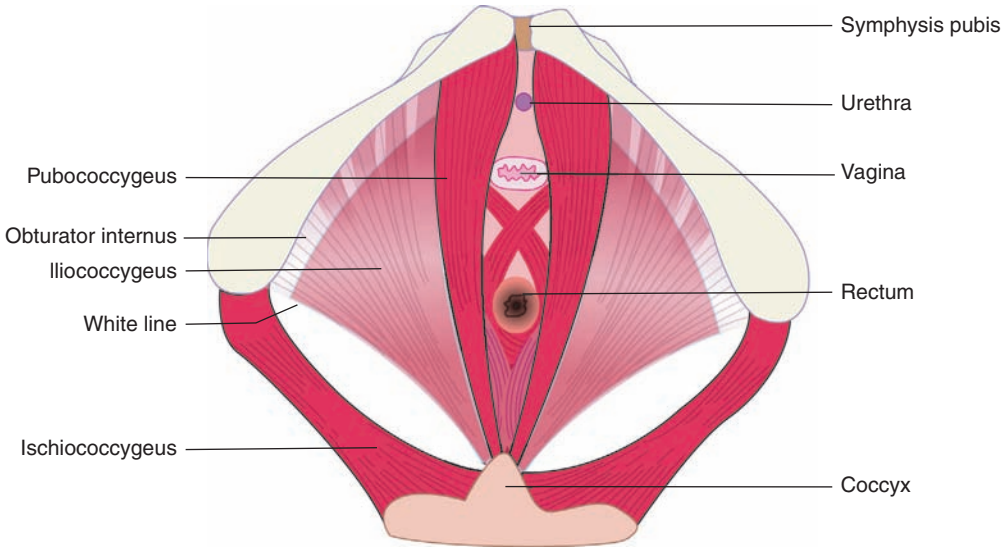


Figure 1.21 The muscular pelvic floor seen from above after the removal of the pelvic viscera and pelvic fascia.

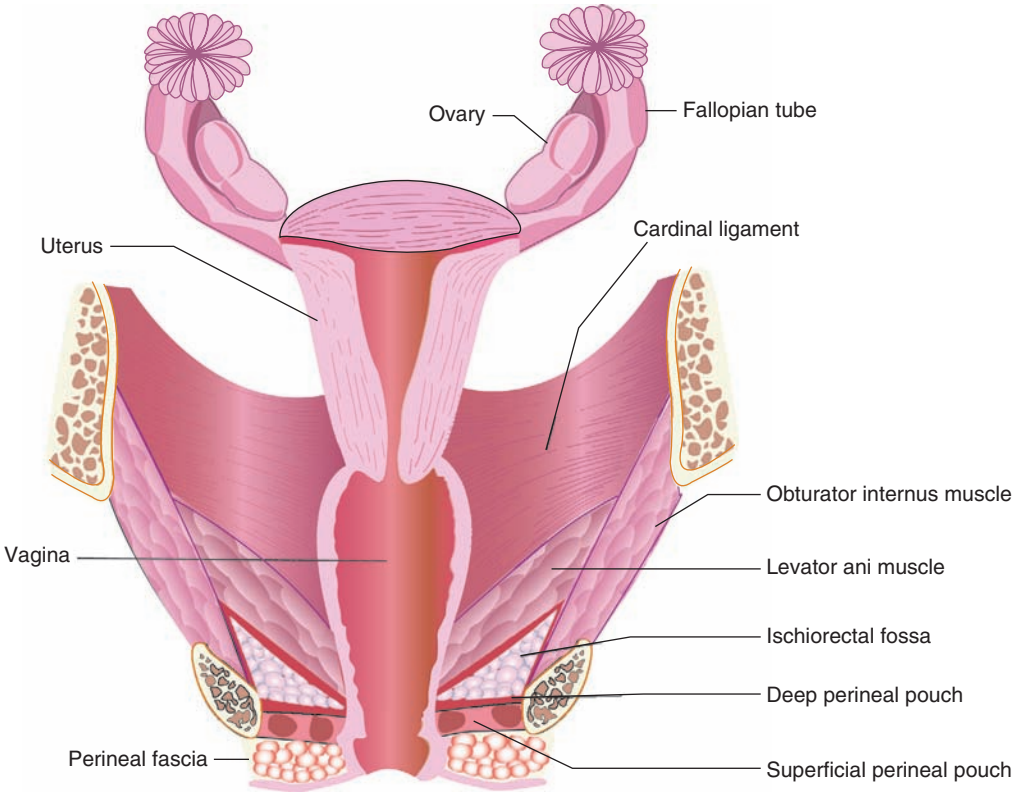


Figure 1.22 Anatomy of the pelvic floor in coronal section.

ramus of the pubic bone. This muscle is so poorly developed that it is difficult to dissect in anatomical specimens and needs a special histological technique for its demonstration. Its functional significance is dubious. The striped muscle or voluntary sphincter of the urethra also lies between the two layers of the triangular ligament.

Superficial Muscles

Four muscles are identified in this layer. The external sphincter muscle of the anus is attached anteriorly to the central point of the perineum and surrounds the anus. The bulbospongiosus muscle, or as it is sometimes called the sphincter vaginae, extends from the central point of the perineum along each side of the vagina to be attached anteriorly to the symphysis pubis. It lies around and lateral to the urethral bulb. The ischiocavernous muscle extends on each side of the ischial tuberosity in relation to the crura of the clitoris to reach it in the midline. The superficial transverse muscle of the perineum passes laterally on each side from the central point of the perineum to the pubic ramus (Figure 1.23). Deep to these superficial muscles and between them and the inferior layer of the triangular ligament lie the vestibular bulb and the greater vestibular glands of *Bartholin*.

The *perineal body* intervenes between the posterior vaginal wall and the anal canal. It is pyramidal in shape with its apex on a level with the junction of the middle and lower thirds of the posterior vaginal wall. The three layers of the muscles of the pelvic floor are represented in the perineal body, and the intervening tissue consisting of fat and fibrous tissue. Superficially, passing from the central point of the perineum are the external sphincter of the anus, the bulbospongiosus and the superficial transverse muscle of the perineum. Deep to this layer lies the fascial layer of the urogenital diaphragm (triangular ligament) enclosing the deep transverse muscle of the perineum. Deeper still, the pelvic diaphragm is represented by the fibres of the levator ani muscles which decussate between the vagina and the rectum. The perineal body is examined by inspection and by palpation. Two fingers are placed in the vagina and flexed laterally; the thumb being applied externally over the labium majus, the levator muscles can be palpated with remarkable ease and the size of the hiatus urogenitalis can be assessed. On asking the patient to contract her pelvic floor muscles, the tone of these muscles can be estimated.

Prolapse of the genital tract, stress incontinence of urine and faecal incontinence are all related to laxity and atonicity of the muscles of the pelvic floor as well as denervation of pelvic nerves during childbirth. Lately, perineal ultrasound and MRI have greatly improved our knowledge of these supportive structures in maintaining the uterine position and continence of urine and faeces.

The Pelvic Cellular Tissue

The pelvic cellular tissue consists of loose areolar tissue which intervenes between the pelvic peritoneum above and the pelvic fascia below. It is continuous with the subperitoneal connective tissue and with the loose tissue of the

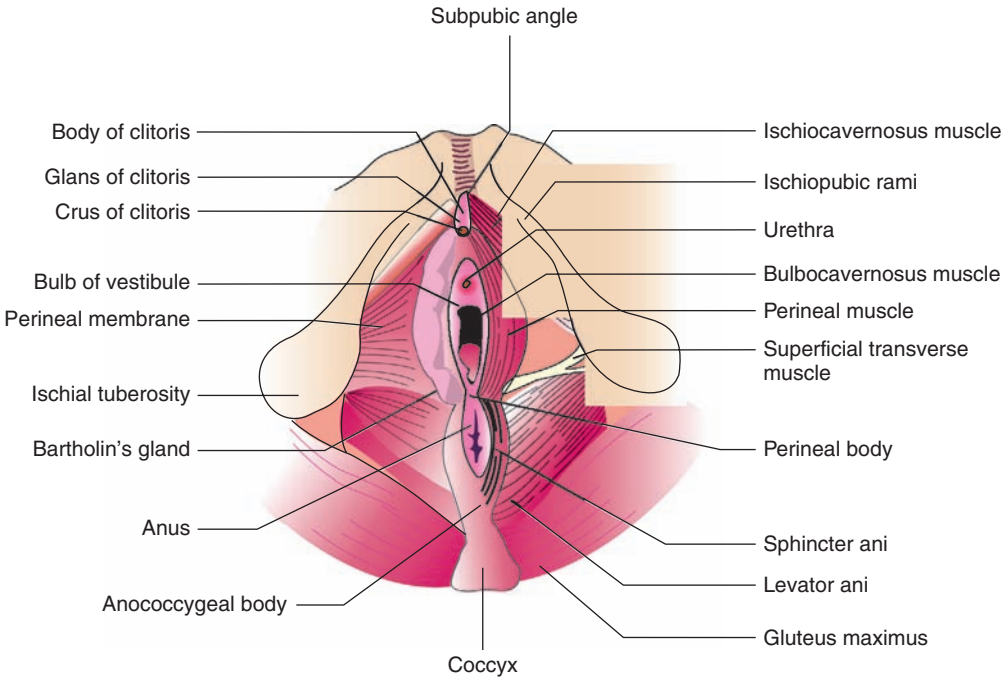


Figure 1.23 The perineum.

perinephric region. The areolar tissue is loose, and when inflamed in the condition of pelvic cellulitis it may lead to the formation of a palpable swelling. As there is a direct continuation between the perinephric and pelvic cellular tissues, effusions arising in either of these situations may track to point as an abscess in the other. In the pelvis, the pelvic cellular tissue is bounded above by the peritoneum and below by the fascia which covers the upper surface of the levator ani muscles. Laterally it is bounded by the pelvic wall, mainly by the fascia which covers the inner surface of the obturator internus while medially it comes into contact with the uterus and the upper part of the vagina.

The **parametrium** is that part of the pelvic cellular tissue which surrounds the uterus. It is by definition extraperitoneal and is most plentiful on each side of the uterus below the level of the internal os. The endopelvic fascia in this region thickens to form ligamentous supports called *Mackenrodt's or cardinal ligaments*. Above this level, the presence of the broad ligaments reduces the amount of parametrium to a minimum. It should be remembered that the level of the levator ani muscle is well below the level of the cervix, being more than halfway down the vagina. The pelvic cellular tissue is usually very plentiful on each side of the vagina, where it is called paravaginal cellular tissue or paracolpos.

A distinction is drawn between the pelvic fascia and the endopelvic fascia. The pelvic fascia consists of the dense connective tissue which covers the surfaces above and below the levator ani and the obturator internus muscles. On the other hand, the endopelvic fascia forms the connective tissue coverings for the vagina, the supravaginal portion of the cervix, the uterus, the bladder, the urethra and the rectum. In addition, condensed bands of endopelvic fascia pass from these moveable organs to the back of the pubic bones, to the lateral walls of the pelvis and to the front of the sacrum. The function of the endopelvic fascia is partly to convey blood vessels to the pelvic organs and partly to support them. Between the different layers of the endopelvic fascia are bloodless spaces which are important to identify in vaginal plastic operations. The term pelvic cellular tissue should be restricted to cellular tissue which intervenes between the different layers of the endopelvic fascia and which lies between the peritoneum above and the true pelvic fascia below.

Anteriorly, the bladder is covered by an endopelvic fascial layer called the vesical fascia while behind it lie the vagina and the supravaginal portion of the cervix covered by their own endopelvic fascial layers.

Immediately behind the uterus and the vagina, the peritoneum which covers the back of the uterus and the posterior vaginal fornix reduces the pelvic cellular tissue to a minimum in these situations. Deep to the uterosacral folds of peritoneum the endopelvic fascia is plentiful, and here it is condensed to form the uterosacral ligaments which pass backwards and upwards from the uterus in the front to reach the sacrum lateral to the rectosigmoid. The uterosacral ligaments help to support the uterus and prevent it from being forced down by intra-abdominal pressure. By their tone they also tend to pull back the cervix and thereby antevert the uterus. Plain muscle fibres can be demonstrated in them. They contain sympathetic and parasympathetic nerves. Mackenrodt ligaments, similar to uterosacral ligaments, help to support the uterus and prevent it from being forced down when the intra-abdominal pressure is raised. They are composed almost entirely of connective tissue and contain very little plain muscle (Figure 1.24).

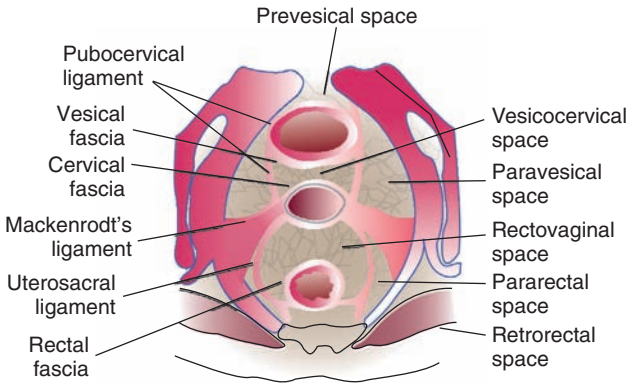


Figure 1.24 The pelvic cellular tissue shown in the cross-section of the pelvis.

A third and equally important part of the supporting mechanism of the pelvic viscera is the pubovesicocervical fascia or the pubocervical fascia. This is a condensation of the endopelvic fascia which passes from the anterolateral aspect of the cervix to be attached to the back of the pubic bone lateral to the symphysis. Some of its cervical attachment fans out laterally and imperceptibly into the transverse cervical or Mackenrodt's ligament. It can, therefore, be regarded morphologically and functionally as a part of this structure.

If Figure 1.24 is studied, the supports of the uterus and the bladder are seen to be triradiate condensation of endopelvic fascia:

1. The anterior spoke is the pubocervical fascia or so-called pubocervical ligament.
2. The lateral spoke is Mackenrodt's ligament.
3. The posterior spoke is the uterosacral ligament.

All these three embrace and insert into the cervix and, when intact, operate on it such as the strings of a hammock, preventing descent. If one or two strings are torn, the contents of the hammock prolapse with resulting descent of the bladder and the uterus.

The endopelvic fascial tissue contains the uterine arteries and veins, together with the venous plexus around the cervix and the lateral fornices of the vagina. The lymphatics from the upper two-thirds of the vagina and from the uterus, the ovaries and the fallopian tubes also pass through the pelvic cellular tissue. On each side of the uterus there is sometimes a small inconstant lymphatic gland known as the gland of the parametrium, about the size of the pin's head, near the ureteric canal. The ureter passes through the parametrium via the ureteric canal in an anteroposterior direction, about 1 cm lateral to the cervix to reach the bladder. It passes below the level of the uterine vessels, which cross it as they run transversely through the pelvis to reach the uterus. Sympathetic nerve ganglia and nerve fibres are plentiful in the parametrium (Frankenhauser's plexus).

In the condition of parametritis, the parametrium is inflamed and thickened. Rarely a large swelling forms which extends as far down as the fascia covering the levator ani muscles, and medially it comes directly into contact with the uterus and the upper part of the vagina. Laterally it extends as far out as the pelvic wall. Posteriorly it extends along the uterosacral ligaments in close relation to the rectosigmoid. Such a swelling may track upwards out of the pelvis to reach the subperitoneal tissues of the iliac region when the effusions may point above Poupart's ligament lateral to the great vessels. In other cases, the swelling may track upwards to the perinephric region. In advanced cases of carcinoma of the cervix, the cancer cells infiltrate the parametrium when they spread either laterally along Mackenrodt's ligaments or posteriorly along the uterosacral ligaments. Clinically, infiltration of the parametrium is detected by determining the mobility of the cervix and the body of the uterus, by palpating in the situation of Mackenrodt's ligament through the lateral fornix of the vagina and by examining the uterosacral ligaments by rectal examination. The fibrosis resulting from chronic parametritis causes chronic pelvic pain and ureteric obstruction (Table 1.2).

TABLE 1.2 Supports of the genital organs

Level I	Uterosacral ligaments and cardinal ligaments support the uterus and vaginal vault
Level II	Pelvic facias and paracolpos which connects the vagina to the white line on the lateral pelvic wall through arcus tendinous
Level III	Levator ani muscles support the lower one third of vagina

The Pelvic Blood Vessels

The ovarian arteries arise from the aorta, just below the level of the renal arteries. They pass downwards to cross first the ureter and then the external iliac artery, and then they pass into the infundibulopelvic fold. The ovarian artery sends branches to the ovaries and to the outer part of the fallopian tubes; it ends by anastomosing with the terminal part of the uterine artery after giving off a branch to the cornu and one to the round ligament.

Internal iliac artery is one of the bifurcations of the common iliac artery. It is 2 cm in length. The ureter lies anterior and the internal iliac vein posterior to it. It divides into an anterior and a posterior branch. The anterior branch supplies the pelvic organs. In obstetric and gynaecological surgery, profuse haemorrhage is controlled by ligating the internal iliac artery on either side. During this procedure, the anterior relation of the ureter to the artery should be remembered and injury to the ureter avoided.

The *uterine artery* arises from the anterior trunk of the internal iliac (or hypogastric artery). Its course is at first downwards and forwards until it reaches the parametrium when it turns medially towards the uterus. It reaches the uterus at the level of the internal os, where it turns upwards, at right angles, and follows a spiral course along the lateral border of the uterus to the region of the uterine

cornu; here it sends a branch to supply the fallopian tube and ends by anastomosing with the ovarian artery. The tortuosity is lost when the uterus enlarges during pregnancy. During the vertical part of its course, it sends branches which run transversely and pass into the myometrium (Figure 1.25). These are called the arcuate arteries and from them arises a series of radial arteries almost at right angles. These radial arteries reach the basal layers of the endometrium where they are termed as the basal arteries. From these the terminal spiral and straight arterioles of the endometrium are derived. The least vascular part of the uterus is in the midline. The vaginal branch of the uterine artery arises before the uterine artery passes vertically upwards at the level of the internal os. It passes downwards through the parametrium to reach the vagina in the region of the lateral fornix. This descending vaginal artery is of great importance during the operation of total hysterectomy since, if not separately clamped and tied, it may lead to dangerous operative haemorrhage. The arcuate arteries that supply the cervix are sometimes called the circular artery of the cervix. From these or the descending vaginal branches the anterior and posterior azygos arteries of the vagina are derived.

The following are the branches of the uterine artery:

- Ureteric
- Descending vaginal—these unite to form the anterior and posterior azygos artery of the vagina
- Circular cervical
- Arcuate → radial → basal → spiral and straight arterioles of the functional layer of the endometrium
- Anastomotic with the ovarian artery

The relation of the uterine artery to the ureter is of great importance. The uterine artery crosses above the ureter in the parametrium where it gives off an important ureteric branch to that structure. The artery runs transversely while the ureter runs approximately anteroposteriorly through the ureteric canal of the parametrium.

Middle sacral artery is a single artery which arises from the terminal aorta. It descends in the middle of the lumbar vertebra and the sacrum to the tip of the coccyx.

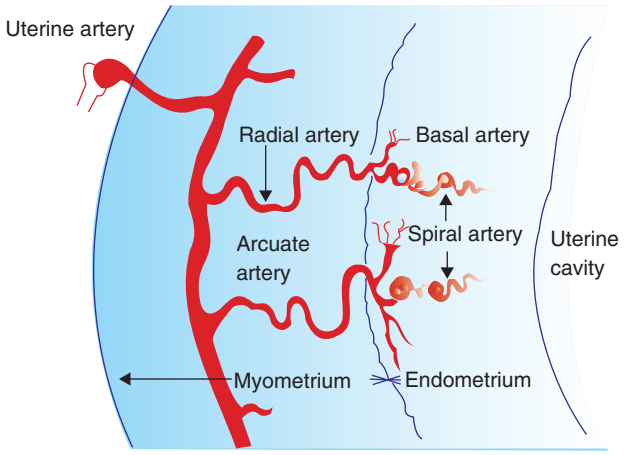


Figure 1.25 The uterine artery and its branches in the uterus.

There is an extensive network of collateral connections in the pelvic arterial vasculature that provides a rich anastomotic communication between major vessel systems. This degree of communication is important to ensure adequate supply of oxygen and nutrients in the event of major trauma or other vascular compromise. Hypogastric (internal iliac) artery ligation continues to be used as a strategy for the management of massive pelvic haemorrhage when other measures have failed. Bilateral hypogastric artery ligation effectively reduces pulse pressure in the pelvis, converting flow characteristics from that of an arterial to a venous system and allowing collateral channels of circulation to provide with adequate blood supply to the pelvic structures. This function is best illustrated by the example of preservation of reproductive functions, followed by successful pregnancies occurring after undertaking the lifesaving operation of bilateral ligation, of both hypogastric and ovarian arteries for uncontrolled atonic PPH after delivery. Details of collateral circulation are given in Table 1.3.

The Vaginal Arteries

Usually the blood supply of the upper part of the vagina is derived from the vaginal branch of the uterine artery. This vessel reaches the lateral fornix of the vagina and then passes downwards along the lateral vaginal wall. It sends branches transversely across the vagina, which anastomoses with branches on the opposite side to form the azygos arteries of the vagina, which run down longitudinally, one in front of the vagina and one behind. These small vessels are encountered in the operations of anterior and posterior colporrhaphy. In some cases, the vaginal artery does not arise direct from the uterine artery but arises from the anterior division of the hypogastric artery, when it corresponds to the inferior vesical artery in the male.

TABLE 1.3 Collateral arterial circulation of the pelvis

Primary Arteries	Collateral Arteries
Aorta	
Ovarian artery	Uterine artery
Superior rectal artery (inferior mesenteric artery)	Middle rectal artery Inferior rectal artery (internal pudendal)
Lumbar arteries	Iliolumbar artery
Vertebral arteries	Iliolumbar artery
Middle sacral artery	Lateral sacral artery
External iliac	
Deep iliac circumflex artery	Iliolumbar artery Superior gluteal artery
Inferior epigastric artery	Obturator artery
Femoral	
Medial femoral circumflex artery	Obturator artery Inferior gluteal artery
Lateral femoral circumflex artery	Superior gluteal Iliolumbar artery

The Arteries of the Vulva and Perineum

The blood vessels of the perineum and external genitalia are derived from the internal pudendal artery, a terminal branch of the anterior division of the internal iliac artery. The artery leaves the pelvis through greater sciatic foramen, winds round the ischial spine and enters the ischiorectal fossa. The main vessel passes forwards in the ischiorectal fossa adjacent to the obturator internus muscle in Alcock's canal. It gives off the inferior haemorrhoidal artery and the transverse perineal artery which supplies the perineum and the region of the external sphincter. It then pierces the urogenital diaphragm and sends another transverse branch to supply the posterior part of the labia and to supply the erectile tissue which surrounds the vaginal orifice. The internal pudendal artery ends as the dorsal artery of the clitoris, supplying the clitoris and vestibule. The tissues around the vaginal orifice, the clitoris and the crura of the clitoris contain a large amount of erectile tissue. Lacerations of the anterior part of the vulva during childbirth may be accompanied by severe bleeding. The terminal branches of the internal pudendal artery anastomose with superficial and deep pudendal arteries which are branches of the femoral artery. This anastomosis is important as it provides an alternative blood supply to the bladder in extended pelvic surgery when the vesical branches of the hypogastric are tied off or even the main trunk of the hypogastric itself may have been ligated at its source.

The Pelvic Veins

The left ovarian vein ends by passing into the left renal vein. The right ovarian vein terminates in the inferior vena cava. The most important feature of the pelvic veins is that they form plexuses. These are well marked in the case of the ovarian veins in the infundibulopelvic fold where they form a pampiniform plexus and cause chronic pelvic pain. Occasionally, this plexus becomes varicose and the large dilated veins form a varicocele similar to the condition seen in the male. The uterine plexus is found around the uterine artery near the uterus and the vaginal plexus around the lateral fornix of the vagina. These venous plexuses are well developed in the presence of large myomas and also during pregnancy when a venous plexus can be distinguished between the base of the bladder and the uterus. The uterine plexus of vein drains into the internal iliac vein. There are two additional channels of venous drainage which are of interest in explaining unexpected sites of metastases in malignant disease of the genital tract:

- A portal systemic anastomosis exists between the hypogastric vein and the portal system via the middle and inferior haemorrhoidal veins of the systemic and the superior haemorrhoidal veins of the portal system. This accounts for some liver metastases of the genital tract malignancies.
- A combination between the middle and lateral sacral and lateral lumbar venous system and the vertebral plexus, which may explain some vertebral and even intracranial metastases, rarely seen in genital tract cancers. In such patients the lungs may escape metastases as they are bypassed by the malignant emboli.
- Uterine veins communicate with the vaginal veins. This explains vaginal metastasis in uterine cancer and endometriosis. The middle sacral veins are two in number on either side of the artery and drain into the left common iliac vein. These veins are encountered during presacral neurectomy, vaginal vault sacropexy and exenteration operation.

The Lymphatic System

The lymphatics and lymphatic glands which drain the female genital organs are of special importance in malignant disease. The surgical removal or radiation should include all the regional glands for curative effect.

The Lymphatic Glands or Nodes

The lymphatic glands which drain the female genital organs are as follows (Figure 1.26).

The Inguinal Glands

This group of glands consists of a horizontal and a vertical group. The horizontal group lies superficially, parallel to Poupart's ligament while the vertical group, otherwise known as the deep femoral glands, follows the saphenous and femoral veins. The uppermost of the deep femoral glands, called the gland of Cloquet or the gland of Rosenmüller, lies beneath Poupart's ligament in the femoral canal between Gimbernat's ligament and the femoral vein. Inconstant deep inguinal nodes are found in the inguinal canal, along the course of the round ligament, and in the tissues of the mons veneris. In such conditions, as primary sore and Bartholin's abscess, the horizontal inguinal group becomes inflamed. There is some evidence that lymphatics from the fundus of the uterus pass along the round ligament and drain into the horizontal inguinal group. It is more likely that these glands will become involved after the appearance of the late suburethral metastasis seen in advanced carcinoma corporis uteri, where the growth has spread down the vagina by retrograde lymphatic spread. The inguinal glands drain the vulva and lower third of the vagina, the lymphatics of the medial portion of the vulva communicate with lymphatics of the opposite side. It is therefore necessary to perform bilateral inguinal lymphadenectomy when cancer occurs in the medial portion of the vulva.

The Glands of the Parametrium

The hypogastric group (internal iliac glands) contains all the regional glands for the cervix, the bladder, the upper third of the vagina and also the greater part of the body of the uterus. This group of glands may be extensively involved in carcinoma of the uterus, cervix and vagina. The glands are most numerous immediately below the bifurcation of the

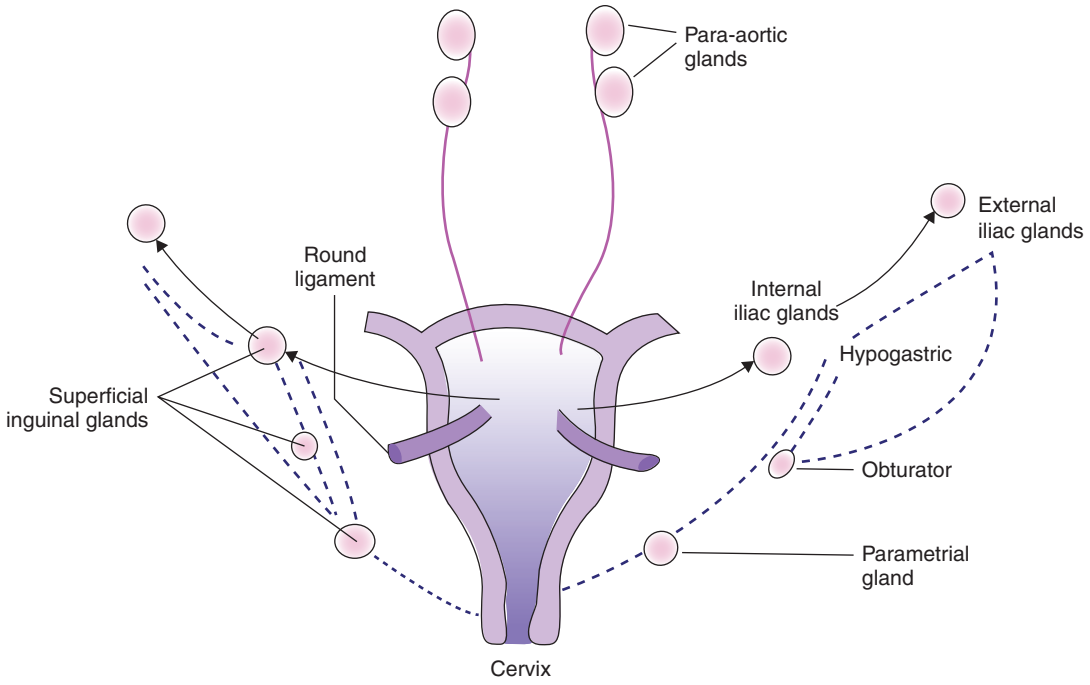


Figure 1.26 Pelvic lymphatic drainage of the cervix.

common iliac group. A further group of these glands situated in the obturator fossa is often called the obturator glands and is frequently the most obviously involved in carcinoma of the cervix. These drain into external and common iliac glands.

External Iliac Glands

This group of glands, several in number, is situated in relation to the external iliac artery and vein. A clean dissection of the external iliac glands can only be made if both vessels are completely mobilized as some of the glands lie lateral to the vessels between them and the lateral pelvic wall. These glands receive drainage from the obturator and hypogastric glands and are involved in late cervical cancer.

Common Iliac Glands

This group is the upward continuation of the external and hypogastric group and, therefore, involved next in genital tract cancer.

The Sacral Group

These glands lie on each side of the rectum and receive lymphatics from the cervix of the uterus and from the upper third of the vagina which have passed backwards along the uterosacral ligaments. Two groups of glands can be recognized, a lateral group lying lateral to the rectum and a medial group lying in front of the promontory of the sacrum. The lymphatics from these glands pass directly either to the inferior lumbar group or to the common iliac group.

The Lumbar Group of Glands

These lymphatic glands are divided into an inferior group that lies in front of the aorta below the origin of the inferior mesenteric artery and a superior lumbar group which lies near the origin of the ovarian arteries. The superior group of lumbar glands receives lymphatics from the ovaries and fallopian tubes as well as from the inferior lumbar glands. The lymphatics from the fundus of the uterus join the ovarian lymphatics to pass to the same group.

The lymphatic glands already mentioned, namely, the glands of the parametrium, the superficial inguinal, the hypogastric, external and common iliac, the sacral and the lumbar receive lymphatics 'direct' from the female generative organs and are known as the 'regional lymphatic glands' of the female genitalia.

These regional lymph nodes are not palpable clinically, but can be identified on CT and MRI scan if they are enlarged to 1 cm or more. At surgery, these glands should be palpated, removed or biopsied. This helps in staging the cancer and in the postoperative radiotherapy.

The Nerve Supply

Both sympathetic and parasympathetic systems supply the female genital organs as well as the bladder (Figure 1.27).

The sympathetic system consists of the presacral nerve which lies in front of the sacral promontory. This nerve plexus divides into two hypogastric nerves which pass downwards and laterally along the pelvic wall to terminate in the inferior hypogastric plexus. This plexus is diffuse and lies in the situation of the uterosacral ligaments. It also receives fibres from the parasympathetic system consisting of sacral fibres 2, 3 and 4. From here, the nerve fibres pass to all the pelvic organs.

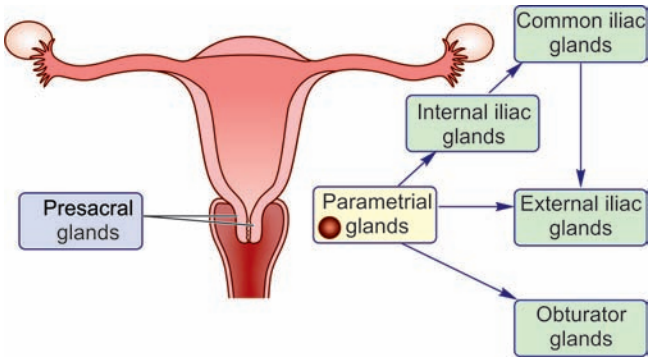


Figure 1.27 Lymphatic drainage of the pelvic lymph nodes.

The cervix is well surrounded by a rich plexus of nerves called Frankenhauser's plexus. The lower vagina is innervated by pudendal nerve.

The ovaries derive their nerve supply from the coeliac and renal ganglia which follow the course of the ovarian vessels.

The ilioinguinal nerve, derived from L1, and the genital branch of the genitofemoral nerve (L1 and L2) supply the mons, the upper and outer aspect of the labia majora and the perineum.

The pudendal nerve derived from sacral second, third and fourth segments supplies the lower vagina, clitoris, posterior part of the labia majora and the perineum. Presacral neurectomy is rarely performed to relieve chronic pelvic pain, and pain due to endometriosis. Pudendal block is needed in operative vaginal deliveries (Table 1.4).

Applied Anatomy and Its Clinical Significance

1. **Vulva.** The skin of the external genitalia is prone to local and general dermatitis. The moist intertriginous parts of the vulva are susceptible to chronic infection. Mucous glands in the vestibular location may become cystic. A cyst of the canal of Nuck may be mistaken for an indirect inguinal hernia. The loose areolar tissue of the vulva and its rich vascularity account for the large haematomas that are formed as a consequence of vascular injury during childbirth or accidental injuries. Vulval cancer is rare and occurs in old age. Lymphatic drainage of vulva is relevant in radical vulvectomy for cancer. Pudendal nerve block is required in episiotomy and forceps delivery. The internal pudendal block is performed by injecting local anaesthetic drug into the nerve at the level of ischial spine, as the nerve winds round this spine.
2. **Vagina.** The posterior vaginal fornix lies in proximity to the peritoneal pouch of Douglas. It is a convenient site for access to the peritoneal cavity, colpopuncture, colpocentesis and diagnostic culdoscopy in the diagnosis of pelvic abscess, ectopic pregnancy and pelvic endometriosis. The ureters have a close relation to the lateral vaginal fornices, particularly in patients with uterine prolapse. Ureteric injury should be guarded against during vaginal surgery on the uterus, as also when attempting to suture vaginal lacerations (colporrhexis) high in the vaginal vault. The anatomic proximity of the bladder base, urethra and vagina and the interrelationship between their vascular and lymphatic networks result in inflammation of the vagina (vaginitis) causing urinary tract symptoms such as frequency and dysuria. Gartner's duct cysts represent a cystic dilatation of the remnants of the embryonic mesonephros. They are present in the lateral walls of the vagina. These are generally asymptomatic, but they may cause dyspareunia or vaginal discomfort. In the lower third of the vagina, Gartner's duct cysts are located anteriorly and may mimic a large urethral diverticulum. Squamous cell carcinoma of vagina is very rare and occurs usually over the decubitus ulcer in a woman with vaginal prolapse.

TABLE 1.4 Nerve supply in the pelvis

Organ	Spinal Segments	Nerves
Perineum, vulva, lower vagina	S2–4	Pudendal, inguinal, genitofemoral, posterofemoral cutaneous
Upper vagina, cervix, lower uterine segment, posterior urethra, bladder trigone, uterosacral and cardinal ligaments, rectosigmoid, lower ureter	S2–4	Pelvic parasympathetics
Uterine fundus, proximal fallopian tubes, broad ligament, upper bladder, caecum, appendix, terminal large bowel	T11–12, L1	Sympathetics via hypogastric plexus
Outer two-thirds of fallopian tubes, upper ureter	T9–10	Sympathetics via aortic and superior mesenteric plexus
Ovaries	T9–10	Sympathetics via renal and aortic plexus and celiac and mesenteric ganglia
Abdominal wall	T12–L1	Iliohypogastric
	T12–L1	Ilioinguinal
	L1–2	Genitofemoral

Adenocarcinoma of vagina has been reported in young girls who were exposed to DES in utero and can occur in the upper part of the vagina. Lymphatic drainage of vulva is relevant in radical vulvectomy for cancer. Pudendal nerve block is required in episiotomy and forceps delivery. The internal pudendal block is performed by injecting local anaesthetist drug into the nerve at the level of ischial spine as the nerve winds round this spine.

3. **Cervix.** The major vascular supply of the cervix is located laterally. Deep lateral sutures placed laterally to include the vaginal mucosa and the substance of the cervix would help to control bleeding during surgical procedures on the cervix such as conization or the surgical evacuation of the cervical canal in cervical ectopic pregnancy. The stroma of the endocervix unlike the ectocervix is rich in nerve endings; hence, manipulation of the cervical canal can cause an unexpected vasovagal attack and severe bradycardia or even cardiac arrest. The lymphatics of the cervix are very complex involving multiple chains of nodes. The principal regional nodes are the obturator, common iliac, internal iliac and visceral nodes of the parametria; others may also be occasionally involved, hence the need for wide nodal dissection during the treatment of cancer cervix employing radical surgery. Squamocolumnar junction is the site of cancer of the cervix. Precancerous lesion of the cervix needs ablation or excision depending upon the age of the woman and its grade (Figure 1.28).

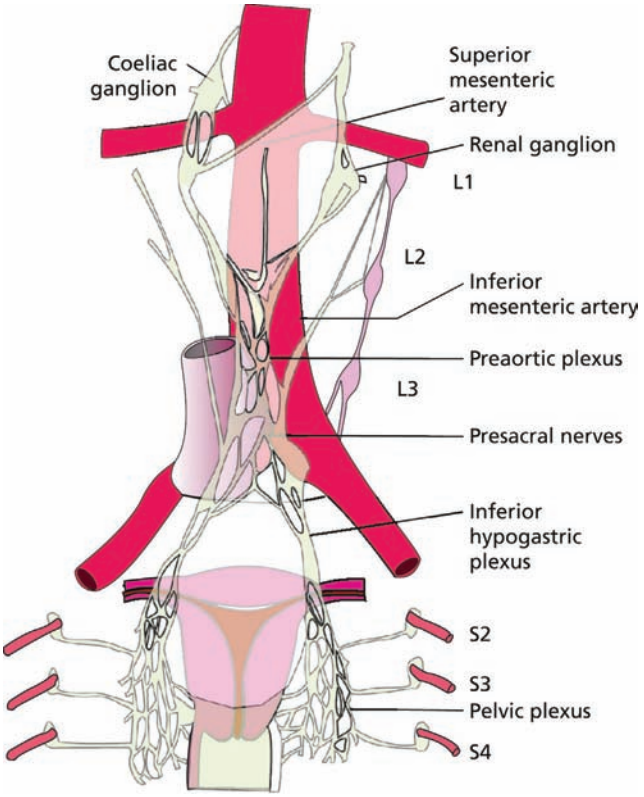


Figure 1.28 Pelvic innervation.

4. **Uterus.** Dysmenorrhoea is not an uncommon symptom, necessitating treatment in day-to-day practice. Whereas, most cases of primary dysmenorrhoea are treated successfully by prostaglandin synthetase inhibitors, there are occasional cases where oral medications may not suffice. In these women, the division of the sensory nerves that accompany the sympathetic nerves can lead to relief. The operations of presacral neurectomy and the endoscopic division of the uterosacral ligaments near the uterine attachment (laparoscopic uterosacral nerve ablation) have been designed to meet this end. The surgeon must be careful to avoid injury to the ureters. Since the uterus receives its main blood supply from the laterally placed uterine arteries, the operation of myomectomy of anterior wall uterine fibroids through a midline incision is attended with the least amount of blood loss. Earlier, it has been discussed that the uterus has a rich blood supply from the branches of the vascular anastomotic arcade between the uterine arteries and the ovarian arteries. There is also presence of an extensive pelvic collateral circulation to ensure enough blood supply in emergency situations wherein bilateral surgical ligation of the hypogastric vessels becomes necessary as a life-saving procedure.
5. **Fallopian tubes.** The right fallopian tube lies in proximity to the appendix. Therefore, it is often difficult to differentiate between acute appendicitis and acute salpingitis. The wide mesosalpinx of the ampullary portion of the tube permits this part to undergo torsion. Mesonephric remnants in the broad ligament may be the cause of formation of parovarian cysts. These often mimic ovarian neoplasms. They have been reported to undergo torsion. Falloscopy visualizes the tubal mucosa and patency of the medial end and salpingoscopy studies the mucosa and patency of the ampullary end of the fallopian tube, and enables us to decide between tubal surgery and in vitro fertilization in tubal infertility.
6. **Ovaries.** There is a wide variation in the size of the ovaries during the childbearing years and after menopause. Atrophic menopausal ovaries are not palpable on vaginal examination. Therefore, any palpable adnexal mass in a postmenopausal woman should be viewed with suspicion and investigated thoroughly to exclude a neoplasm. The location of the ovary in the ovarian fossa lies in proximity to the ureters. Hence, during pelvic surgical procedures for severe endometriosis or pelvic inflammatory disease that involve the ovaries, great caution must be exercised to avoid ureteric injury. Ultrasound scanning for any adnexal mass, polycystic ovarian disease and ovulation monitoring is possible and is easy, cost effective, accurate and noninvasive. Additional hormonal monitoring is, however, required in in vitro fertilization programme.
7. **Surgical precautions during gynaecological operations.** The anatomic proximity of female reproductive organs with the ureters, urinary bladder and rectum in

the pelvis is a major consideration during gynaecologic surgery. Surgical compromise of the ureter may occur during clamping or ligation of the infundibulopelvic folds, clamping and ligation of the cardinal ligaments, reperitonealization of the lateral wall following hysterectomy or during wide approximation of endopelvic fascia during anterior colporrhaphy repair.

At the base of the broad ligaments, the uterine artery crosses the ureter. During Wertheim's operation, when in doubt whether the structure under view is a blood vessel or the ureter, the feel of the structure is helpful; also, mild stroking lengthwise invokes a wave of peristalsis in the ureter. During abdominal hysterectomy for benign uterine disease, the practice of intrafascial clamping of the parametrium also helps to prevent ureteric injury. Subtotal hysterectomy in younger women in whom the cervix is healthy (Pap test normal) has the advantage of retaining the cervix for sexual reasons and for reducing the risk of future vault prolapse. The urinary bladder if well drained during pelvic surgery will be less vulnerable to inadvertent trauma. During colposuspension operations for stress urinary incontinence, there may be significant venous bleeding in the cave of Retzius. If proper drainage is not provided, there is a possibility of occurrence of a large subfascial haematoma that may extend up to the umbilicus. Rectal injuries occur most frequently during vaginal hysterectomy associated with high posterior colporrhaphy and enterocele repair. The rectum is also vulnerable to injury in the presence of wide adhesions, obliterating the pouch of Douglas in cases of extensive pelvic endometriosis, chronic pelvic inflammatory disease or advanced pelvic malignancy.

The genital prolapse is caused by atonicity, relaxation or damage to the nerve of the pelvic floor muscles and the supporting ligaments. The knowledge of these anatomical structures is necessary in the repair of various types of prolapse and in enhancement and buttressing these structures.

Stress incontinence of urine can be cured by elevating the neck of the bladder and mid-urethral ligamentary suspension.

Key Points

- Anatomical knowledge of the pelvic organs is essential to interpret the clinical findings as well as those of ultrasound, CT and MRI to make an accurate gynaecological diagnosis.
- Normal vaginal secretion is small in amount and varies with the phase of the menstrual cycle. Döderlein's bacilli predominate. They are Gram-positive and grow anaerobically in an acid medium of 4.5 pH. Low acidity does not allow other organisms to grow and cause vaginitis.
- Normal cervix has several physiological functions. The alkaline secretion attracts sperms at ovulation and sieves out the abnormal sperms in their ascent. The plug of mucous prevents entry of sperms as well as bacteria, and prevents pregnancy and pelvic inflammatory disease. The internal os remains competent during pregnancy, but effaces as its collagen dissolves near term. Capacitation of sperms occurs in the cervical canal.
- Fallopian tube. The nutritive secretion of endosalpinx, peristaltic movements of the musculature and ovarian fimbria play important roles in fertility.
- Knowledge of lymphatic drainage of the pelvic organs is important in staging, removal or radiation of lymphatic metastasis in genital organ malignancies. CT and MRI are used in mapping the lymph nodes involved in genital tract cancers.
- Remnants of the Wolffian body and its duct can cause parovarian cyst and Gartner's duct cyst.
- The pelvic portion of the ureter lies close to the genital organs. It is recognized by its pale glistening appearance and peristalsis. It needs to be dissected and protected against injury during gynaecological surgery.
- Pelvic floor muscles and fasciae hold the pelvic organs in place. Prolapse, stress incontinence of urine and faeces are related to the laxity and atonicity of these structures. Denervation of the pelvic nerves during childbirth is also responsible.
- The bladder, rectum and anal canal share the same muscular and ligamentary supports. Laxity of these supportive structures causes genital prolapse as well as urinary, faecal incontinence.
- Breast examination now falls in the domain of the gynaecologists. It is therefore important to know the structure of the breasts and changes that occur at different age groups.

Self-Assessment

Q.1 Describe the anatomy of Bartholin's gland and its clinical significance.
Q.2 Describe the pelvic diaphragm and its importance in preventing genital prolapse.
Q.3 Describe the course of the ureter in the pelvis. Where is it vulnerable to injury during pelvic surgery?
Q.4 Describe the pelvic cellular tissue supports of the uterus.

Suggested Reading

Cunningham FG, Leveno KL, Bloom SL et al. (eds). William's Obstetrics. 23rd Ed. New York, McGraw Hill, 2010; 14–35.
Schorge JO, Schaffer JI, Halvorson LM et al. (eds). William's Gynaecology. 1st Ed. New York, McGraw Hill, 2008; 798.

Chapter 2 Normal Histology

CHAPTER OUTLINE

Histological study of the endometrium is needed to detect the hormonal causes of infertility and abnormal menstrual patterns. However, lately, studying ovulation pattern in infertility by endometrial examination has lost considerable importance and is superseded by ultrasonic scanning, which is noninvasive and accurate in detecting the timing of ovulation and the result is available on the spot. Endometrial study is needed in suspected genital tract tuberculosis and cancer. The morphological study of the ovary and adnexal mass is also possible with ultrasound scanning.

The Ovary of the Newborn

At term, the fetal ovary measures 10–16 mm in length and is situated at the level of the brim of the pelvis. If a section is taken through the ovary and examined histologically, the following can be recognized.

The surface epithelium. This is a single layer of cuboidal cells, which later gives rise to the surface epithelium of the adult ovary. It is morphologically continuous with the mesothelium of the peritoneum.

The subepithelial connective tissue layer. This layer gives rise to the tunica albuginea of the adult ovary and to the basement membrane beneath the surface epithelium.

The parenchymatous zone. This area is the cortex and also the most important area, as it contains the sex cells. It can be divided into the following zones:

- Immediately beneath the surface epithelium, the sex cells are still grouped together in bunches to form egg nests.
- Below this area, the sex cells take the form of primordial follicles and are packed together without orderly arrangement (Figure 2.1).
- Developing follicles are seen in the deeper parts (Figure 2.2). Rete ovary in the medulla represents primary sex cords. Leydig cells, analogues of testis, are also seen in the medulla.

Zona vasculosa. This contains the blood vessels. It constitutes the medulla of the ovary (Figure 2.3). A few hilar cells homologues to interstitial cells of the testes are present in the medulla and rarely cause hilar cell tumour of the ovary.

The Primordial Follicle

As early as the third week of gestation, primordial germ cells appear in the endoderm of the yolk sac, and these migrate along the dorsal mesentery to the urogenital ridge by the eighth week. The first evidence of primordial follicle appears at about 20 weeks of fetal life. The fetal ovary contains 7 million primordial follicles but most degenerate, and the newborn contains only 2 million follicles. The primordial follicle consists of a large cell, the primordial ovum (oogonia), which is surrounded by flattened cells, best termed as the *follicle epithelial cells*. The follicle epithelial cells give rise to the granulosa cells of the Graafian follicle.

The primitive ovum (primary oocyte) is roughly spherical in shape and measures 18–24 μ in diameter, the nucleus 12 μ and nucleolus 6 μ. It has a well-defined nuclear membrane and its chromatin stains clearly. The primary oocytes remain in the prophase of first meiotic division until puberty.

The ovary of the newborn is packed with primordial follicles, approximately 2 million, dropping to a few hundreds at puberty. One of the most curious features of the ovary is the tendency of the sex cells to undergo degeneration. An

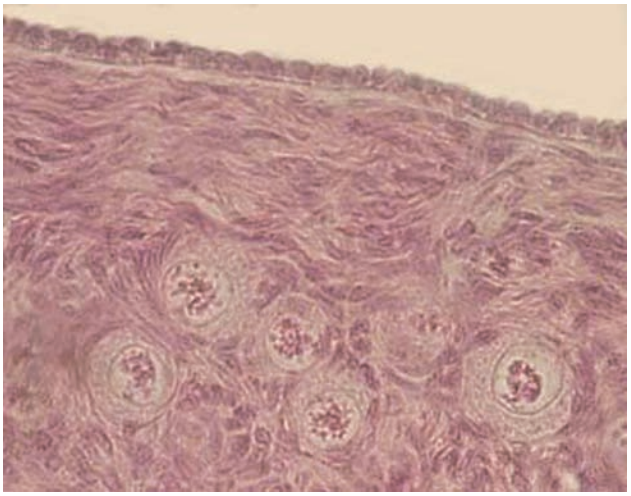


Figure 2.1 Ovary of a newborn child showing germinal epithelium and the stroma packed with primordial follicles. (Source: Andrei Gunin, MD, PhD, Dr Sci, Professor, Department of Obstetrics and Gynecology, Medical School Chuvash State University.)

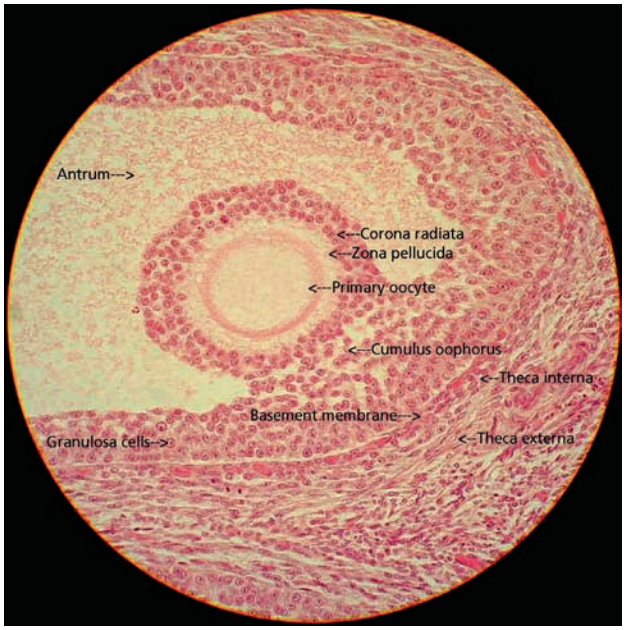


Figure 2.2 Graafian follicle. Discus proligerus showing granulosa cells, the ovum and the membrana limitans externa. Theca interna cells are few. (Source: David B Fankhauser, PhD.)

enormous number disappears during intrauterine life (IUL), and this process of degeneration continues throughout childhood and the childbearing period, with the result that no ovum can be detected in the ovaries of a woman who has passed the menopause. At birth, about 2 million follicles seen are reduced to 400,000 at puberty; only 400 follicles are available during the childbearing period for fertilization. The oogonia enter the prophase of the first meiotic division and remain so until puberty.

The Graafian Follicle (Figure 2.2)

The Graafian follicle, described by Regnier de Graaf in 1672, is a vesicle whose size measures on an average between 12 and 16 mm in diameter after puberty. Before puberty it seldom reaches more than 5 mm in diameter.

The mature Graafian follicle is spheroidal or ovoid in shape and contains pent-up secretion, the liquor folliculi. The lining consists of two layers: (i) theca interna and (ii) granulosa layer. The outer or *theca interna* layer consists of cells that are derived from the stroma cells of the cortex. The theca cell is responsible for the production of ovarian hormones, oestrogen and progesterone, sometimes extended to the production of androgens. Within the theca interna layer lies the *granulosa cell layer,* which consists of cells that have a characteristic appearance. The cells are 8–10 μ in diameter. The nuclei always stain deeply and the cells contain relatively little cytoplasm. In one area, the granulosa cells are collected together to form a projection into the cavity of the Graafian follicle. This projection is referred to as the *discus proligerus or cumulus oophorus*. The ovum itself lies within the discus proligerus. With the exception of the area around the discus proligerus, the peripheral granulosa cells form a layer only a few cells in thickness, whereas at the discus, the cells are between 12 and 20 layers thick. The granulosa layer itself is nonvascular and capillaries cannot be identified in it. Scattered amongst the granulosa cells, particularly in the vicinity of the discus proligerus, are small spherical globules around which the granulosa cells are arranged radially. These structures form Call-Exner bodies. The formation of *Call-Exner bodies* is a distinct feature of granulosa cells and can be readily recognized in certain types of granulosa cell

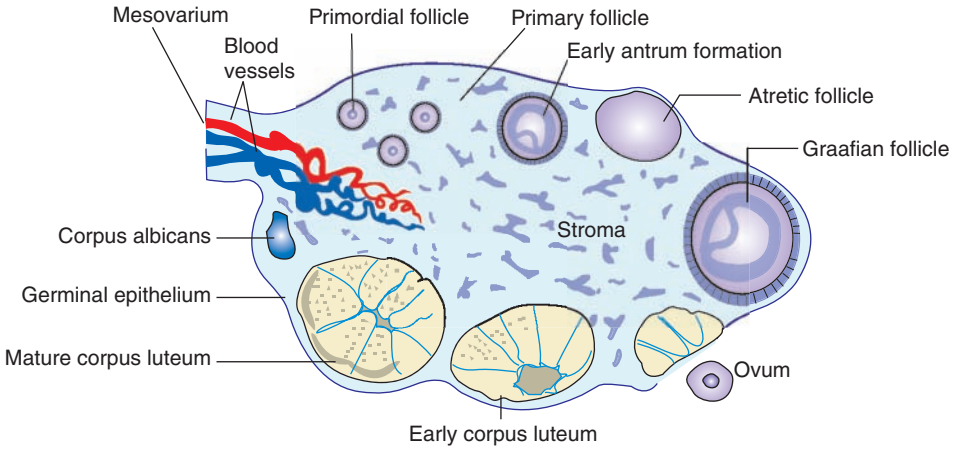


Figure 2.3 Structure of the adult ovary.

tumours. Between the granulosa layer and the theca interna is a basement membrane called the *membrana limitans externa,* upon which lies the basal layer of granulosa cells (Figure 2.4).

The mature ovum measures 120–140 μ in diameter and its nucleus 20–25 μ. At the periphery of the deutoplasm is a vitelline membrane outside which a clear translucent capsular acellular layer known as the zona pellucida enveloping the ovum. The granulosa cells surround the entire periphery of the ovum (Figure 2.5). The ovum remains in the meiotic arrest until about 36 h before ovulation when first meiotic division is completed and first polar body is extruded. Second meiotic division occurs only if the sperm penetrates the zona.

Those granulosa cells, which are immediately adjacent to the ovum, have a radial arrangement and form the corona radiata. The corona radiata remains attached to the ovum after its discharge into the peritoneal cavity at ovulation. The theca interna cells enlarge during the maturation of the follicle, and shortly before ovulation, they are larger than the granulosa cells. A third layer, the theca externa, is ill-defined in the ovary.

The liquor folliculi is a clear fluid-containing protein which coagulates after formalin fixation. It is secreted by the granulosa cells and contains the ovarian hormone oestrogen.

The Fate of the Graafian Follicle

The process whereby a primordial follicle is converted into a Graafian follicle, follicularization, can be recognized as early as the 32nd week of IUL. Until puberty most primordial follicles in the ovary undergo retrogression by a process which is termed as follicle atresia. Ovulation, whereby the follicle discharges its ovum into the peritoneal cavity, is first seen at puberty and is restricted to the childbearing period of life. The development of a primordial follicle into a Graafian follicle is under the control of the follicle-stimulating hormone (FSH) secreted by the anterior pituitary gland. Several follicles commence to develop in each menstrual cycle. In response to FSH, small gap junctions develop between the granulosa cells and the oocyte, and these gap junctions provide a pathway for nutrition and metabolic interchange between them. Of the several follicles developing in both ovaries, one follicle grows faster than the rest and produces more

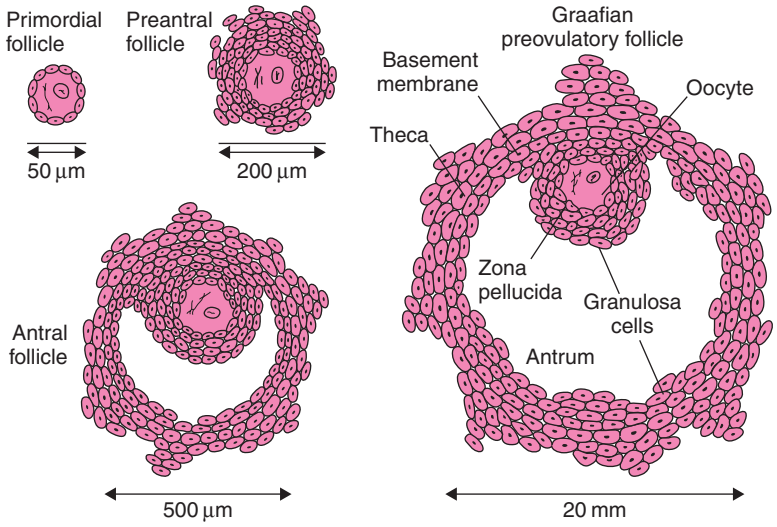


Figure 2.4 Follicular development: Graafian follicle showing granulosa cells, the ovum and theca interna cells. Graafian follicle measures 20 mm at ovulation.

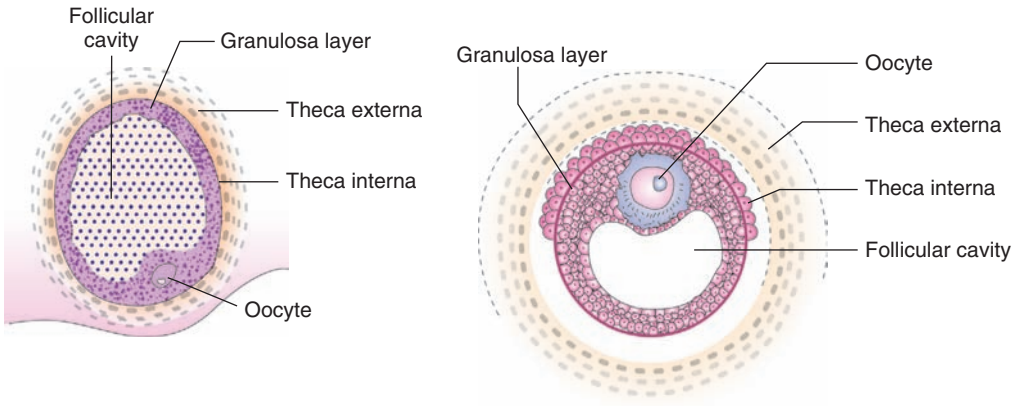


Figure 2.5 Oocyte.

FSH receptors and oestrogen. The rising oestrogen level stimulates luteinizing hormone (LH) receptors in the theca cells but causes a negative feedback to the anterior pituitary gland leading to a progressive fall in the level of FSH and gonadotropic support to the other lesser developed follicles which atrophy. The number of follicles that develop in any one cycle depends upon the levels of FSH and LH as well as the sensitivity of the follicles. Induction of multiple ovulations in in vitro fertilization is based on this observation. In a spontaneous normal menstrual cycle, only one dominant follicle develops into a Graafian follicle resulting in a single ovulation. Follicular atresia begins first in the ovum and later in the granulosa cells. Hyaline degeneration occurs and hyaline tissue is deposited as a glass membrane. Gradual absorption of liquor folliculi causes collapse of the follicle. The theca interna cells persist longer as dark-stained interstitial cells at the periphery of the follicle.

Ovulation

Ovulation occurs when the ovum surrounded by the corona radiata escapes out of the Graafian follicle. It is quickly picked up by the tubal fimbria, which hugs the ovary at ovulation (Figure 2.6). The peak level of 75 ng/mL of LH is required for ovulation. LH peak lasts 24 h.

The rupture of the Graafian follicle occurs because of contraction of micromuscle present over the theca externa. The contractions are brought about by prostaglandin secreted under the influence of LH. The process of maturation and ovulation can be minutely studied by serial ultrasonography. The Graafian follicle grows at the rate of 1–2 mm daily and attains the size of 20 mm or more at ovulation. The sudden shrinkage in size of a follicle, appearance of free fluid in the pouch of Douglas and regrowth of the collapsed cyst thereafter suggest that ovulation has occurred. Knowledge of the timing of ovulation is needed in in vitro fertilization, in artificial insemination and in the control of fertility. Ovulation is estimated to occur 14 days before the first day of the succeeding cycle, and this interval is more or less fixed. In case of irregular cycles, it is the follicular phase which varies, but the luteal phase remains more or less constant at 14 days. However, we do encounter cases of infertility with a short luteal phase, when menstruation begins in less than 14 days after ovulation.

Normally, *one single ovum* is discharged from the Graafian follicle. However, multiple ovulations can occur and result in a multiple dizygotic pregnancy. Multiple ovulations can also be therapeutically induced with hormones during in vitro fertilization.

The aperture through which an egg escapes from the ovary is called the stigma, appearing on laparoscopy as a red spot that heals in 3–4 days' time. The indirect methods of detecting ovulation are based on serial vaginal cytology, serial cervical mucus study, premenstrual endometrial biopsy, observing daily basal body temperature (BBT) and estimation of blood progesterone levels (or urinary pregnanediol levels) in the postovulatory or immediate premenstrual phase. Rarely, rupture of the Graafian follicle fails, but the follicle grows into a corpus luteum. This is termed luteinized unruptured follicle, which causes infertility.

The most important physiological marker of imminent ovulation is LH surge and not E_2 peak, as the latter may not always culminate into ovulation. LH surge causes the following:

1. Completion of meiosis of ovum
2. Ovulation
3. Development of corpus luteum

Anovulation occurs in about 10% cases of infertility, and sporadically during the childbearing years, but its occurrence is not uncommon for a few cycles after the menarche and just prior to the onset of menopause.

Unless fertilized, the ovum does not survive for more than 24 h. Thereafter it degenerates in the fallopian tube without leaving behind any trace.

Corpus Luteum (Figure 2.7A and B)

Soon after ovulation, the Graafian follicle cyst collapses and luteinization of the theca cells and the granulosa cells takes

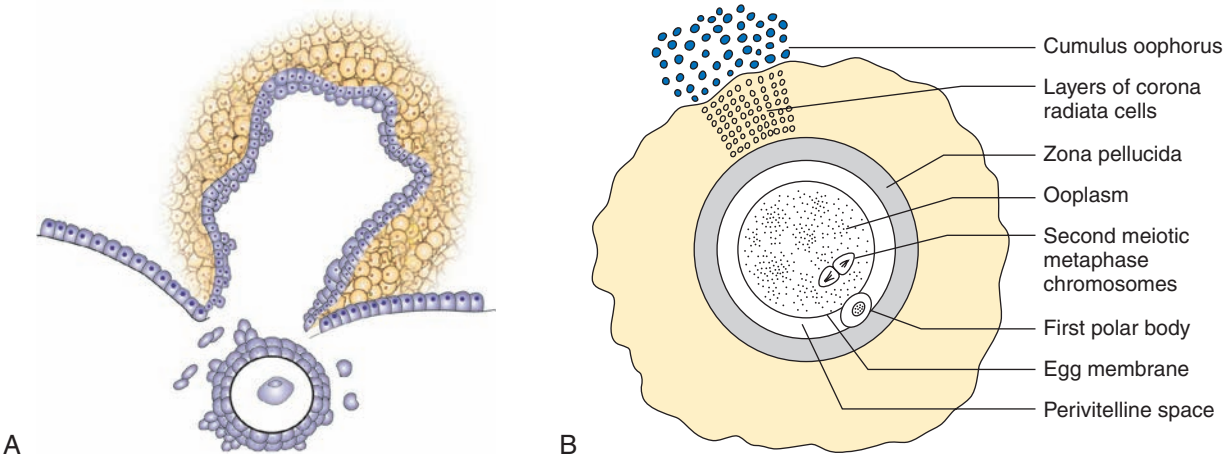


Figure 2.6 **(A)** Ovulation. **(B)** Freshly ovulated ovum.

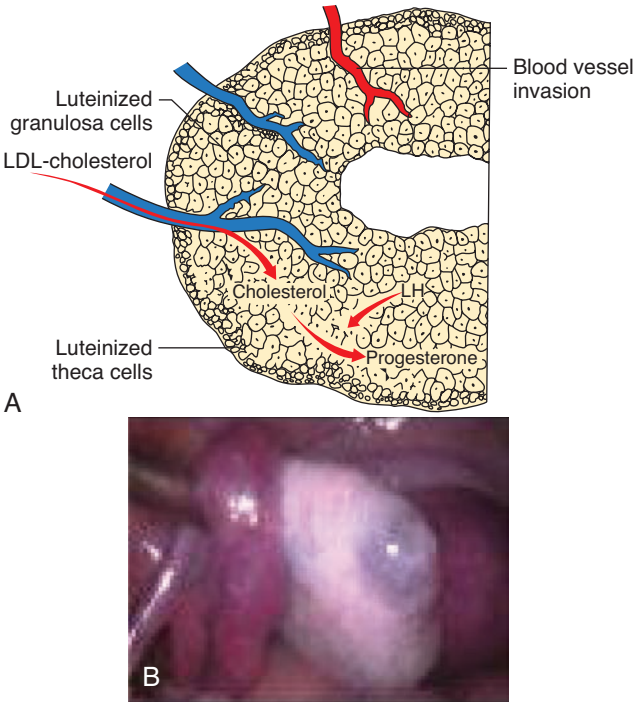


Figure 2.7 **(A)** Formation of corpus luteum. **(B)** Laparoscopic appearance of Graafian follicle at the time of ovulation. (Courtesy (B): Dr Shyam Desai, Mumbai.)

Figure 2.8 Corpus atreticum. The end result of atresia of a Graafian follicle. The granulosa cells have disappeared and a hyaline lamina has been deposited. The follicle is in the process of collapse.

place. The cells bloat up and increase in size, with pale staining cytoplasm. The nuclei therefore appear small. The cells proliferate and become eightfold to tenfold in size, due to which the cyst wall becomes crenated. At the same time, the corpus luteum becomes vascularized from the vessels in the theca interna layer. Some bleeding may occur in the cavity of the cyst. The corpus luteum reaches maximum maturity by the 22nd day of the normal cycle, when it attains the size of 2 cm or more. If pregnancy fails to occur, by the eighth postovulatory day, the corpus luteum starts degenerating and hyalinization sets in. The corpus luteal fluid contains phospholipid, cholesterol and carotene. Although it appears initially grey, later the corpus luteum acquires a yellow colour due to carotene, also known as lutein. During the last premenstrual week, vascularity of the corpus luteum diminishes when atrophy and degeneration of granulosa cells can be demonstrated in the form of vacuolated cells. Later hyaline tissue is deposited, and this hyaline body is known as the corpus albicans. Retrogression of the corpus luteum is a slow process and it is calculated that 9 months may elapse before it is completely replaced by hyaline tissue (Figure 2.8). The regression is attributed to fall in the LH level and rise in the level of oestrogen and $PGF_{2\alpha}$.

Menstruation

Menstruation is brought about by the fall in the levels of oestrogen and progesterone following the degeneration of the corpus luteum. In anovulatory cycles, fall in the level of oestrogen alone can bring about withdrawal bleeding in the form of menstruation. However, the oestrogen withdrawal bleeding is far heavier than the progesterone withdrawal bleeding.

Corpus Luteum of Pregnancy

Following fertilization, the corpus luteum continues to grow and forms the corpus luteum of pregnancy. This corpus luteum is larger and more cystic than the corpus luteum of menstruation and may attain the size of 2.5 cm. The convolutions are larger and more intricate. The individual granulosa cell is also large and measures as much as 40–50 μ. The secretion also increases. The theca cells are seen up to the 20th week, but thereafter they cannot be identified.

The corpus luteum of pregnancy is functionally active up to the 10th to 12th week in human beings. Thereafter, the placenta takes over the secretory function and carries pregnancy to term. Extirpation of the corpus luteum after the 14th week in humans will not therefore induce an abortion.

The Endometrium of the Uterus

The endometrium is the special epithelial lining of that part of the cavity of the uterus which lies above the level of the internal os. It consists of a surface epithelium, glands and stroma. It was not until 1907 that the variations in the histological structure of the endometrium during the menstrual cycle were established by Hitschmann and Adler. This formed the basis upon which much of the modern work on the sex hormones rests.

The endometrium of the body of the uterus can be divided into two zones: a superficial termed the functional layer and a deeper one termed the basal layer, which lies

adjacent to the myometrium. The stroma cells of the basal layer stain deeply and are packed closely together. Islands of lymphoid tissue are found in the basal layer.

The vascular system of the endometrium is of great importance. Two types of arteries supply the endometrium. One of these is restricted to the basal third and consists of small, straight and short arteries. The superficial two-thirds of the endometrium is supplied by coiled arteries.

The Proliferative Phase

The phase of the menstrual cycle which starts when regeneration of menstruating endometrium is complete and lasts until the 14th day of a 28-day cycle is referred to as the proliferative or oestrogenic phase. At the end of menstruation, which may occupy from 3 to 5 days, the necrotic superficial layers have been exfoliated and the endometrium is represented by only the deep or basal layer. The coiled arteries have been lost and the terminal ends of the straight arteries sealed off by fibrin. The stroma is heavily infiltrated with leucocytes and red cells. Regeneration is remarkably rapid and all elements of the endometrium including glands and new sprouting vessels are present at the end of 48 h. The proliferative phase therefore starts and proceeds rapidly for about 3–5 days, and not later than 7 days after the start of the menstrual cycle. During proliferation the functional and the basal layers are well defined. The basal layer measures 1 mm in thickness, while the functional layer, commencing with an average of 2.5 mm, reaches about 3.5 mm by the 14th day, and during the secretory phase, it hypertrophies still further, so that immediately before menstruation its average thickness is about 8–10 mm. During the proliferative phase, the glands of the functional layer are simple tubules with regular epithelium (Figure 2.9). About the 10th day of the cycle, the glands become slightly sinuous and their columnar epithelium becomes taller than before. The glands sometimes show a characteristic appearance in the later proliferative phase as if the glandular epithelium has been telescoped into the lumen, rather like an intussusception. This appearance is false and this telescoping is in reality due to the tuft of epithelium which has budded off from the gland wall. It is, therefore, merely an evidence of oestrogenic activity in the glandular epithelium. The stroma becomes extremely oedematous with wide separation of individual cells. During the first postmenstrual week, the coiled arteries extend only half way through the endometrium. Afterwards they grow more rapidly than the endometrium so that they become more coiled and spiralled. In some cases, the vascularity is so intense that blood oozes into the cavity of the uterus at the time of ovulation to be discharged from the vagina. Regular intermenstrual bleeding of this kind is a well-known clinical symptom and is due to the intense hyperaemia at the end of the proliferative phase. It almost certainly indicates that ovulation has occurred.

The Secretory Phase

Progesterone induces secretory changes only if the endometrium is primed by oestrogen, which produces progesterone receptors in the endometrial cells. The secretory phase of the endometrium begins on the 15th day and persists until the onset of menstruation. The most characteristic signs of this phase are found in the glands. Their epithelial cells develop spherical translucent areas between the nuclei and the basement membrane which contain the precursors of the glandular secretion and which persist until about the 21st day of the cycle. This characteristic appearance is called subnuclear vacuolation and is presumptive evidence of progesterone activity and, therefore, of ovulation. The fluid in these subnuclear vacuoles consists of mucin and glycogen (Figure 2.10), the function of which is presumably to provide nutrition to the fertilized ovum. The phase of subnuclear vacuolation is rapidly followed by an increase in intracellular secretion which pushes the nuclei to the basement membrane and fills the cell. The subnuclear vacuole

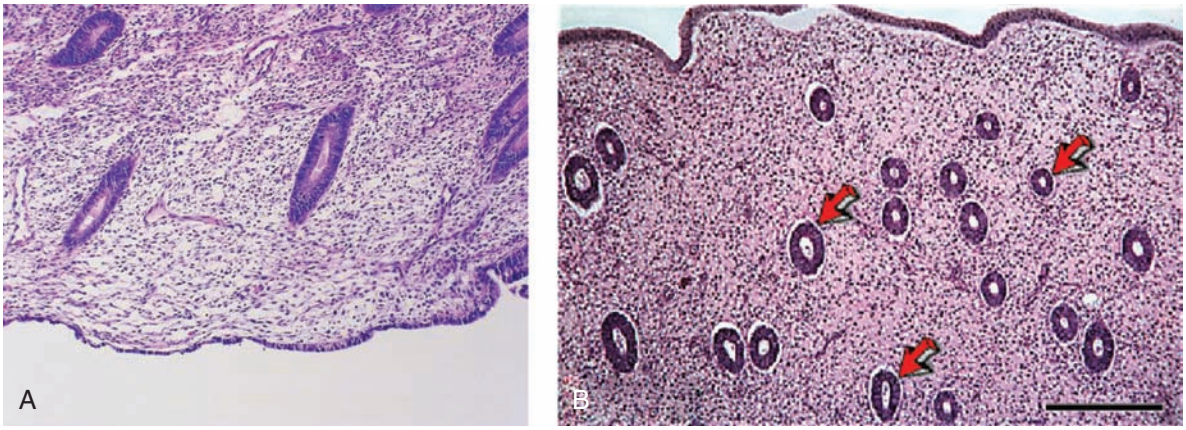


Figure 2.9 **(A)** Normal endometrium in the proliferative phase. **(B)** The glands are simple tubules and are shown in longitudinal and transverse section (×66). (Source: The image belongs to Rex Bentley, MD, Department of Pathology, Duke University Medical Center taken from link: http://www.pathologypics.com/PictView.aspx?ID=1149, Copyright © University of Kansas Medical Center, Department of Anatomy and Cell Biology.)

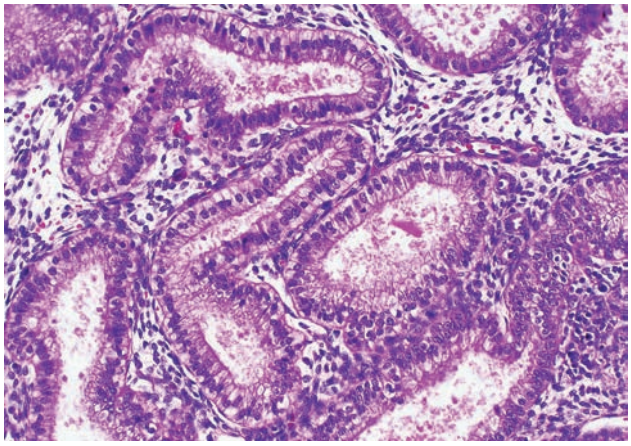


Figure 2.10 Endometrium—secretory hypertrophy (early stage). The gland is crenated, the lumen contains mucous secretion and the inner border of the cells is irregular. Subnuclear vacuolation is well seen. The surrounding stroma is oedematous and the hypertrophied stroma cells are widely separated from each other (×200). (Source: The image belongs to Rex Bentley, MD, Department of Pathology, Duke University Medical Center taken from link: http://www.pathologypics.com/PictView.aspx?ID=1149.)

later migrates past the nucleus to the surface of the cell. In the latter part of the secretory phase, the inner border of the epithelial cells become irregular through the discharge of the secretion into the lumina of the glands, which shortly before menstruation are full of coagulated secretion that stains deeply with eosin. The glands become crenated and assume a characteristic corkscrew-shaped form (Figure 2.11A and B). The stroma of the functional layer remains oedematous, but further interstitial haemorrhage is rare except immediately prior to the onset of menstruation. The coiled arteries become more spiral and form closely wound perpendicular columns through the mucosa. The stroma cells become swollen, and after the 21st day of the cycle they tend to be collected immediately beneath the surface epithelium where they surround the ducts of the glands in such a way that the functional layer can be subdivided into two zones: the superficial or compact zone, and a deeper spongy layer. The swollen stroma cells of the compact part of the functional layer represent young decidual cells, and in every respect the reaction of the compact zone corresponds to what is found in this part of the endometrium during pregnancy. The islands of lymphoid tissue in the basal layer of the endometrium scatter lymphocytes into the functional layer so that at this stage, there is a well-marked lymphocytic infiltration of the whole of the endometrium. The endometrium measures 8–10 mm in thickness in the secretory phase. The endometrial thickness can be studied ultrasonically. This study is useful in indicating the optimal time for embryo transfer in in vitro fertilization (Figure 2.12). In spite of the intense secretory activity of the functional layer, the basal layer glands are not similarly affected and retain nonsecretory pattern and mitosis is rare in this phase.

The secretory phase reaches its peak by the 22nd day of the cycle after which no further growth ensues. About the 24th day of the cycle some shrinkage of the glands is apparent,

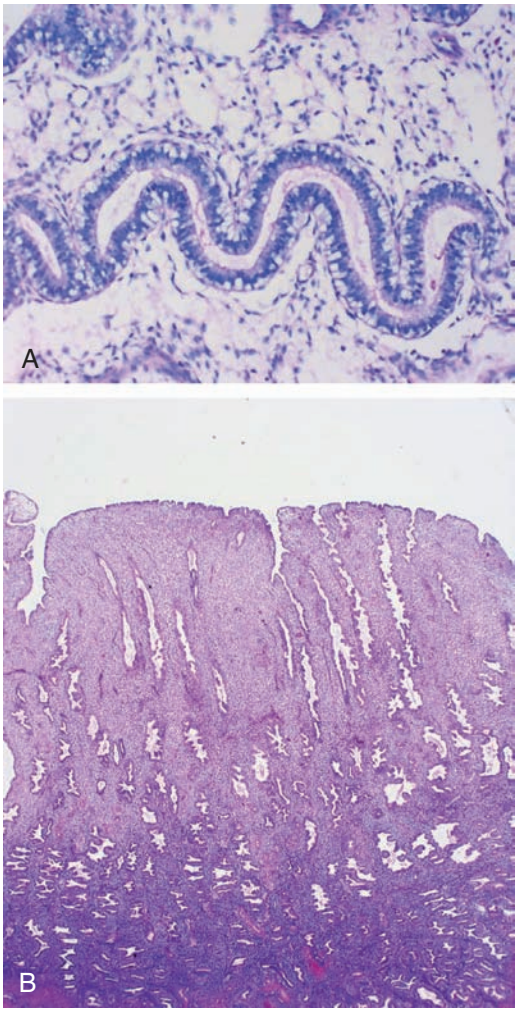


Figure 2.11 **(A)** Endometrium—secretory hypertrophy—at a slightly later stage than Figure 2.10. The secretory vacuoles are now near the apex of the cell (×124). **(B)** Endometrium showing compacta, spongiosa and basalis layers. (Source: The image belongs to Rex Bentley, MD, Department of Pathology, Duke University Medical Center taken from link: http://www.pathologypics.com/PictView.aspx?ID=1149.)

partly due to the dehydration of the stroma. The corkscrew pattern now becomes saw-toothed. No superficial necrosis has yet occurred but the superficial layers are noticeably less vascular. Just before menstruation there is a well-marked local leucocytic infiltration.

Dating of the endometrium and the diagnosis of luteal phase defect (LPD) are recognized by correlating the post-ovulatory endometrial picture with the menstrual date. A lag of 2 or more days is confirmative of corpus LPD. The estimation of progesterone level in the mid-secretory phase also indicates progesterone deficiency.

The Menstruating Endometrium

The menstrual changes in the endometrium are essentially degenerative. The spiral-coiled arteries undergo vasoconstriction a few hours before the onset of menstrual bleeding

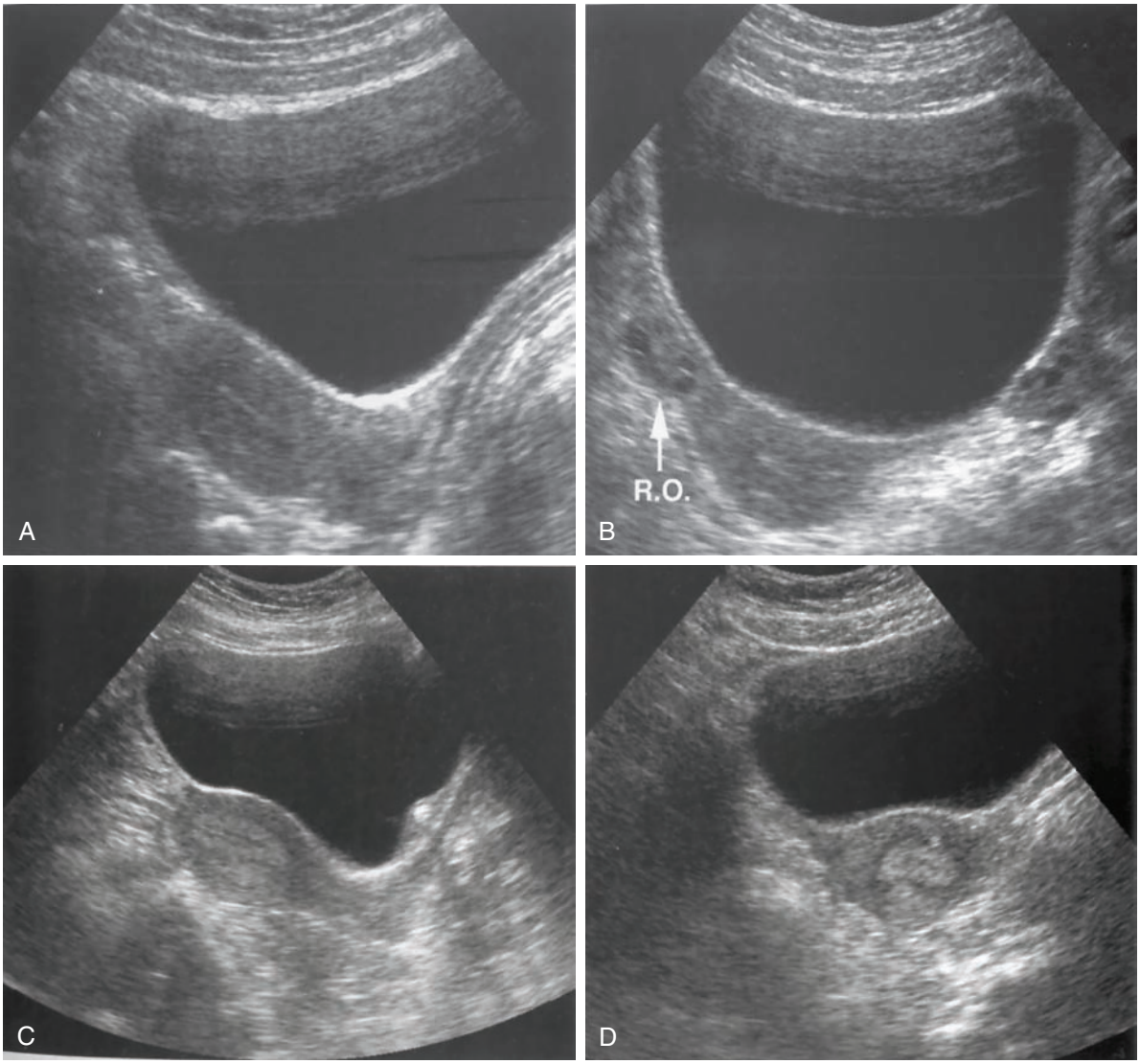


Figure 2.12 Pelvic sonography showing normal anteverted position of the uterus in sagittal views **(A** and **C)** of two separate patients. Note the polycystic (right) ovary adjacent to the uterus in the sagittal view **(B)** and the thickened endometrial linings in the views **(C** and **D).** (Courtesy: Dr Ketan Gundavda, Mumbai.)

under the influence of prostaglandin $F_{2\alpha}$. It is believed that the ischaemia thereby produced leads to the necrosis of zones in the walls of the small arteries in the superficial part of the endometrium. In addition, the buckling of the coiled arteries produces blood stasis, which may also cause necrosis. This buckling results from the decrease in the depth of the endometrium as a whole and causes further tightening of the arterial coils. Several additional coils may be detected in a single vessel. Bleeding from the endometrium is restricted only to the times when the coiled arteries relax and when the blood is discharged from the artery through the damaged necrotic areas in its wall. The straight arteries immediately beneath the coiled arteries undergo vasospasm at the time of the menstrual bleeding and thereby provide a simple safety mechanism for haemostasis. This vasospasm limits the menstrual loss. Deficiency of the mechanism may account for some forms of menorrhagia. The vasospasm is selective as it only affects the superficial layers and does not extend to the basal layer, which is thereby assured of an adequate blood supply necessary for regeneration. The compact zone of the functional layer becomes infiltrated with a large number of cells, and the surface epithelium may be pushed away from the subadjacent stroma. A little later the glands of the spongy zone of the functional layer disintegrate so that the epithelial cells separate from each other and become scattered amongst the red blood cells, leucocytes and the cells of the stroma (Figure 2.11B). The degenerative process is rapid, so that by the second day of the period of bleeding, the compact zone and the superficial part of the spongy zone have degenerated and a large part of it has been discharged into the cavity of the uterus. It is certain that the whole of the compact zone of the functional layer is shed, and probably most of the spongy zone of the endometrium is also shed. The basal layer is not shed during menstruation. On the third day of the period of bleeding, the surface of the endometrium is raw and the

patulous glands of the functional layer open directly into the cavity of the uterus. Active degeneration seems to be restricted to the first 2 days of menstruation. The subsequent bleeding is the result of oozing from the capillaries of the denuded stroma. It is common to find relics of the glands and stroma of the endometrium in the shreds and clots passed on the fifth day of the period of bleeding, which affords conclusive proof that a large part of the endometrium is shed in normal menstruation. There is reason to believe, however, that in some cases of abnormal uterine haemorrhage, the disintegration process is not spread uniformly over the entire endometrium, but may be localized to limited areas.

The menstrual blood loss is controlled by interaction between PGE_2, $PGF_{2\alpha}$ and PGI_2 (prostacyclin) secreted by the endometrium. Whereas PGE_2, $PGF_{2\alpha}$ and thromboxane cause vasoconstriction of the vessels, prostacyclin causes vasodilation and menorrhagia. The combined oral contraceptive pills (OCPs) cause atrophic endometrium. PGE_2 predominates in the proliferative phase and $PGF_{2\alpha}$ in the luteal phase.

Regeneration

Regeneration of the denuded epithelium is already in progress before the menstrual bleeding has stopped and is completed 48 h after the end of menstruation. Repair is brought about by the glandular epithelium growing over the bare stroma (Figure 2.13). This is brought about by vascular endothelial growth factor (VEGF) produced by oestriol stimulation. It is not uncommon for relics of crenated glands to be found in the endometrium during the first 2 days following menstruation, and one of the great characteristics of the endometrium at this time is the presence of a large number of lymphocytes in the stroma. The relation of the cyclical changes between the ovaries and the endometrium is discussed in Chapter 3.

Endometrium

Using magnetic resonance imaging (MRI) technique, Haicak described three layers of endometrium: (1) high-intensity endometrial strip; (2) medium signal intensity over the myometrium; and (3) in between these two layers, a 'junctional zone' or 'subendometrial halo'. Ultrasound shows peristaltic movements in this subendometrial halo zone. These movements are under hormonal influence. This zone is thin before puberty and after the menopause, and also those on oral combined pills. It increases in size during pregnancy and becomes vascular, under oestrogen influence. This zone is maximum at the time of ovulation. At this time the increased peristaltic movement helps in the transport of sperms into the fallopian tubes. The peristaltic movements diminish during the luteal phase under the effect of progesterone and help in implantation of the fertilized egg.

The contractions or these movements in the subendometrial zone have important bearing on reproductive process. They help in the rapid transport of sperms to the fallopian tubes within a few minutes during ovulation, but help in implantation during the luteal phase.

Abnormal function of this zone is one of the factors responsible for failure of conception in IVF programme, or occurrence of a tubal pregnancy.

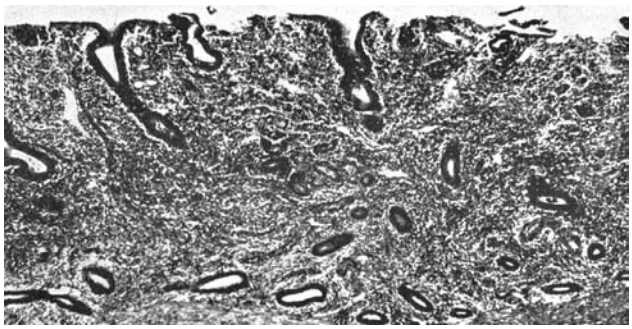


Figure 2.13 Endometrium on the last day of the period of bleeding illustrating the compact stroma and the method by which the denuded area is covered by the epithelium which grows over it from the glands.

The Decidua of Pregnancy

In the early weeks of pregnancy, the structure of the endometrium is very similar to that found in the late secretory phase. The division into compact and spongy zones of the functional layer is more clearly defined. The basal layer can still be identified, but its glands, although staining more deeply than the hypertrophied glands of the spongy layer, show some degree of crenation and contain secretion. The lymphoid islands of the basal layer are not easily identified, for in the early weeks of pregnancy lymphocytes are disseminated extensively into the stroma of the spongy layer. The glands of the spongy layer retain the general form found in the late secretory phase, but they are much more crenated, so much that the impression is given that they have increased in number. The cells lining the glands are irregular in shape and tend to be elongated with irregular processes projecting into the lumina of the glands and discharging secretion. It is not uncommon for small papillae to be formed which project into the glands, but in spite of the activity of the epithelium, the basement membrane remains well defined. Activity is not restricted to the immediate vicinity of the implanted ovum, but is distributed uniformly throughout the endometrium of the body of the uterus. The compact layer shows the typical decidual reaction of pregnancy. The decidual cells are derived from stroma cells: they are stellate in shape, contain glycogen and are surrounded by an intercellular fibrillary ground substance and by lymphocytes (Figure 2.14).

Ectopic Decidual Cells

Decidual cells are not restricted to the endometrium of the body of the uterus. Decidual reaction has been demonstrated in various ectopic situations in the pelvis. The best example of ectopic decidual reaction is found on the surface of the ovaries during pregnancy, when small irregular reddish areas are easily recognized with the

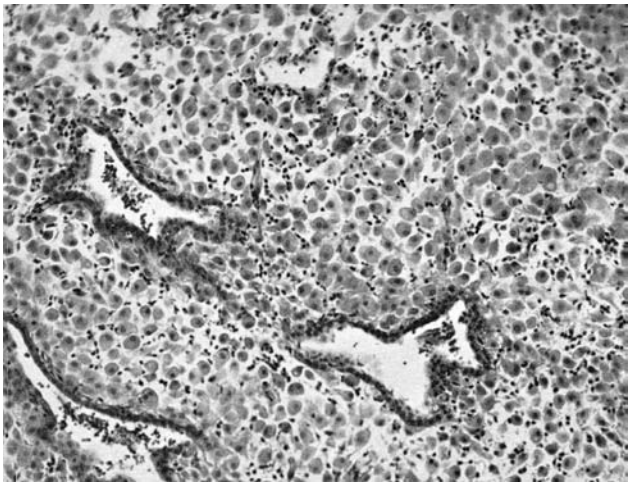


Figure 2.14 Decidua of early pregnancy. The large decidual cells have a faintly staining cytoplasm which is eosinophilic. They are always surrounded by lymphocytes and the cells fuse with an intercellular matrix (×110).

naked eye and show typical decidual reaction on histological examination. In the ovaries, the decidual reaction is limited to the surface with very little invasion of the cortex. Ectopic decidual reaction is always very well-marked beneath the peritoneum of the back of the uterus in the pouch of Douglas. It has been demonstrated in adenomyomas, in the walls of chocolate cysts, on the uterovesical fold of peritoneum and in the omentum. Decidual reaction can invariably be demonstrated in the isthmical region of the endometrium during pregnancy, but only rarely is the typical reaction found in the glands of the cervical canal. Decidual reaction occurs in the fallopian tube in an ectopic pregnancy, but it is incomplete and deficient. A thick decidua develops in hydatidiform mole under the influence of the hormones. The significance of ectopic decidual cells is unknown. The decidual reaction is controlled by the corpus luteum, but it is unknown why only cells with this curious distribution respond to the stimulus.

Vaginal Epithelium

The upper portion of the lateral vaginal epithelium displays cyclic changes in response to the ovarian hormones. These changes can be studied cytologically by scraping this portion of the vaginal epithelium and staining it with Shorr stain. Details of vaginal cytology are discussed in Chapter 10.

Ovarian Function

Apart from producing an ovum monthly, ovaries produce hormones responsible for maturation of the Graafian follicle, ovulation, menstruation and maintenance of pregnancy in the early weeks of gestation. The steroidal hormones are oestrogen and progesterone. Oestrogen is mainly secreted by the Graafian follicle in the follicular phase (preovulatory phase). A small amount is also secreted by the corpus luteum in the premenstrual phase. Progesterone is secreted by the corpus luteum, and the absence of progesterone in the premenstrual phase denotes anovulation. The control of these hormones is described in Chapter 3. Inhibin is a nonsteroidal hormone present in the Graafian follicle. It is a protein that inhibits FSH and stimulates LH secretion by the anterior pituitary. Excess of inhibin seen in polycystic ovarian disease (PCOD) is responsible for the high level of LH.

The other hormones which the ovary produces in small amounts are testosterone and androstenedione, mainly secreted by the stromal cells and stimulated by LH. Androstenedione gets converted peripherally into oestrone through aromatization in the fat tissue. After menopause, ovarian oestrogen level falls as Graafian follicles disappear, and progesterone fails to be produced. The increased stromal cells of the menopausal ovary continue to produce some androstenedione which gets converted into oestrone. Though a weak oestrogen, oestrone is capable of exerting oestrogenic effect on the target tissues. Obese women have therefore more oestrone than a lean woman and hence a greater tendency to endometrial hyperplasia and malignancy.

Pregnancy

In some cases of uterine and ectopic pregnancies, the endometrium shows intense adenomatous and hypersecretive activity within the glandular epithelium. The cells are enlarged; epithelial nuclei show mitosis, hyperchromasia, polyploidy and atypical cell types. The cells are hypersecretive without glycogen content. This condition is called *Arias-Stella reaction*. These changes are focal and often associated with decidual reaction in the stroma. Besides pregnancy, this endometrial reaction is seen in endometriosis, reaction to oestrogen and to gonadotropins, as well as in gestational trophoblastic disease (GTD).

Menopausal Endometrium

In the majority of women, oestrogen withdrawal at menopause causes endometrial atrophy, and the endometrium is only 1–3 mm in thickness. The atropic endometrium is susceptible to infection resulting in senile endometritis, and postmenopausal bleeding. In rare cases, the endometrium becomes hyperplastic under the influence of extragenital oestrogen (oestrone) produced in the peripheral fat from epiandrostenedione. The postmenopausal endometrium measuring more than 4 mm is considered abnormal. Endometrial hyperplasia and polyp also occur when tamoxifen is administered to a woman with breast cancer.

Cervical Mucus

In 1948, Papanicolaou described the fern test and the cyclical changes in the cervical mucus under the influence of

various hormones. A drop of cervical mucus spread and dried on a glass slide in the preovulatory phase (oestrogenic phase) presents a palm leaf or fern type of reaction, due to the presence in it of sodium chloride (Figure 2.15). This reaction disappears after ovulation under progesterone influence. Under the influence of progesterone, the cervical mucus becomes thick and tenacious and impenetrable to sperms and bacteria. The details of cervical mucus are described in Chapter 19.

Endocervical lining does not exhibit cyclical changes like the endometrium. In pregnancy, however, adenomatous hyperplasia may occur, and decidual changes are seen in 10% of the patients.

Oral combined hormonal pills over the years also cause hyperplasia of endocervical epithelium and an abnormal 'Pap smear'. Lately, an increased incidence of endocervical carcinoma has been observed in young women who have been on hormonal contraception use. Contrary to this, the pills cause atrophic endometrium in the body uterus.

Process of Fertilization

Certain changes are necessary before the primary oocyte can mature for fertilization. Oogonia that enter the prophase of the first meiotic division are known as primary oocytes. Whereas those oogonia which do not begin the first meiotic division and those not surrounded by granulosa layer undergo atrophy. At puberty, under the LH surge, primary oocyte completes the first meiotic division and gives rise to secondary oocyte, containing most of the cytoplasm, 23X chromosomes and a small polar body. This secondary oocyte completes its second meiotic division only after fertilization, and gives out second polar body.

Thus, the first stage of maturation of the oocyte occurs within the Graafian follicle, but the second division occurs only after the fertilization in the fallopian tube.

Testis

Each testis is divided into:

(a) Tubular compartment (85%) responsible for spermatogenesis.
(b) Interstitial compartment (15%) for steroidogenesis and secretion of testosterone.

Tubular compartment is divided into 250–300 lobules, each lobule containing 1–3 convoluted seminiferous tubules. The seminiferous tubule contains Sertoli cells and germ cells.

The Sertoli cells at the base support the tubule and secrete Müllerian inhibiting factor (MIF) which inhibit development of Müllerian system in a male. The diploid germ cells undergo mitosis to produce primary spermatocytes. Further meiotic division results in secondary spermatocytes, spermatids and a mature sperm.

The seminiferous tubule is surrounded by myofibroblasts which contract and propel the sperms into rete testis. More description is provided in the chapter on infertility.

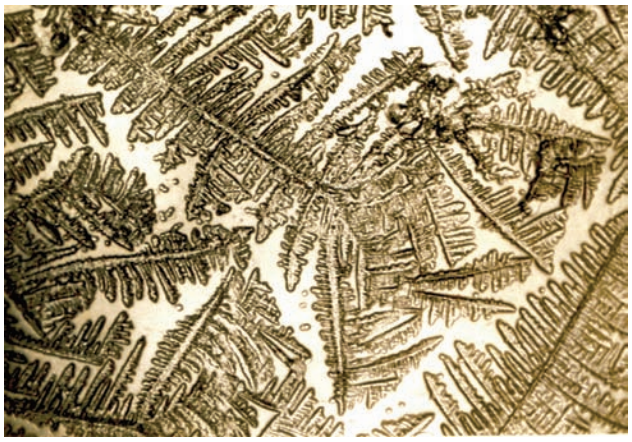


Figure 2.15 Microscopic appearance of dried cervical mucus showing the 'fern appearance'.

Key Points

- The ovary of the newborn has about 2 million primordial follicles. These are reduced to about 400,000 at puberty and of these around 400 are available during the reproductive lifespan.
- Cyclic changes in the Graafian follicle—leading to ovulation, corpus luteum formation and menstruation—are under the control of the hypothalamus, which controls the release of gonadotropins from the anterior pituitary.
- Oestrogen causes regeneration of the endometrium and the proliferative phase. Progesterone is responsible for secretory transformation of the endometrium rendering it favourable for implantation of the fertilized ovum.
- Peak level of 75 ng/mL of LH is needed for ovulation.
- In present-day practice, serial ultrasound monitoring of the Graafian follicle is used to detect ovulation in patients undergoing treatment for infertility.
- Endometrial histology is required to diagnose endometrial tuberculosis, endometrial cancer and hormonal dysfunction.
- Endometrial thickness of 8–12 mm is considered normal in the premenstrual phase. In menopausal women, endometrial thickness should not exceed 4 mm.
- LH surge is an important indicator of imminent ovulation.

Self-Assessment

1. Describe the microscopic appearance of the endometrium during the proliferative phase.
2. Describe the histological appearance of the endometrium in the secretory phase.
3. Describe the microscopic appearance of the menstruating endometrium.

4. Describe the endometrial changes during pregnancy.
5. What is the significance of cervical mucus forming in clinical practice?

Suggested Reading

Berek JS, Adashi EY, Hillard PA (eds). Novak's Gynecology. 13th Ed. Philadelphia, PA, Williams & Wilkins, 2004.

Mishell DR Jr, Davajan V (eds). Infertility, Contraception and Reproductive Endocrinology. 2nd Ed. Oradell, NJ, Medical Economics Books Oradell, 1986.

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Chapter 3 Physiology

CHAPTER OUTLINE

Neuroendocrinology with vast hormonal interactions is responsible for menstrual cycle and reproductive functions in a woman.

It is now well established that a normal menstrual cycle depends on cyclical ovarian steroid secretions, which in turn are controlled by the pituitary and the hypothalamus and, to some extent, are influenced by the thyroid and adrenal glands. It is therefore essential to understand the hypothalamus–pituitary–ovarian axis in normal women (H–P–O) and apply this knowledge in therapeutic management in infertility, family planning and various gynaecological disorders.

Hypothalamus

Hypothalamus with its several nuclei and extrinsic connections is now considered the main neuroendocrine gland and the regulatory factor in the chain of hypothalamic–pituitary–ovarian–uterine axis. Hypothalamus regulates the functions of the anterior pituitary gland through portal vessels by releasing both the stimulatory and the inhibitory hormones that in turn influence the functions of the target tissues through the systemic circulation (Figure 3.1A and B). These hormones in turn are controlled by positive and negative feedback loops from ovarian hormones. External and internal stimuli further modify or influence hypothalamic functions.

Hypothalamus is located at the base of the brain behind optic chiasma and below the thalamus above the pituitary and forms the base of the third ventricle. The base of the hypothalamus forms tuber cinereum, which merges to form the pituitary stalk. The origin of this stalk is known as median eminence, which is rich in capillary loops as well as nerve endings. Median eminence is an important site of storage of chemical signals, which get transferred into portal circulation to reach the anterior pituitary gland. Schally and Guillemin were the first to discover a decapeptide called gonadotropin-releasing hormone (GnRH) in 1971. GnRH is secreted by the median eminence and the arcuate nucleus, which modulates the neural control of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary gland. It (arcuate nucleus) also secretes prolactin-inhibiting factor (PIF), which is dopamine that inhibits the release of prolactin. During late pregnancy and lactation, a low or absent inhibitory factor leads to a high secretion of prolactin that initiates and maintains lactation.

Hypothalamus is also responsible for secretion of thyrotropin releasing factor, corticotropin releasing factor, insulin-like growth factor and melanocyte releasing factor.

Hypothalamus is connected to the anterior pituitary gland through special hypophysis pituitary portal system of vessels but connected directly to the posterior pituitary gland (neurohypophysis) by the supraoptic and paraventricular nuclei (Figure 3.2).

GnRH (decapeptide) is synthesized in arcuate nucleus and is released at the nerve endings near tuber cinereum. GnRH has a half-life of 2–4 min and is therefore difficult to assay. Its level is assessed through the LH level. It is released in a pulsatile manner into the portal vessels and reaches the anterior pituitary gland. *The pulsatility and amplitude of its release vary with the various phases of the menstrual cycle*. In the preovulatory phase (follicular phase), it pulses once in

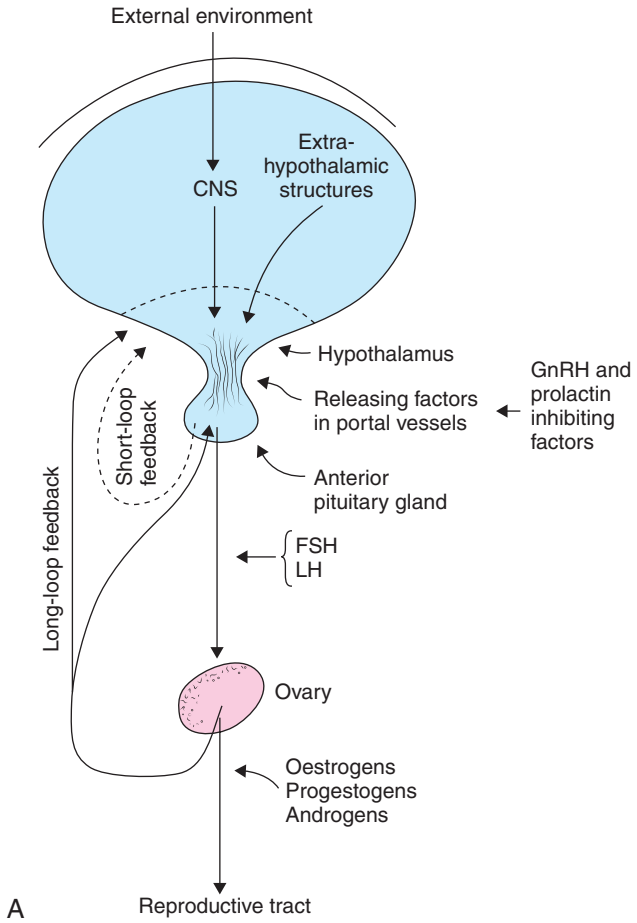

Figure 3.1 **(A)** Hypothalamic–pituitary–ovarian axis.

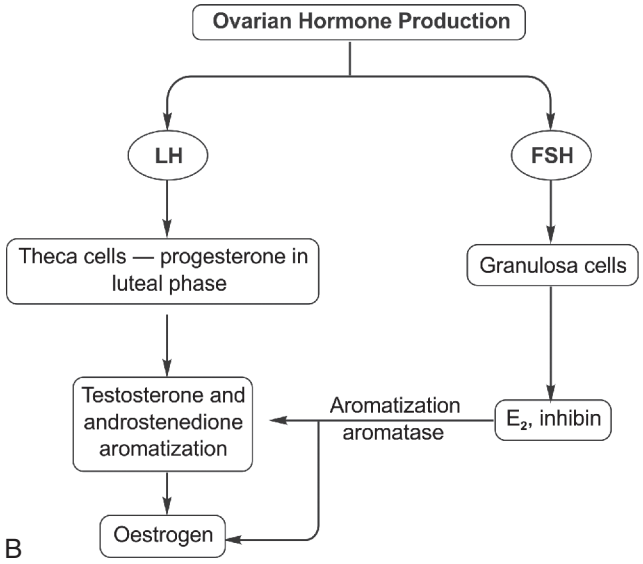

Figure 3.1 **(B)** Ovarian hormone production.

every 60 min, but it slows down to once in 3 h in the luteal phase, with increased amplitude of each pulse.

GnRH exhibits different actions depending on the manner in which it is released. Its continuous release causes suppression of gonadotropins and thereby the ovarian functions through the process of 'down-regulation' or desensitization

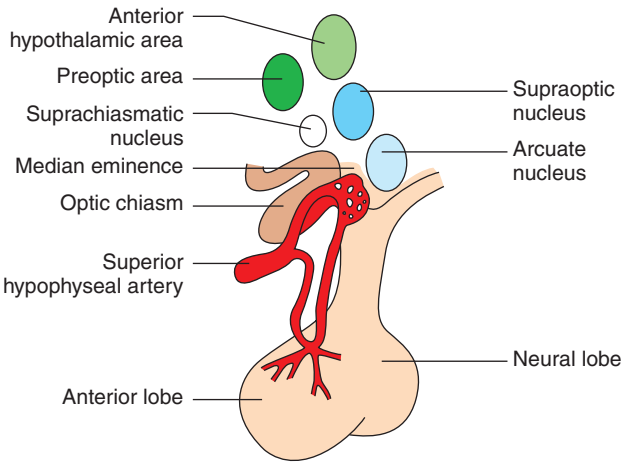

Figure 3.2 Hypothalamic nuclei.

of pituitary hormones. This mode of administration is now employed in therapy using synthetic analogues of GnRH in regulating ovulation in in vitro fertilization and suppressing menstruation in precocious puberty, in reducing the size of the uterine fibroids and in causing shrinkage of endometriosis. Its suppressive effect on ovulation is also being tried as a contraceptive, but the drug has proved expensive as of today. The pulsatile administration, on the other hand, causes cyclical release of gonadotropins, FSH first and later LH which induces ovulation and the possibility of a pregnancy. This therapy is applied in women with anovulatory infertility.

Hypothalamus can be influenced by the higher cortical centres, especially the temporal lobe. Emotional upsets are known to stimulate or depress the H–P–O axis and disturb the menstrual cycles. Neuro-endocrine system works through several loops, both positive and negative.

- Long loops through oestrogen and progesterone
- Short loop through anterior pituitary gland
- Ultrashort loop within the hypothalamus

Epinephrine and oestrogen stimulate whereas dopamine, serotonin and opioides inhibit the release of GnRH by the hypothalamus. Gonadotropins also inhibit GnRH secretion.

Until puberty, the hypothalamus is in a dormant state under the inhibitory influence of adrenal cortex, and the higher cortical centres, or it may be insensitive and nonresponsive to these stimuli. It becomes gradually sensitive around 8–12 years and starts its hormonal functions, fully establishing the H–P–O axis by the age of 13–14 years. What triggers GnRH to start functioning is not clear, but perhaps leptin produced by the adipose tissue that initiates the response. Initially, GnRH is released in a pulsatile manner during sleep, but later throughout 24 h. In the follicular phase, with low oestrogen (E_2) level, pulsatility is every 90 min, and with rise in E_2 level, the frequency rises to every 60 min. In the luteal phase, the frequency slows down to 1 in 3 h. Hypothalamus is sexually differentiated at birth. GnRH secretion is continuous in males, but pulsatile in females. Administration of testosterone to a female rat at birth is shown to cause a continuous secretion of GnRH in later life and alter the hormonal function to a male type.

Synthetic analogues of GnRH are nanopeptides and are now available and are used in the following:

- Preoperative shrinkage of uterine fibroids
- Shrinkage of endometriosis
- Shrinkage of endometrium prior to endometrial ablation
- Hirsutism
- Precocious puberty
- In vitro fertilization
- Prostatic cancer

Prolonged administration over 6 months can cause oestrogen deficiency and osteoporosis, and therefore the therapy should be used on a short-term basis. This peptide is degraded in the gastrointestinal tract and is therefore given intravenously, subcutaneously or intranasally. Its short life mandates repeated administration at short intervals. However, depot monthly injections are available.

Side effects of GnRH are as follows:

- Insomnia
- Nausea
- Osteoporosis caused by oestrogen deficiency, but reverts to normal after stoppage of the drug
- Decrease in breast size—reversible
- Myalgia, oedema
- Dizziness
- Decreased libido
- Decrease in high density lipoprotein (HDL) and increase in cholesterol by 10% each

The drugs and their administration are as follows:

- Nafarelin 200 mcg intranasally daily for 6 months.
- Buserelin 300 mcg TID subcutaneously daily × 5 days.
- Depot injection of goserelin IM or implant 3.6 mg monthly.
- Leuperide 3.75 mg IM monthly × 5 months.
- Triptorelin 3.7 mg IM 4 weekly.
- Antagon is GnRH antagonist used in down-regulation in in vitro fertilization.

Pituitary Gland (Adenohypophysis)

Pituitary gland lies in the sella turcica. It measures 1.2 × 1 × 0.6 cm and weighs 500–900 mg. It comprises the anterior pituitary gland (adenohypophysis) and the posterior pituitary gland (neurohypophysis). The anterior pituitary gland originates at the roof of the embryonic pharynx called Rathke's pouch and contains chromophil and chromophobe cells. The posterior lobe develops from the floor of the brain. The two lobes of the pituitary gland develop independently of each other. The anterior lobe is ectodermal in origin.

The anterior pituitary gland measuring 30 × 6 × 9 mm in size is located at the base of the brain in a bony cavity called sella turcica below the hypothalamus. It consists of three histologically distinguishable cells: (i) the chromophobe or parent cell, (ii) the chromophil cells described as eosinophil or alpha (α) cells and (iii) basophil or beta (β) cells. The β-cells secrete the gonadotropins that control the ovarian function and menstrual cycles. These gonadotropins are FSH, LH, thyroid-stimulating hormone (TSH) and corticosteroid hormone. Each of these hormones has α- and β-fractions. Whereas α-fraction is identical in all (contains 92 amino acids), β-fraction is specific in its action.

Follicle-Stimulating Hormone

FSH is a water-soluble glycoprotein of high molecular weight and is secreted by the β-cells; it contains 115 amino acids in β-fraction. The carbohydrate fraction is mannose. FSH controls the ripening of the primordial follicles, and in conjunction with the LH, it activates the secretion of oestrogen. Its activity builds up as the bleeding starts to cease reaches a peak around the seventh day of the cycle (40 ng/mL) and then declines to disappear around the 18th day. Another small peak occurs after ovulation, perhaps as a result of a fall in the level of oestrogen in the premenstrual phase. The half-life of FSH is 4 h. Low FSH causes defective folliculogenesis and short or defective corpus luteal phase. Oestrogen suppresses FSH secretion through negative feedback mechanism. It develops LH receptors in the granulosa cells.

Gemzell initially isolated FSH from the pituitary of human cadavers at autopsy, but it required 10 pituitaries to produce enough FSH for one ovulation. FSH is now commercially obtained from the urine of menopausal women. The preparation contains both FSH and LH. Pure FSH is now available on the market but is very expensive.

Luteinizing Hormone

LH is a water-soluble glycoprotein of high molecular weight secreted by β-cells; it also contains 115 amino acids. The carbohydrate fraction is mannose. LH pulse occurs only during sleep initially, but later extends throughout the day. LH surge initiated by oestrogen lasts for 48 h and is preceded by a small amount of progesterone 2 h earlier. LH level doubles in 2 h and the peak plateaus for 14 h before declining. Progesterone secretion begins 34 h after LH peak. In conjunction with FSH, it activates the secretion of oestrogen, brings about the maturation of the ovum and causes ovulation. LH stimulates the completion of the reduction division of the oocyte. Following ovulation, it produces luteinization of the granulosa and the theca cells and initiates progesterone secretion. The LH surge precedes ovulation by 24–36 h (mean 30 h) and a minimum of 75 ng/mL is required for ovulation. This time relationship of LH peak to ovulation is helpful in predicting the exact time of ovulation in infertile women on gonadotropin therapy, making it possible to retrieve ova in in vitro fertilization and to arrange for timely artificial insemination to enhance chances of conception. LH stimulates the secretion of testosterone and androstenedione in the ovarian stroma (theca cells), which diffuse into the follicular fluid and are aromatized into oestradiol.

Today, for diagnostic and therapeutic purposes, a rapid, visual semiquantitative enzyme immunoassay dipstick test,

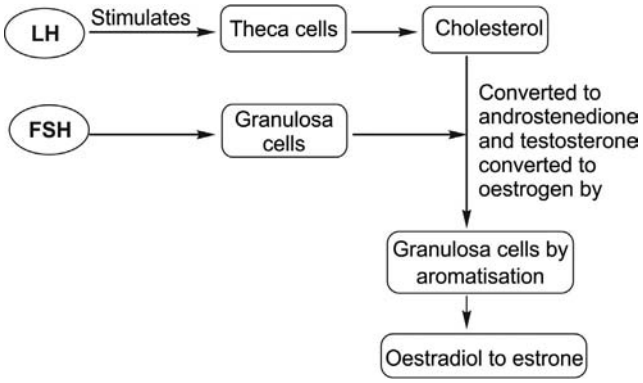

Figure 3.3 Two-cell two-gonadotropin theory of ovarian steroidogenesis.

called OvuSTICK, is available for testing urine to detect the LH surge by undertaking daily LH estimations around the period of ovulation. These kits are expensive. The half-life of LH is 30 min (Figure 3.3).

Human Chorionic Gonadotropin (hCG)

Secreted by the trophoblastic tissue in pregnancy, human chorionic gonadotropin (hCG) has a luteinizing action and is available in injectable form for use in cases of anovulatory infertility, in vitro fertilization, corpus luteal insufficiency and habitual abortions. hCG contains α- and β-fractions. The α-fraction resembles LH and TSH, but the β-fraction is exclusively specific to chorionic tissue. It is commercially obtained from the urine of pregnant women. The level is increased in trophoblastic tumours and some ovarian tumours. Recombinant hCG is now available, which has less side effects at the site of injection.

Prolactin

Prolactin is an alcohol-soluble protein (polypeptide) (198 amino acids) without a carbohydrate fraction and with a half-life of 30 min. It is secreted by α-cells. Its main action is on lactation. It has a suppressive effect on the pituitary–ovarian axis, and therefore the patient who suffers from hyperprolactinaemia may develop amenorrhoea or oligomenorrhoea due to anovulatory cycles, with or without galactorrhoea. Normal prolactin level is 25 ng/mL. Up to 100 ng/mL occurs in hyperprolactinaemia but over 100 ng/mL is seen in pituitary tumours. The prepubertal level of 7 ng/mL rises to 13 ng/mL at puberty and 25 ng/mL in an adult woman. Active prolactin is present in the form of monomer or 'little prolactin' (50%), whereas dimeric and multimetric (big prolactin) forms have negligible biological activity. Normally, the prolactin is under tonic hypothalamic inhibitory factor (PIF), which is probably dopamine and is released into the portal system. The level of prolactin is raised during sleep, nipple stimulation and the secretion of thyroid-releasing hormone, β-endorphin, serotonin and oestrogen.

Prolactin level does not fluctuate much during the menstrual cycle. It suppresses LH but not FSH, so hyperprolactinaemia decreases the LH/FSH ratio.

Growth hormone, insulin-like growth factor, epidermal growth factor, adrenal cortex and *TSH* also participate in the endocrinological functions in a woman, through their action on the hypothalamus and anterior pituitary gland. A high level of TSH stimulates prolactin secretion and causes ovulatory and menstrual dysfunction. Interleukin-1 is a cytokine with antigonadotrophic activity and it prevents luteinization of granulose cells.

Posterior Pituitary Gland (Neurohypophysis)

Oxytocin and vasopressin are nonapeptides formed in the hypothalamus and released directly into the posterior pituitary gland. Oxytocin is produced by the paraventricular nucleus and vasopressin by the supraoptic nucleus of the hypothalamus.

Oxytocin

Oxytocin acts mainly on the smooth muscle of the uterus, causing contraction of the muscles and controlling the bleeding in the third stage of labour. By intermittent uterine contractions and relaxation, it induces and enhances the labour pains, in the first and second stage of labour. It causes contraction of the myoepithelial cells lining the mammary ducts and ejects milk during suckling.

Vasopressin

Vasopressin maintains the blood volume and blood pressure. Both have antidiuretic action when given in large quantities (over 20 units of oxytocin in 24 h). The therapeutic applications of these hormones are described in Chapter 43.

Ovarian Steroidogenesis

The active hormones of the ovary are the steroids derived from cholesterol. These include oestrogens, progesterone, testosterone and androstenedione (Figure 3.1A).

Oestrogen

Natural oestrogens are C18 steroids, the main source of which are the theca and granulosa cells of the Graafian follicles and corpus luteum, while the adrenal cortex is the secondary source of supply. Oestrogen is secreted as oestradiol. It is bound to albumin (30%) and sex-hormone-binding globulin (SHBG, 69%), and only 1% is biologically active. It acts by binding to cytoplasmic receptors in the cells. It is inactivated by the liver and excreted as conjugates of oestrone, oestradiol and oestriol

in the urine and bile (85% in urine, 10% in faeces). The plasma oestradiol level rises approximately 6–7 days before ovulation from 50 mcg daily to the peak level of 300–600 mcg about 2 days before ovulation and approximately 24 h before the LH peak (level up to 350 pg/mL). Thereafter, the oestradiol concentration falls to 150–200 mcg daily, but a small rise is seen again in the mid-luteal phase. The urinary excretory level follows the pattern seen in the plasma. The oestradiol peak seen before ovulation is not as a good marker for indicating ovulation as LH, because follicular maturation does not always end in ovulation. A serum level of oestrogen with ultrasonic monitoring is used to monitor the optimal time to administer hCG for the therapeutic induction of ovulation. Whereas oestradiol, which is 10 times as potent as oestrone, is present during reproductive period, it is oestrone derived from peripheral aromatization of androstenedione that is predominant in menopausal women. The placenta is the main source of oestriol. Each cycle produces 10 mg of oestradiol.

Synthetic oestrogens are readily available in the market and are used in various gynaecological disorders. They are absorbed orally and through vagina and skin.

Actions of Oestrogens (Figure 3.4)

1. **Feminization and secondary sex characteristics.** The texture of the female skin and hair and the shape of the female form are considerably influenced by oestrogen.
2. **Specific action on the genital tract.**

Vulva and vagina

- Development of the vulva.
- Vascular stimulation of the vulva and vagina.
- Epithelial stimulation of the vulva and vagina.
- Cornification of the superficial layers of the vagina, which appear as acidophilic polyhedral cells with a small pyknotic nucleus. Oestrogen raises the karyopyknotic index in vaginal cytology (Ch. 6).
- Deposition and metabolism of intracellular glycogen in the vaginal epithelium.

Uterus

- Causes myohyperplasia of the myometrium and cervix.
- Increases uterine vascularity.
- Regenerates the endometrium after menstruation and is responsible for the proliferative (preovulatory) growth of the endometrium. Oestrogen causes proliferation of epithelial lining, glandular cells and stroma and mitosis. Spiral vessels elongate and stretch the entire length of endometrium, and dilate.
- Stimulant effect on the glands of the endocervix and their mucous secretion.

Fallopian tubes

Oestrogen stimulates the tubal musculature, which is, in fact, morphologically specialized myometrium.

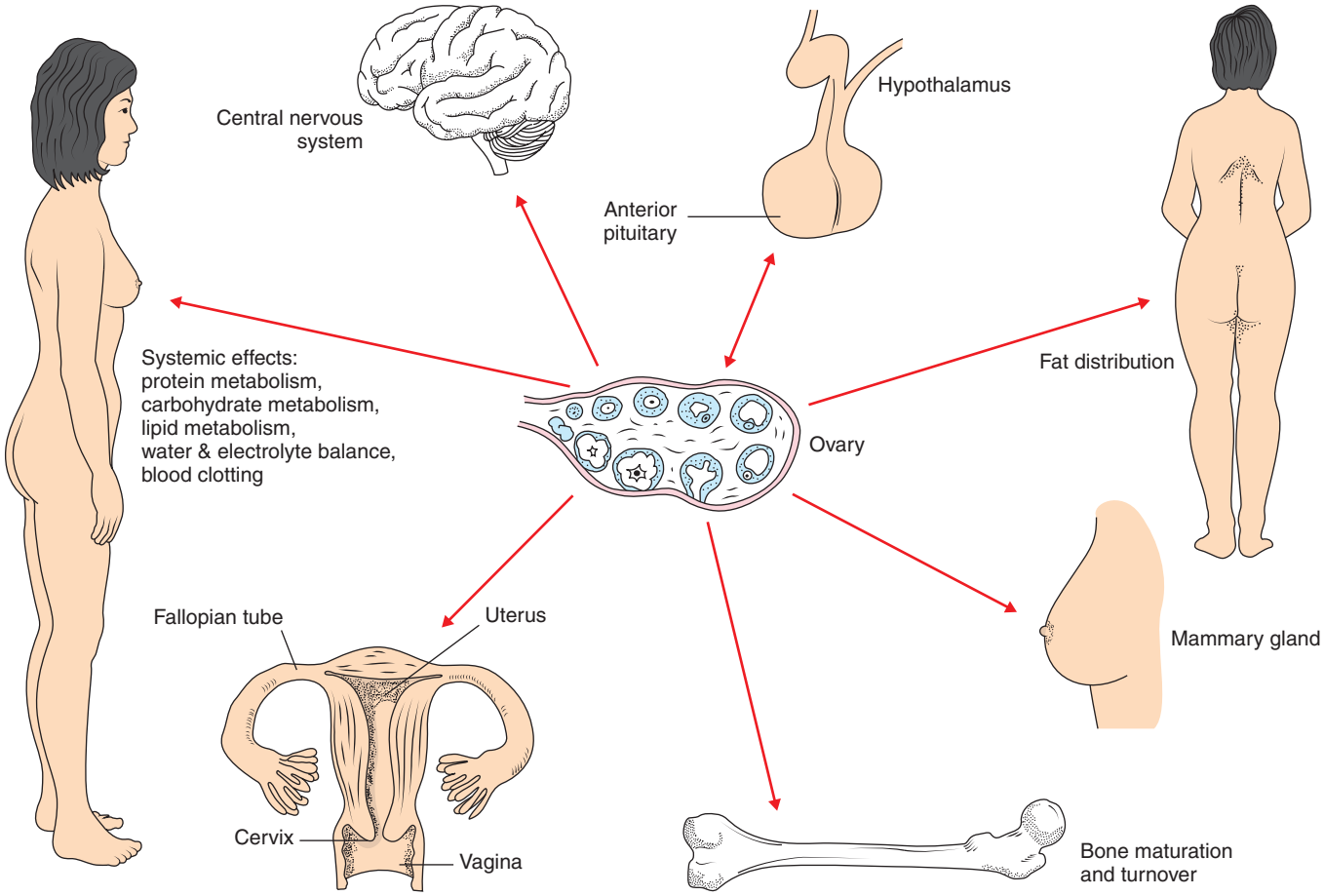

Figure 3.4 Physiological effects of oestrogen.

Ovary
No action.

3. **Breast**. Hypertrophy of the ductal and parenchymal tissue of the breast, increased vascularity, areolar pigmentation, but no galactogenic effect. Large doses suppress lactation.
4. **Action on other endocrine glands**. Oestrogen suppresses FSH and thyrotropic hormones. It can be used to inhibit ovulation as also production of milk in the puerperal patient. It is stimulant to the LH and thereby corpus luteum formation and, to a lesser extent, to ACTH.
5. **Skeletal system**. It increases calcification of bone and the closure of epiphyses in the adolescent and is antagonistic to somatotropin. In the postmenopausal women, decalcification of bone (osteoporosis leading to kyphosis) is, in fact, due to oestrogen deficiency.
6. **Water and sodium metabolism**. Oestrogen tends to cause water and sodium retention. An example is premenstrual tension, which is caused by congestion and water retention. It also causes calcium and nitrogen retention.
7. **Blood cholesterol**. Blood cholesterol levels are to a small extent controlled by oestrogen, hence the importance of ovarian conservation when performing hysterectomy in a young woman. HDL increases under oestrogen influence and is cardioprotective.
   - Oestrogen improves the skin by producing collagen.
   - By raising fibrinogen level, it can cause thromboembolism and is a major side effect of oestrogen.
   - It increases SHBG by the liver.

Progesterone

The corpus luteum is the main source of progesterone and a small amount is derived from adrenal gland (2–3 mg), seen in the proliferative phase. Although progesterone is an important intermediary product in the synthesis of adrenal corticosteroids, it has little, if any, biological action from this extra ovarian source. The plasma level of progesterone rises after ovulation and reaches a peak level of 15 ng/mL at mid-luteal phase. With the degeneration of the corpus luteum, its level falls and this brings about menstruation. In an anovulatory cycle, progesterone is absent or is in negligible amount (from extra ovarian sources). Menstruation is then brought about by a fall in the level of oestrogen. If pregnancy occurs, the corpus luteum persists, even enlarges and continues to secrete progesterone. This high level of hormone prevents menstruation and leads to amenorrhoea of pregnancy. It is excreted in the urine as sodium pregnanediol 3-glucuronide and recovered as such for assay in the secretory phase of the menstrual cycle. Progesterone is bound to albumin (80%) and corticosteroid-binding globulin (20%). Daily production in the luteal phase is 20–40 mg and daily urine excretion is 3–6 mg. Mid-luteal phase level of less than 15 ng/mL suggests corpus luteal phase defect (LPD) and ovulatory dysfunction.

Radioimmunoassay is currently used to estimate the plasma progesterone levels in mid-luteal phase in cases of infertility. However, with development of enzyme immunoassay, a home 'dip-stick' test can estimate urinary pregnanediol to determine occurrence of ovulation. Salivary progesterone level is estimated by direct use of solid-phase enzyme immunoassay (Dooley). Several synthetic progesterones (progestogens) are now available for commercial use (Figure 3.1A and B) .

Actions of Progesterones

Endometrium. Progesterones cause secretory hypertrophy and decidual formation if the endometrium has been previously primed with oestrogen. Glycogen and mucus collect in the tortuous glands.

Pregnancy. Progesterone initially from the corpus luteum and later from the placenta is essential for the continuation of pregnancy.

Uterus. Progestogens cause myohyperplasia of the uterus. They increase the strength but diminish the frequency of uterine contractions.

Fallopian tube. Progestogens cause hyperplasia of the muscular lining of the fallopian tube and make peristaltic contractions more powerful as well as increase the secretion by the tubal mucous membrane.

Cervix. Progestogen causes hypertrophy of the cervix and makes the cervical mucus more tenacious. It renders the internal os competent and holds the pregnancy to term.

Vagina. During early pregnancy the vagina becomes violet coloured due to venous congestion. The epithelial cells fail to mature and cornify. They are classically basophilic with fairly large nuclei and folded edges. Karyopyknotic index falls to below 10%.

Breasts. Progestogens, with oestrogen, cause breast hypertrophy. They increase acinar epithelial growth.

Pituitary. The exact action of progestogens on the pituitary is not known. Progestogens may inhibit the production of FSH and suppress ovulation. A certain percentage of progestogens is metabolized to oestrogen, and it may well be that the oestrogen so produced is responsible for inhibiting pituitary activity.

Fluid retention. Progestogens cause water and sodium retention and is a contributory factor in premenstrual tension and weight gain.

Smooth muscle. Progestogens relax smooth muscles. The uterine muscles therefore relax in pregnancy. Ureter dilates under its effect.

Thermogenic. Progestogens raise the body temperature by 0.5°C. Basal body temperature (BBT) chart is based on its thermogenic effect during the menstrual cycle.

Anabolic effect. Progestogens exert anabolic effect and this partly accounts for some of the weight gain which may follow their administration.

Libido. Diminution of libido infrequently occurs.

Virilization. While part of the administered progestogen is metabolized to oestrogen, it is also partly metabolized to testosterone. If administered to a patient during pregnancy, some progestogens have virilizing effect upon a female fetus.

- Lipid metabolism decreases HDL but increases low-density lipoprotein. Thus, it is harmful to the heart.
- It improves the immune response.

Side Effects

If given in large doses, progestogen can cause gastrointestinal symptoms, nausea and vomiting. Headache and mild elevation of temperature are also seen. In fact, all symptoms of pseudopregnancy state may be observed—water retention, breast enlargement and tenderness, and moderate uterine enlargement. Virilism has been reported with some synthetic progestogens, especially 19-nortestosterones. Some exhibit adverse effects on lipid metabolism and increases the risk of breast cancer. Thrombosis of deep veins, pulmonary embolism and arterial thrombosis are rare but are reported with third generation of synthetic progestogens (gestodene, desogestrel) (Table 3.1).

Relaxin

This hormone relaxes the connective tissue and is probably secreted by the ovary. Relaxin is a water-soluble protein and nonsteroid. It may have a role in pregnancy and may be responsible for relaxation of pelvic joints and pelvic floor muscles.

Inhibin

Inhibin is a nonsteroidal water-soluble protein (peptide) secreted by the Graafian follicle. McCullagh identified this protein and named it inhibin, because it is known to suppress pituitary FSH. Inhibin consists of two peptides, namely inhibin A (α-fraction) and inhibin B (β-fraction). In normal ovarian folliculogenesis, FSH and LH initiate secretion of oestrogen by the Graafian follicle. Oestrogen is responsible for secretion of inhibin in the Graafian follicle, which in turn suppresses FSH but stimulates LH secretion. Administration of inhibin in the early follicular phase can delay folliculogenesis and inhibit ovulation and luteinization. Inhibin may have an important role in the control of fertility both in the males and the females. It causes agglutination of sperms, prevents cervical mucus penetration and interferes with egg interaction. In polycystic ovarian disease (PCOD), there is an increased secretion of inhibin. This causes a low FSH but a high LH secretion by the anterior pituitary gland and is responsible for anovulation. Although the extraction of purified inhibin is not yet successful, there is a possible hope of its availability in the near future. Normal level of 50 pg/mL (>45 pg) drops to less than 15 pg/mL after menopause due to oestrogen deficiency. It is studied by ELISA test.

TABLE 3.1 Effects of oestrogen and progesterone on the female genital tract

Organ	Oestrogen	Progesterone
Breasts	Ductal/stromal growth	Alveolar growth
Vagina	Superficial cells with glycogen	Intermediate cells
Cervix	Abundant mucus thin, viscous, penetrable to sperms	Thick tenacious mucus, impenetrable to sperms
Uterus	Myohyperplasia	Myohyperplasia
Endometrium	Proliferative endometrium	Secretory endometrium
Fallopian tube	Secretion	Increased peristaltic movements
Ovary	No action	No action

Activin

Activin is secreted by the anterior pituitary gland and the granulosa cells, and stimulates FSH release, and enhances action in the ovary.

Follistatin suppresses FSH activity by acting against activin.

Anti-Müllerian Hormone (AMH)

AMH is a peptide secreted by the Sertoli cells in the testis and granulosa cells in the ovary. In the male, AMH starts to be secreted by the seventh week of intrauterine life and it continues until puberty. It inhibits the development of **Müllerian** system. Absence of AMH results in hermaphrodite.

In the female, AMH is secreted by the granulosa cells after puberty. It helps in the follicular development and oocyte maturation.

Normal value is 2–6.8 ng/mL; level <1 ng/mL shows poor ovarian reserve, >10 ng/mL is seen in PCOD and hyperstimulation syndrome. Its level is related to precocious and delayed puberty, infertility and premature menopause. Its level is related and reflects the number of growing follicles.

Estimation of serum AMH is used in the study of ovarian reserve in an infertile woman and a woman with secondary amenorrhoea. In in vitro fertilization programme, it carries a prognostic value and helps to decide on donor egg.

Sex Hormone-Binding Proteins

Most of oestrogens and androgens are bound to sex hormone-binding protein (SHBP) secreted by the liver and remain inactive. Only free hormones are biologically active and influence their target organs (1–2%). Oestrogen and thyroid hormones increase the secretion of these proteins, but androgens lower their levels.

Testosterone

Fifty per cent testosterone comes from the ovaries and the rest from adrenal gland. The ovarian stromal tissue secretes androgenic products, namely testosterone, dehydroepiandrosterone (DHEA) and androstenedione. Androstenedione gets converted in the peripheral fat to oestrone. The normal increase in stromal tissue at ovulation causes a slight increase in the secretion of these hormones. After the menopause, the increased ovarian stroma is responsible for the rise in these hormones and development of hirsutism in some postmenopausal women. Total daily

production of testosterone is 0.2–0.3 mg and plasma level is 0.2–0.8 ng/mL. The daily production of androstenedione is 3 mg and plasma level is 1.3–1.5 ng/mL. Normal 17-ketosteroid level is 5–15 mg in 24 h. More than 25 mg indicates adrenal hyperplasia. Plasma level of DHEA sulphate over 5 mcg/mL is seen in adrenal hyperplasia.

Eighty to eighty five per cent androgens are bound to SHBP and 10–15% to albumin. One to two per cent free testosterone remains biologically active and acts at the peripheral targets, i.e. hair growth and acne by conversion to dihydrotestosterone by hydroxylase enzyme. Clinically, administration of androgen causes follicular atresia and anovulation.

Physiology of Menstruation

The proliferative phase of the endometrium represents the oestrogenic part of the menstrual cycle. It is initiated and controlled by oestrogen. The secretory phase of the endometrium is controlled by progesterone, although the effect of progesterone is obtained only after the endometrium has been sensitized with oestrogen. This is because oestrogen produces progesterone receptors to which progesterone acts.

Although the activity of the endometrium is directly controlled by the ovarian function and by the two hormones secreted by the ovary, the ovary itself is activated by the pituitary gland, the secretion of which is under the nerve control of the hypothalamus.

At birth, the ovaries are populated with lifetime complement of eggs located in the primordial follicles, but most of these follicles undergo atresia throughout childhood and only about 400 of these primordial follicles are present during reproductive age. At puberty, the hypothalamus starts a pulsatile secretion of GnRH, resulting in the activation of H–P–O uterine axis and in the establishment of menstrual cycles.

Pulsatile GnRH initiates secretion of FSH and LH. FSH released by the anterior pituitary gland stimulates the growth of a few primordial follicles into Graafian follicles. Multiple follicles start growing in both the ovaries, but only one dominant Graafian follicle is selected which ripens to full maturity and ovulates, whereas other follicles become atretic. The Graafian follicles under the influence of FSH together with only a minimal amount of the LH secrete 17-β-oestradiol (Figure 3.5A and B). 17-β-Oestradiol has several functions: in the first place, it produces proliferative changes in the endometrium, it

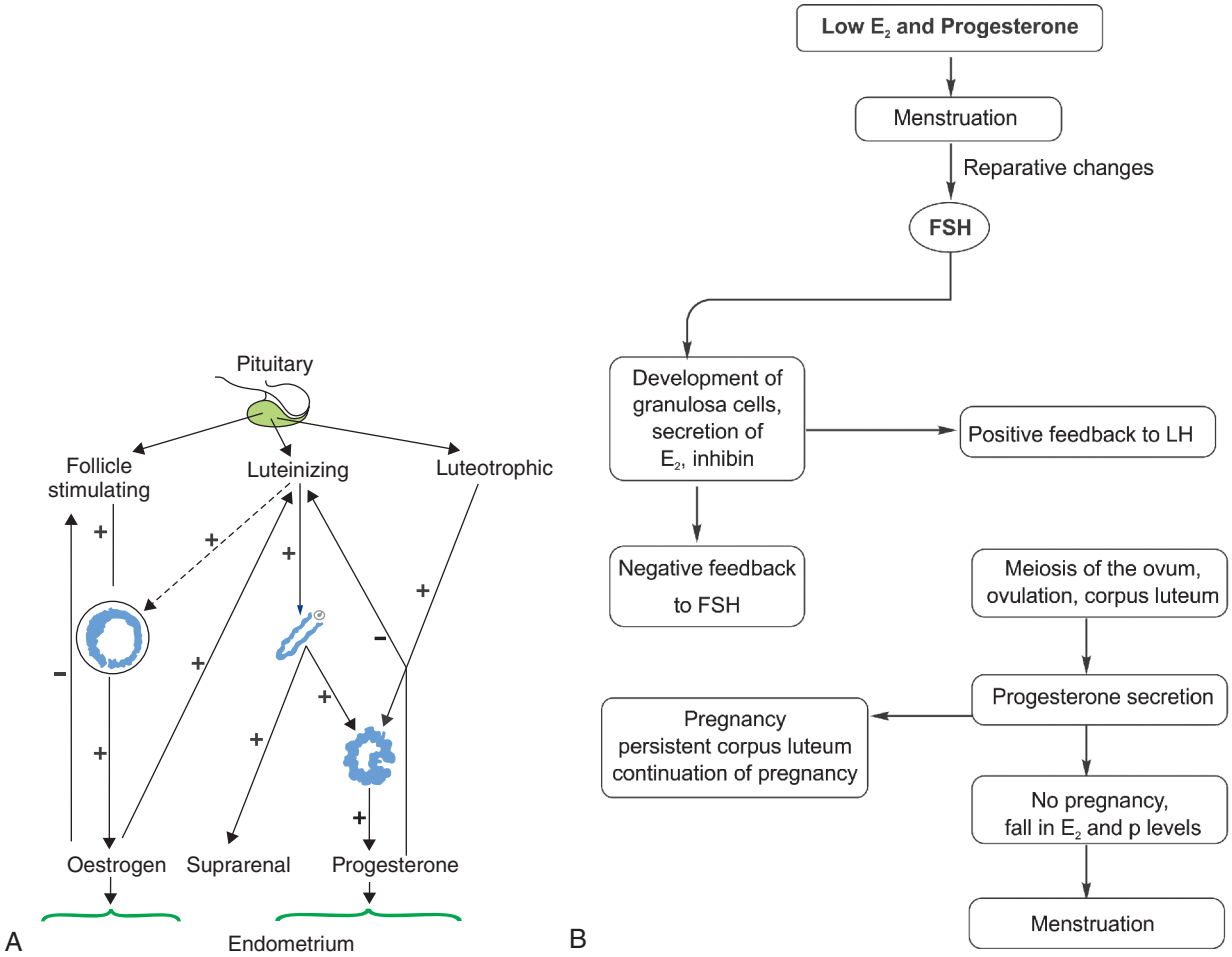

Figure 3.5 **(A)** A scheme illustrating interrelation of pituitary gonadotropic hormones. '+' indicates stimulation and '–' indicates inhibition. **(B)** Flowchart of menstruation.

secretes inhibin and inhibits further secretion of FSH by the anterior pituitary and it stimulates LH receptors in the theca cells and stimulates anterior pituitary to secrete LH. Inhibin produced by the Graafian follicle under oestrogenic effect is also responsible for a fall in the FSH level and stimulation of LH secretion. The maximum peak of oestrogen secretion is seen about 48 h before ovulation, whereas the LH peak occurs about 24–36 h before ovulation. LH has following functions. In the first place, it stimulates a Graafian follicle to secrete 17-β-oestradiol, and secondly, it causes the follicle to rupture at ovulation and to form a corpus luteum (Figure 3.6). It also stimulates the secretion of testosterone and androstenedione by theca cells.

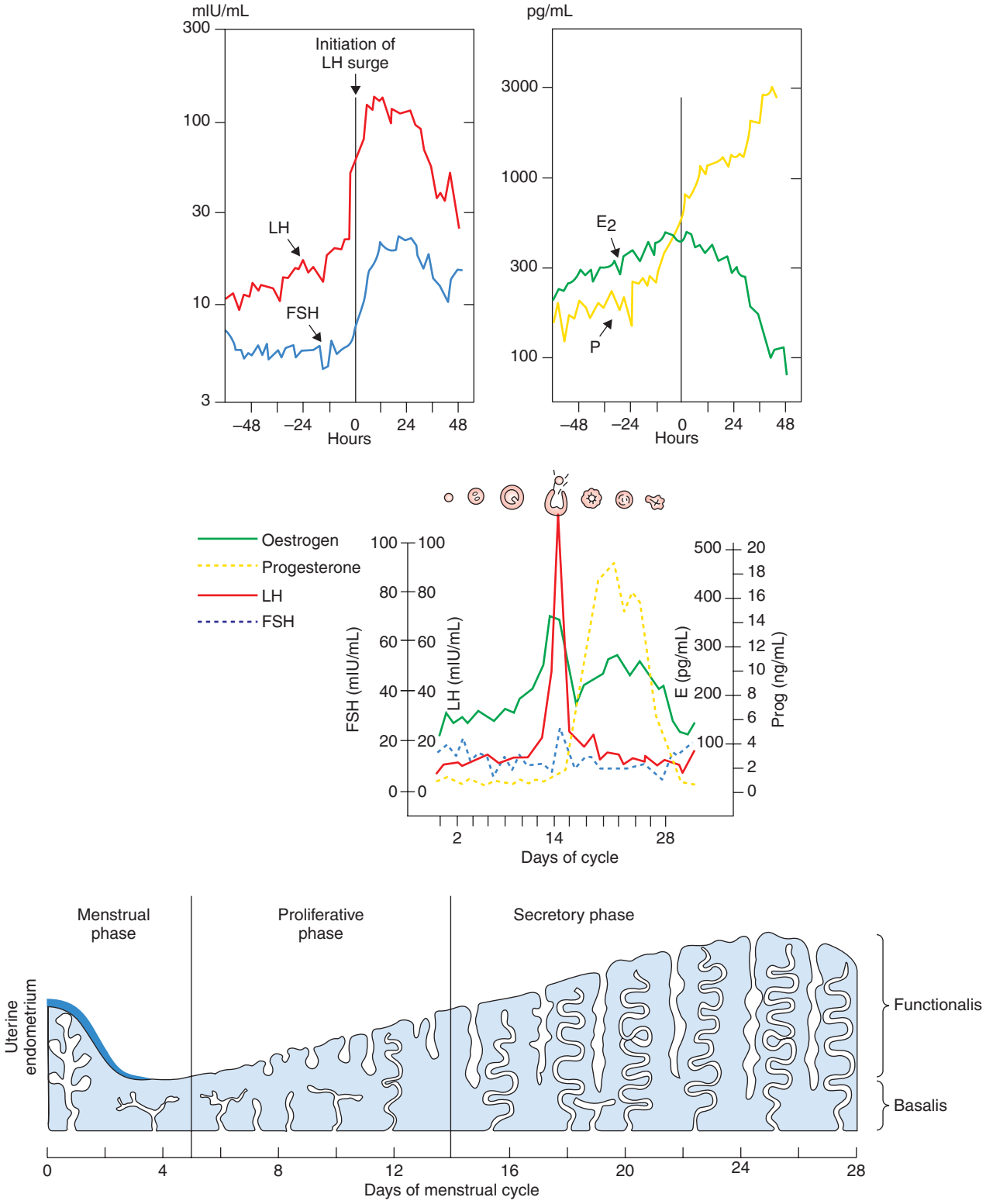

Figure 3.6 Plasma hormone levels in the normal menstrual cycles.

The corpus luteum secretes progesterone, the level of which starts rising. The hormone progesterone has two functions. In the first place, it stimulates the endometrium to undergo secretory hypertrophy, and secondly, it inhibits further production of LH by the anterior pituitary. *The gonadotropins seem to have no direct effect upon the endometrium of the uterus* (Figure 3.6).

In the absence of pregnancy, both oestrogen and progesterone levels decline gradually and the fall in the level of these hormones brings about menstruation. A fall in the level of these hormones also starts off a fresh positive feedback mechanism and triggers the hypothalamus to release gonadotropin. This is how a menstrual cycle is regulated. The luteal phase, i.e. time between ovulation and menstruation, is fairly constant at 14 days in a menstrual cycle. The growth of the ovarian follicles and endometrial thickness can be studied by serial ultrasound. Oestrogen, LH and mid-luteal progesterone levels can be conveniently and speedily measured by radioimmunoassays (Figure 3.7; Table 3.2).

As mentioned earlier, thyroid hormones and adrenal hormones react with sex hormones and alter the H–P–O pathway by inhibiting GnRH secretion. Oral combined pills, by virtue of inhibiting GnRH and preventing ovulation,

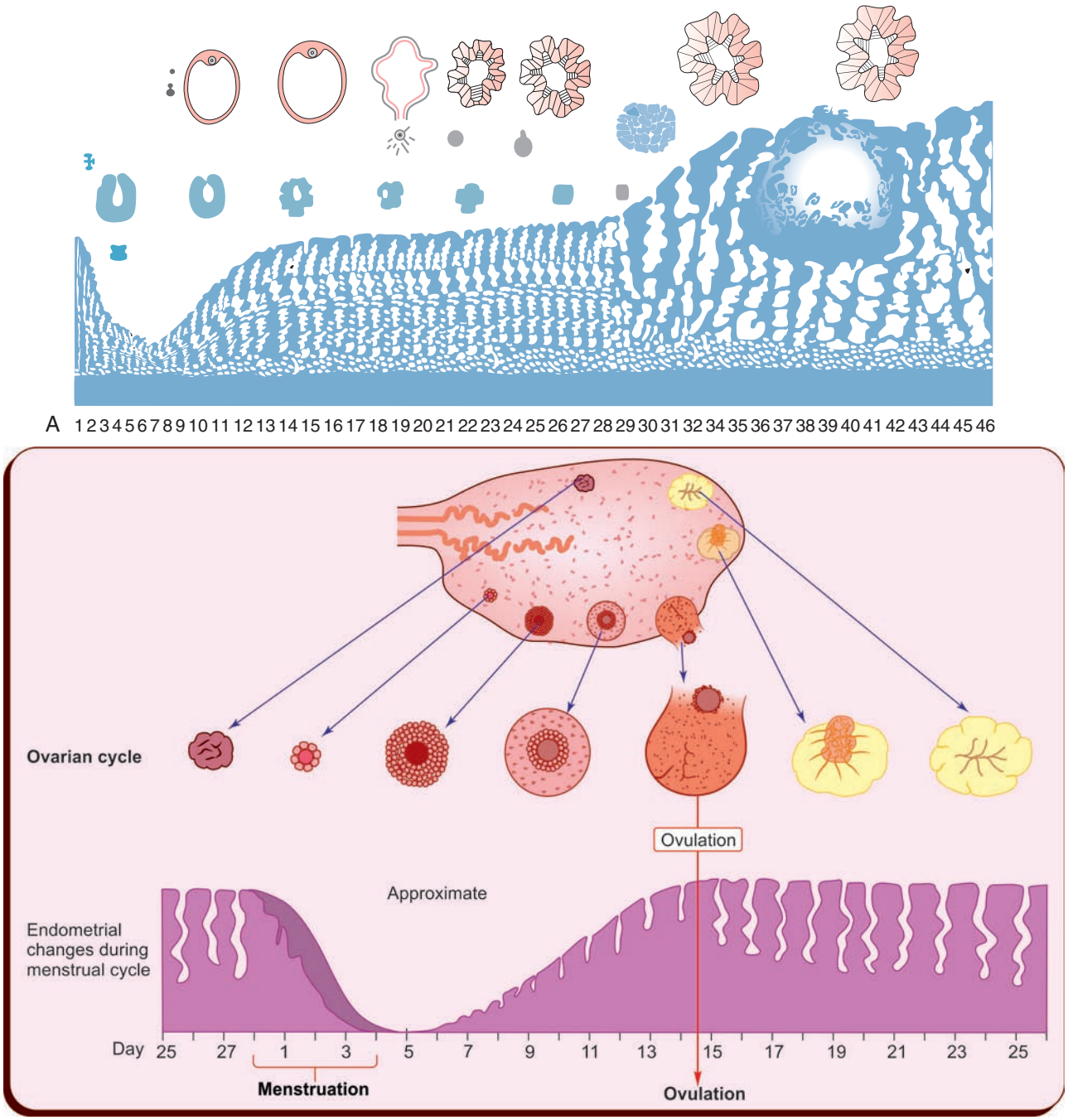

Figure 3.7 **(A)** Schroder's illustration of the relation between ovarian function and the changes in the endometrium during early pregnancy. **(B)** Ovarian cycle with corresponding endometrial thickness.

TABLE 3.2 Hormonal levels in different phases of menstrual cycle

	NORMAL			
Hormone	**Follicular Phase**	**Ovulation**	**Luteal Phase**	**Menstrual Phase**
FSH	5–15 mIU/mL	12–30	2–9	3–15 mIU/mL
LH	6–14 mIU/mL	25–100	2–13	3–12 mIU/mL
E_2	100/200 pg/mL	300–500 pg/mL	100–200	–
P	1 ng/mL	–	15 ng/mL	–
17 ketosteroid	Normal	5–10 mg/daily	–	>25 mg in adrenal hyperplasia
Testosterone	Normal	0.2–0.8 ng/mL	–	>2 ng/mL in ovarian tumours
Androstenedione	Normal	1.3–1.5 ng/mL	–	–
DHEA	Normal	<5 mcg/mL	–	>5 mcg in adrenal hyperplasia
Cortisol	–	<5 mcg/dL	–	–
DHEAS	800 ng/mL	–	–	Adrenal hyperplasia, tumour

cause atropic endometrium. Continuous oestrogen stimulation leads to endometrial hyperplasia (Figure 3.8).

Feedback Mechanism in the H–P–O axis

As mentioned in the beginning, the various hormones liberated by the hypothalamus, anterior pituitary gland and the ovaries are dependent upon each other, each reaching in positive as well as negative feedback at different levels.

The following are the feedbacks:

1. Long feedback mechanism from the ovaries to pituitary and hypothalamus.
2. Short feedback mechanism between the anterior pituitary gland and hypothalamus.
3. Ultrashort feedback mechanism.

Autoregulation of release of GnRH by hypothalamus. Increased secretion of GnRH suppresses its own synthesis and vice versa.

Leptin

Since its discovery in 1994, leptin (adipocyte protein hormone) is linked to nutrition and may bear an important role in the control of hypothalamic–pituitary–ovarian axis. A diet restriction has a negative impact on hypothalamus and decreases LH secretion causing amenorrhoea as seen in anorexia nervosa. Leptin is found in the follicular fluid in the ovaries and presumably stimulates pulsatile secretion of GnRH around puberty. Hence, an obese adolescent reaches menarche earlier than a lean girl. Lean girls have a delayed puberty. More research is required in this field.

Menstruation

Menstruation is the end point in the cascade of events starting at hypothalamus and ending in the uterus. The menstrual cycle is usually of 28 days, measured by the time between the first day of one period and the first day of the next. The duration of bleeding is about 3–5 days and estimated blood loss is between 50 and 200 mL. The regular cycle of 28 days is seen only in a small proportion of women. A deviation of 2 or 3 days from the 28-day rhythm is quite common. The menstrual rhythm depends on the H–P–O function, whereas the amount of blood loss depends upon the uterine condition.

A study of the coiled arteries of the endometrium shows that there is a slight regression of endometrium shortly after ovulation and that a rapid decrease in thickness can be demonstrated even before menstruation starts. In the regression that starts a few days prior to the onset of menstruation, there is a decreased blood flow which may cause shrinkage of the endometrium from dehydration. During menstruation itself, the reduction in the thickness of the endometrium is determined by both desquamation and resorption. The coiled arteries become buckled with subsequent stasis of blood flow. The necrosis of the superficial layers of the endometrium is produced either by local stasis or by the clearly demonstrated vasoconstriction of the coiled arteries. Menstrual bleeding occurs when the open arteries damaged by necrosis relax and discharge blood in the uterine cavity. Some degree of venous haemorrhage also occurs. Fragments become detached from the superficial layer of the endometrium by the end of the first day (Figures 3.7–3.9).

The important feature of the menstrual changes is the contraction and constriction of the coiled arteries. The ischaemia causes necrosis and disintegration of the superficial zone. The regeneration of the vascular system is probably brought about by the development of anastomosing arteries. The re-epithelialization is brought about by the cells growing from the mouth of the base of the glands that remain in the unshed basal layer of the endometrium.

In anovulatory menstruation, there is the same shedding of a thin necrotic superficial layer of the endometrium, and it is to be presumed that exactly the same factor is at work to cause the vascular changes with resultant ischaemia.

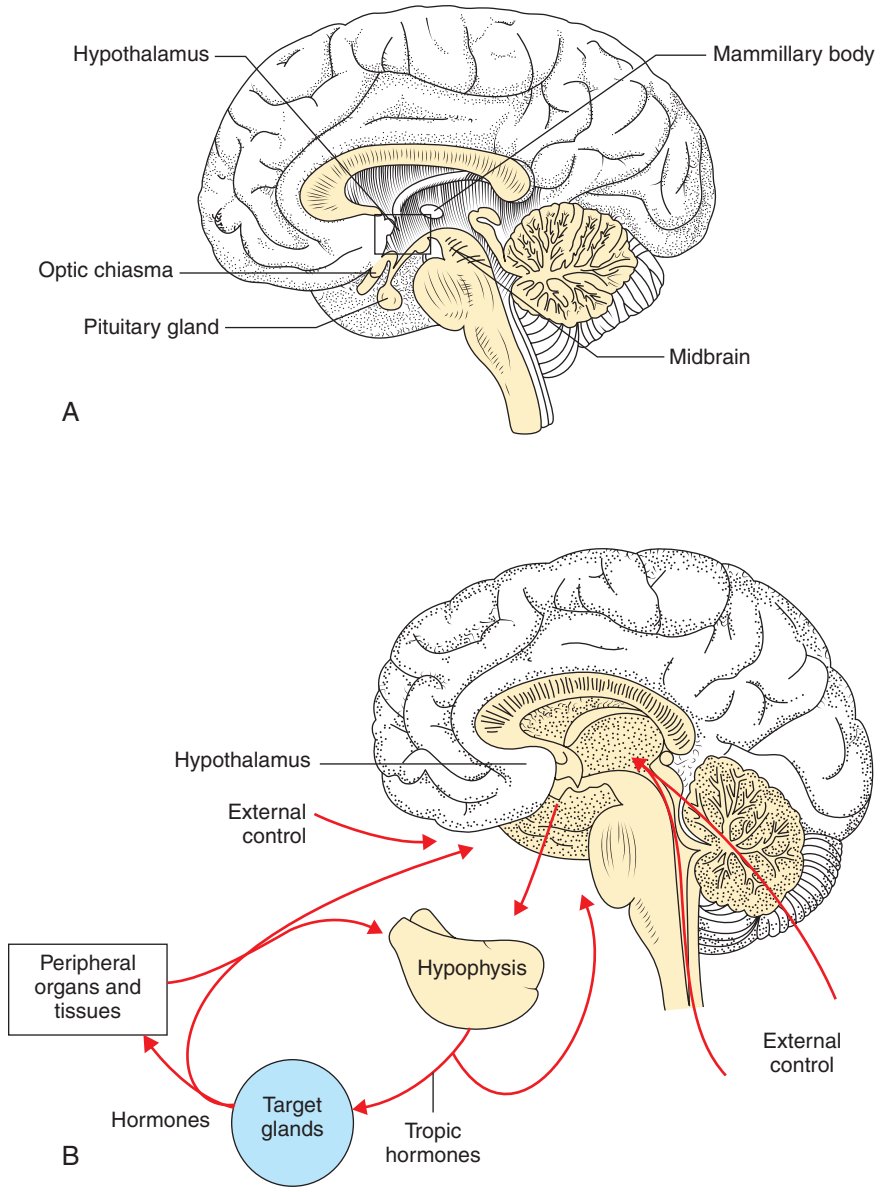

Figure 3.8 Neuroendocrine control of menstruation.

The vascular changes in the endometrium and the amount and duration of the menstrual bleeding are controlled by the interaction of different prostaglandins secreted by the endometrium.

Prostaglandin E_2 (PGE_2) causes myometrial contractions but vasodilatation of the vessels. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) causes vasoconstriction as well as myocontraction. Prostacyclin (PGI_2) is responsible for muscle relaxation and vasodilatation. According to this, PGE_2 and $PGF_{2\alpha}$ are responsible for dysmenorrhoea, and PGI_2 can cause menorrhagia.

Improved ultrasonic imaging and colour Doppler study of the endometrium have improved our knowledge related to menstrual disorders.

Menstrual Fluid in 'Stem Cell' Therapy

The stem cells are the basic building blocks of every other cell in the body. Whereas organ cells have specific functions, the stem cells are 'blank' but have the potential to take up any function. Under suitable environment and surrounded by specific organ cells, the stem cells divide into either stem cells or another type of cells with their attached functions. Thus, the stem cells have a vital role in 'regenerative medicine' in degenerative and life-threatening diseases such as Alzheimer disease, atherosclerosis, diabetes, heart disease, bowel disease, Parkinsonian disease and rheumatoid arthritis.

The sources of stem cells were until recently seen in bone marrow, embryo, amniotic fluid and umbilical cord blood but now in menstrual fluid as well. The menstrual fluid contains mesenchymal cells such as mononuclear cells and fibroblasts. These cells, however, deteriorate with advancing age. Therefore, cells from young women are suitable for donation, and self-use at a later age if needed. The kit contains antibiotics to prevent infection, and the menstrual fluid is cryopreserved and harvested. The procedure is simple, noninvasive and painless as well as possible.

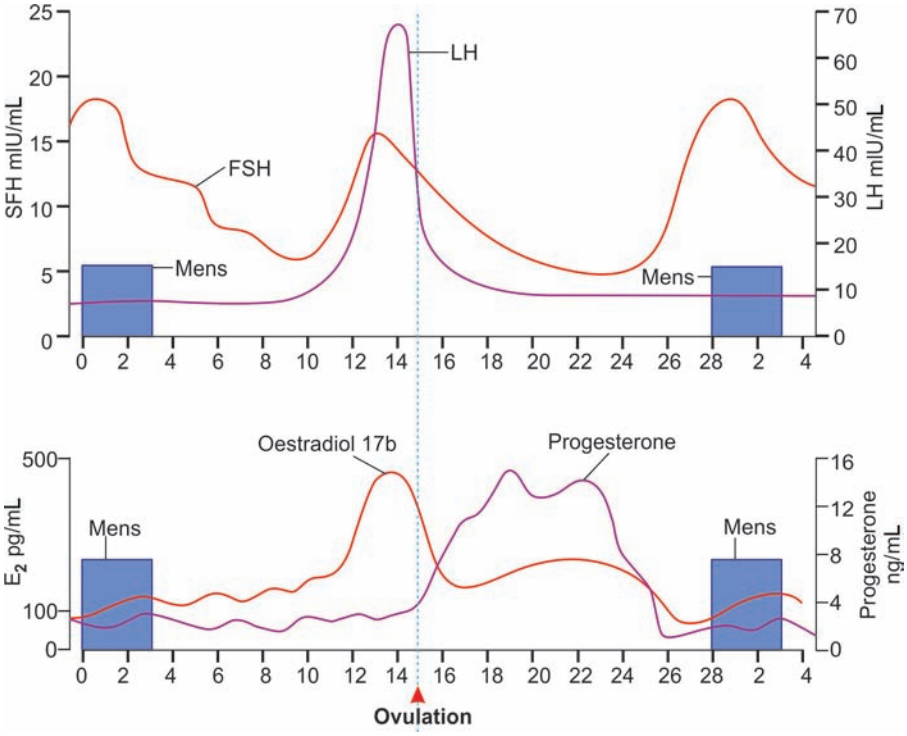

Figure 3.9 Hormonal level during menstrual cycle.

Key Points

- Neuroendocrinology with its vast hormonal network is key to normal menstrual cycles and reproductive function in a woman.
- Hypothalamus, with its secretion of GnRH (decapeptide), is the main neuroendocrine gland and regulatory factor in the chain of hypothalamic–pituitary–ovarian axis. The higher cortical centres can modify or influence hypothalamic secretion.
- Proliferative phase of endometrium represents oestrogenic action of the ovary.
- Progesterone causes secretory endometrium only if the latter is primed with oestrogen.
- Therapeutic management in infertility, family planning and gynaecological disorders is based on the knowledge of neuroendocrinology and the interaction of various hormones.
- Synthetic analogues of GnRH, FSH and LH are used in infertility and amenorrhoea.
- Oestrogen and progesterone have specific roles in the menstrual cycle and in the development of genital organs.
- Other hormones participate in the maintenance of normal menstruation.
- LH surge is the key marker of imminent ovulation.
- LH causes maturation of Graafian follicle, meiosis of ovum before ovulation, ovulation and development of corpus luteum.
- Leptin appears to have a role in the development and onset of puberty.
- Menstrual fluid is recently discovered to contain the stem cells and may prove useful in stem cell therapy. Only young women are suitable for donation.
- Fifty per cent of total testosterone and a small amount of androstenedione produced in the stroma by LH are needed for conversion to oestrogen by the granulosa cells. Excess of production causes acne and hirsutism.

Self-Assessment

1. Describe the neuroendocrine control of the menstrual cycle.
2. Describe the formation and processes that lead to the formation of the Graafian follicle.
3. Describe the mechanism of ovulation.
4. Describe the microscopic appearance of the endometrium during the various phases of the menstrual cycle.
5. Describe the rheological properties of cervical mucus during different phases of the normal menstrual cycle.

Suggested Reading

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Chapter

4

Puberty, Paediatric and Adolescent Gynaecology

CHAPTER OUTLINE

Introduction

It is being increasingly recognized as a fact that gynaecologic disorders can have their origin in childhood disorders such as congenital defects, neglected infections acquired in childhood, failure to diagnose and treat endocrinopathies in childhood, tumours overlooked and a general tendency to belittle physical and psychological trauma of sexual abuse. All these can cast their shadow on future reproductive health of the individual during adult life. The understanding of the role of the gynaecologist in the timely detection of these problems, instituting preventive and timely therapeutic interventions to correct the same if possible and counselling the parents about the likely sequelae as well as measures to mitigate their consequential ill-effects can all contribute towards improving the future quality of life. These should be the goals of the clinician practicing this subspecialty.

Reproductive Endocrinology of the Growing Girl Child

During childhood, the endocrine changes in the growing female child are directed towards preparing her for the maturation of the hypothalamus–pituitary–ovarian–uterine axis to achieve full reproductive potential. The fetal hypothalamus (arcuate nucleus) begins to produce gonadotropin-releasing hormone (GnRH) by the 10th week of gestation, gonadotropin secretion follows, levels of circulating follicle-stimulating hormone (FSH) and luteinizing hormone (LH) steadily rise up to the 20th week of gestation when the fetal hypothalamus becomes increasingly sensitive to the negative feedback inhibition of the placental steroids resulting in rapid decline in levels of the circulating gonadotropins. With the birth and expulsion of the placenta, its inhibitory effect ceases and there is once again a transient rise in circulating levels of gonadotropins and a gradual decline to nadir by the age of 2–3 years. Throughout early childhood the levels of circulating gonadotropins continues to remain low, there is minimal pituitary response to administered GnRH and the hypothalamic secretion of GnRH is profoundly suppressed.

The transition to puberty is characterized by episodic LH secretion associated with the circadian sleep-wake cycle. The rise in LH values becomes 2–4 times higher during sleep as compared to the waking hours. This change is noted during the early phase of onset of puberty. Gradually, the levels of FSH begin to rise and reach a plateau at mid-puberty, and the LH levels continue to rise even thereafter until late puberty. Such changes are observed even in girls suffering from Turner's syndrome indicating that these are not dependent on the ovarian steroid hormones but represent the effects of the rapidly maturing hypothalamic–pituitary relationship.

The sequential changes occurring in the growing girl child indicate that the initial development begins with progressively increasing GnRH secretion, which leads to increased pituitary sensitivity and responsiveness to GnRH

stimulation. This results in rise in levels of circulating gonadotropins, which promote follicular development in the ovaries. The ovaries in response to the above stimulus produce oestrogens that act on the uterine endometrium to initiate proliferation and endometrial growth, a prelude to menarche. In time, the pulsatile secretion of GnRH is established followed by cyclic ovarian function and regular menstrual cycles.

Once the hypothalamus becomes active, GnRH may prime the pituitary gonadotrops and increase its sensitivity to subsequent GnRH stimulation. A pulsatile pattern of GnRH secretion slowly evolves. The fact that earlier in the course of development, the GnRH manifests as low-frequency pulses favours FSH secretion, explaining why this is the first gonadotropin to register a rise. Later as the GnRH pulsatile frequency enhances, there is a greater rise in LH surges and establishment of the adult pattern of gonadotropin release. The positive feedback to oestrogen develops and the cyclic pattern of gonadotropin release and normal menstrual cyclicity gets established (Figures 4.1 and 4.2).

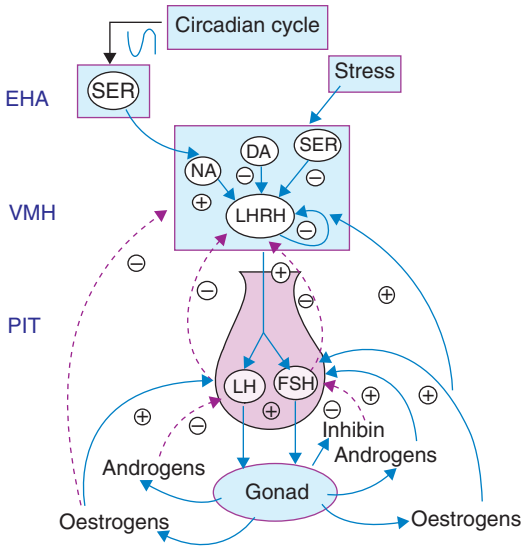


Figure 4.2 Hypothalamic–pituitary–ovarian axis regulatory control. EHA: extrahypothalamic areas, VMH: ventral medial hypothalamus, PIT: pituitary, SER: serotonin, DA: dopamine and NA: noradrenalin.

The Newborn Female Infant

History and physical examination—the newborn: The best time to begin documenting clinical observations is at birth. General examination should assess the gestational maturity of the neonate and document any abnormal findings such as webbing of the neck, ectopia vesicae, congenital ureteric fistula, imperforate anus, vaginal anus, congenital adrenal hyperplasia, presence of inguinal hernia, umbilical hernia or abdominal mass suggestive of a genital tract abnormality, a bulging hymen (mucocolpos), clitoromegaly, ambiguous external genitalia, heterosexuality or true intersex. General physical examination begins with examination of the breasts. At birth the breast nodule can be felt easily, and on squeezing, some clear to milky secretion can be often seen from the nipples (witch's milk) because of exposure of the fetus in utero to the high-circulating levels of maternal oestrogens during pregnancy. This effect is transient and spontaneously resolves with passage of time. Repeated attempts to squeeze breast secretions should be stoutly resisted as this may result in bruising, infection and breast abscess formation. The external genitalia should be examined under a good light keeping the newborn supine with the thighs well flexed against the abdomen. Once again oestrogen effects on the genitalia are apparent, the labia majora appear thick and full and tend to cover the labia minora, the clitoris appears prominent—the clitoral index (glans width × length) should not exceed 6.0 cm^2. Values exceeding this call for further investigations as clitoromegaly may be due to a serious underlying cause such as congenital adrenal hyperplasia, which demands immediate attention and treatment in contrast to other causes such as true hermaphroditism and maternal exposure to androgens (teratogens—drugs having androgenic side effects or androgen-secreting tumours of the adrenals or ovaries).

On separation of the labia, it is not uncommon to observe a white mucoid discharge/blood which may persist for about 7–10 days. The vaginal orifice may be somewhat difficult to visualize, pressure on the vestibule often results in expression of mucus discharge, which confirms patency of the outflow tract; ultrasound examination of the pelvis clarifies the doubt. Assigning correct sex gender at birth is crucial.

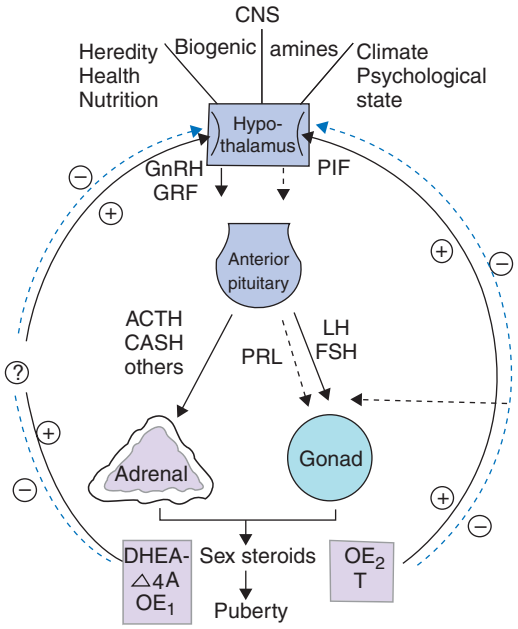


Figure 4.1 Neuroendocrinologic control of puberty. CASH: corticoadrenal stimulating hormone.

The Growing Girl Child

A young prepubertal girl child may be brought with complaints related to her private parts such as swelling, itching, offensive vaginal discharge, bleeding or injury. Examination of the prepubertal child calls for patient persuasion, gentleness, reassurance and skill and goes a long way in accomplishing a satisfactory examination. Sometimes the clinician may have to resort to sedation or even anaesthesia.

A vaginoscope/colposcope may be used to inspect the lower genital tract. Distension of the vagina with saline can be accomplished by holding the labia tightly around the vulval introitus; this may allow sufficient distension for satisfactory inspection of the cervix, vaginal vault, health of the vaginal walls, detection of any neoplasm or presence of any foreign body inserted inadvertently into the vagina. Endoscopic examination may be a satisfactory alternative to a difficult clinical examination.

The preschool girl child is best examined supine with her hips well abducted and the feet apposed (frog leg position), older child is best examined supine with her legs supported in stirrups. In young prepubertal girls, the labia majora appear flattened, the labia minora are thin and relatively prominent and the clitoris is small. On parting the labia or drawing the lower parts of the labia downwards and outwards, the vaginal orifice can be well visualized. The vaginal walls appear thin and congested, the transverse rugae present in adults are not seen, a midline longitudinal ridge may be present. If vaginal discharge is required for testing, this should be collected with a moist cotton tipped applicator, rubbing should be avoided as this not only causes discomfort but can be traumatic to the thin and delicate vaginal epithelium. In the young prepubertal girl child, the vagina measures 4–5 cm, the cervix is twice the length of the uterus; the ovaries are located high up at the pelvic brim. Endocrine activity of the pituitary, ovaries and adrenal glands becomes increasingly manifest between the ages of 7 and 10 years when increases in oestrogen effects on the genitalia become evident clinically. In case of suspected child sexual molestation or rape, the child may be better examined in the knee chest position. In this position, the vagina balloons out and the introitus and hymen are easily visualized, the trauma of forced sexual assault is often apparent as laceration or tear of the introitus posteriorly. In this position it is easier to collect discharge from the vagina for culture and forensic tests. The pelvic examination should be avoided in an adolescent girl, but when required, it is done under sedation of anaesthesia.

The vagina lengthens to 10–12 cm in a fully grown adolescent, the vagina becomes more capacious, the vaginal epithelium is thick with presence of rugae and covered with a white acidic discharge and the vagina shows presence of a mixed flora of nonpathogenic organisms. The cervix feels like a knob at the top of the vaginal vault and the uterus to cervix ratio reverses to 2:1. With approaching puberty, the ovaries descend into the pelvis and the ovaries show evidence of commencing follicular function.

Common Paediatric Gynaecologic Problems

The prepubertal girl child: The common problems for which medical opinion is sought include broadly:

- Vulvovaginal infections and leucorrhoea
- Vaginal bleeding
- Ambiguous genitalia
- Abdominal neoplasms
- Sexual abuse
- Sex education—sexuality

The common gynaecologic problems affecting the prepubertal girl child for which consultation may be sought usually involve vulval pruritus, vaginal bleeding or discharge, developmental anomalies, suspected abdominal lump, precocious or late puberty and suspected sexual assault.

Although the genital structures are in the resting state during early childhood, they are not immune to diseases. The prepubertal female genitals are delicate and are prone to infection and bleeding.

1. Vulvovaginal infections, pruritus and discharge: Irritation or inflammation of the vulva may result from numerous causes. Infections (*molluscum contagiosum*, condylomata acuminata, herpes genitalis and gonorrhoea) may be transmitted through sexual or nonsexual close contact with the child. Poor personal hygiene may lead to candidal vulvovaginitis, vulval irritation may follow worm infestation such as pin worms or thread worms secondary to anorectal contamination. Poor sexual hygiene may lead to chronic nonspecific vulvovaginitis and irritation leading to vulvitis causing labial adhesions. Exposure to chemicals (deodorants/antiseptics) may cause atopic dermatitis leading to a chronic discharge, vulvar skin excoriation and over time cause labial adhesions, or eczematoid changes.

Vaginal discharge: This is generally the result of infection caused by nonspecific causes, generally resulting from poor hygiene or as a result of specific infections.

Nonspecific vulvovaginitis: This is best treated by initially improving perineal hygiene such as warm sitz baths, cleaning the perineal area with bland olive oil followed by soap and water, keeping the parts dry, and the use of clean cotton undergarments. Often these measures suffice. Vulvar medications should be prescribed sparingly as the skin of the genital region is very sensitive in children. In case of unsatisfactory response in 2–3 weeks, consider topical application of an oestrogenic cream (Premarin/Dienesterol/Evalon). This brings about a thickening of the vaginal mucosa, lowers the vaginal pH and encourages growth of lactobacilli which in turn helps overcome offending bacterial infection. Oestrogen also helps to improve the vulvovaginal vascularity and produce rapid clinical improvement. Nonspecific vulvovaginitis can sometimes cause copious foul-smelling bloodstained discharge secondary to anorectal contamination with *Escherichia coli, Streptococcus faecalis* or by *shigella* organisms or by *intestinal parasites* such as thread worms or pin worms which respond to anthelmintic drugs. Finally, any offensive vaginal

discharge that follows retention of a *foreign body* responds promptly to its removal.

Specific vulvovaginitis: Diagnosis should precede treatment. Sexually transmitted disorders require specific treatment. Early diagnosis and treatment prevent sequelae. These infections have been specified in Chapter 11.

2. Vaginal bleeding: This can be the result of simple treatable causes or be indicative of a more serious underlying cause requiring thorough investigation and timely treatment.

Diagnostic approach: A history of the nature of bleeding and a general physical examination are essential to begin with. Smear and culture of the discharge if serosanguinous or purulent bloodstained and offensive are of fundamental importance. Smear of the discharge for cytologic evaluation is necessary whenever a neoplasm is suspected.

In difficult cases where localization of the cause of bleeding is not possible, a thorough examination under anaesthesia under a good light, and if necessary a direct endoscopic visualization using a paediatric cystoscope/hysteroscope helps to clear the diagnosis.

Common causes include endocrine causes, trauma, prolapsed urethra and neoplasms.

Endocrine causes include transient neonatal vaginal bleeding as a result of maternal circulating oestrogens in the newborn. Precocious puberty has been reported as early as the age of 6 years; however, the presence of other endocrine stigmata helps to resolve the diagnosis. Accidental ingestion of the mother's oral contraceptive pills resulting in bleeding has also been reported.

Trauma: This may be accidental, straddle-type injuries resulting from falling astride a sharp object may result in minor injuries such as lacerations, or a blunt injury may result in a vulval haematoma; the injuries caused by penetrating objects may be serious and may result in peritoneal trauma involving internal viscera requiring laparotomy. Self-inflicted during play or following sexual abuse may not be reported by the child for fear of remonstration. Examination under a good light coupled with a detailed history help to arrive at the cause. Precautions must be taken to ascertain and exclude the possibility of foreign body inserted in the vagina being overlooked.

Prolapsed urethra may follow undue physical exertion when the child complains of painful micturition, vulvar pain and bleeding. Separation of the labia reveals a mulberry like protrusion at the site of the urethral orifice. It is possible to pass a soft rubber catheter through the centre of the mass and the bladder decompressed. The catheter may be left in situ for a few days, suitable antibiotic cover and analgesics should be prescribed. The oedematous mass may subside or undergo necrosis when after a few days it can be excised at the line of demarcation with a cutting cautery knife.

Condylomata acuminata. These warty or granular lesions may bleed at times in a prepubertal child.

Sarcoma botryoides also known as grape-like sarcoma is a rare and highly malignant tumour of childhood carrying a serious prognosis.

3. Ambiguous genitalia: The recognition of genital abnormalities at an early age is important to determine the sex of rearing of the infant, and to chalk out plans for their correction, long-term management, prognosis and parental counselling.

Examination of the external genitalia is of primary importance. An enlarged phallus at birth raises the first doubt about ambiguous genitalia and the need for proper assigning of the sex of the child. The commonest cause of ambiguous genitalia (>90% cases) is adrenal hyperplasia which can have a serious prognosis if not promptly recognized and treated. The immediate concerns of the clinician in the salt-wasting type are to prevent rapid dehydration leading to fluid and electrolyte imbalance. The parents should be counselled that the external genitalia are incompletely formed and further investigations are warranted. As a working clinical rule, presence of a midline frenulum on the phallus is strongly indicative of the infant being a genetic male, whereas paired attachment of the labia to the phallus suggests a genetic female. Clitoral enlargement with ambiguous genitalia at birth may be due to female pseudohermaphroditism, mixed gonadal dysgenesis, male pseudohermaphroditism and rarely true hermaphroditism. Usually the more pronounced the ambiguity, the simpler it is to raise the child as a female regardless of its genetic sex. History and clinical physical examination often throw considerable light on the possible cause—for example, history of administration of large doses of progestogens to the mother in early first trimester, or a family history of sexual ambiguity in other female relatives or a maternal aunt or another female relative who suffered from amenorrhoea or infertility with ambiguous genitalia is indicative of the possibility of a recessive genetic disorder. A history of surgery for inguinal hernia in early infancy with the unexpected finding of an undescended testis helps to identify the underlying aetiology.

The importance of examination of the newborn should include a rectal examination to determine the presence of the uterus at birth. Visualization of the hymen and testing its patency as discussed earlier is important. In case of doubt - sex chromatin studies and karyotype, imaging studies using ultrasound or MRI, hormone assays of gonadotropins (FSH and LH), 17-ketosteroids and 17 a-hydroxyprogesterone (which is elevated in 21-hydoxylase deficiency) are indicated for formulating a diagnosis. Estimations of serum electrolytes and blood glucose are important in the management of the salt wasting variety of adrenal hyperplasia. Other investigational aids which may be of use include vaginoscopy, colpogram and laparoscopy. Rarely is an exploratory laparotomy required for diagnostic purposes alone. It is advisable to adopt a multidisciplinary approach to tackle the long-term management of the child. In the newborn infant, the diagnosis of the salt loosing adrenal hyperplasia as early as possible is important to institute prompt treatment to avoid a serious outcome.

An imperforate hymen needs to be tackled at the time of puberty to forestall hydrocolpos/haematocolpos. Vaginal anomalies detected at birth do not call for immediate surgical

intervention. Let the child grow up to the age of puberty. If pelvic imaging shows the presence of a well-developed uterus and ovaries, then the consideration for plastic surgery for an artificial vaginal reconstruction (partial or complete) becomes mandatory; however, in case of congenital absence of the vagina, in the absence of the uterus, postponing of the surgical procedure until the time of marriage is important, as coital frequency helps to maintain the patency of the vagina.

It must be remembered that in the case of suspected hermaphroditism, the undescended testis in the inguinal canal or intra-abdominal situation should be surgically removed at the appropriate time as it is prone to malignant change with advancing age.

4. Tumours of gynaecological origin in children: The role of the gynaecologist is to be aware of the possible occurrence of tumours in childhood, and to be familiar with the investigations to arrive at the proper diagnosis and management plan. A large variety of swellings and tumours of diverse origins have been recognized in infancy and childhood. Many of these are not strictly of gynaecologic origin but enter the domain of differential diagnosis or are seen by the gynaecologist first, hence the need about their awareness. These include sacrococcygeal tumour, duplication cysts of the gastrointestinal tract (GI tract), urachal cyst, umbilical hernia, Wilms' tumour, single pelvic kidney, lymphoma, haemangioma, chordoma, neuroblastoma, meningioma and hamartoma. Sarcoma botryoides is a rare and highly malignant tumour of childhood, it generally presents as a polypoidal of grape-like neoplasm protruding through the vulva.

A distended urinary bladder can present as a swelling in infancy and childhood. Ovarian tumours, both cystic and solid, are known to occur in children, and account for 1.0% of all neoplasms in premenarcheal children. Girls with ovarian neoplasms generally present with abdominal enlargement and pain. In the prepubertal child, the bulk (over 60%) of these tumours are of germ-cell origin (dermoids are the commonest; however, immature teratomas, embryonal cell tumours, endodermal sinus tumours, dysgerminomas, choriocarcinomas and gonadoblastomas have been recognized in childhood, many of these are malignant). Many of these tumours secrete substances such as alfa fetoproteins, carcinoembryonic antigen and human chorionic gonadotropin hormone which serve as tumour markers and help to arrive at a diagnosis. With approaching adolescence, the incidence of epithelial cell tumours of the ovary begin to make their appearance, so that in adult life epithelial tumours of the ovary predominate and account for almost 80% of all ovarian neoplasms. In India, the incidence of ovarian neoplasms under the age of 20 years of age account for about 4–14% of all ovarian neoplasms. About a third of the tumours tend to be malignant. Bulk of these is the germ cell tumours (dysgerminomas predominant); endodermal sinus tumours, teratomas and mixed cell types have a dismal outlook. The survival rates are encouraging in girls treated early for the disease.

Ultrasound examination of the abdomen and pelvis and CAT/MRI scans are useful in establishing the diagnosis of ovarian neoplasms and assessing areas of solid and cystic components. Areas of calcification in degenerated parts of these tumours are not infrequent. A rare tumour of the lower genital tract namely sarcoma botryoides also affects children; it is a tumour posing a grave prognosis and should be tackled in a paediatric oncologic setting.

In general, all treatments should aim at conserving reproductive potential as far as possible without jeopardizing the patient's life. This is important to enable the growing child to achieve maturity and preserve future childbearing potential. The ovarian tumours have been detailed in Chapter 33.

5. Child sexual abuse: Two basic forms of sexual abuse are recognized. The first involves victimization by a stranger; it may involve any form of sexual activity brought about by enticement, coercion or force. Such acts are usually reported by the child. This situation must be handled very tactfully. Appropriate medical examination and tests performed, counselling offered and efforts undertaken to bring the offender to book. The second form of sexual abuse rampant in society, and under reported is incest.

Incest occurs frequently in families with social problems of alcoholism, drug abuse, physical abuse, broken homes, violence, delinquency, mental retardation and an atmosphere of violence. Father-daughter relationships are the commonest, but it may involve any close male relative. Among children of incestuous relationship only 10% have normal psychological development. Anger, guilt feelings, mood swings, depression, lying, cheating and stealing are some bad habits these children develop; poor school performance often follows and unexplained physical complaints, sleep disturbances and aggressive behaviour are frequent manifestations. Rape leads to immediate emotional shock and a feeling of anger all around. Tactful handling and timely psychiatric help give the child the best chance of coming out of the experience unscathed.

6. Sex education and female sexuality: Fifty years ago, parental supervision and early marriages prevented young individuals from experimenting with sexuality. Changes in societal behaviour, freer interaction between the sexes, influence of the media and greater involvement of women in the workforce have led to changing moral and ethical values and altered adolescent behaviour. The fact that almost 10% of pregnancies occur in teenagers, nearly 5–8% of reported medical termination of pregnancy (MTPs) are in teenagers and 6% of all deaths from unsafe abortions occur in teenagers emphasizes the need for imparting sex education to senior school and college-going adolescents to prevent unwanted pregnancies, MTPs, sexually transmitted diseases and HIV (Mukherjee, 1999).

Puberty and Adolescence

Biological Sequential Events Observed during Puberty

Adolescence is the age between 10 and 19 years. Puberty is the period of transition from childhood to adult sexual maturation. It is the process of biological, psychological

and physical development through which sexual reproduction becomes possible. Progression occurs through sequential changes described as thelarche → adrenarche → peak growth spurt → menarche → ovulation. Hormonal events earlier described play a key role in orchestrating this transition. Profound bodily changes, sexual development and altered emotional and behavioural changes are observed during this maturational period. Besides endocrinal influences, genetic, nutritional and other environmental factors play an important role during this transitional period of life.

Endocrine mechanisms underlying puberty: These have been highlighted in the following:

- Early in puberty, the sensitivity of the gonadostat to the negative effects of low estradiol (E_2) gradually decreases.
- Late in puberty, maturation of positive E_2 feedback initiates the LH surge.
- Basal levels of pituitary gonadotropins increase throughout puberty due to enhanced hypothalamic GnRH pulse amplitude rather than frequency.

Age of onset of puberty: The age of onset is influenced by nutritional status, genetic and environmental influences including racial and cultural background, climate and residence. Hence a great deal of variations is observed in the evolution of puberty changes. Normal age of puberty varies between 9 and 13 years, and the duration lasts 2–3 years. Though the beginning of puberty is subtle and cannot be dated precisely, the end point is menstruation (menarche).

Over the last century, the age of menarche has progressively lowered; this has been very evident in the developed world including the West and Japan. Also menarche occurs later in women residing at higher altitudes as seen in Eskimos. A critical body mass has to be achieved prior to menarche, obesity predisposes to earlier age of menarche (minimum of 45 kg).

When environmental factors are optimal, puberty is controlled by genetic factors as witnessed by the fact that the age interval between the times of menarche in identical twins is 2.2 months that between dizygotic twins is 8.2 months.

Factors Affecting Time of Onset of Puberty

- Genetics
- Race. The African-American girls enter puberty about 1–1.5 years earlier than the White American girls
- Nutritional status. Puberty sets in earlier in moderately obese girls and is delayed in malnourished girl. Leptin (peptide) secreted by the fat cells stimulate GnRh secretion and induce early puberty. Minimum of a 45 kg body weight is required to induce pubertal changes. Macrosomic babies tend to grow obese and have early menarche thereby.
- General health status
- Altitude. Delayed in Eskimo girls as compared to girls living in the tropics
- Psychological state. Exposure to education, media
- Exposure to light (blind individuals enter puberty earlier than sighted individuals)

Growth spurt and menstruation: The starting of the physical growth curve is soon followed by typical sequence of development of female secondary sexual characteristics, which include thelarche, adrenarche, continuing growth spurt genital organ growth and menarche. These will hereafter be discussed at length.

Tunner and Marshall described five stages of pubertal changes—these are in the following sequences (Figure 4.3A):

- Physical growth and weight gain
- Development of breasts
- Pubic and axillary hair
- Development of ovaries and genital organs
- Growth of sport and menstruation

Gordon et al. (2002) depicted the physical changes occurring during puberty as under:

A comparison of the growth rates in male and female growing children reveals a similar curve until the age of 10.5 years (the male growth being somewhat ahead throughout, thereafter the growth spurt in the female child overtakes that of the male child for 1–2 years before it plateaus out). However, the growth curve in the male child demonstrates the final spurt a couple of years later before plateauing. Thus, the average mean height of a fully grown man is greater than that in woman as shown in Figure 4.4.

Physical Growth and Body Weight

The growth in the height and weight in the female child begins on average around the age of 10.5 years (average of 9–11 years) and is completed by the age of 14 years. During this period, the height growth that stabilizes at 4–10 cm/year before puberty doubles during puberty (5–10 cm/year). Growth is attributed to growth-promoting hormone of the anterior pituitary, and also by insulin-like growth factor (IGF-1). The body shape also takes on the feminine configuration. *The bone mass during adolescence increases by 50%, emphasizing the importance of providing adequate calcium, iron and nutritional needs during the growing years of adolescence. Iron requirement increases by 15%.*

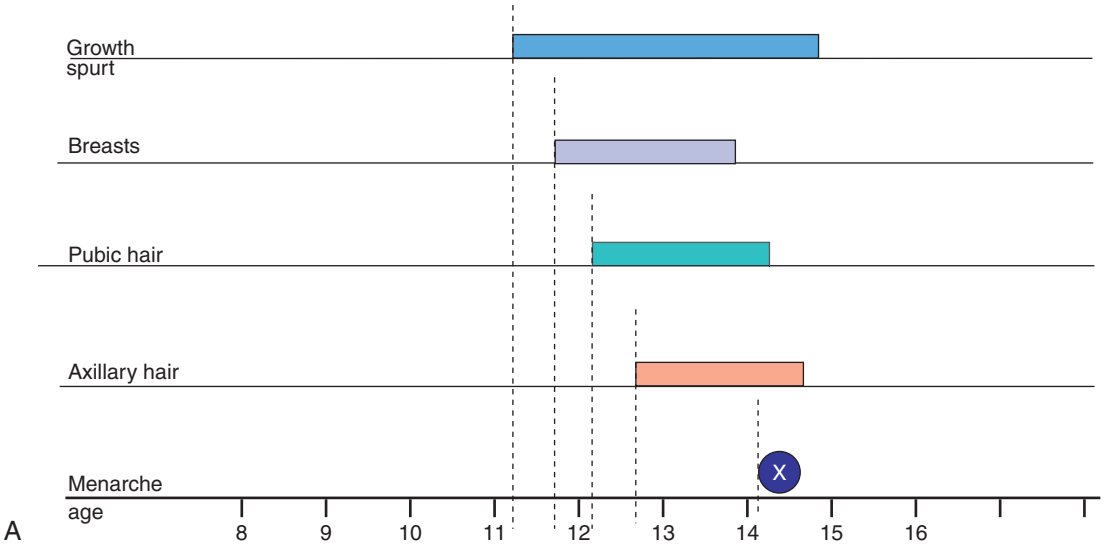
Secondary Sex Characters (SSC)—Tanner Classification of the Sequence of Development

Thelarche

The first sign of puberty is the development of the breasts. Breast budding usually appears between the ages of 9–11 years; it is indicative of the competency of the hypothalamic–pituitary–ovarian axis. The adolescent breast development is divided into 5 stages:

B1—denotes the prepubertal breast. At this infantile stage only the papilla is elevated.

B2—denotes thelarche. The breast buds are palpable, areola enlarges and the breast is elevated like a small mound.



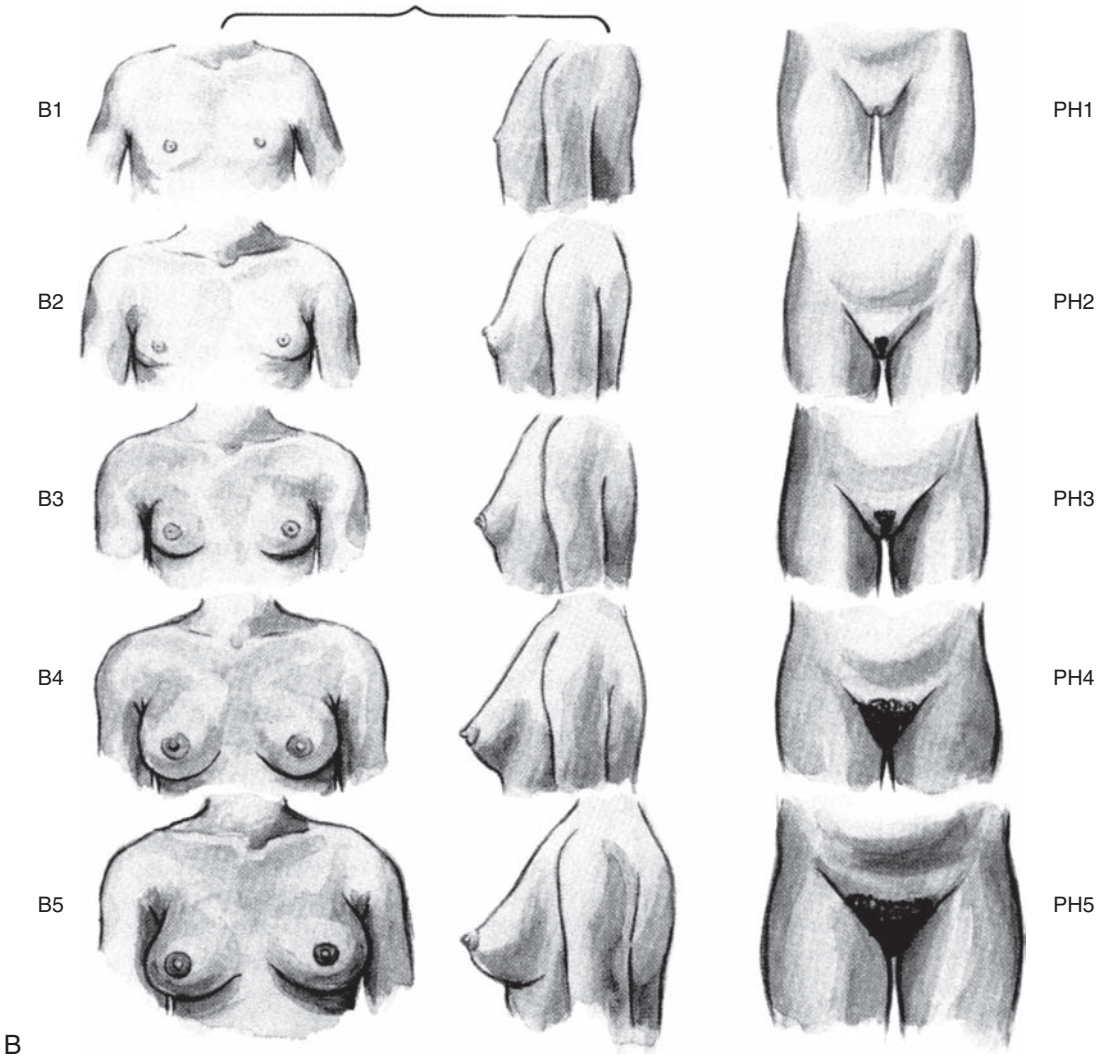


Figure 4.3 **(A)** Development of secondary sex characters related to age. **(B)** Pubertal changes in the breasts and pubic hair.

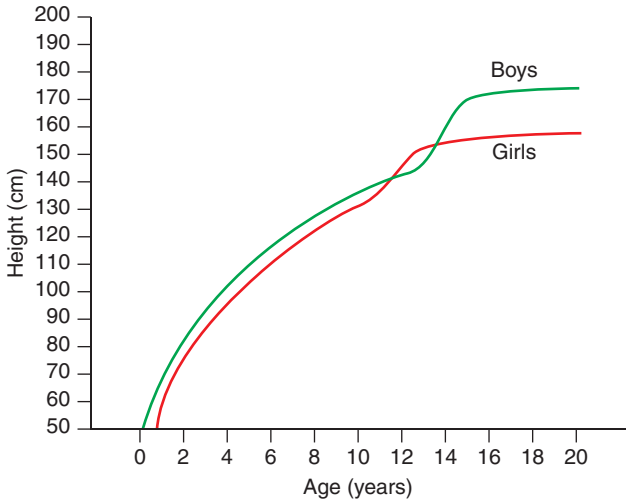


Figure 4.4 Height attained growth curves for boys and girls showing growth spurt.

B3—there is further enlargement of the breast and its areola without separation of its contours.
B4—preferential growth of the areola and nipple leads to formation of a secondary mound over the mound of the breast.
B5—formation of the mature adult breast. There is recession of the areola into the general contour of the breast because of greater growth of the breast tissue (Figure 4.3B).

Adrenarche

The adrenals are the main source of androgens, which are responsible for the growth of pubic and axillary hair. Pubic hair generally make its appearance about 6 months after thelarche at the B4 stage. Axillary hair generally make their appearance 1–2 years after pubarche. Rarely axillary hair development precedes pubic hair development.

Pubic Hair Development

The stages of pubic hair growth are as follows:

P1—prepubertal stage when there are no coarse pubic hair present, the vellus hair present over the pubic area are similar to the ones seen over the abdominal wall.
P2—pubarche denotes the appearance of long or slightly curved and pigmented hair sparsely over the labia.
P3—darker, coarser and curly hair are seen spread over the mons pubis.
P4—the preadult stage when thick dark growths of curly hair are seen covering the area short of the inverted triangle.
P5—adult inverted triangular distribution of thick, coarse, dark curly hair spreading out towards the medial aspects of the thighs is evident.

Axillary Hair Development

The sequence of axillary hair development is as follows:

A1—prepubertal stage. No axillary hair present.
A2—appearance of sparse axillary hair.
A3—adult distribution of thick, coarse and dark pigmented hair.

Genital Organs:

- Vulva—vulval skin under the influence of oestrogen becomes keratinized and resistant to infection. Fat is deposited in the labia majora.
- Vaginal mucosa becomes multilayered with the formation of superficial layer containing glycogen and PH is maintained at 4.5 by Döderlein's bacillus acting on glycogen.
- The uterus grows rapidly, and prepubertal ratio of uterus/cervix of 1:1 changes to 2:1 or 3:1.
- The ovaries start developing primordial follicles into Graafian follicles. However, a dominant follicle with ovulation occurs in 50% cases. Rest take 1–2 years for ovulatory cycles to occur.

Menarche

The first menstrual period generally follows thelarche by about 2 years, when growth development is almost complete and breast development reaches the adult mature stage. The initial menstrual cycles are generally anovulatory for about 12–18 months after menarche.

Skeletal Age

Sexual maturation correlates more with bone age than chronological age.

Determination of bone age provides a better marker for prediction of the remaining growth potential and the final adult height.

Management

Although puberty is a transitional physiological period, lack of knowledge regarding various physical changes and fear of future impose stress and anxiety in these adolescent girls, though lately they have acquired a better knowledge than before.

- Sex education is very useful in schools. The knowledge regarding sexually transmitted disease (STD), HIV and risk of pregnancy will dissuade them from indulging in premarital sex. Where promiscuity prevails, contraceptives should be encouraged. Barrier method protects against STD, and oral pills protect against pregnancy.
- Nutrition from protein, calcium, and iron are required for the growth and maintaining haemoglobin; calcium need increases by 50% and iron by 15%.
- Lately, HPV vaccination is strongly recommended for adolescents, especially if they indulge in sexual activity.
- Quadrivalent vaccine is given at 0, 2, 6 months.
- Bivalent vaccine is given at 0, 1, 6 months.

Puberty—Anomalies of Gonadal Function

Delayed puberty is defined when the secondary sexual characters do not appear by the age of 14 and menarche is not established by 16 years of age (10%).

Primary amenorrhoea and delayed puberty: Causes for these conditions can be broadly divided into hypogonadal

and eugonadal varieties. Patients with hypogonadism may have hypergonadotropism secondary to ovarian failure (Turner) or hypogonadism as a result of failure of maturation of the hypothalamic–pituitary–ovarian relationship. The eugonadal variety consists of patients with evidence of steroidogenesis but delayed menarche. In this group the possibility of primary amenorrhoea due to other causes like Müllerian developmental anomalies leading to outflow obstruction, less commonly testicular feminization syndrome (androgen insensitivity), failure of development of the positive feedback mechanism in spite of adequate endogenous oestrogen production and hyperprolactinaemia often resulting from a pituitary neoplasm (prolactinoma) should be suspected. Malnutrition and anorexia nervosa are other genital causes. Details are described in chapter on amenorrhoea.

Aetiology of delayed puberty:

- Commonly, it is familial or idiopathic (60%).
- Hypothalamic and pituitary inadequacy. CT, MRI of sella turcica, FSH, LH level confirm the diagnosis.
- Ovarian causes—Turner's syndrome, Swyer syndrome, resistant ovary, autoimmune disease, testicular feminizing syndrome, high FSH.
- Polycystic ovarian disease.
- Development of secondary sexual characters, but no menstruation—absent uterus or cryptomenorrhoea, abstruction in the lower genital tract.
- Malnutrition, anorexia nervosa, childhood illness and vigorous exercise.
- Hypothyroidism.

Investigations and management—see Chapter 23 (Amenorrhoea).

Anorexia nervosa is being increasingly recognized and treated with the help of a psychiatrist. Identification of the group of patients who exhibit pubertal maturation but fail to develop a positive feedback system for establishing appropriate LH surges required for triggering ovulation. In the long term, these individuals with chronic anovulation are at risk of developing endometrial hyperplasia and malignancy.

Approach to diagnosis: All patients after the age of 14 years manifesting absence of breast development and oestrogen effects need to be investigated. Besides a detailed history and physical examination including record of height in centimetres and weight in kilograms, the following investigations are recommended:

1. Serum FSH, LH, PRL and TSH, steroid hormone assays including androgens
2. CT scan of the skull
3. Buccal smear for sex chromatin determination
4. Karyotype, G-banding, polymerase chain reaction and fluorescent Y testing
5. Ultrasound to detect uterine anomalies and the presence of the ovary
6. Laparoscopy in selected patients

Precocious puberty: This is defined as the appearance of any of the secondary sexual characteristics before the age of 8 years or the occurrence of menarche before the age of 10 years (Figure 4.5). It is not a common clinical entity.

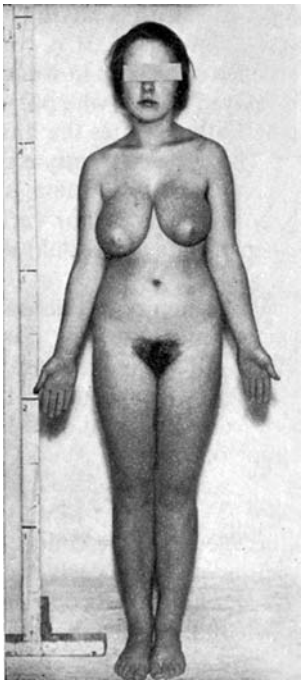


Figure 4.5 Precocious puberty—a girl aged 11. Note well-marked breast development and adult pubic hair growth.

Broadly speaking, precocious puberty can be divided into two types. The first variety (known as true, complete or isosexual precocious puberty) results from the premature activation of the endocrine pathway comprising the hypothalamic–pituitary–ovarian axis. In such girls, the total growth spurt and potential increase in height is not achieved, hence it is necessary to identify the possibility early and advocate prompt treatment to delay the maturation process to enable the child to achieve increase in height. In contrast, the second variety known as the pseudo or incomplete precocious puberty is the result of sex steroid stimulation independent of the above axis.

Aetiological classification of precocious puberty: The various causes are as follows:

1. *Complete precocious puberty:*	a) Idiopathic, familial or sporadic, genetic (75%) b) Congenital lesions of the *hypothalamus–pituitary* Acquired lesions—trauma, infection, neoplasm—tuberculosis (TB) meningitis in childhood c) Part of a specific syndrome—McCune-Albright (5%), von Recklinghausen's neurofibrobromatosis d) Other causes—endocrine/metabolic disorders
2. *Incomplete precocious puberty:*	a) Premature thelarche b) Premature adrenarche c) Premature menarche

3. *Pseudoprecocious puberty: (GnRH independent)*
   a) Feminizing ovarian tumours (10%) (hormone secreting)
   b) Adrenal hyperplasia/ neoplasm—20%
   c) Hypothyroidism
   d) Hepatoblastoma producing gonadotropins
   e) Iatrogenic–oestrogen administration

In over 90% of cases, no organic lesion is detected. The hypothalamus-pituitary-ovarian axis and the adrenal functions mature early resulting in precocious puberty.

Pregnancy in a young girl aged 6 years has been recorded. Investigations reveal that gonadotropins and ovarian steroid hormones are secreted in adult quantities.

A number of skull problems such as rickets can cause precocious puberty. Tumours at the base of the brain such as craniopharyngioma, pituitary tumours, optic glioma, teratomas and astrocytomas may be contributory causes. Infections such as encephalitis, meningitis and hydrocephalus have also been implicated.

Clinical features of precocious puberty: The commonest variety termed constitutional precocity tends to run in families. It must be borne in mind that this diagnosis is one of exclusion. Long-term follow-up is recommended as some of the cerebral conditions come to light only in adulthood. Sexual precocity is consistent with normal reproductive function, and is not related to early onset of menopause. In these children, the sequence of events of sexual maturation follows the normal standard pattern. Since the growth spurt occurs at an earlier age, there is a transient but short-lived increase in height. As the epiphysis of the long bones fuse early under premature oestrogen effects, there is an eventual stunting of the height. Intellectual, psychosexual and emotional development correspond to the chronological age, hence these youngsters and their families have to face potentially difficult social and emotional situations.

McCune-Albright syndrome affects about 5% of children with precocious puberty. Multiple cystic bone lesions are seen. Café-au-lait spots on the skin may be evident at birth. Menstruation sets in early independent of the customary sequence events of thelarche and adrenarche preceding menarche. This is attributed to the autonomous production of oestrogens by the ovaries. Eventual fertility remains unimpaired and the adult height attained.

In every case of sexual precocity, the possibility of an underlying functional hormone secreting tumour of the ovary must be entertained and its possibility excluded.

Investigations: The following investigations are recommended:

1. Radiograph of the wrist to establish bone age.
2. Thyroid function tests—T_3, T_4, and TSH. TSH stimulates FSH receptors.
3. EEG and CAT/MRI scan of the skull.
4. Adrenal function tests to exclude heterosexual precocity.
5. Pelvic sonography to exclude pelvic neoplasms.
6. GnRH test to exclude autonomous ovarian cysts from those secondary to gonadotropin stimulation. GnRH test—IV 20 mcg/kg GnRH—estimate LH level 30 min later; level > 9.2 IU/L indicates true precocious puberty (GnRH related).
7. FSH, LH, oestrogen levels.

Management: Precocious puberty is a disturbing development for the parents and child. All efforts must be undertaken to detect the underlying cause. However, the cause may not be apparent and may be detected only later in life. Parents should be counselled accordingly. Parents should be warned that the child is vulnerable to sexual assault and needs careful supervision.

Proper treatment should be instituted for hypothyroidism, adrenal hyperplasia and surgical intervention for tumours of the ovary, adrenals or of neurological origin.

Drug treatment of constitutional precocity includes:

1. Inj. depot medroxyprogesterone acetate (DMPA) 100–200 mg, IM every 2–4 weeks to induce regression of these changes and cessation of menstruation. It is however not very efficient in inhibiting bone growth. Treatment depresses adrenocortical and hypothalamic pituitary activities. Instead of injection, daily or cyclical progestogen avoids injections, but are not convenient.
2. Cyproterone acetate exerts antiandrogenic and antigonadotropin effects. Oral administration of 70–150 mg/m^2/day has been found to be superior to DMPA. It also helps in increase of height and stature. Adrenal suppression is a known side effect.
3. GnRH agonists (Buserelin) form the mainstay of treatment in present day practice.

   The monthly administration of depot preparations allows pubertal development to be arrested temporarily until the full height potential has been achieved and the child reaches the appropriate age for the onset of puberty.
   - Buserline 100 mcg nasal spray daily.
   - Leuprotide 7.5 mg monthly. A single implant of histrelin—effect lasts for 1 year.
   - Triptorelin 11.25 mg 3 monthly for 1 year with calcium and vitamin D to prevent osteoporosis 20 mcg.

In precocious puberty, future reproductive capacity is not compromised and premature menopause is not documented.

Calcium and vitamin D supplementation is required to prevent drug-related osteoporosis.

Adolescent Contraception

This is a complex subject. Cultural, religious, socioeconomic and educational factors impact it. Understanding adolescent sexuality and the emotional need of youth help in the proper and effective implementation of this increasingly important social and health goal. Teenage sex can be

viewed as a normal behaviour development and milestone, or a risk behaviour pattern which may lead to serious consequences beyond the adolescent's comprehension.

Children from poor socioeconomic strata of society, living in crowded localities, disrupted families and states of depression and unhappiness as well as teenagers from the affluent classes are prone to experiment with sex.

Premarital sex can end in acquiring sexually transmitted diseases and unwanted pregnancy.

Recommended contraceptive methods: Adolescents should be informed about sexuality, the importance of self-control and abstinence until a more responsible age. However, growing adolescents resent sermonizing and are more responsive when their individuality is respected. Information about contraception is necessary to equip them to face real life situations.

Oral contraceptives (O.C.) are in general preferred as these safeguard the adolescent girl against any unwanted pregnancies. These O.C. pills also confer the advantage of regular periods with modest flow, and freedom from discomfort. In case of girls in an unstable relationship with a male partner, insistence on the additional use of barrier contraception by the male partner is desirable to protect her against STDs.

Emergency contraception should be made available in case of contraception failure such as condom slippage/condom bursting/forgotten use. The contraceptives for adolescents have been detailed in Chapter 20.

MTP services. Access to these back-up services should be available to unmarried adolescents (Ch. 20).

Miscellaneous Problems

Apart from the more pertinent problems discussed earlier, adolescents are subject to other health problems which will be discussed briefly hereafter.

1. ***Puberty menorrhagia:*** Soon after the menarche, the early menstrual cycles tend to be irregular and often prolonged leading to severe anaemia.
2. ***Dysmenorrhoea:*** In adolescents the menstrual cycles tend to be irregular and anovulatory to begin with, however, in the following 12–18 months, with maturing of the endocrine axis, the cycles become more regular, ovulation sets in and the periods become painful. Spasmodic dysmenorrhoea can be severe enough to require medication. Drugs such as mefenamic acid 500 mg, twice daily, help to control the pain. This drug acts by virtue of inhibiting the enzyme prostaglandin synthetase.
3. ***Hirsutism:*** The causes of the masculine distribution of coarse hair can be psychologically disturbing to the individual. The causes can be broadly classified as follows:
   1. Idiopathic
   2. Ovarian (a) Polycystic ovarian disease
      (b) Pure gonadal dysgenesis
      (c) Virilizing ovarian tumours like arrhenoblastoma, hilar cell tumour, gynandroblastoma, lipoid cell tumour
   3. Adrenal (a) Congenital adrenal hyperplasia of the delayed variety
      (b) Virilizing adrenal tumours
      (c) Cushing's syndrome
   4. Iatrogenic (a) Anabolic agents
      (b) Androgenic drugs such as danazol (Ch. 10)
4. ***Endometriosis:*** Thought to be of rare occurrence in India, recent investigational advances such as pelvic sonography and laparoscopy have revealed that this disease can also occur in adolescence and be the cause of severe dyspareunia, dysmenorrhoea and chronic pelvic pain.

Acne is common amongst adolescent girls. For treatment, refer to Chapter 10.

Development and Growth in a Male

Spermatogenesis

Spermatogenesis occurs in the seminiferous tubules of the testis. The primordial germ cells appear in the yolk sac in the third week of embryo and migrate along the dorsal mesentery to the genital ridge. These germ cells divide by mitosis into 1300 primordial cells or spermatogonia by sixth week. These remain quiescent in the seminiferous tubules throughout childhood.

Near puberty, spermatogonia divide by mitosis into primary spermatocytes. Meiosis occurs only at puberty and smaller secondary spermatocytes containing haploid number of chromosomes are formed. These develop into spermatids. The spermatozoa develop by acquiring an acrosome cap, elongation and condensation of sperm nucleus and a tail. The development of sperms take 72 days (Figure 4.6) and entire spermatogenesis including transit time in the duct takes 3 months.

Structure of the Sperm (Figure 4.7)

The mature sperm has a head with an acrosome covering, mid-piece and a tail which allows motility. Acrosome membrane contains enzyme hyaluronidase, acrosin and other proteases, which allow acrosin reaction, break down of acrosome membrane and penetration of sperm into zona pellucid. Hyaluronidase dissolves corona radiata cells. The sperms are stored in the epididymis. One spermatocyte produces four spermatids, and one spermatid produces four spermatozoa.

Spermatogenesis beginning at puberty is a continuous process unlike ovulation, which occurs once a month, and continues with senescence though with less efficiency. The testes show germ cells in different stages of maturation at any given time, and the sperms mature in the testes as well as the accessory organs, and undergo capacitation in the cervix before they are capable of fertilization.

The seminiferous tubules are lined by germ cells and Sertoli cells lying adjacent to germ cells. The Sertoli cells produce androgen-binding protein by FSH and bind testosterone to this protein causing a high level of testosterone within the testes as compared to that in the blood. The

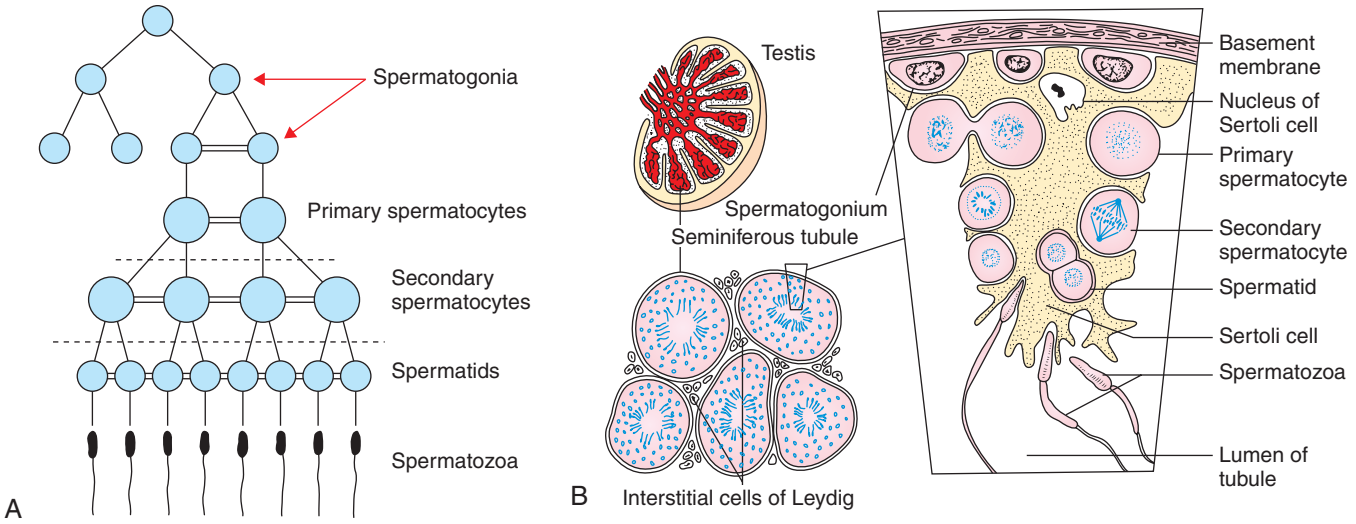


Figure 4.6 **(A)** Sequence of cell stages during spermatogenesis. **(B)** Cell stages during spermatogenesis.

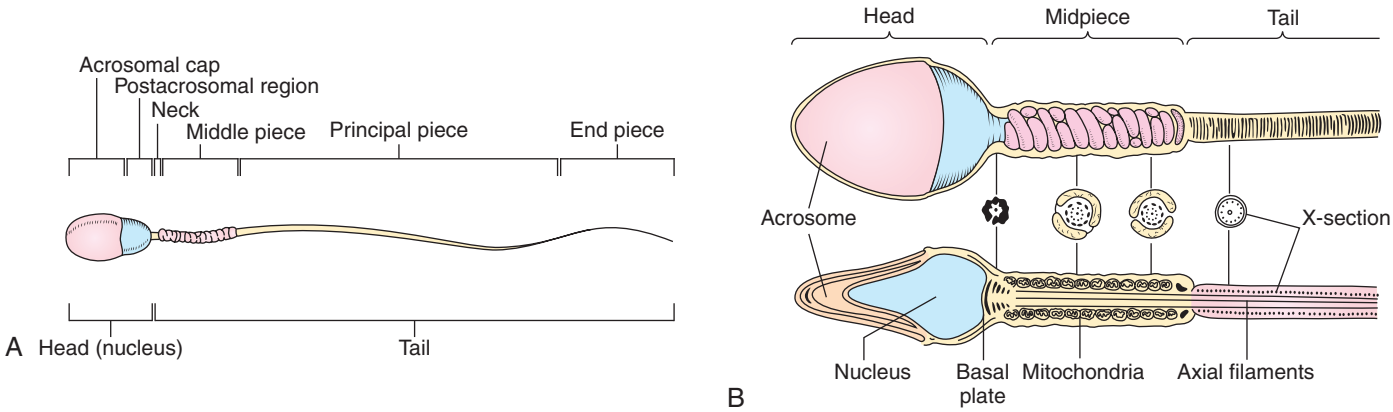


Figure 4.7 **(A)** Human spermatozoa. **(B)** Diagram of fine structure of human spermatozoa.

interstitial cells (Leydig cells) produce testosterone by LH (Figure 4.8).

Pubertal changes:

- The spurt is the height 2 years later as compared to girls.
- There is no end point such as menarche seen in female.
- Testosterone is responsible for growth and maturation of accessory organs.
- Secondary sex characters develop at puberty. These are deepening of voice, development of pubic hair and male distribution such as moustache and facial hair.

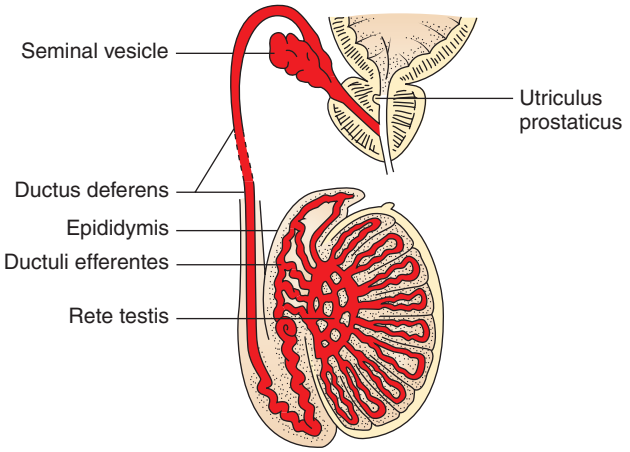


Figure 4.8 The testis and epididymis.

Endocrine Control (Figure 4.9)

Hypothalamus is critical in the development of male organs and spermatogenesis, and GnRH is produced continuously and, not in a pulsatile fashion as in a female. FSH is not essential for spermatogenesis; it acts on the Sertoli cells and produces androgen-binding protein mentioned above. Sertoli cells also produce anti-Müllerian inhibiting hormone, (MIH) and inhibin which inhibits FSH. MIH inhibit development of Müllerian system.

LH stimulates testosterone secretion by the Leydig cells.

Hypothalamic failure leads to loss of spermatogenesis and testosterone production.

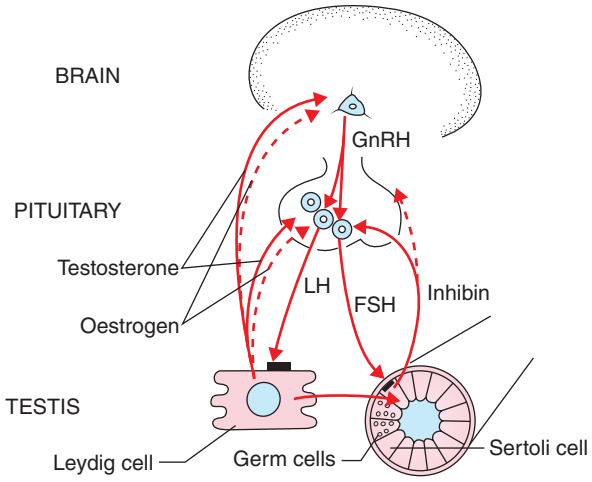


Figure 4.9 Endocrine control of spermatogenesis.

Key Points

- Puberty is a change from childhood to adulthood and involves physical, biological, endocrinological and psychological changes.
- Normal age of puberty in a female is 13–14 years. Puberty is precocious when the secondary sexual characters appear before the age of 8 and menstruation begins at 10 years. The most common cause is constitutional, but other causes should be excluded. It is desirable to suppress menstruation until the appropriate age is reached to allow the girl to reach the height.
- Delayed puberty after the age of 16 years may be familial or idiopathic, but requires investigations.
- Constitutional and hereditary delay or precocious puberty does not adversely affect the menstrual or reproductive function. Menopause age is not also influenced.
- Spermatogenesis takes 72 days and is a continuous process after puberty.
- Hypothalamic pituitary axis produces testosterone in the Leydig cells necessary for spermatogenesis.
- Puberty menorrhagia can cause anaemia.
- Acne may be due to PCOD and should be treated.

Self-Assessment

Q.1 Describe the endocrinology of puberty
Q.2 Describe Tanner's classification of development of female secondary sex characteristics.
Q.3 Describe the causes associated with causation of anomalies of puberty.
Q.4 Write short notes on adolescent contraception.
Q.5 Discuss the problems of teenage pregnancies.
Q.6 Describe the clinical manifestations and management of haematocolpos.
Q.7 Discuss the causes and management of abnormal uterine bleeding in adolescence.
Q.8 Enumerate the varieties of ovarian tumours seen in young adolescent girls. Discuss the management of such cases.
Q.9 What are the common causes of hirsutism/virilization in female adolescents?
Q.10 What are the hazards of STD in adolescent girls? How would you counsel young females to avoid STDs?

Suggested Reading

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Chapter

5

Perimenopause, Menopause, Premature Menopause and Postmenopausal Bleeding

CHAPTER OUTLINE

Introduction

The process leading to the final onset of menopause is determined by the number of Oogonia present in the ovaries at birth, the rate of atresia during reproductive years and the hormonal interplay regulated by the hypothalamic–pituitary–ovarian axis.

Perimenopause

Perimenopause is a period 3–4 years before menopause and followed by 1 year of amenorrhoea. This period is associated with mild ovarian hormonal deficiency leading to anovulation and menstrual disorders, especially menorrhagia.

Apart from general health check up to rule out cardiovascular disorder, diabetes, hypertension, pelvic examination, mammography, ultrasound, bone density and Pap smear may be advisable to assure the woman of her good health.

Management comprises the following:

- Diet, advice on smoking, alcohol, extra calcium and exercise will help. Smoking is toxic to the follicles and causes rapid metabolism of oestrogen in the liver and is antioestrogen.
- Counselling on contraception will help. Intrauterine contraceptive devices and oral combined pills are not recommended on account of irregular bleeding and risk of thrombosis, respectively. Surgical method is not required for a short period of fertility. Progestogen-only pills may cause irregular bleeding. Barrier contraceptive is the safest method.
- If a woman has fibroids, a short course of GnRH or Mirena IUCD can shrink the fibroid and avoid hysterectomy. Dysfunctional uterine bleeding requires investigations.
- The woman needs guidance on menopausal symptoms. The need for hormone replacement therapy (HRT) will be discussed later.

Prediction of Approaching Menopause

1. A fall in the level of Inhibin B (not inhibin A) causes a rise in follicle-stimulating hormone (FSH) level.

2. A fall in the level of anti-Müllerian hormone suggests low ovarian reserve and low antral follicular count.
3. Rise of FSH level and more than normal luteinizing hormone (LH) level

Study of FSH level on day 2–5 after last menstrual period detects premenopausal stage.

Menopause

Menopause is defined as the time of cessation of ovarian function resulting in permanent amenorrhoea. It takes 12 months of amenorrhoea to confirm that menopause has set in, and therefore it is a retrospective diagnosis.

Climacteric is the phase of waning ovarian activity, and may begin 2–3 years before menopause and continue for 2–5 years after it. The climacteric is thus a phase of adjustment between the active and inactive ovarian function and occupies several years of a woman's life, and it involves physical, sexual and psychological adjustments.

Demography

Sixty million women in India are above the age of 55 years. With women living longer than before, a majority would spend one-third of their life in the postmenopausal stage. The health problems cropping up during this period and related to oestrogen deficiency of menopause are now obvious and better understood. It is important therefore to address all these menopause-related diseases and apply prophylactic measures so that these women can lead an enjoyable and healthy life. An average Indian woman now lives up to 65 years of age, whereas in developed countries a lifespan up to 80 years is possible.

Age

Menopause sets in when the follicular number falls below 1000. Menopause normally occurs between the ages of 45 and 50 years, the average age being 47 years. It is not uncommon, however, to see a woman menstruate well beyond the age of 50. This delayed menopause may be related to good nutrition and better health. Late menopause is also common in women suffering from uterine fibroids and those at high risk of endometrial cancer. Menopause setting before the age of 40 is known as premature menopause.

Menopausal age is not related to menarche, race, socioeconomic status, number of pregnancies and lactation, or taking of oral contraceptives. It is however directly associated with smoking and genetic disposition. Smoking induces premature menopause.

Pathophysiology

During climacteric, ovarian activity declines. Initially, ovulation fails, no corpus luteum forms and no progesterone is secreted by the ovary. Therefore, the premenopausal menstrual cycles are often anovulatory and irregular. Later, Graafian follicles also fail to develop, oestrogenic activity is reduced and endometrial atrophy leads to amenorrhoea. Cessation of ovarian activity and a fall in the oestrogen and inhibin levels cause a rebound increase in the secretion of FSH and LH by the anterior pituitary gland. The FSH level may rise as much as 50-fold and LH 3–4 fold. Menopausal urine has become an important commercial source of human menopausal gonadotropin (hMG). With further advancing years, gonadotropin activity of the pituitary gland also ceases, and a fall in FSH level eventually occurs.

Hormone Levels

There is 50% reduction in androgen production and 66% reduction in oestrogen at menopause. The oestrogen level may remain low at 10–20 pg/mL. Some oestrogen comes from the ovary, but most of it is oestrone (E_1) derived from peripheral conversion of androstenedione secreted by the ovary, and its level varies between 30 and 70 pg/mL. The ovary also secretes a small amount of testosterone which causes mild hirsutism at menopause. The FSH appears in high concentration in the urine (more than 40 IU/l). E_2/E_1 ratio maintained over 1 in the premenopausal period is reduced to less than 1 in the menopausal age, causing an oestrogen deficiency state. Oestrogen level of over 40 pg/mL exerts bone and cardiotrophic effect, but the level below 20 pg/mL may predispose to osteoporosis and ischaemic heart disease (Table 5.1). Low level of growth hormone causes ovarian failure.

Risk factors for menopause-related diseases are as follows:

- Early menopause.
- Surgical menopause or radiation.
- Chemotherapy especially alkalytic agents.
- Smoking, caffeine, alcohol.
- Family history of menopausal diseases (genetic).
- Drugs related such as GnRH, heparin, corticosteroids and clomiphene (antioestrogen) when given over a prolonged period (over 6 months) can lead to oestrogen deficiency.
- Diabetes.

TABLE 5.1 Hormone levels in a menopausal woman

E_2	5–25 pg/mL
Oestrone	20–70 pg/mL—more in obese women
FSH	>40 mIU/mL
Androgen	0.3–1.0 ng/mL
Testosterone	0.1–0.5 ng/mL
LH	50–100 mIU/mL
Androstenedione	800 pg/mL
Growth hormone	Low
Inhibin B	
Anti-Müllerian hormone	

Anatomical Changes

The genital organs undergo atrophy and retrogression. The ovaries shrink and their surfaces become grooved and furrowed. The tunica albuginea thickens. The menopausal ovary measures less than 2 × 1.5 × 1 cm in size (8 mL in volume) as seen on ultrasound. Fifteen years later, it should not measure more than 2 mL. The plain muscle in the fallopian tube undergoes atrophy, cilia disappear from the tubal epithelium and the tubal plicae are no longer prominent.

The uterus becomes smaller through atrophy of its plain muscle, so that the connective tissues are more conspicuous. The endometrium is represented by only the basal layer with its compact deeply stained stroma, and a few simple tubular glands. The lymphoid tissue and the functional layer disappear. It is common for the endometrial glands to dilate before menopause sets in, and cystic glandular hyperplasia reported in some premenopausal women causes metropathia haemorrhagica, with irregular heavy bleeding. The pre-existing fibromyoma gradually shrinks.

The cervix becomes smaller and its vaginal portion is represented by a small prominence at the vaginal vault. The cervical stenosis and pyometra are not uncommon. The vaginal fornices gradually disappear as the cervix shrinks after the menopause. The vagina becomes narrow and its epithelium becomes pale, thin and dry and gets easily infected causing senile vaginitis (Figure 5.1). The vulva atrophies and the vaginal orifice narrow and this can cause dyspareunia. The skin of the labia minora and vestibule becomes thin, pale and dry, and there is considerable reduction in the amount of fat contained in the labia majora. The pubic hair is reduced and becomes grey. The red patches seen around the urethra and introitus are caused by senile vulvitis, and a urethral caruncle may be produced. The pelvic cellular tissue becomes lax and the ligaments that support the uterus and vagina lose their tone, and these conditions predispose to prolapse of the genital organs, stress incontinence of urine and faecal incontinence.

Apart from the atrophy of the genital organs, general disturbances that develop are almost certainly caused by alterations in the endocrine balance maintained during the childbearing period. Fat is deposited around the breasts, hips and abdomen. Although the mammary glandular tissue atrophies, deposition of fat often makes the breasts more pendulous. Whereas, glandular tissue constitutes 30% of the breast volume, it is reduced to only 5% after the menopause. The skin wrinkles and hair grow around the chin and lips. Hypertension, cardiac irregularities and tachycardia are at times noticed after menopause. Arthritis and osteoporosis of the vertebral bones, upper end of the hip joint and wrist are related to oestrogen deficiency after menopause.

Tooth decay, keratoconjunctivitis and cataract are related to menopausal oestrogen deficiency.

Menopausal Symptoms (Table 5.2)

Menstrual

The three classical ways in which the menstrual period ceases are as follows:

- Sudden cessation
- Gradual diminution in the amount of blood loss with each regular period until menstruation stops
- Gradual increase in the spacing of the periods until they cease for at least a period of 1 year

Although by definition, menopause is said to have set in if amenorrhoea lasts for a year, a woman who bleeds after a gap of 6 months is considered to have postmenopausal bleeding and should be thoroughly investigated. Continuous bleeding, menorrhagia or irregular heavy bleeding in the perimenopausal period are considered abnormal and should be investigated for malignancy of the genital tract.

Hot Flushes

Almost 60–70% women go through menopausal period without problems. Rest need guidance and treatment. The most common and the most noticeable symptoms of hot flushes and sweating are the hallmark of the climacteric in

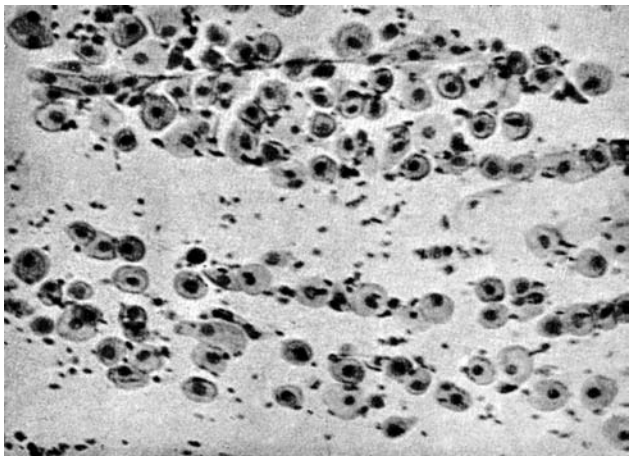

Figure 5.1 Cytology of senile vaginitis.

TABLE 5.2 Early features of menopause

- Hot flushes
- Sweating
- Insomnia
- Headache
- Psychological
- Cancer phobia
- Dyspareunia, decreased libido
- Pseudocyesis
- Irritability
- Depression, insomnia, tiredness
- Lack of concentration, loss of memory
- Urinary stress incontinence, dyspareunia

85% women. Hot flushes are the waves of vasodilation affecting the face and the neck and these last for 2–5 min each. These are followed by severe sweating. Several of these flushes occur in a day, but are more severe during the night, and can disturb sleep. The hot flushes are sometimes preceded by headache. Palpitation and anginal pains may be felt. Mental depression due to disturbed sleep or otherwise, irritability and lack of concentration are noticed. With passage of time, the frequency and severity of flushes diminish over a period of 1–2 years. Hot flushes are caused by noradrenaline, which disturbs the thermoregulatory system. Oestrogen deficiency reduces hypothalamic endorphins, which release more norepinephrine and serotonin. This leads to inappropriate heat loss mechanism.

Other causes that can be associated with the symptom of hot flushes include: thyroid disease, epilepsy, pheochromocytoma, carcinoid syndromes, autoimmune disorders, mast cell disorders, insulinoma, pancreatic tumours and even leukemias.

The vasomotor symptoms are more severe in surgical menopause than natural menopause.

Other Symptoms

Some women develop a condition of pseudocyesis, when they fear pregnancy and attribute amenorrhoea and increased abdominal girth to pregnancy.

Cancer phobia may also develop; the woman starts worrying over her looks.

Neurological

Vasomotor symptoms and paraesthesia take the form of sensations of pins and needles in the extremities.

Libido

Sexual feeling and libido may increase in some, if they feel happy to get rid of menstruation and fear of pregnancy. Many however notice decreased libido after menopause (15%; lack of orgasm and arousal.)

The symptoms which develop little later are as follows:

- Urinary such as dysuria, stress incontinence and urge, recurrent infection (urethral syndrome)
- Genital such as dry vagina, dyspareunia, loss of libido
- Faecal incontinence
- Thyroid dysfunction

Urinary Tract

Oestrogen deficiency can cause urethral caruncle, dysuria, with or without infection, urge and stress incontinence. The stress incontinence is caused by poor vascularity and tone of the internal urinary sphincter. These urinary symptoms are clubbed together under the term 'urethral syndrome'.

Genital

Atrophic vagina reduces the vaginal secretion, and dry vagina can cause dyspareunia. Loss of libido adds to sexual dysfunction. Rarely, senile vaginitis can cause vaginal bleeding (Figure 5.1). Prolapse of genital tract and stress incontinence of urine and faeces are mostly menopausal related.

Neurological

Depression, loss of memory, irritability, poor concentration and tiredness.

Late Sequelae

Menopausal women with chronic oestrogen deficiency are liable to develop the following:

- Arthritis, osteoporosis and fracture, backache
- Cardiovascular accidents such as ischaemic heart disease, myocardial infarction, atherosclerosis and hypertension
- Stroke
- Skin changes
- Alzheimer's disease
- Ano-colonic cancer
- Tooth decay
- Prolapse genital tract, stress incontinence of urine and faecal incontinence
- Cataract, glaucoma and macular degeneration

Locomotor system disorders: Menopausal arthropathy, osteoarthritis, fibrositis and backache may be age related.

Osteoporosis (Figure 5.2). It is an incipient slowly progressing skeletal disorder characterized by microarchitectural deterioration of bone mass resulting in increased fragility and predilection to fracture in the absence of significant trauma. About 15% of elderly women suffer from osteoporosis and almost three times as many suffer from osteopenia (deficient bone mass). Both osteopenia and osteoporosis predispose to fractures. These constitute a significant cause of morbidity such as pain, deformity and impaired respiratory and other bodily functions. Hip fractures are often associated with a high rate of mortality.

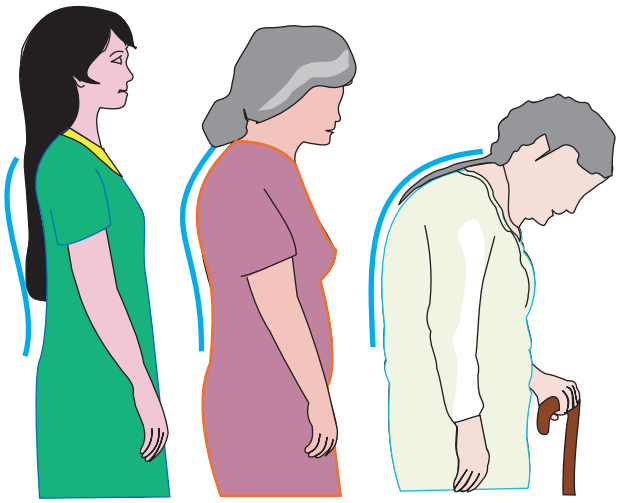

Figure 5.2 Osteoporosis of the vertebral column.

With increasing longevity of women in India, the medical practitioners will be called upon more often to care for osteoporosis-related problems.

Osteoporosis is defined as a condition in which there is a fall in bone mass exceeding 2.5 standard deviations (SD) below the mean for young adults. WHO has defined low bone mass as *osteopenia* and *osteoporosis* on the basis of axial skeleton (bone mineral density, BMD) to facilitate screening and identification of individuals at risk. These definitions apply specifically to T-scores derived from the use of dual-energy X-ray absorptiometry (DEXA) of the lumbar spine. WHO defines osteopenia as a BMD between 1 and 2.5 SD below the young adult mean peak and osteoporosis as BMD which is 2.5 SD or more below the standard adult mean values.

PATHOPHYSIOLOGY. Bone is not an inert supporting tissue. *Bone remodelling* takes place constantly. At the cellular level, bone remodelling is a balance between bone resorption (osteoclastic activity) and bone formation (osteoblastic activity) while the main functions of the osteocytes and lining cells are metabolic, subserving the nutrition of bone and the maintenance of calcium homeostasis. After cessation of adult growth, the skeleton consolidates to reach peak bone mass (PBM) at the age of 35–40 years. Thereafter, slow subsequent age-related loss of bone mass occurs in everyone at the rate of 0.4% annually, but women are additionally exposed to an accelerated rate of bone loss during the perimenopausal age and the initial 5–8 years of the early menopause (2% cortical bone and 5% trabecular bone). Oestrogen deficiency is the dominating factor contributing to osteoporosis in women. Additional contributing factors such as calcium and vitamin D deficiency also need consideration. At the age of 40 years, bone calcium amounts to 1200 g. When the level drops below 750 g, fracture of the bone is liable to occur.

Figure 5.3 shows that women live a third of their lifespan in menopause. Elderly women suffer from vertebral fractures leading to gibbus formation, a bent spine and shortening of height.

The other high-risk factors for osteoporosis are as follows:

- Family history of osteoporosis.
- Low calcium intake in diet.
- Smoking and excess of caffeine and alcohol intake.
- Early menopause.
- Low weight.
- Surgical menopause following hysterectomy with or without oophorectomy. It is now believed that even if the ovaries are conserved, the disturbance in their vascularity leads to ovarian atrophy.
- Radiation menopause.
- Woman on GnRH, heparin and corticosteroids, danazol, clomiphene.
- Thyrotoxicity.
- Sedentary lifestyle, diabetes.

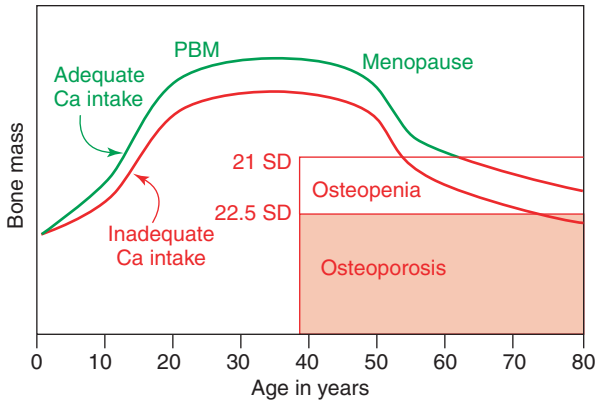

Figure 5.3 Bone mineral density—age related.

Diminished BMD can be studied by DEXA and single- or dual-photon absorptiometry for spine, neck of the femur and radius. This technique detects bone loss of as little as 1–5% compared to plain radiography, which shows loss of bone mass only at 30% loss.

Cardiovascular Disease. Oestrogen is cardioprotective by maintaining a high level of high density lipoprotein (HDL) and lowering the low density lipoprotein (LDL) and triglycerides. Oestrogen deficiency therefore can cause atherosclerosis, ischaemic heart disease and myocardial infarction. Obese women with hypertension and previous thromboembolic episodes are liable to cardiovascular accidents. Oestrogen prevents atherosclerosis through its antioxidant property.

Stroke. The incidence of stroke also increases in menopausal women.

Skin. Collagen content is reduced, causing skin to wrinkle. The 'feminine forever' thought applies to oestrogen cream to delay the age-related skin changes. However, it is observed that after a few months the skin actually thins out, and oestrogen cream may be beneficial temporarily and only in the initial phase of treatment.

Alzheimer's Disease. Lately, it is reported that Alzheimer's disease is precipitated by oestrogen deficiency at menopause, and hormonal therapy is beneficial in preventing or delaying its onset. It is beneficial only if given in the perimenopausal age or soon after menopause. Giving hormone later is not effective:

- Tooth decay
- Keratoconjunctivitis, cataract, glaucoma and macular degeneration

Ano-colonic cancer and teeth decay are known to increase after menopause.

Endocrine System. Mild virilization as seen in the form of hirsutism is probably adrenal in origin, as also is obesity, especially the deposit of fat around the hips. Hypothyroidism with low basal metabolic rate (BMR), high cholesterol

level, dryness of skin, brittleness of hair and lack of concentration are noticed in a few menopausal women.

Pyometra. Years after menopause, a woman may develop senile pyometra caused by cervical stenosis, and needs drainage by cervical dilatation under general anaesthesia.

Investigations

Investigatory procedures are as follows:

- History of various symptoms.
- General examination includes blood pressure recording, palpation of the breasts, weight and hirsutism.
- Pelvic examination such as Pap smear.
- Blood sugar, lipid profile, ECG.
- Mammography, pelvic ultrasound.
- Bone density study. DEXA is a quick test with less radiation.
- Oestrogen (E_2) and FSH levels to decide on the need of HRT.
- Endometrial biopsy in women on HRT and tamoxifen.

Management

The clinician should adopt a holistic approach towards management of health problems of menopausal women and selectively prescribe hormone therapy according to the requirement. Minimal required dose avoids risks while conferring the beneficial effects.

Counselling

The woman often develops pregnancy and cancer phobia. It is the duty of the gynaecologist to convince her, after thorough examination and investigations, that all is well with her. It is a good practice to document baseline recordings of pelvic ultrasound, which includes the ovarian size and the endometrial thickness, mammography as well as E_2 and FSH levels, when HRT is considered. Regular counselling may be required until the woman is well settled in menopause.

The advice on contraceptives is necessary. Until menopause is well established and amenorrhoea has lasted for 12 months, the couple is advised to use barrier method. Hormonal pills may not be safe from the point of view of thromboembolism. Progestogen pills or depot injections may be the alternative, but they cause irregular bleeding and depression.

Diet should include at least 1.2 g of calcium, vitamin A, C, E and 400 mg of vitamin D. Soya beans are good (discussed later). Weight-bearing exercises (walking and aerobic) delay onset of osteoporosis.

Mild Tranquillizers

These relieve woman's anxiety, sleeplessness and depression. Antidepressants such as sulpiride may be needed.

Antidepressant drugs—Venlafaxine 30–150 mg daily, Paroxetine 10–20 mg daily, Gabapentin 300 mg three times a day.

Hormone Replacement Therapy

Not all women require HRT. Besides, HRT does not suit all, and it may cause complication and be harmful. However, it is logical to prescribe HRT and not withhold it when one needs it in the minimal effective dose for the shortest needed duration under supervision while on therapy.

Initially, every menopausal woman was advised to go on HRT as soon as menopause set in to be taken for several years. Newer researches and their observations reveal that a few women need prophylactic and therapeutic HRT, but 70–85% of women remain healthy and need only good nutrition and healthy lifestyle.

Who Needs HRT?

- Symptomatic women who suffer from oestrogen deficiency (therapeutic).
- High-risk cases for menopausal complications such as cardiovascular disease, osteoporosis, stroke, Alzheimer's disease and colonic cancer (prophylactic).
- Premature menopause, spontaneous or following surgery (hysterectomy, tubectomy). The surgical procedures disturb and compromise the blood supply to the ovaries. Menopause caused by radiotherapy and chemotherapy for cancer, especially alkylating agents (prophylactic).
- Gonadal dysgenesis in adolescents (therapeutic).
- Women demanding HRT as prophylaxis.

The type of hormone, route of administration and duration of treatment depend upon the purpose for which it is used, i.e. prophylactic or therapeutic.

Symptomatic women who suffer vasomotor symptoms, urinary symptoms and sexual disharmony with dyspareunia, as well as psychosomatic problems need to be treated with HRT on a short-term basis for a period varying between 3 and 6 months. Most improve by the end of 6 months after which the woman usually gets adjusted and settles down well in the menopausal phase of life.

The high-risk cases for osteoporosis have already been mentioned. The women with atherosclerosis, hypertriglyceridemia and ischaemic heart disease may benefit from cardioprotective effect of prophylactic oestrogen. However, HRT is not recommended for women who are already suffering from ischaemic heart disease.

Recently, it was proved that prophylactic HRT may delay or prevent the occurrence of Alzheimer's disease and allow the woman at risk to lead a comfortable life for years.

There are women who are healthy and at no risk of the above diseases. They do however feel inclined to take HRT with the belief that they will have the feeling of well-being and can lead an enjoyable life. These women need a proper screening before prescribing the hormones. They should be counselled regarding the benefit, side effects and the cost, and the need for periodic check up while on hormones. Certain contraindications to be noted for oestrogen therapy are as follows:

- Breast cancer, uterine cancer or family history of cancer
- Previous history of thromboembolic episode

- Liver and gall bladder diseases
- Uterine fibroids—the fibroids may enlarge in size

Hypertension, diabetes and smoking are not contraindications, provided they are regularly monitored. Rather cardiac disease, stroke and smoking may be the indications for oestrogen therapy to derive benefit and improve their health from oestrogen deficiency.

Uses of HRT

- Short term—hot flushes, vasomotor symptoms
- Dyspareunia, libido
- Urethral syndrome
- Long term—osteoporosis
- Cardiovascular
- Alzheimer's disease

Osteoporosis

HRT is the cornerstone in the prophylaxis and treatment of osteoporosis. After menopause, the woman loses on an average 3% BMD every year causing osteopenia and eventually osteoporosis and fracture of the vertebra, femur and of the wrist. The trabeculated bone is most affected. The morbidity arising from fracture is considerable. The benefit of HRT is proved beyond doubt in preventing or delaying bone resorption. When to start HRT remains a controversial point. Although earlier it was recommended in the perimenopausal age or soon after menopause, the poor compliance over a long period, the cost and the limited benefit of up to 8–10 years have now altered the decision by some gynaecologist to follow-up the woman with regular study of bone density mass and prescribe when osteopenia is observed. This allows an optimal benefit of HRT (around the age of 60). Natural oestrogen, progestogen, tibolone and raloxifene are beneficial in osteoporosis, if it occurs early in menopause. Osteoporosis occurring late in menopause benefits from bisphosphonates, as primary treatment.

It is observed that benefit of HRT lasts while the woman continues to take HRT, and the bone loss resumes once she stops taking drugs. Since the prolonged therapy beyond 8–10 years is not beneficial but perhaps harmful, most gynaecologists now follow-up the woman for osteopenia and prescribe HRT when osteopenia occurs.

Oestrogen delays or protects against osteoporosis by 50% in all skeletal bones, and not restricted to trabecular bones of spine, wrist and upper hip bones.

Prophylaxis of Osteoporosis

- Oestrogen hormone therapy-ERT (hysterectomized)
- Oestrogen + progesterone (HRT)
- Tibolene
- Raloxifene
- Soya
- Bisphosphonates for late osteoporosis
- Calcitonin
- Parathyroid
- Diet

Risks of HRT:

- Endometrial cancer
- Breast cancer
- Ovarian cancer
- Thromboembolism
- Lipid profile dysfunction
- Gall stones, liver dysfunction

Cardioprotective Effect of HRT

Oestrogen deficiency increases the risk of atherosclerosis, ischaemic heart disease and angina in a postmenopausal woman. Oestrogen is therefore cardioprotective in prevention of cardiovascular disease. It also increases HDL and decreases LDL, cholesterol and triglycerides. Oestrogen is most effective when taken orally as far as its effect on lipid profile is concerned. Oestrogen and tibolone are strongly cardioprotective in menopausal women. However, a woman with previous ischaemic heart disease does not benefit from HRT and its use is not recommended.

Drugs, Dosage and Route of Administration

Oestrogen Therapy. Short-term therapy is required to relieve the woman of hot flushes, night sweats, palpitations and disturbed sleep. Oestrogen should however be given in the smallest effective dose for a short possible period of 3–6 months. Natural oestrogens are used. Oral Premarin (E_1—natural equine-conjugated oestrogen) in the dose of 0.625 mg daily, increasing to 1.25 mg if necessary, ethinyl oestradiol 0.01 mg, micronized oestrogen (1–2 mg) or Evalon 1–2 mg are effective. Progestogen such as Duphaston/medroxyprogesterone 10 mg or Primolut-N 2.5 mg daily for 10–12 days each month should be added to prevent endometrial hyperplasia and carcinoma. This therapy can still cause endometrial hyperplasia in 5% and atypical hyperplasia in 0.7% cases. Because of this, some prefer to give a combined hormone therapy (Femet) containing 2 mg 17β-oestradiol and 1 mg of norethisterone acetate, which is known to cause endometrial atrophy. *Progesterone is not required in a hysterectomized woman*. Cyclical combined HRT causes cyclical bleeding. Period-free HRT can be attained if the combined hormones are taken continuously.

Dyspareunia, urethral syndrome and senile vaginitis respond well to local oestrogen cream, which is preferred to oral therapy. Oestriol base cream 1/2 g is applied every day for 10–12 days each month for a period of 3–6 months until the symptoms disappear. Estring (vaginal ring) releases 5–10 mcg oestrogen and is 90% effective over a period of 3 months.

LONG-TERM THERAPY. Long-term oestrogen therapy is beneficial in delaying osteoporosis and reducing the risk of cardiovascular disease in a postmenopausal woman. However, it is observed that *extending the medication beyond 8–10 years does not confer any further benefit*.

ORAL ROUTE. Orally administered oestradiol gets extensively metabolized into oestrone in the intestine and the liver so that only 10% reaches the systemic circulation as

TABLE 5.3 Advantages and disadvantages of oral and transdermal route of oestrogen

Oral	Transdermal
Advantages	**Advantages**
• Cheap • Easy to take • Can be withdrawn quickly in presence of side effects • Good for lipid profile and cardiovascular protection	• Low-dose oestradiol • Avoids first-pass effect and liver metabolism • Reduces triglycerides • No thromboembolic risk or hypertension
Disadvantages	**Disadvantages**
• High dose required • First-pass effect in liver • Daily intake • Tablet contains lactose, and not suited to women who are allergic to lactose • High incidence of side effects • ↑ Hypertension • ↑ Thromboembolism	• Costly • Not tolerated in warm climates • Variable absorption

oestradiol. Larger doses therefore need to be given orally as compared to the nonoral route (Table 5.3). This metabolism in the gut and the liver is known as 'first-pass' effect, and this also increases certain liver proteins, alters the clotting factors and increases the secretion of renin. However, given orally, it improves the lipid profile except serum triglyceride and improves the cardioprotective effect. Very recently, however, the controversy has been raised regarding its protective role in a woman already suffering from cardiovascular disease, and HRT is not recommended for them.

TRANSDERMAL PATCH (ESTRADERM). It avoids the first-pass effect of liver metabolism, and the hormone reaches the systemic circulation as oestradiol. The risk of thromboembolic episode and probable hypertension is eliminated. It reduces serum triglyceride level as well.

Estraderm patch contains 3–4 mg of oestradiol and releases 50 mcg each day. The disadvantage of skin reaction with alcohol-based patch is now avoided by newer transdermal system, but it cannot be reapplied after being taken off the skin during bath. The patch needs to be changed twice a week. The cost prohibits many women from using them. It should be applied away from the breasts, on the arms, legs and thighs.

Gel (100 mg contains 60 mg β-oestradiol) is applied to the skin for improving the collagen content and avoid wrinkles (two measures of 0.75 mg oestradiol). The plasma level is maintained at 60–80 pg/mL.

VAGINAL CREAM. Oestriol cream is used in urethral syndrome and dry vagina. About 1/2 g is applied daily for a few days each month on a short-term basis. Premarin is also available as cream.

VAGINAL RING. Oestrogen supplementation can be effectively achieved by inserting a vaginal ring that releases 17β-oestradiol @ 0.0075 mg daily for 90 days. This form of medication should be considered in the management of menopausal vaginal symptoms.

IMPLANT. Implant containing 25–50 mg oestradiol is effective for 6 month each, and maintains the E_2 level at 50–60 pg/mL. A minor operation is required for insertion and removal. It is suitable in hysterectomized women.

Intranasal 300 mcg of oestrogen raises the level of hormone in 30 min, and becomes effective. However, breakthrough bleeding, sneezing and itching occur in 1–3% cases and 55% have stopped the therapy by the end of 1 year.

The oestrogen therapy reduces the incidence of fracture by 50% at the end of 5 years (90% vertebra and 50% hip). Similarly, cardiovascular complications have been reduced by 40–50% with oestrogen therapy.

Unfortunately, compliance of long-term use of hormone therapy is marred by vaginal bleeding. To overcome this problem, '*period-free*' HRT is now produced by the combination of oestrogen and progesterone taken continuously instead of cyclically. Not only continuous progestogen suppresses oestrogen-stimulated endometrium, it also allows a smaller dose of oestrogen and progestogen and lesser side effects. Even then, vaginal bleeding may occur up to 6 months of this regime, followed by amenorrhoea. Any bleeding after that requires investigations.

The risks of HRT are follows:

- Vaginal bleeding with continuous HRT (period-free HRT) is more common if the therapy is started within 1 year of menopause, and may last up to 6 months. After the first year of menopause, there is less risk of vaginal bleeding. Persistent vaginal bleeding requires endometrial biopsy. The bleeding can however be avoided by decreasing oestrogen dose or increasing the dose of progestogen. With 'period-free' HRT, 75–100% women become amenorrhoeic by the end of 1 year.

Gabapentin is a nonhormonal anticonvulsant that reduces hot flushes by 50% if given in a dose of 900–2400 mg daily. Dizziness (14%) and drowsiness (12%), tiredness, headache, blurred vision, dry mouth and memory problem gradually disappear after a week or so.

- Thromboembolism.
- Endometrial cancer if E_2 is taken alone and the risk last for 10 years after stoppage of therapy.
- Breast cancer is due to progestogen if HRT is taken over 5 years.
- The possibility of coronary heart disease in a woman with cardiovascular disease has caused a great concern regarding the use of HRT in these women. HRT is contraindicated in these cases.
- Increased risk of ovarian cancer.

Progestogens. Progestogens are used for 10–12 days in each cycle to avoid the risk of endometrial hyperplasia and cancer in nonhysterectomized women. If given for 7 days in each cycle, the risk of endometrial hyperplasia is reduced to 4%, but if given for 12 days in each cycle, the risk is further reduced less than 2%. It does so through

enzyme 17β-hydroxydehydrogenase, which inactivates E_2 and controls the mitotic activity within the endometrial cells. They do reduce the bone resorption, but not to the extent seen with oestrogen therapy. Some of them have an adverse effect on lipid profile (Figure 5.4).

The drugs used are Primolut-N 2.5 mg, medroxyprogesterone and Duphaston, 10 mg. Progestogen implants are also available for those intolerant to oestrogen. Progestogens cause bloated feel, weight gain and depression and may adversely alter the lipid profile. Medroxyprogesterone has no adverse effect on lipids but reduces the bone density. To avoid the systemic side effects and poor compliance with oral progestogen, *Mirena IUCD containing levonorgestrel is inserted for 5 years in HRT programme*. Micronized progesterone is not useful in HRT.

Drospirenone, a new progestogen, has no androgenic and adverse lipid effect. A dose of 3 mg combined with 30 mcg oestradiol (yasmin, janya, tarana) has been tried in menopausal women, but more research is desirable.

Testosterone implant and combined tablet with oestrogen are used to improve libido. The role of Viagra to improve libido is controversial at present.

Yohimbine resembles reserpine, an indole alkyl amine alkaloid derived from the bark of tree *Rauwolfia*. It improves libido. A dose of 6–10 mg daily at night is prescribed. Tolerance develops with this drug. Risk of hirsutism should be borne in mind.

Other Drugs

1. **Tibolone** (Livial) is a synthetic derivative of 19-nortestosterone and has a weak oestrogenic, progestogenic and androgenic action. The tablet containing 2.5 mg does not cause endometrial hyperplasia but causes irregular bleeding in 15% cases. It also elevates the mood, relieves the vasomotor symptoms, improves the sex drive and reduces bone resorption. Its main action is cardioprotection by reducing the level of triglycerides. Side effects include weight gain, oedema, tenderness in the breast, gastrointestinal symptoms and vaginal bleed (15%). The greasy skin and increased hair growth are due to androgenic action. It should be initiated only after 1 year of menopause to avoid vaginal bleeding. It may perhaps increase the risk of breast cancer.
2. **Raloxifene,** a nonsteroidal compound (Evista), is a selective oestrogen receptor modulator (SERM), which reduces the risk of fracture by 50%, especially vertebra by increasing BMD by 2–3%. It causes 10% reduction in total cholesterol and LDL and raises HDL level. It does not raise the level of triglycerides. It is therefore cardioprotective in long term. It has a very low risk of endometrial and breast cancer. It is mainly beneficial in reducing osteoporosis and is given 60 mg daily with calcium and vitamin D. It is absorbed from the gastrointestinal tract (60%), and glucuronidation occurs in the liver and is excreted in the faeces. Toremifene 20 mg daily is effective in 60% cases. *Side effects* are hot flushes, cramps, increased incidence of venous thrombosis and retinopathy. It does not control vasomotor symptoms. Contraindications are as follows:
   - Venous thrombosis.
   - It should not be given with oestrogen.
   - Hepatic dysfunction.
   - Stop the drug 72 h before surgery.
   - Not to be given with drugs such as indomethacin, naproxen, ibuprofen and diazepam.
3. **Soya.** Soya beans contain isoflavone (phytoestrogens, genistein and daidzein). About 11 g soya contains 2–4 mg phytoestrogens, which is strongly oestrogenic, though it is a nonsteroidal plant product. About 45–60 mg soya daily is protective without the potential risk of breast cancer, liver disease and other side effects of oestrogen. It is a safe alternative to hormonal therapy. It also decreases cholesterol, LDL and triglycerides with a marginal increase in HDL. It also has antiviral, antifungal and anticarcinogenic effects. It is also present in lentil and chick peas.
4. **Bisphosphonates** such as etidronate and tiludronate reduce bone resorption through the inhibition of osteoclastic activity. Etidronate 10 mg/kg body weight (approximately 400 mg orally daily) is given for 2 weeks followed by a gap of 2–3 months (3-month course), and this course is repeated for 10 such cycles. The drug should not be given with calcium, because its absorption is reduced. Calcium should be taken in the morning and etidronate swallowed (not chewed) in the afternoon, on an empty stomach with a glass of water in the upright position; stay upright for half an hour. This reduces the oesophageal irritation. The tablet should not be swallowed with coffee, tea or juice. Overdose causes hypocalcaemia. Milk and antacid can reduce gastric irritation. It is recommended that HRT should be prescribed in early menopausal age. After 60 years, osteoporosis should be managed with bisphosphonates. **Alendronate** is given as either 5 mg daily or 35 mg weekly. Overdose causes hypocalcaemia. **Risedronate** has reduced gastric side effects and is effective in a dose of 5 mg daily or 35 mg once a month. **Zoledronic acid** is used therapeutically once a year as intravenous infusion of 5 mg over 15 min, but osteonecrosis of the jaw and visual disturbances are

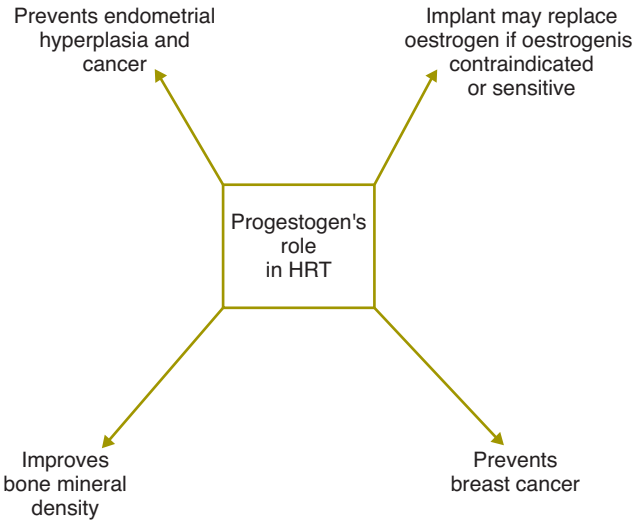

Figure 5.4 Role of progestogen in HRT.

the major side effects, though very rare. Ibadronate sodium is given 2.5 mg daily or 150 mg monthly orally or 3 mg intravenously three monthly. **Calcitonin** is a peptide produced by thyroid C cells. It inhibits osteoclast activity and inhibits bone resorption. It is given as a nasal spray at a single dose of 200 IU daily for 3 months. Nasal spray can cause flushes, rhinitis, allergic reaction and nasal bleeding. It reduces the incidence of fracture by 30%. **Subcutaneous injection** of calcitonin is also available, but gastrointestinal symptoms, anaemia and inflammation of joints cause poor compliance so also the high cost. **Teriparatide** is the recombinant formation of parathyroid hormone. About 20 mcg once-daily subcutaneous injection decreases vertebral fracture by 65% and others by 50% if used less than 2 years. Nausea and headache are the complications. **Strontium ranelate** given 1–2 g daily orally increases BMD by 50%. However, it is very expensive and not easily available. **Clonidine** is an imidazoline derivative used to treat hot flushes. It is also effective in hypertensive women not responding to oestrogen. Clonidine lowers blood pressure in addition to relieving hot flushes. Dose of 0.2–0.4 mg daily suffices. It acts centrally. Side effects are dry mouth, dizziness and nausea. Androgens improve libido, but carries the risk of hirsutism.

Conclusions

- Not every menopausal woman needs HRT.
- A symptomatic woman due to oestrogen deficiency requires HRT for 3–6 months. The duration and route of HRT depend upon the purpose for which the therapy is prescribed.
- Total duration of prophylactic therapy beyond 8–10 years has not proved beneficial, but side effects may harm the woman.
- The benefit of therapy should be balanced against the risks of breast and endometrial cancers and venous thromboembolism.
- Phytoestrogen is available as 'Femarelle', one tablet to be taken twice a day.
- Therapy should be individualized according to the need.

Lately, once a *month oral ibandronate* is made available which improves bone density (ibandronate is marketed as IDROFOS-150 mg).

The drug increases the BMD by 5–10% and also prevents recurrence of fracture. Nonresponse is seen in 10% cases.

Alendronate is the third generation of bisphosphonates (nonhormonal) and is 1000 times more potent than etidronate with no side effects. It is marketed as Osteofos (5, 10, 35 and 70 mg).

Hormone Replacement Therapy and Breast Cancer

- The risk of breast cancer is not increased up to 3 years of HRT and 5 years of oestrogen alone replacement therapy.
- Lower risk is seen with use of dydrogesterone in HRT.
- HRT can cause recurrence of breast cancer and is therefore contraindicated in a woman who has been treated for breast cancer. Tibolene is safe.
- HRT increases the density of breast tissue and impede screening programme of mammography subsequently.
- Breast cancer developing following HRT is of low grade with good prognosis.

Hormone Replacement Therapy and Endometrial Carcinoma

- ERT can cause well-differentiated carcinoma.
- Minimum of 12 days of progesterone added to ERT reduces the risk of endometrial cancer to 2%.
- Combined oestrogen and progesterone provides a better protection against endometrial cancer.
- Tibolene is a safe drug and does not cause endometrial hyperplasia.
- Raloxifene, unlike tamoxifen exercises antioestrogen action on endometrium.
- The risk of cancer with ERT is dose and duration dependent.

Premature Menopause

Premature menopause is defined as ovarian failure occurring 2 SD in years before the mean menopausal age in a population. It is clinically defined as secondary amenorrhoea for at least 3 months with raised FSH level, raised FSH/LH ratio and low E_2 level in a woman under 40 years of age.

The incidence is 1%. Before the age of 30 years the incidence is 1:1000, at 35 it is 1:250 and just before 40 years it is 1%.

Aetiology

Some causes of premature menopause are known:

- Fewer germ cell migration from the yolk sac
- More apoptosis of germ cells

1. Genetic disorders such as chromosomal abnormalities are reported in 10–20% of cases involving X sex chromosomes. Autosomal dominant sex-linked inheritance is known. Ovarian dysgenesis is seen in 30% cases.
2. Autoimmune diseases are reported in 30–60% cases. Mumps, thyroid dysfunction, hypoparathyroidism and Addison disease may account for a few cases. The ovarian biopsy shows infiltration of the follicles with plasma cells and lymphocytes. Raised CD_8 count and low CD_4 count suggest autoimmune disease. Antiovarian antibodies are present.
3. Tuberculosis of the genital tract involving the ovaries can cause secondary amenorrhoea and ovarian failure.
4. Smoking is known to induce premature menopause, and the age when it occurs depends upon the degree of smoking.

5. Radiation and chemotherapy can cause premature menopause, but the effect is reversible and the ovary may resume ovulation and menstruation after about a year of amenorrhoea. Radiation of up to 400–500 rads restores normal ovarian function in 50% cases after a period of 1 year or 2, and pregnancies have occurred. Alkalytic agents are strong inducers of premature menopause.
6. Ovarian failure following hysterectomy is known to occur in 15–50% cases and is caused by kinking and blockage of ovarian vessels. Tubectomy can also produce similar effect.
7. Prolonged GnRH therapy may lead to ovarian suppression and failure.
8. Enzyme defects such as 17-α-hydroxylase deficiency and galactosaemia have adverse effect on oocytes, but more often cause primary amenorrhoea.
9. Resistant ovary: This terminology is used less frequently these days and it is presumed that the follicles fail to respond to gonadotropin stimulation.
10. Induction of multiple ovulations in infertility can cause premature menopause when the follicles get exhausted.

Pathophysiology

Lack of receptors is explained as the cause of nonresponse of follicles. In others, exhaustion of primordial follicles is responsible.

Clinical Features

Hot flushes and sweating occur in 75% cases and may be more severe than seen in natural menopause. Libido is diminished in 10–20% cases. Vaginal dryness and urinary symptoms are less complained of.

Investigations

- FSH level: 40 mIU/mL or more
- E_2 level: 20 pg/mL or less
- Thyroid function, calcium level, chromosomal study and thyroid antibodies
- Blood sugar
- X-ray pituitary fossa for the tumour
- BMD study is not always necessary, and it is an invasive procedure
- Ovarian biopsy
- Ultrasound
- Prolactin level

Complications

The risks of osteoporosis and cardiovascular diseases increase in premature menopause.

Management

1. The cause of premature menopause should be ascertained and the cause treated. Follicular maturation, ovulation and menstruation have been restored following the treatment of the cause.
2. Oophoropexy and ovarian shield during radiotherapy protect ovaries.
3. Progestogen challenge test will indicate if menstruation can be induced, provided endometrium is primed with oestrogen.
4. Corticosteroid therapy is effective in autoimmune disease if antibodies to sex hormones are present in the blood. Plasmapheresis has also been attempted.
5. A woman with hypo-oestrogenism may require HRT or other drugs to prevent osteoporosis. Oestrogen implant with progestogen or Mirena IUCD offers long-term HRT.

Specific management according to the need:

1. An older woman or a parous woman not interested in pregnancy or menstrual functions may require HRT if she develops menopausal symptoms. She may require prophylactic HRT if she is a high-risk case of cardiac complication, or osteoporosis.
2. Libido improves with testosterone and E_2 therapy.
3. A woman not interested in pregnancy, but requests for restoration of menstrual cycles, should receive oestrogen progesterone cyclical therapy or cyclical progesterone alone.
4. A young woman interested in pregnancy should be offered either ovulation induction therapy (if ovarian reserve present) or be offered donor eggs in in vitro fertilization.
5. Ovarian transplant is being experimented.
6. In a young woman with diminished ovarian reserve, Dehydroepiandrosterone (DHEA) 25 mg + folic acid (OVOSTORE) three times a day for 4–5 months per stimulation of ovary improves the pregnancy rate (30–50%) by increasing the oocyte and embryo quality. It also reduces aneuploidy in embryos.

Late Menopause

It is defined as a condition in which menstruation continues beyond 52 years. Late menopause occurs in women with fibroids and is seen in women who develop endometrial cancer. Often it is constitutional. Beyond 52 years, endometrial biopsy is required to rule out endometrial pathology.

Benefits of late menopause are:

- Late ageing—better quality of life
- Cardioprotective, delay in osteoporosis

Disadvantages—increased risk of breast, uterine and ovarian malignancies.

Postmenopausal Bleeding

Normally a 1-year period of amenorrhoea after the age of 40 is considered as menopause. However, vaginal bleeding occurring anytime after 6 months of amenorrhoea in a

menopausal age should be considered as postmenopausal bleeding and investigated. Even without amenorrhoea or irregular bleeding, if a woman over the age of 52 years continues to menstruate, she needs investigations to rule out endometrial hyperplasia and malignancy of the genital tract.

Aetiology

Several causes account for genital tract bleeding in a postmenopausal woman:

1. Vulva—trauma, vulvitis, benign and malignant lesions.
2. Vagina—foreign body such as ring pessary for prolapse, senile vaginitis, vaginal tumour (benign as well as malignant) and postradiation vaginitis.
3. Cervix—cervical erosion, cervicitis, polyp, decubitus ulcer in prolapse and cervical malignancy.
4. Uterus—senile endometritis, tubercular endometritis, endometrial hyperplasia (10%), polyp, endometrial carcinoma and sarcoma and mixed mesodermal tumour.
5. Dysfunctional uterine bleeding, metropathia haemorrhagica, uterine polypi and endometrial hyperplasia.
6. Fallopian tube malignancy.
7. Ovary—benign ovarian tumour such as Brenner tumour, granulosa and theca cell tumour and malignant ovarian tumour.
8. Hypertension and blood dyscrasia.
9. Urinary tract—urethral caruncle, papilloma and carcinoma of the bladder may be mistaken for genital tract bleeding.
10. Bowel—bleeding from haemorrhoid, anal fissures and rectal cancer may be misleading.
11. An important reason for postmenopausal bleeding is indiscriminate or prolonged use of oestrogen unopposed by progestogens, and HRT when applied cyclically. Tamoxifen causes endometrial hyperplasia and cancer.

Thirty to fifty per cent of postmenopausal bleeding is attributed to malignancy of the genital tract, the most common being endometrial cancer, cervical cancer and ovarian tumours. Common benign conditions are endometrial hyperplasia and polypi and dysfunctional uterine bleeding. Postmenopausal bleeding due to oestrogen and Tamoxifen are not uncommon, others are rare.

Clinical Features

History

The age of menarche and menopause, history of taking oestrogen and tamoxifen and prolapse details should be elicited. Abdominal pain and foul-smelling discharge are noticed in malignant tumours. Urinary and rectal symptoms are also important features to be noted.

Examination

1. Blood pressure.
2. General examination includes obesity and diabetes, which are prone to endometrial cancer.
3. Abdominal palpation will reveal a tumour.
4. Speculum and bimanual examination may reveal an obvious cause in the lower genital tract.

Investigations

Excluding malignancy is the main aim of investigations:

1. Blood count and smear will reveal blood dyscrasia.
2. Blood sugar levels.
3. Cervical cytology for cervical lesion.
4. Endometrial study.
5. Sonosalpingography for endometrial polyp.
6. Ultrasound—endometrial thickness of more than 4 mm indicates the need of endometrial biopsy.
7. CA 125 serum levels.

Several methods are now available to obtain endometrial tissue for histological examination. Although many endometrial benign lesions cause bleeding, the main objective is to exclude malignancy:

- Dilation and curettage (D&C)—fractional curettage comprising separate scrape of endometrium and endocervix not only allows the exact site of malignancy if present, but also detects the extent of spread of the tumour and staging. The curettage requires general anaesthesia and hospitalization.
- Uterine cavity aspiration and endometrial sampling avoid anaesthesia and can be performed as an outpatient case.

Vibra aspirator, Gravlee's jet washer, Isaac's aspirator and Pipelle aspirator are used to obtain endometrial sampling.

Aspiration is mainly employed in screening women on HRT and tamoxifen. D&C is best to rule out cancer when postmenopausal bleeding is reported.

None of these methods is 100% fool proof, and some cases may fail to detect the cause of bleeding.

1. To improve the predictive value of endometrial study, hysteroscopic inspection and selective biopsy are now considered the gold standard in the diagnosis of endometrial lesion, though 1–3% false-negative findings are reported.
2. Ultrasound, CT and MRI. Transvaginal ultrasound is an adjunct to other investigations, in detecting the endometrial thickness and irregularity and pelvic tumour. In case endometrial cancer is detected, CT and MRI are useful preoperative investigations and these detect the extent of spread of the tumour to the myometrium and the lymph nodes. Doppler ultrasound with increased diastolic blood flow and low resistant index suggest malignant growth.
3. Diagnostic laparoscopy will be required to study the nature of the tumour and its spread if ultrasound picks up a pelvic tumour.
4. When the genital tract as a cause of bleeding has been excluded, cystoscopy and proctoscopy may discover the cause of bleeding.

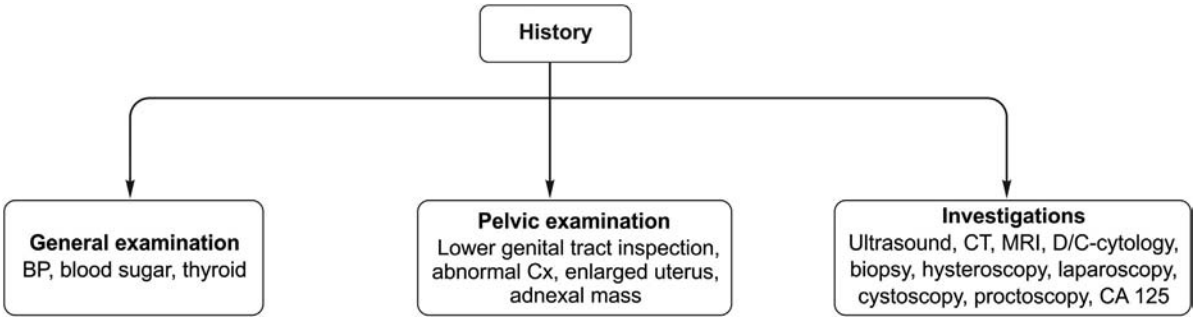

Figure 5.5 Flowchart of postmenopausal bleeding.

Detection of a benign lesion should not deter further investigations to rule out malignancy of the genital tract, as both may coexist. Postmenopausal bleeding is explained in Figure 5.5.

Management

1. Treat the cause.
2. When no cause is found, and if there has been only one bout of bleeding, the patient should be kept under observation. About 80% of these cases do not bleed again. If the woman continues to bleed, or bleeding recurs, it is advisable to perform a laparotomy. An undiagnosed small tumour may be discovered and dealt with appropriately. Otherwise abdominal hysterectomy with bilateral salpingo-oophorectomy should be performed and the specimen sent for histopathological study.

Other menopausal problems encountered in gynaecology are as follows:

- Genital prolapse and rectal prolapse
- Stress incontinence
- Malignancy of the genital tract
- Breast cancer
- Decreased libido and dyspareunia

These are described in their respective chapters.

Key Points

- Normal menopause sets in around 45–47 years.
- Premature menopause before 40 years can cause menopausal symptoms, osteoporosis and cardiovascular diseases. Late menopause is a high-risk factor for uterine malignancy and breast cancer.
- Thirty to forty per cent of postmenopausal bleeding is caused by cancer, and needs detailed investigations.
- Urethral syndrome, dry vagina with dyspareunia and menopausal symptoms require short-term oestrogen therapy.
- Long-term HRT is protective against osteoporosis, cardiovascular accidents, stroke, Alzheimer's disease and colon cancer.
- A proper diet, exercise and HRT help in delaying menopausal diseases. Oestrogen cream, oral tablets with progestogen and skin patches are available. The implants and Mirena have recently been introduced in HRT. Other optional drugs are tibolone (Livial), raloxifene (SERM), phytoestrogens and bisphosphonates.
- Not all require hormone therapy. Rational thinking and recommendation is 'selective use of HRT' with minimal dose for minimum required period. The side effects and contraindications to hormone therapy should be known. A regular follow-up is necessary in women on HRT. Proper counselling is mandatory. The type of hormone, dosage and route of HRT is prescribed according to the need of the individual.
- Nonhormonal prophylactic therapy may be used instead of HRT.
- A woman may spend one-third of her life in oestrogen deficiency state and pose health problems. High-risk cases need monitoring and prophylactic therapy so that she leads a healthy life.

Self-Assessment

1. Define menopause. Describe the anatomical changes and alterations in the hormonal profile that characterize menopause.
2. Enumerate the symptoms associated with onset of menopause.
3. Describe the pathophysiology of postmenopausal osteoporosis and its management.
4. Describe the commonly prescribed regimes of HRT. Enumerate its advantages and limitations.
5. Briefly describe the use of medications prescribed in the management of osteoporosis.

Suggested Reading

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Chapter

6

Gynaecological Diagnosis

CHAPTER OUTLINE

The term *gynaecology* (from the Greek, *gynae* meaning woman and *logos* means discourse) pertains to the diseases of women and is generally used for diseases related to the female genital organs.

The interaction of the patient with a physician can often be an anxiety-producing event, particularly so in the practice of gynaecology because of the sensitive nature of the problems that need to be discussed; hence, the observance of the highest standards of ethical and professional behaviour is called for to establish rapport, while at the same time not creating a hostile environment in which the patient feels embarrassed or uncomfortable to permit a meaningful assessment of her underlying medical problem.

Three ethical principles must be integrated into the care and nature of services offered to every patient.

1. **Respect:** Today, counselling forms an important aspect of consultation. The nature of the gynaecological ailment, reason for a particular investigation and its predictive value should be discussed. The discussion on treatment options with their demerits and merits will enable the woman to choose the treatment she considers best for her. The gynaecologist should, however, guide her in making the right decision. The clinician must respect the patient as an individual. Remember that the patient has the right to make decisions about her health care. It is not ethically or morally right to enforce the physician's opinion on the patient. This will safeguard against any charge of negligence if a medicolegal problem arises at a later date. The records should be properly maintained and the documents preserved. The patient should feel assured at all times about 'privacy and confidentiality'.
2. **Beneficence:** The medical attendant must be vigilant to ensure that the therapeutic advice rendered to the patient should be in 'good faith'. It should be aimed at benefiting her. All medical measures adopted during the course of medical treatment should be guided and evaluated on the basis of the principle of the cost/benefit ratio accruing out of the medical advice given.
3. **Justice:** This is rendered when the physician makes access to care, the type of care, the attention provided and the cost of care equitable to the needs of the patient.

History and physical examination constitute the fundamental tools on which rest the tentative diagnosis, the tests to be undertaken and the treatment to be recommended (Table 6.1).

History

Careful history and physical examination form the basis of patient evaluation, clinical diagnosis and management. Investigations are employed to confirm the diagnosis and for the follow-up of treatment.

It is advisable to ask the patient to describe her main complaint in her own words and take her own time narrating the evolution of the problem, the aggravating and relieving factors and the investigations and treatment she has already undergone. Good and patient listening is essential to obtain maximum cooperation during the subsequent pelvic examination.

TABLE 6.1 History: Gynaecological case record form

Registration No:			
Name in full:			
Address:			
Tel. No.:	Name and contact of next of kin:		
Insurance details:			
Demographic data:			
Age:	Marital status:	Parity:	Occupation:
Chief complaints:			
Origin, duration and progress:			
Past history:			
Medical illnesses:			
Surgical illnesses:	Allergy to drugs and previous blood transfusion		
Personal history:			
Diet:			
History of blood transfusion in the past:			
Bowels and micturition:			
Habits/addictions:			
Medications:			
Allergies:			
Marital history:			
Sexual intercourse:			
Dyspareunia:			
Contraceptives used:			
Sexual disorders: vaginal discharge			
Family history:			
Diabetes:	Hypertension:	Allergies:	Tuberculosis:
Genetic disorders:			
Carcinoma:	Multiple births:	Others:	
Menstrual history:			
Age at menarche:			
Past menstrual cycles:			
Present menstrual cycles:			
Date of the last menstrual period:			
Obstetric history:			
Full-term deliveries:	No.	Outcome:	
Preterm deliveries:	No.	Outcome:	
Abortions:	Interventions with details:		
Number of living children:	Date of last delivery:		

History begins with the recording of the basic information about the patient as shown in the sample proforma (Table 6.1).

Present Illness

The clinician must record the patient's complaints in the sequence in which they occurred, noting their duration, their aggravating and relieving factors and their relation to menstruation, micturition and defaecation. The investigations performed and the response to treatment given so far should be noted.

Past and Personal History

Past medical and surgical problems may have a bearing on the present complaints. For example, a history of diabetes may suggest that pruritus vulva may be due to genital candidiasis, and history of sexually transmitted disease (STD) may have a direct bearing on future infertility.

History of pelvic inflammatory disease (PID) or puerperal sepsis may be associated with menstrual disturbances, lower abdominal pain, congestive dysmenorrhoea and infertility. Tuberculosis may lead to oligomenorrhoea and infertility. History of endocrinopathy may affect her sexual functions. Medical diseases such as hypertension, cardiac

disease, anaemia, diabetes, asthma and the like will require to be controlled prior to a planned surgery. Previous blood transfusion and drug allergy should be noted. This has special reference to HIV and hepatitis B infection.

Previous abdominal surgery such as caesarean section, removal of the appendix, excision for ovarian cyst, etc. may lead to pelvic adhesions, which may be the cause of abdominal pain, backache, retroverted fixed uterus, infertility and menstrual disturbances. Dyspareunia is often the result of pelvic adhesions.

Allergies to any drug, current medication, use of alcohol, smoking and life style have relevance in the management.

Family History

Certain problems run in families, e.g. menstrual patterns tend to be similar amongst members of the family. Premature menopause, menorrhagia and dysmenorrhoea may occur in more than one member in a family. Similarly, female members of some families are more prone to cancer of the ovary, uterus and breast. Diabetes, hypertension, thyroid disorders, allergic diathesis and functional disorders are often familial in nature. Genetic and hereditary disorders affect more than one member in the family, e.g. thalassaemia. Tuberculosis may affect many in the family.

Marital and Sexual History

Note the details of her marital life, such as the frequency of coitus, dyspareunia, frigidity, achievement of orgasm, libido, use of contraceptives and the method used. Relevance of dyspareunia to infertility should be noted.

Menstrual History

Normal menarche and menstrual cycle have been described in Chapters 2 and 3.

The term *menorrhagia* denotes excessive blood loss (increase in duration of bleeding/heavier blood flow) without any change in the cycle length. The term menorrhagia is now replaced by 'abnormal uterine bleeding' (AUB) and will be addressed in this chapter. The term *polymenorrhoea or epimenorrhoea* refers to frequent menstrual cycles as a result of shortening of the cycle length. Sometimes women suffer from a menstrual disorder characterized by shorter duration of the cycles coupled with heavier flow or prolongation in the duration of the flow; this condition is termed as *polymenorrhagia*. The severity of AUB can be assessed by taking into account the number of sanitary pads required per day, history of passing blood clots, presence of anaemia and evaluating for the presence of accompanying symptoms such as fatigue, palpitation, dizziness, breathlessness on exertion and the presence of pallor. Menorrhagia and polymenorrhagia are frequently present in women with myomas, adenomyosis and PID in women wearing intrauterine contraceptive devices (IUCDs) and also due to hormonal imbalance causing dysfunctional uterine bleeding (DUB) in perimenopausal women. AUB now replaces the word DUB.

Oligomenorrhoea is the term used to describe infrequent menses. In this condition, the cycle length is prolonged without affecting the duration and amount of flow. *Hypomenorrhoea* refers to the condition in which the cycle length remains unaltered, however the duration of bleeding or the amount of blood loss, or both are substantially reduced. When complete cessation of menstruation occurs, the condition is described as amenorrhoea. *The problems of oligomenorrhoea and hypomenorrhoea are encountered in conditions such as polycystic ovarian disease (PCOD), hyperprolactinaemia and genital tuberculosis, in women on oral contraceptive pills, in association with certain neoplasms of the pituitary or ovary, in functional hypothalamic disorders and in psychiatric disorders*. Drugs may occasionally be implicated. Oligomenorrhoea and hypomenorrhoea may occasionally progress to amenorrhoea. Amenorrhoea is physiological during pregnancy, lactation, prior to puberty and after menopause. *Metrorrhagia* (now addressed as intermenstrual bleeding) means the occurrence of intermenstrual bleeding, and it may occur in association with ovulation (mittelschmerz); however, it is commonly associated with the presence of neoplasms such as uterine polyps, carcinoma cervix and uterine and lower genital tract malignancy. It may occur with conditions such as vascular erosions, using intrauterine devices or breakthrough bleeding in oral pill users. However, this symptom calls for thorough investigation because of a possible malignant cause. Sometimes the patient may present with the complaint of *continuous bleeding,* so that the normal pattern can no longer be distinguished. Such episodes may be of functional origin due to hormonal disturbances often witnessed as puberty bleeding and perimenopausal bleeding disorders (DUB). However, during the childbearing years, conditions due to complications of early pregnancy such as ectopic pregnancy and abortion often present in this manner. Genital tract neoplasms such as submucous polyps and genital malignancies may present with continuous bleeding. *Postmenopausal bleeding* is often related to genital malignancy in 30–40%; hence, this symptom should not be treated lightly, it should be evaluated carefully and all efforts made to exclude such a possibility. Postcoital bleeding often suggests cervical lesion, i.e. erosion, polyp and cancer.

The presence of dysmenorrhoea and dyspareunia may have organic cause in the pelvis, i.e. endometriosis, fibroid and PID.

Vaginal discharge is common in lower genital tract infections.

Obstetric History

Record the details of every conception and its ultimate outcome, the number of living children, the age of the youngest child and the details of any obstetric complications encountered, e.g. puerperal or postabortal sepsis, postpartum haemorrhage (PPH), obstetrical interventions, soft tissue injuries such as cervical tear, an incompetent cervical os and repeated abortions, genital fistulae, complete perineal tear and genital prolapse, stress urinary

incontinence and chronic backache. Severe PPH and obstetric shock may lead to pituitary necrosis and 'Sheehan's syndrome'. *Thus, many a gynaecological problem has its beginnings rooted in earlier inadequate obstetric care.*

Medical termination of pregnancy and spontaneous abortions should also be enquired into.

Abdominal pain: Abdominal pain is a complaint in pelvic tuberculosis, PID and endometriosis. Acute lower abdominal pain occurs in ectopic pregnancy, torsion or rupture of an ovarian cyst and chocolate cyst.

Physical Examination

Physical examination (Table 6.2) includes general examination, systemic examination and gynaecological examination

TABLE 6.2 Physical examination

1. General examination:		
Height in cm:	Weight (in kg), gait:	
Build: Weight	Nutritional status:	Appearance:
Pallor:	Lymphadenopathy:	Oedema of the feet—varicose veins
Stigmata of disease: Breasts, thyroid, hirsutism		
Vital parameters:	Temperature:	Pulse rate:
Respiratory rate:	Blood pressure:	
2. Systemic examination:		
Cardiovascular system:		
Respiratory system:		
Liver palpation in malignancy		
3. Gynaecological examination:		
Abdomen:		
Inspection:		
Shape:	Umbilicus:	Movement with breathing:
Scars:	Lump:	
Palpation:		
Tenderness:		
Rigidity and guarding:		
Palpable lump: Ascites due to tuberculosis, ovarian malignancy and Meig syndrome		
Auscultation:		
Peristalsis:	Bruit:	
Pelvic examination:		
External genitalia:		
Appearance:		
Discharges:		
Scars:		
Perineum:		
Bimanual examination:		
Cervix:		
Uterus:		
Fornices:		
Speculum examination:		
Cervix:		
Vagina:		
Pap smear:		
Vaginal discharge:		
Rectal examination if necessary:		
4. Clinical diagnosis:		
Provisional:	Final:	
Investigations: These are planned in accordance with the provisional diagnosis.		

with a female attendant present to assist the patient and reassure her, particularly so when the attending clinician is a male doctor.

General Examination

General examination includes data mentioned in the proforma (Table 6.2). Pallor of the mucous membranes, the tongue and conjunctivae together with pale appearance of the skin and nails is highly suggestive of anaemia fullness of the neck is suggestive of a thyroid enlargement and enlarged lymph nodes are indicative of chronic infection, tuberculosis or metastasis following malignancy. Bilateral oedema of the feet may be found in women with large abdominal tumours, and unilateral nonpitting oedema is highly suggestive of malignant growth involving the lymphatics. Breast examination should be included in general examination. Hirsutism is a feature of PCOD. Breast secretion is noted in hyperprolactinaemia an important feature in amenorrhoea.

Systemic Examination

All gynae patients must be examined as a whole. This includes the examination of the cardiovascular and respiratory systems. Presence of any neurological symptoms calls for a detailed neurological evaluation, otherwise testing of the reflexes should generally suffice.

Abdominal Examination

Inspection

Many gynaecological tumours arising out of the pelvis grow upwards into the abdominal cavity. They cause enlargement of the abdomen, particularly the lower abdomen below the umbilicus, and their upper and lateral margins are often apparent on inspection. However, very large tumours can give rise to a diffuse enlargement of the entire abdomen. Pseudomucinous cystadenomas of the ovary can enlarge to mammoth proportions, sometimes to an extent of causing cardiorespiratory distress. Eversion of the umbilicus can occur as a result of raised intra-abdominal pressure and is observed with large tumours, ascites and pregnancy. The mobility of the abdominal wall with breathing should be observed carefully. In case of an intra-abdominal tumour, the abdominal wall moves over the tumour during breathing so that its upper margin is apparently altered. In case of pelvic peritonitis, the movements of the lower abdomen below the umbilicus are often restricted. The presence of striae is seen in parous women, pregnant women, in obese subjects and in women harbouring large tumours.

Palpation

With the clinician standing on the right side of the patient, it is desirable to palpate for the liver, spleen and kidneys with the right hand, and to use the sensitive ulnar border of the left hand from above downwards to palpate swellings arising from the pelvis. The upper and lateral margins of such swellings can be felt, but the lower border cannot be reached.

Myomas feel firm and have a smooth surface, unless they are multiple, when they present a bossed surface. Ovarian neoplasms often feel cystic, and may be fluctuant. The upper margin of these swellings is often well felt, unless the swelling is too large. The pregnant uterus feels soft and is known to harden intermittently during Braxton Hicks contractions; this is characteristic of pregnancy. The full bladder bulges in the lower abdomen and feels tense and tender. Extreme tenderness on palpation below the umbilicus is suggestive of peritoneal irritation, seen in women with ectopic pregnancy, PID, twisted ovarian cyst, a ruptured corpus luteum haematoma or red degeneration in a fibroid often associated with pregnancy. In women with an acute surgical condition, guarding in the lower abdomen and rigidity on attempting deep palpation are noted.

Percussion

Uterine myomas and ovarian cysts are dull to percussion, but the flanks are resonant. Dullness in the flanks and shifting dullness indicate the presence of free fluid in the peritoneal cavity. *Ascites may be associated with tuberculous peritonitis, malignancy or pseudo-Meig's syndrome.*

Auscultation

This reveals peristaltic bowel sounds, fetal heart sounds in pregnancy, souffle in vascular neoplasms and pregnant uterus. Hyperperistalsis may indicate bowel obstruction; feeble or absent peristalsis indicates ileus, calling for aggressive attention. Return of peristaltic sounds following pelvic surgery is a welcome sign of recovery and an indication to start oral feeds.

Gynaecological Examination

Most prefer dorsal position, so that bimanual examination of the pelvic organs can be conducted following abdominal examination without changing the position. Some may prefer left lateral (Sims' position). Verbal consent should be obtained for bimanual examination.

External Examination

It is a good practice to inspect the external genitalia under a good light. Notice the distribution of pubic hair. Normal pubic hair is distributed in an inverted triangle, with the base centred over the mons pubis. Extension of the hair line upwards in the midline along the linea nigra up to the umbilicus is seen in about 25% of women, especially in women who are hirsute or mildly androgenic as in PCOD. With the patient in lithotomy and her thighs well parted, note the various structures of the vulva. Look for the presence of any discharge or blood. Ask the patient to bear down and observe for any protrusion due to polyp or genital descent such as cystocele, rectocele, uterine descent or procidentia.

Separate the labia wide apart and examine the fourchette to see whether it is intact or reveals an old healed tear.

Speculum Examination

Speculum examination should ideally precede bimanual vaginal examination especially when the Papanicolaou (Pap) smear and vaginal smear need to be taken.

A bivalve self-retaining speculum such as the Cusco's speculum is ideal for an office examination (Figures 6.1 and 6.2). It allows satisfactory inspection of the cervix, taking of a Pap smear, collection of the vaginal discharge from the posterior fornix for hanging drop/KOH smear and colposcopic examination.

The Sims' vaginal speculum (Figure 6.3) with an anterior vaginal wall retractor can be used for the above examination. It permits an assessment of vaginal wall for cystocele and rectocele. However, an assistant is required to help the clinician during this examination and the woman needs to be brought to the edge of the table. Stress-incontinence should be looked for especially in presence of vaginal prolapse. In this case, the patient is examined with a full bladder.

Figure 6.1 Cusco's speculum.

Bimanual Examination

After separating the labia with the thumb and index fingers of the left hand, two fingers of the right hand (index and forefinger), after lubrication, are gradually introduced beyond the introitus to reach up to the fornices. If the fingers encounter the anterior lip of the cervix first, it denotes the cervix is pointing downwards and back towards the posterior vaginal wall, and that the uterus is in the anteverted position, conversely when the posterior lip of the cervix is encountered first, it is indicative of a retroverted uterus. The clinician next observes the consistency of the cervix: it is soft during pregnancy and firm in the nonpregnant state. Observe whether the movements of the cervix during the examination cause pain; this is seen in an ectopic pregnancy, as also in women with acute salpingo-oophoritis. The examining fingers now lift up the fornices and thereby elevate the uterus towards the left hand, which is placed over the lower abdomen and brought behind it (Figure 6.4). The uterus can thus be brought within reach of the abdominal hand and palpated for position, size, shape, mobility, tenderness and presence of any uterine pathology, e.g. fibroids (Figure 6.5).

In case of the retroverted uterus, it will be felt through the posterior fornix.

Thereafter, the clinician directs the tips of the examining fingers in the vagina into each of the lateral fornices and, by lifting it up towards the abdominal hand, attempts to feel

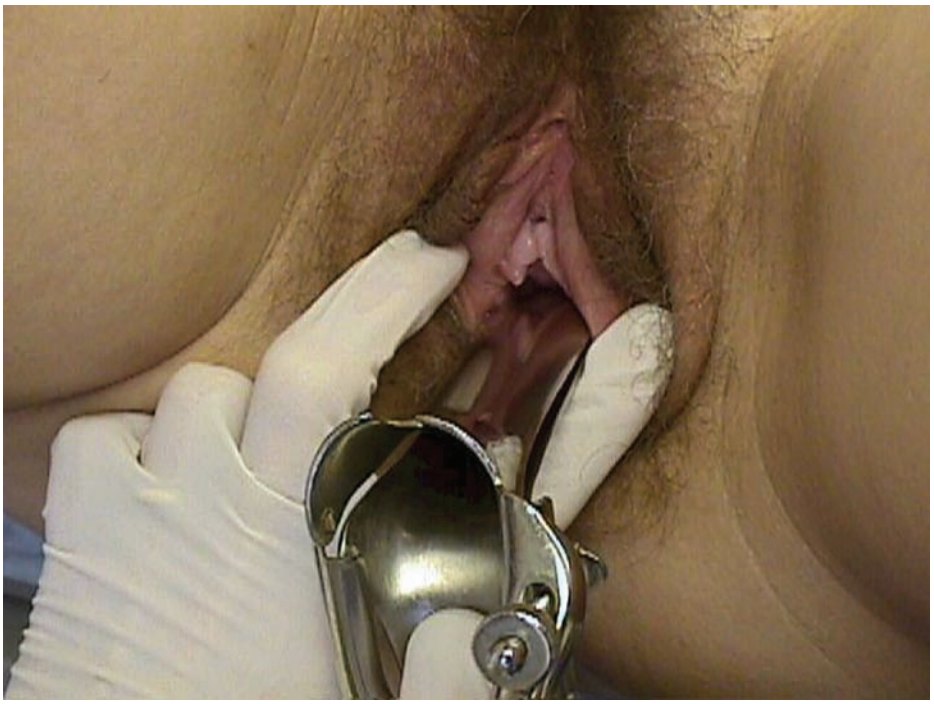

Figure 6.2 Speculum examination of the cervix. The patient is lying in the dorsal position and a Cusco's speculum has been inserted into the vagina. (Source: Mike Hughey, MD, President, Brookside Associates, Ltd.)

Figure 6.3 Sims' speculum.

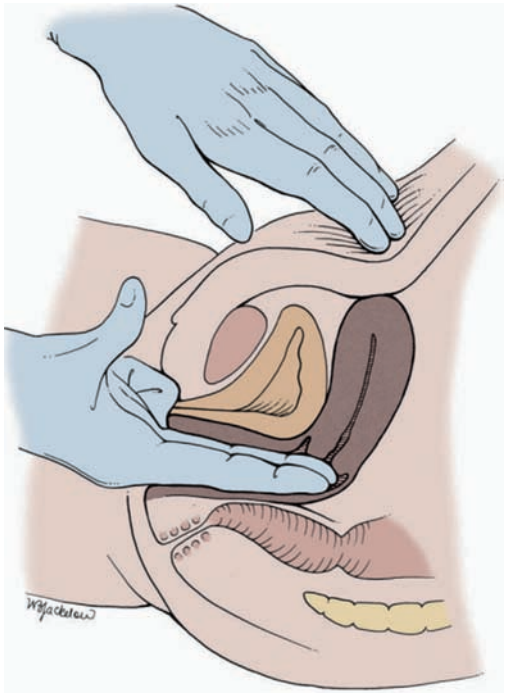

Figure 6.4 Bimanual examination of the pelvis in the female. Two fingers of the right hand are introduced into the vagina and the left hand is placed well above the symphysis pubis. (Source: Swartz MH: Textbook of Physical Diagnosis. Philadelphia, WB Saunders, 1989, p 405, Copyright © 2007 Saunders, An Imprint of Elsevier.)

for masses in the lateral part of the pelvis between the two examining hands. Should this reveal the presence of a swelling separate from the uterus, then the presence of some adnexal pathology is confirmed. The common swellings identified include ovarian cyst (Figure 6.6) or neoplasm, a paraovarian cyst, e.g. fimbrial cyst, tubo-ovarian masses (Figure 6.7), hydrosalpinx, and swelling in chronic ectopic pregnancy.

The appendages are normally not palpable unless they are swollen and enlarged. The ovary is not easily palpable; however, when palpated, it evinces a peculiar painful sensation that makes the patient to wince. Next in turn is the palpation of the posterior fornix. This enables the palpation of the contents of the pouch of Douglas. The most common swelling is the loaded rectum, particularly if she is constipated. Others in order of diminishing frequency include a

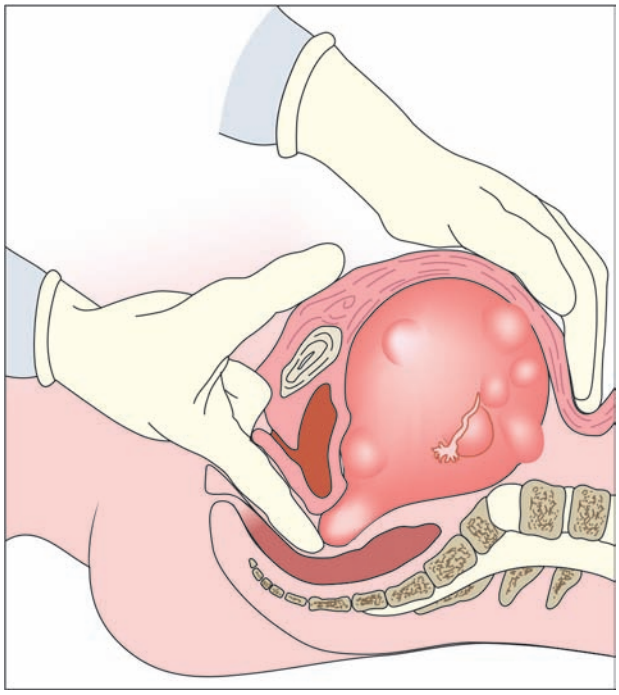

Figure 6.5 Bimanual examination in the case of multiple uterine myomas. Note how the external hand is placed high in the abdomen, well above the level of the tumour. Movements are transmitted between the two hands directly through the tumour.

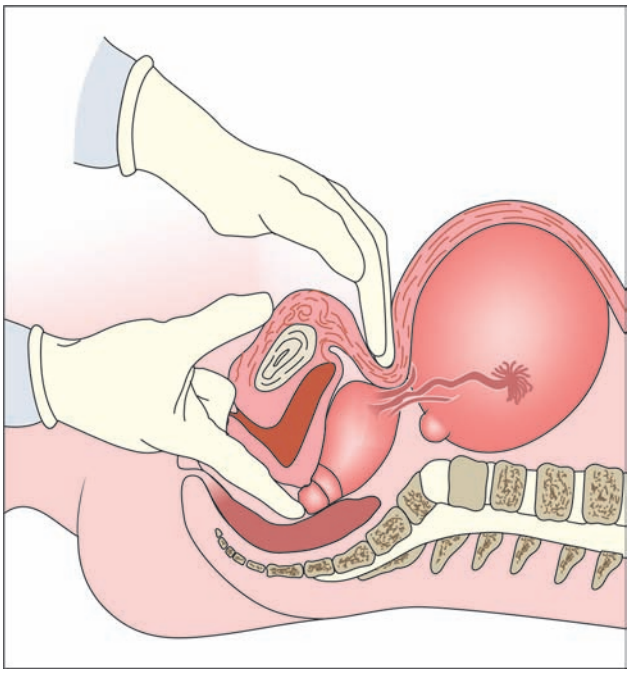

Figure 6.6 Bimanual examination in the case of an ovarian cyst. The nature of the tumour is determined on bimanual examination because the uterus can be identified apart from the abdominal tumour. Compare Figure 6.5. In some cases the pedicle can be distinguished if the fingers in the vagina are placed high up in the posterior fornix. Movements of the abdominal tumour are clearly not transmitted to the cervix.

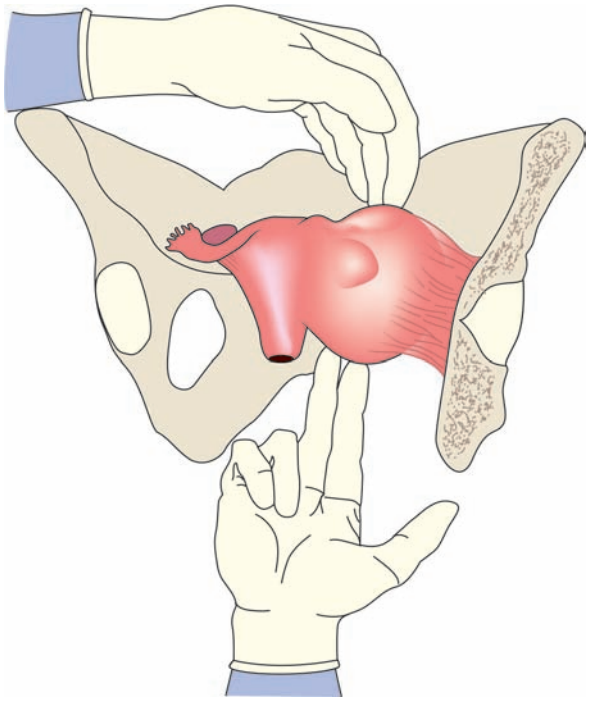

Figure 6.7 Bimanual examination in the case of a pyosalpinx. Note that the uterus is displaced to the opposite side. The fingers in the vagina are moved to one side of the cervix, and they feel the lower pole of the swelling.

retroverted uterus, ovaries prolapsed into the pouch of Douglas, uterine fibroid, ovarian neoplasm, chocolate cyst of the ovary, endometriotic nodules, pelvic inflammatory masses resulting from the adhesions of tubo-ovarian masses to the posterior surface of the uterus and the floor of the pouch of Douglas, pelvic abscess pointing in the posterior pouch and pelvic haematocele commonly associated with a ruptured ectopic pregnancy. To recognize the uterus from the adnexal mass, push the cervix upwards, and if this is transmitted to the swelling it is the uterus. Alternately, pushing down the uterus causes the cervix to move down. Adnexal mass does not move with cervical or uterine movement.

Rectal Examination

In virgins, a vaginal examination is avoided. Instead a well-lubricated finger inserted into the rectum can be used for a bimanual assessment of the pelvic structures. Today, practically all gynaecologists prefer ultrasonic scanning to rectal examination, which, apart from being unpleasant, is not that accurate. A rectal examination is a very useful additional examination whenever there is any palpable pathology in the pouch of Douglas. It often allows the ovaries to be more easily identified. In parametritis and endometriosis, the uterosacral ligaments are often thickened, nodular and tender. It confirms the swelling to be anterior to the rectum, and if the rectum is adherent to that swelling. This is important in case of carcinoma of the cervix to determine the extent of its posterior spread. A rectal examination is mandatory in women having rectal symptoms. This should begin by inspecting the anus in a good light, when lesions such as fissures, fistula-in-ano, polyps and piles may come to light. Introduction of a well-lubricated proctoscope to inspect the rectum and anal canal helps to complete the examination. *Ultrasound today has reduced the importance of rectal examination except in cancer cervix and pelvic endometriosis.*

Investigations

Detailed history and clinical examination often clinch the diagnosis or reduce the differential diagnosis to a few possibilities. However, investigations may be necessary to confirm the diagnosis, to assess the extent of the disease, to establish a baseline for future comparison regarding the response to therapy and finally to determine the patient's fitness to undergo surgery.

Common disorders: Age related:

Preoperative investigations are described in the chapter on preoperative and postoperative care. Special investigations are discussed below.

Special investigations:

- **Special tests** such as tumour markers: CA-125 in suspected adenocarcinoma of the ovary; carcinoembryonic antigen (CEA), α-fetoproteins and β-hCG in suspected ovarian teratomas.
- **Bacterial examinations of the genital tract**. These include the following: (a) examination of the vaginal discharge for trichomoniasis; (b) 10% KOH-treated smear for detecting candida; (c) 1% brilliant cresyl violet for staining trichomonad, but not the other bacteria and leucocytes; (d) platinum loop for collection of discharge (in suspected gonorrhoea) from the urethra, ducts of Bartholin and the endocervical secretion for culture on chocolate agar; (e) immunofluorescent examination of the discharge of endocervical cells for suspected chlamydial infection and (f) microscopic examination of the clue cells for diagnosis of bacterial vaginosis (Ch. 10).

Feinberg–Whittington medium is used for trichomonad and Nickerson–Sabouraud for moniliasis. The presence of clue cells indicates bacterial vaginosis.

Polymerase chain reaction (PCR) staining has been extensively utilized in the diagnosis of various infections.

Special Tests

Hanging Drop Preparation

In women complaining of leucorrhoea, the discharge collected from the posterior fornix on the blade of the speculum should be suspended in saline and submitted to microscopic examination. Normal vaginal discharge shows the presence of exfoliated vaginal epithelial cells and presence of large rod-like lactobacilli known as the Döderlein's bacilli. A fresh suspension of the discharge may reveal the motile flagellated organisms known as *Trichomonal vaginalis.* Another common cause of vaginal infection is fungal infection or *vaginal candidiasis*;

this can also be detected on microscopic examination of the vaginal discharge. To the suspension of the vaginal discharge, add an equal amount of 10% KOH solution. Place a drop of the mixture on a slide, cover it with a cover slip, warm the slide and examine it under the low power of the microscope. The KOH dissolves all cellular debris, leaving behind the more resistant yeast-like organisms. Typical hyphae or mycelia and budding spores can be easily detected. Many cases of vaginitis are attributed to *bacterial vaginosis* (nonspecific vaginitis); also known as *Gardnerella vaginalis*. The visualization of 'clue cells' seen preferably in a stained smear of the vaginal discharge is highly suggestive of the infection. Vaginal infections have been discussed later in detail in Chapter 10.

Schiller Test. This test detects the presence of glycogen in the superficial cells of the vaginal epithelium. The vaginal wall is stained with Lugol's iodine. The vaginal epithelium takes mahogany brown colour in presence of glycogen. Unstained areas (negative test) are abnormal and require biopsy for histological examination.

Papanicolaou Test

Screening for cancer. First described by Papanicolaou and Traut in 1943, this screening test is often referred to as the 'Pap test' or a surface biopsy or exfoliative cytology (cytology is a Greek word, meaning study of cells). It forms a part of the routine gynaecological examination in women. All women over the age of 35 years should undergo an annual check-up with the Pap test. Aside from premalignant and malignant changes, other local conditions can often be recognized by the cytologist. The Pap smear is a screening test only. Positive test (abnormal cells) requires further investigations like colposcopy, cervical biopsy and fractional curettage. Unfortunately, a Pap test can detect only about 60–70% of precancer and cancer of the cervix and less than 70% of endometrial cancer. Reliability of the report depends upon the slide preparation and the skill of the cytologist. Whereas a single test yields as much as 10–15% false-negative reading, it is reduced to only 1% with repeated tests. A false-positive finding is reported in the presence of infection. A yearly negative Pap smear for 3 years is assuring, and thereafter 5 yearly test is adequate.

Pap smear should be obtained prior to vaginal examination, because the fingers may remove the desquamated cervical cells and give a false-negative report, lubricant may prevent detection of organisms and any vaginal bleeding during examination may preclude proper visualization of the cervix. The patient should not have intercourse or touch for 24 h prior to Pap test. The best time to do Pap smear is around ovulation, but any other time can also do. The patient is placed in the dorsal position, with the labia parted, and the Cusco's self-retaining speculum is gently introduced without the use of lubricant or jelly. The cervix is exposed; the squamocolumnar junction is now scraped with Ayre's spatula by rotating the spatula all around (Figure 6.8). The scrapings are evenly spread onto a glass slide and immediately fixed by dipping the slide in the jar containing equal parts of 95% ethyl alcohol and ether. After fixing it for 30 min, the slide is air-dried and stained with Pap or short stain. The slide is considered satisfactory if endocervical cells are seen. To improve the predictive valve, endocervix is also scraped with a brush and added to the slide. Nowadays, a fixative spray (cytospray) is available and can be used conveniently in an office set-up. For hormonal cytological evaluation, the scrapings are taken from the upper lateral part of the vaginal walls; three types of cells are found in the normal smear: (i) the basal and para basal cells are small, rounded and basophilic with large nuclei, (ii) the cells from the middle layer are squamous cells, transparent and basophilic with vesicular nuclei while and (iii) the cells from the superficial layer are acidophilic with characteristic pyknotic nuclei. In addition, endometrial cells, histocytes, blood cells and bacteria can be seen. Malignant cells are hyperchromatic with a great increase in chromatin content. The nuclei vary in size and there is usually only a small amount of cytoplasm in the undifferentiated malignant cell (Figures 6.9 and 6.10). The nucleus/cytoplasmic ratio is increased in malignant cells.

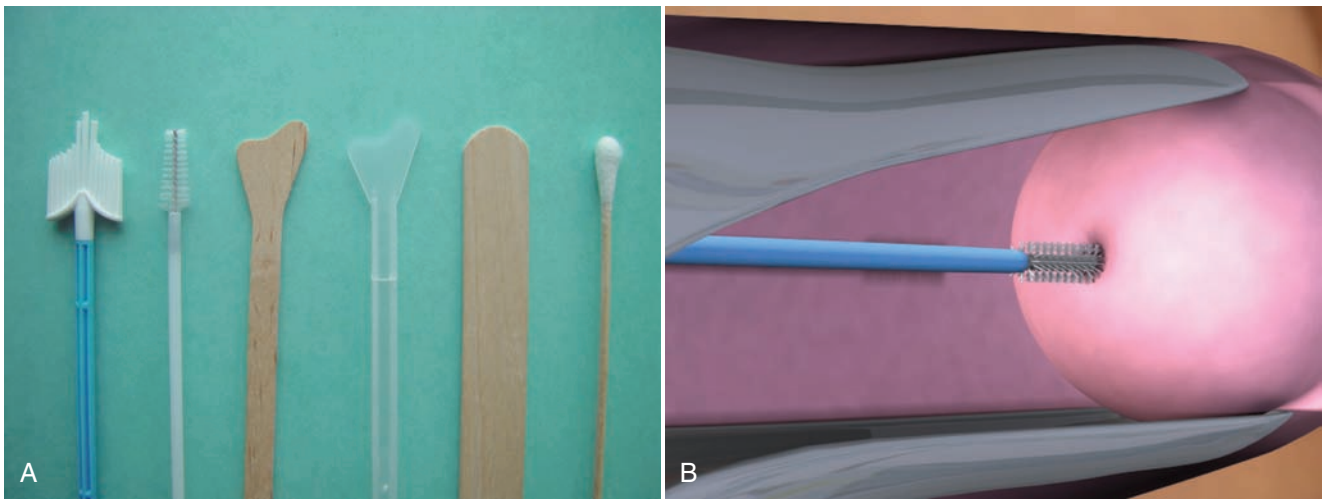

Figure 6.8 **(A)** Papanicolaou sampling devices. Left to right: Cervix-Brush, Cytobrush, wooden spatula, plastic spatula, tongue blade and cotton swab applicator. (From Figure 16, Pre-procedure. Procedure Consult. Pap Smear. Editors: Michael L Tuggy and Jorge Garcia.) **(B)** Pap smear with a brush. (From Figure 1, Pre-procedure. Procedure Consult. Papanicolaou Testing. Editors: Todd W Thomsen and Gary S Setnik.)

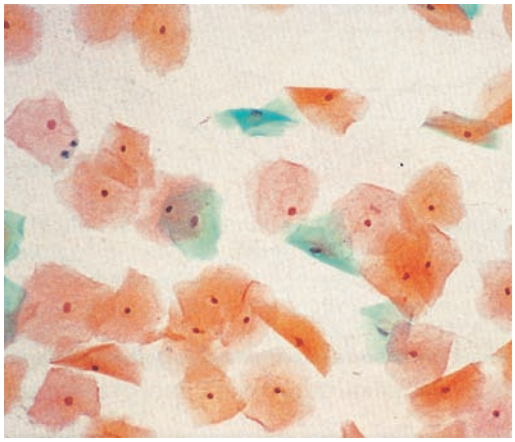

Figure 6.9 Normal cervical smear showing superficial (pink) and intermediate (blue/green) exfoliated cervical cells (low power magnification). (From Figure 20-5, Ian Symonds and Sabaratnam Arulkumaran: Essential Obstetrics and Gynaecology, 5th Ed. Elsevier, 2013.)

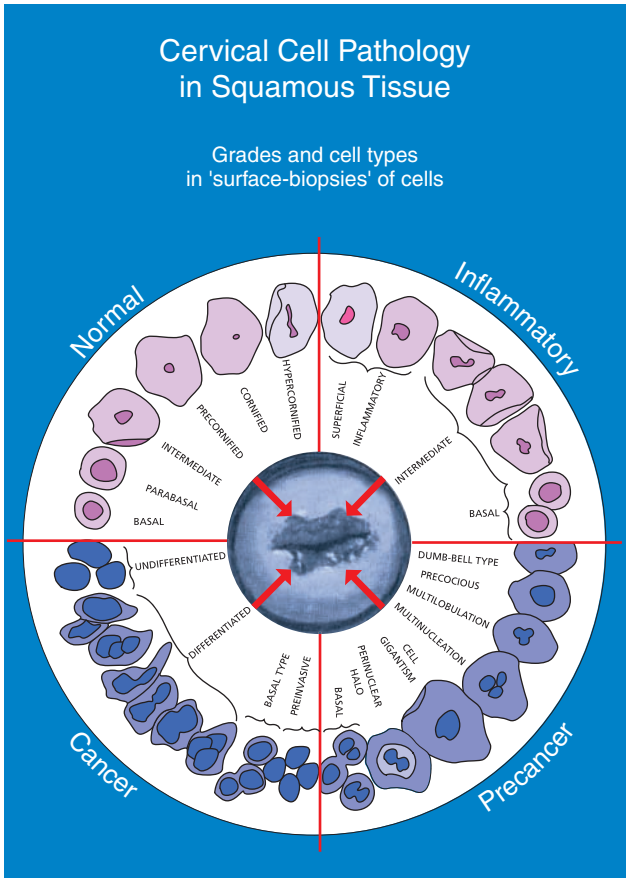

Figure 6.10 Illustration of pathological grades of epidermoid cells in the squamocolumnar junction of the cervix. Cells arising in this location were produced by a uniform cell-scraping technique. Classification of cell types is based upon thorough study, evaluation of cell characteristics and pathological features and is finally correlated with corresponding histological studies of the tissue. No attempt is made to classify cells exfoliated from other tissue areas, such as the endometrium. The squamocolumnar junction is a vital zone to the female, since this is the focal point where cancer arises. Grading of cells depends upon knowledge of origin of cell sample, on securing a rich concentration of cells, and of greatest importance, correct correlation with histological findings.

Papanicolaou classification:

Grade I Normal cells (Figure 6.9)
Grade II Slightly abnormal, suggestive of inflammatory change; repeat smear after treating the infection
Grade III A more serious type of abnormality, usually indicative of the need for biopsy
Grade IV Distinctly abnormal, possibly malignant and definitely requiring biopsy
Grade V Malignant cells seen (Figure 6.10)

A newer classification (Table 6.3) describes the cytology smears as follows:

1. Normal cytology
2. Inflammatory smear
3. Cervical intraepithelial neoplasia (CIN I) or mild dysplasia
4. CIN II, III and carcinoma in situ nuclear abnormalities
5. Malignant cells and tadpole cells with nuclear abnormalities

It is reasonable to enquire about the percentage of unsuspected cancers, including carcinoma in situ, that are likely to be diagnosed on routine cytology. The Indian Council of Medical Research (ICMR), New Delhi, screened the population of women over the age of 30 years and found 5–15 smears to be abnormal per 1000, women examined. The incidence of dysplasia reported at the All India Institute of Medical Sciences, New Delhi, was 16/1000 patients screened. In a postmenopausal woman, if the squamocolumnar junction is indrawn due to oestrogen deficiency, a 10-day course of oestrogen cream exposes the squamocolumnar junction better and yields an accurate result. Postradiation cytology is difficult to sample because of scarring and atrophy of the vagina. The cells are often enlarged, vacuolated with multiple nucleation and nuclear wrinkling. Inflammatory cells may be present (Table 6.4).

Liquid-based cytology using a thin preparation is superior to Pap smear (Figure 6.11). The liquid is used to screen for papilloma virus. Cancer cervix screening is described in Figure 6.12. This is described in detail in Chapter 38. Other methods of cervical screening are also described in Chapter 38.

TABLE 6.3 Comparison of different classification

Pap Smear (1943)	CIN (WHO 1975)	SIL Bethesda (1988)
I	Normal	Normal
II	Inflammatory	Inflammatory −HPV −ASCUS
III	CIN I	Low SIL
IV	CIN II, CIN III, CIS	High SIL
V	SCC	SCC

ASCUS: atypical squamous cell of undetermined significance; CIN: cervical intraepithelial neoplasia; CIS: carcinoma in situ; SIL: squamous intraepithelial lesion and SCC: squamous cell carcinoma.

TABLE 6.4 Bethesda classification

- Sample—adequate, unsatisfactory
- Squamous cell abnormalities
  - Atypical squamous cells (ASC)
- Atypical squamous cells of undetermined significance (Ascus-U.S.)
- ASC—cannot exclude high grade lesion (Ascus-H)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- Squamous cell carcinoma
- Adenocarcinoma

Source: Bethesda Guidelines.

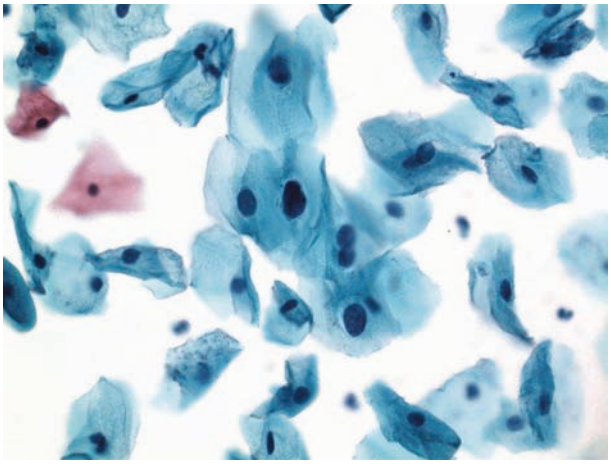

Figure 6.11 Liquid-based cytology classified as epithelial cell abnormality, low-grade squamous intraepithelial lesion (LSIL). Note particularly the cells in the centre. They have enlarged nuclei compared with those in the cells to the left and below. This feature is required for a diagnosis of LSIL. The nuclear contours are irregular. One cell to the right of centre is binucleated, a common feature in LSIL. (From Figure 12-1, Barbara S Apgar, Gregory L Brotzman and Mark Spitzer: Colposcopy: Principles and Practice, 2nd Ed. Saunders: Elsevier, 2008.)

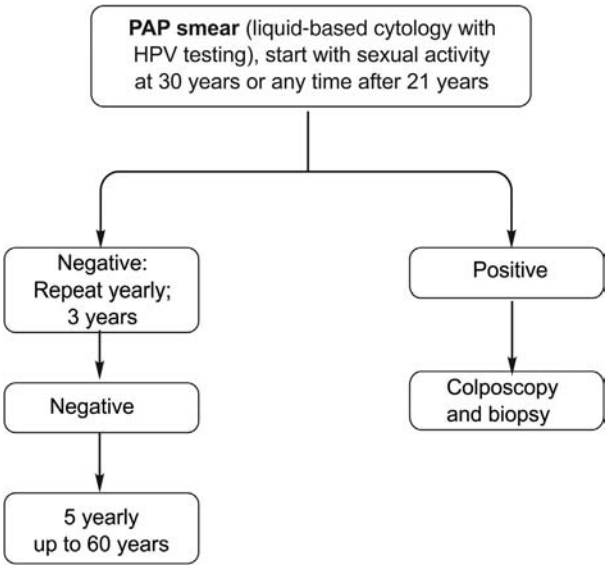

Figure 6.12 Cancer cervix screening.

Cytohormonal Evaluation

The ovarian hormones oestrogen and progesterone influence the vaginal mucosa; thus, the epithelial cells exfoliated in the vagina reflect the influence of the prevailing dominant hormone in the system at that time. The oestrogen-dominated smear appears clean and shows the presence of discrete cornified polygonal squames. The progesterone-dominated smear appears dirty and reveals the predominance of intermediate cells. During pregnancy, the cytology smear shows intermediate cells and navicular cells. After the menopause due to the deficiency of the ovarian hormones, the vaginal *mucosa* thins down and the exfoliated cells are predominantly parabasal and basal types. In human papilloma virus (HPV) infection, one can recognize koilocytes with perinuclear halo and peripheral condensation of cytoplasm. The nucleus is irregular and hyperchromatic (Figure 6.10).

Karyopyknotic index or KPI (maturation index). It is the ratio of mature squamous cells over the intermediate and basal cells. It is more than 25% in proliferative (oestrogenic) phase (Figure 6.13) and low in secretory (progestational) phase (Figure 6.14) and during pregnancy. During pregnancy, a ratio of more than 10% indicates progesterone deficiency. Normally, peak value of KPI is reached on the day of ovulation (2 days after serum E_2 peak).

Uterine Aspiration Cytology

Perimenopausal and postmenopausal women on hormone therapy are now being screened for endometrial cancer. The uterine aspiration syringe or brush is found to be satisfactory for obtaining adequate samples. It can be utilized as an office procedure; about 90% accuracy with no false-positive findings is claimed with this procedure.

Colposcopy

The colposcope is a binocular microscope giving a 10–20 times magnification. It is useful in locating abnormal areas and accurately obtaining directed biopsy from the suspicious areas on the cervix in women with positive Pap smears. This

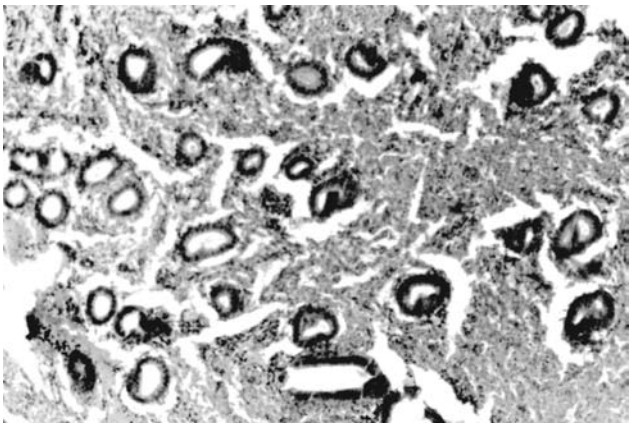

Figure 6.13 Histology of proliferative phase.

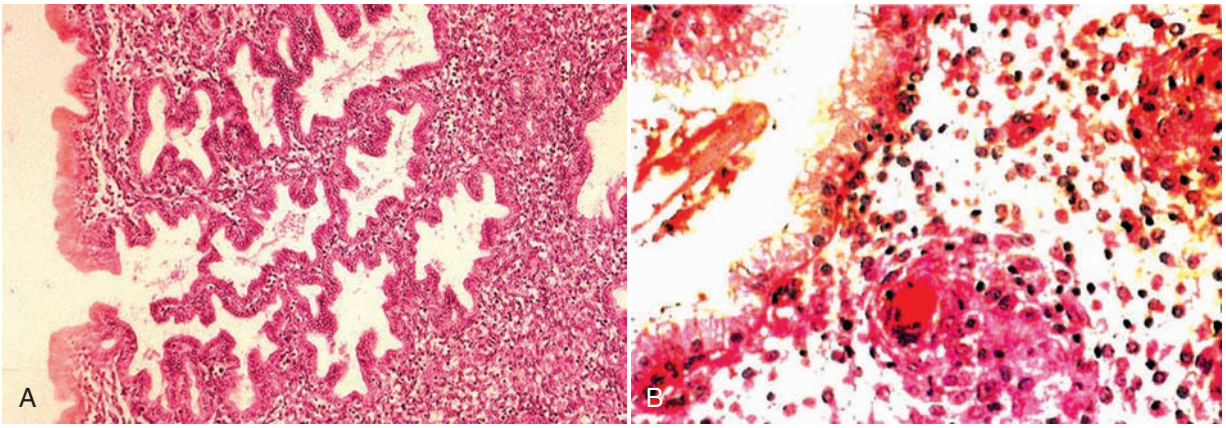

Figure 6.14 **(A)** Histology of secretory phase. (Source: Copyright 2009 by the University of Florida.) **(B)** Midsecretory endometrium.

way the frequency of false-negative biopsy is reduced, so also the need for conization, a procedure that is accompanied with considerable amount of bleeding and morbidity (Ch. 35).

Endometrial Biopsy (Figure 6.14A and B)

An office or outpatient procedure was at one time very popular in the investigations of the female partner for infertility. It is performed in the premenstrual phase. A fine curette is introduced into the uterine cavity to obtain a small strip of the endometrial lining for histopathological examination. With the availability of ultrasonic noninvasive method for detection of ovulation, this procedure is now generally not employed. It is still used if tubercular endometritis is suspected. It is useful in the diagnosis of corpus luteal phase defect.

Hormonal Assays

In present-day practice, it is possible to study the levels of several hormones using radioimmunoassays and/or the ELISA tests. The commonly assayed hormones include FSH, LH, PRL, ACTH, T_3, T_4, TSH, progesterone, oestradiol, testosterone, cortisol, aldosterone, hCG, dehydroepiandrosterone and androstenedione. These assays are used in the diagnosis of menopause, PCOD and prolactinomas, and for monitoring treatment regimes in induction of ovulation and in assisted reproduction.

Ultrasonography

Ultrasonography is a simple noninvasive and painless diagnostic procedure that has the advantage of being devoid of any radiation hazard. The pelvis and the lower abdomen are scanned in both the longitudinal and transverse planes. Generally, this scan is done when the patient's bladder is full as it helps to elevate the uterus out of the pelvis, and displaces the gas-filled bowel loops away, thus providing the sonologist with a window to image the pelvic organs. In most cases, a transvaginal probe can be usefully employed to obtain finer details of the pelvic organs. The bladder need not be full, if the vaginal probe is used. The scan can collaborate the clinical impression or uncover a hitherto unsuspected pathology. Lately, rectal and perineal routes are also available. D3 ultrasound is now capable of providing three-dimensional images of the pelvic organs. Ultrasound is recently available. Ultrasound is also used in certain therapeutic procedures such as in vitro fertilization and aspiration of a cyst or pelvic abscess.

Other Imaging Modalities

Radiological investigation such as hysterosalpingography is utilized for studying the patency of the fallopian tubes in an infertile patient. CT scan and MRI are advanced investigations which determine the extent of tumours and their spread. For details, refer to Chapter 8. Sonosalpingography is employed in women with infertility and when uterine polyp is suspected.

Gynaecological Endoscopy

Both diagnostic laparoscopy and hysteroscopy are established useful tools in the armamentarium of the gynaecologist. For details, refer to Chapter 7 (Endoscopy in Gynaecology).

Aspiration of Pouch of Douglas

Aspiration of pouch of Douglas is required in the diagnosis of the following:

- Pelvic abscess
- Ectopic pregnancy in haematocele
- To detect malignancy in ascites with ovarian cyst

The only therapeutic purpose is to drain the pus in pelvic abscess.

The woman is placed in the lithotomy position and the posterior lip of the cervix drawn downwards and forwards with the vulsellum forceps while the speculum retracts back the posterior vaginal wall. After disinfecting the area,

a long needle attached to an aspiration syringe is inserted into the pouch of Douglas, and aspiration done. The examination is best done in the operation theatre under full aseptic precaution with all readiness to proceed to laparoscopy or laparotomy if indicated.

Pregnancy Test

The first morning sample of urine is used in rapid immunological test to confirm pregnancy, by detecting the presence of human chorionic hormone. The pregnancy test becomes positive by the beginning of sixth week, from the last menstrual period.

Key Points

- Most gynaecological diseases can be diagnosed by a proper and detailed history and pelvic examination.
- A wide range of investigations are now available with the gynaecologists which finally confirm the diagnosis, detect the extent of the disease and help in planning the management.
- Pap smear is now an established screening procedure in carcinoma cervix.
- Ultrasound examinations have simplified gynaecological diagnosis.
- Selective gynaecological endoscopy helps definitive diagnosis.
- Hormonal assays are necessary in in vitro fertilization and various hormonal disturbances.
- CT and MRI have added to the imaging modalities.

Self-Assessment

1. Enumerate the details of history taking in gynaecological history taking.
2. Outline details of documentation of physical examination observations in practice.
3. What information can be obtained on routine speculum examination?
4. Describe the importance of Pap smears in clinical practice.
5. What is the role of endoscopy and ultrasonography in the clinical practice of gynaecology?

Suggested Reading

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Chapter 7 Endoscopy in Gynaecology

CHAPTER OUTLINE

Endoscopes are telescopes designed to view the interior of body spaces or viscera. Although attempts at endoscopy date back to over a hundred years, the potential of this method as diagnostic and therapeutic tools was appreciated and came to the forefront only in the last three decades. When used appropriately, endoscopic surgery offers the advantages of a more accurate diagnosis, less invasiveness, reduced pain, faster recovery and shortened hospital stay or a day care. Advances in instrumentation and techniques now enable the endoscopist to accomplish several operative procedures hitherto performed only by open surgery, including cancer surgery. Some of the advances are harmonic scalpel, suture materials and laser.

Minimal invasive surgery (MIS) implies avoiding an abdominal scar, minimal handling of pelvic and abdominal organs, less pain and thereby fast recovery.

Advantages of laparoscopy: (a) lesser pain, (b) few analgesics, (c) short hospital stay, (d) quick return to daily work, (e) no scar—no scar hernia, (f) good cosmetic and (g) less pelvic adhesions.

Disadvantages: (a) Longer procedure, more anaesthesia, expensive, expertise required.

Laparoscopy

Laparoscopy was developed by the 1970s, and operative laparoscopy has started gaining ground in the last two decades. Advances in technology led to the development of high-resolution cameras, video laparoscopy, the development of safe instruments permitting the use of electrical and laser energy and harmonic scalpel for cutting and cauterizing tissues or achieving haemostasis.

Its role in the management of infertility stands undisputed, so also the benefits of laparoscopy over laparotomy of being minimally invasive and having a lower incidence of adhesion formation and infection renders endoscopy to be an attractive alternative procedure in many gynaecological diseases.

Despite these advantages, there are potential limitations. For example, the exposure to the operative field may be reduced, manipulation of the pelvic viscera often restricted and tissue apposition during suturing not as accurate. Moreover, the feel of tissues experienced by the surgeon during open surgery lacks during endoscopic surgery.

The endoscopic surgeon in the making has to go through supervised training and acquire the skills over a period of time. There is a learning curve during which the endoscopist in training understands the limitations of the procedure and knows when to stop. Thereafter, the incidence of complications during endoscopy begins to decline and progressively more complex procedures can be successfully undertaken.

Laparoscope (Figure 7.1). Laparoscope is a rigid telescope varying in diameter between 4 and 10 mm and it is 30 cm long, incorporating an optical system as a means of illumination. The light is transmitted from an external source to the distal lens by means of fibreglass cables. Light source of 300 W is used for illumination of abdominal cavity. Photography requires light source of 1000 W. Other instruments include Veress needle, trocar and accessories to perform therapeutic procedures (Figure 7.1). A long Veress needle is available for obese woman and for posterior colpopneumoperitoneum. CO_2 machine to create pneumoperitoneum is specially

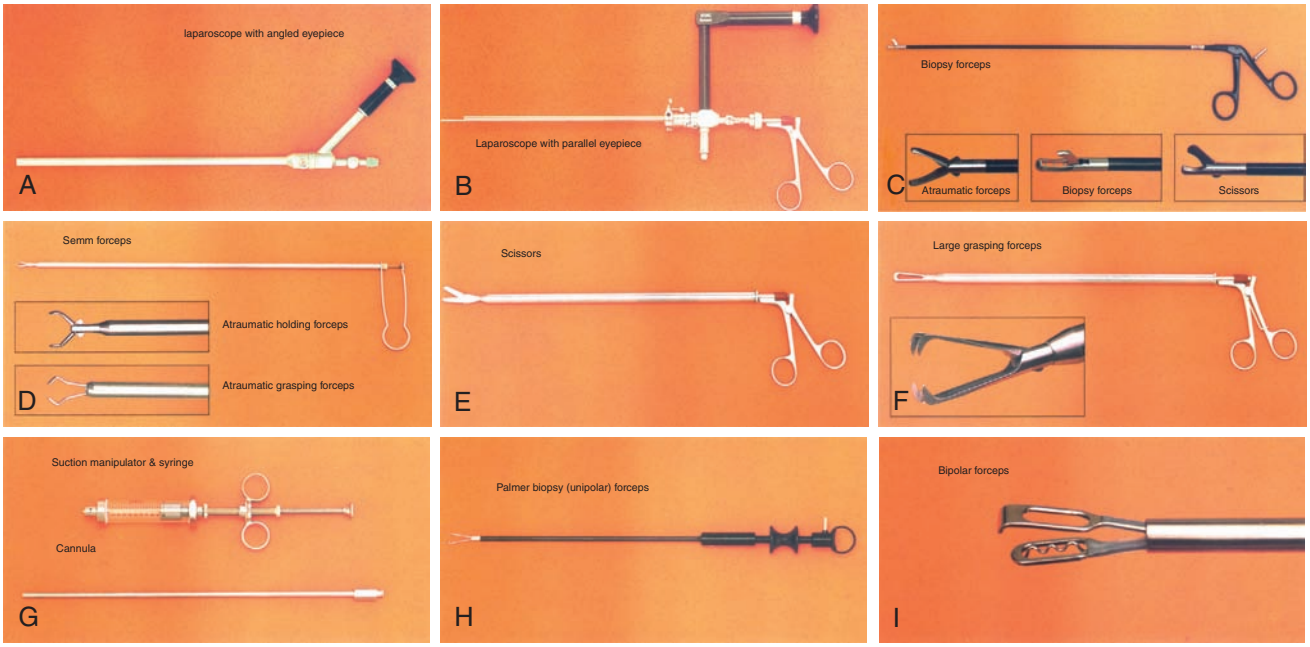

Figure 7.1 Laparoscope and commonly used accompanying instruments. **(A)** Laparoscope with angled eyepiece. **(B)** Laparoscope with parallel eyepiece. **(C)** Biopsy forceps. **(D)** Semm forceps. **(E)** Scissors. **(F)** Large grasping forceps. **(G)** Suction manipulator and syringe. **(H)** Palmer biopsy (unipolar) forceps. **(I)** Bipolar forceps.

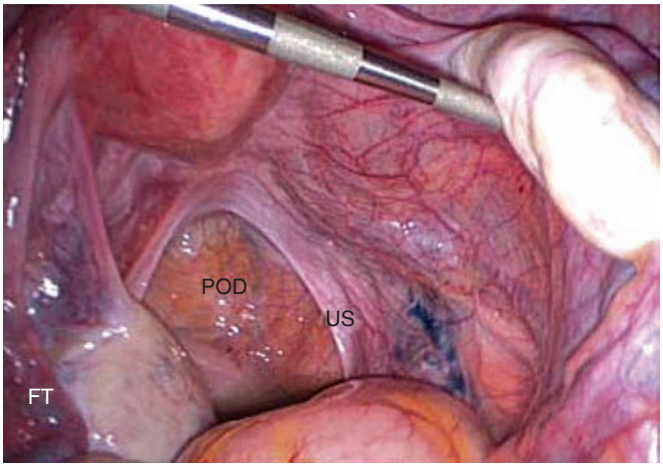

Figure 7.2 View of the pelvis with uterus anteverted from laproscopy. Right ovary turned over with probe to expose right pelvic sidewall. (FT, fallopian tube; POD, pouch of (From Figure 1-1. Douglas; US, uterosacral ligament.) Robert W Shaw, David Luesley and Ash Monga: Gynaecology, Fourth Edition, Elsevier, 2011.)

designed for laparoscopy. About 100 mL/min is instilled into the peritoneal cavity, maintaining intraperitoneal pressure below 15 mmHg. About 1000 mL is required for adequate pneumoperitoneum (Figure 7.2).

Indications for Laparoscopy

The laparoscope has emerged as an invaluable tool in the armamentarium of the gynaecologist, both for diagnostic and for therapeutic uses (Table 7.1).

Diagnostic Laparoscopy

The common indications for diagnostic laparoscopy include the following (Figures 7.3–7.7).

TABLE 7.1 Indications of laparoscopy

Diagnostic	Therapeutic
• Infertility—tubal patency adhesions, pathology uterine disease ovulation, PCOD • Ovary—PCOD size, volume adhesions • Pelvic endometriosis • Chronic pelvic pain • Ovarian malignancy tumour nature benign, malignant extent, staging Ca second-look surgery • Uterus—malformations, absent uterus, septate fibroid, adenomyosis perforation during surgery • Tubal—infertility PID—ectopic pregnancy • Pelvic tuberculosis • Prior to tuboplasty to study the feasibility	• Pelvic adhesiolysis • Ablation of endometriosis • PCOD—drilling • Ovarian cystectomy ovariotomy, surgery • Lymphadenectomy in cancer cervix uterus, ovary • Myomectomy • Myelinolysis • Gift in infertility • Septate uterus • Ectopic pregnancy • Tuboplasty • LAVH • Hysterectomy • Removal of hydrosalpinx and pyosalpinx • Vault prolapse • Stress incontinence • LUNA (laparoscope uterosacral nerve ablation in dysmenorrhoea)

Infertility and Tubal Disease. Laparoscopy is indicated if hysterosalpingography reveals abnormal or ambiguous findings. Laparoscopy can reveal peritubal adhesions not detectable by hysterosalpingography. Chromopertubation using methylene blue dye is a part of diagnostic laparoscopy for infertility evaluation to determine tubal patency.

A band is recognized extending from the right tube to the under surface of the liver in pelvic inflammatory disease (PID) caused by gonococcal and chlamydia infection. This goes by the name Fitz-Hugh–Curtis syndrome. The relationship between the ovary and the ovarian fimbria

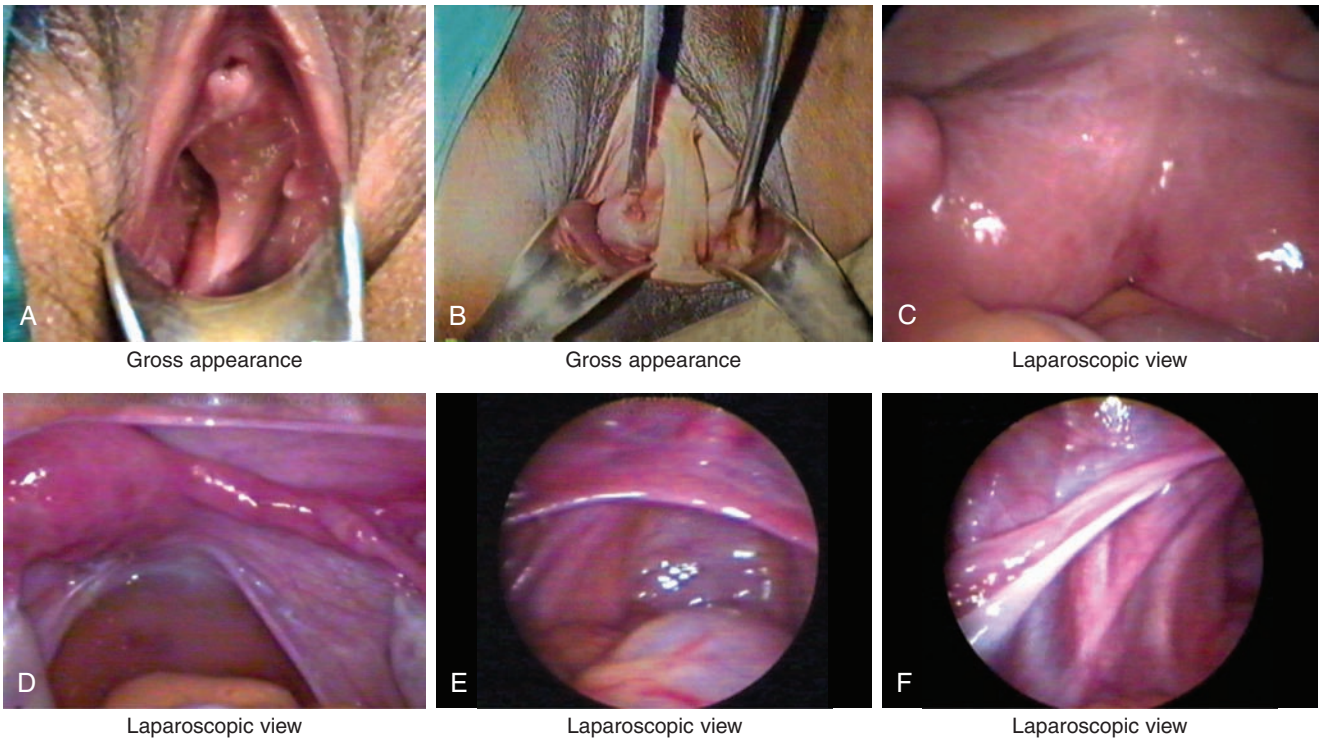

Figure 7.3 **(A)** to **(F)** Gross and laparoscopic appearance of genital tract abnormalities. **(A)** Septate vagina. **(B)** Two cervices with two vaginas. **(C)** Bicornuate uterus. **(D)** Bicornuate uterus with rudimentary horn. **(E)** Rudimentary uterus (RKH syndrome). **(F)** Streak ovary.

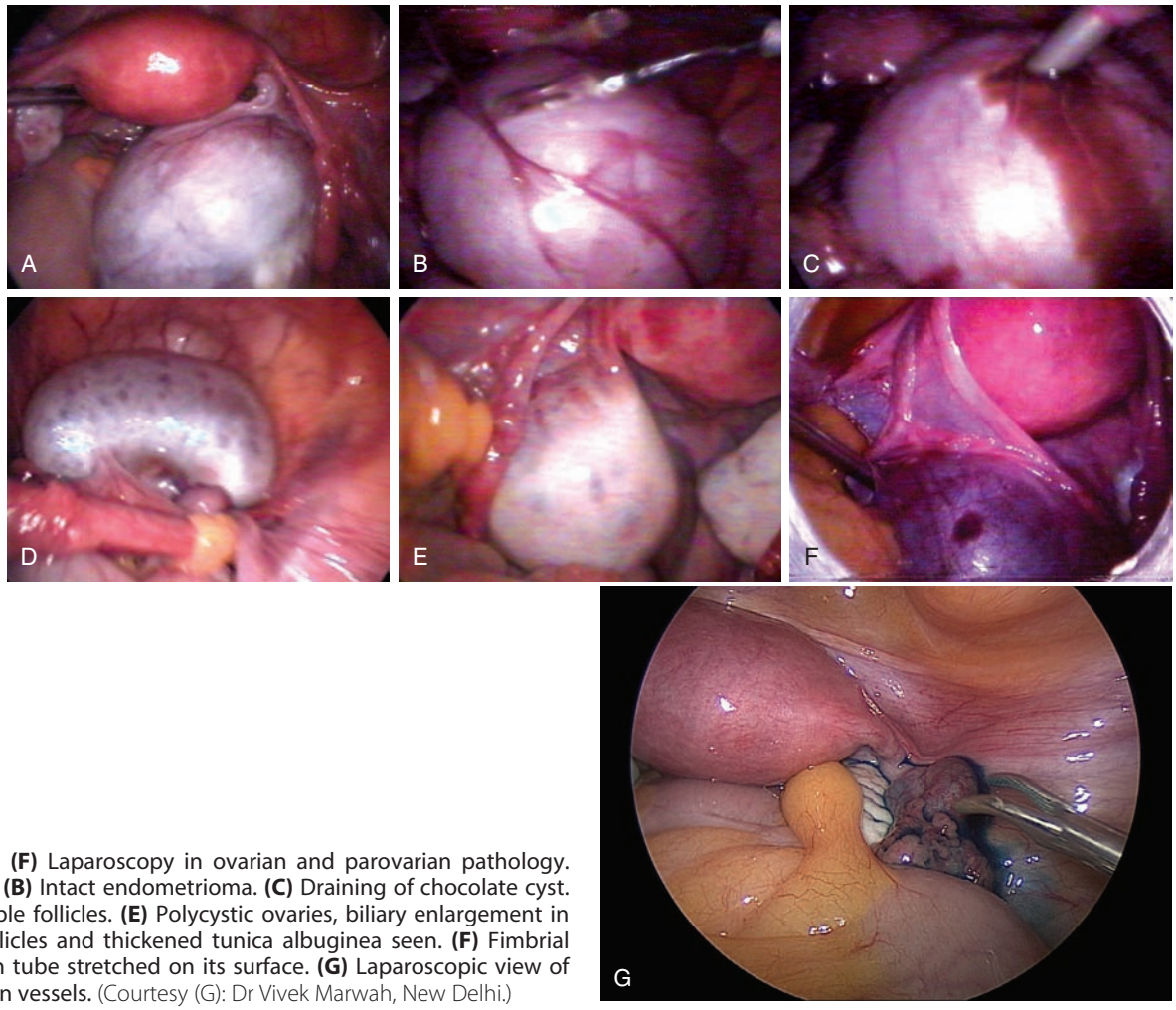

Figure 7.4 **(A)** to **(F)** Laparoscopy in ovarian and parovarian pathology. **(A)** Dermoid cyst. **(B)** Intact endometrioma. **(C)** Draining of chocolate cyst. **(D)** PCOD—multiple follicles. **(E)** Polycystic ovaries, biliary enlargement in size—multiple follicles and thickened tunica albuginea seen. **(F)** Fimbrial cyst with fallopian tube stretched on its surface. **(G)** Laparoscopic view of the twisted ovarian vessels. (Courtesy (G): Dr Vivek Marwah, New Delhi.)

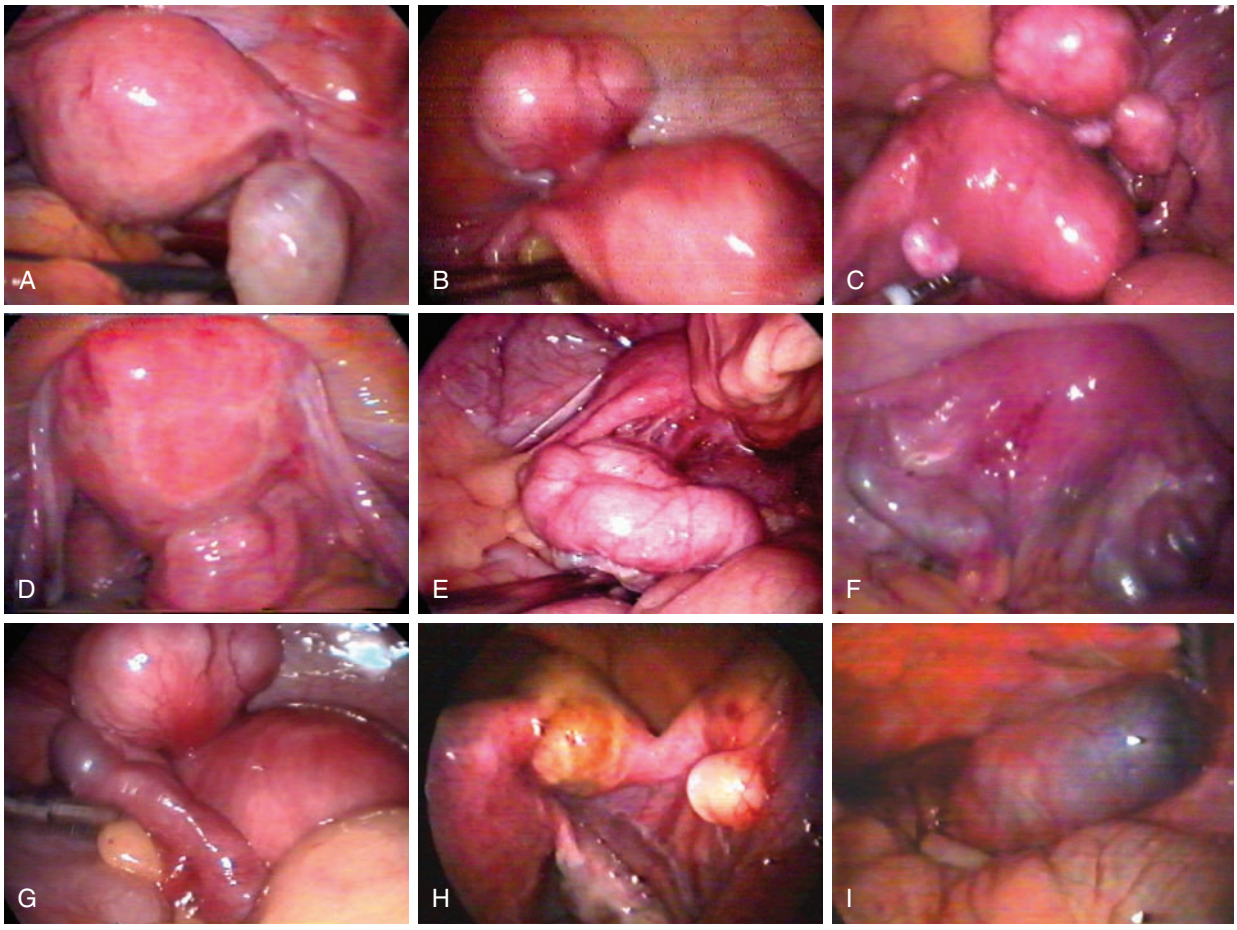

Figure 7.5 **(A)** to **(I)** Laparoscopy in uterine and tubal pathology. **(A)** Diffusely enlarged uterus due to adenomyosis. **(B)** Anterior wall subserous pedunculated fibromyoma of the uterus. **(C)** Multiple fibroids—uterus subserous and intramural. **(D)** Posterior isthmical fibromyoma. **(E)** Tubal pyosalpinx. **(F)** Bilateral tubal hydrosalpinx. **(G)** Tubo-ovarian mass. **(H)** Genital tuberculosis—tuberculous pyosalpinx. **(I)** Unruptured tubal ectopic pregnancy.

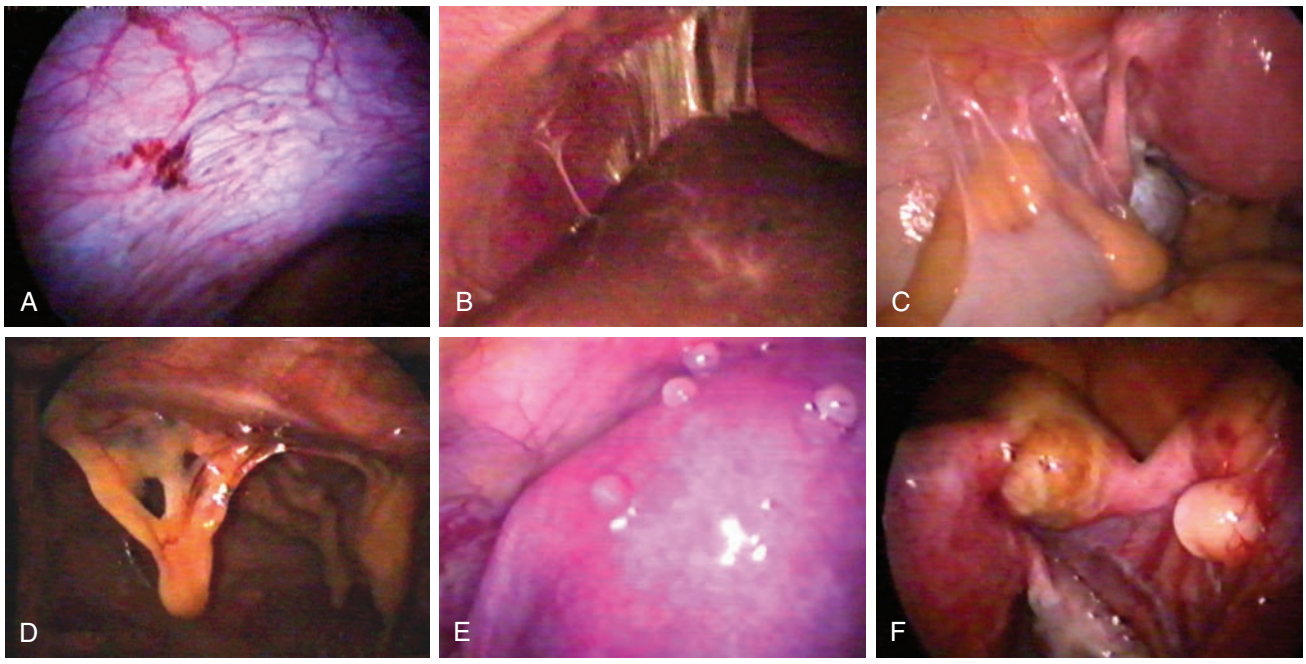

Figure 7.6 **(A)** to **(I)** Laparoscopy: Miscellaneous. **(A)** Endometriosis: peritoneal implant. **(B)** Chronic PID: perihepatic adhesions. **(C)** Chronic PID: pelvic adhesions. **(D)** Abdominal Koch's disease: peritoneal adhesions. **(E)** Genital Koch's disease: tubercles on the uterine serosa. **(F)** Genital Koch's disease: beaded tuberculous fallopian tube.

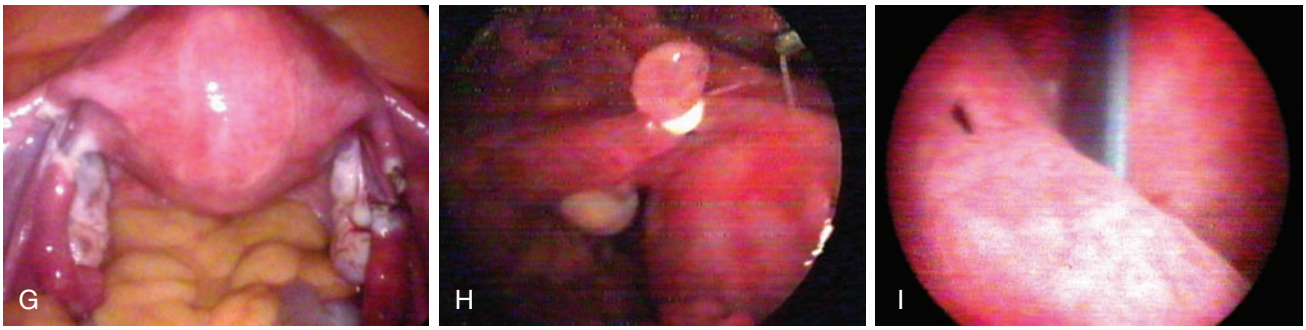

Figure 7.6, cont'd **(G)** Family planning: tube occlusion with bipolar cautery and cutting. **(H)** Family planning: tube occlusion with silastic band. **(I)** Cystoscopy: ureteric orifice seen—probe in vesicovaginal fistula.

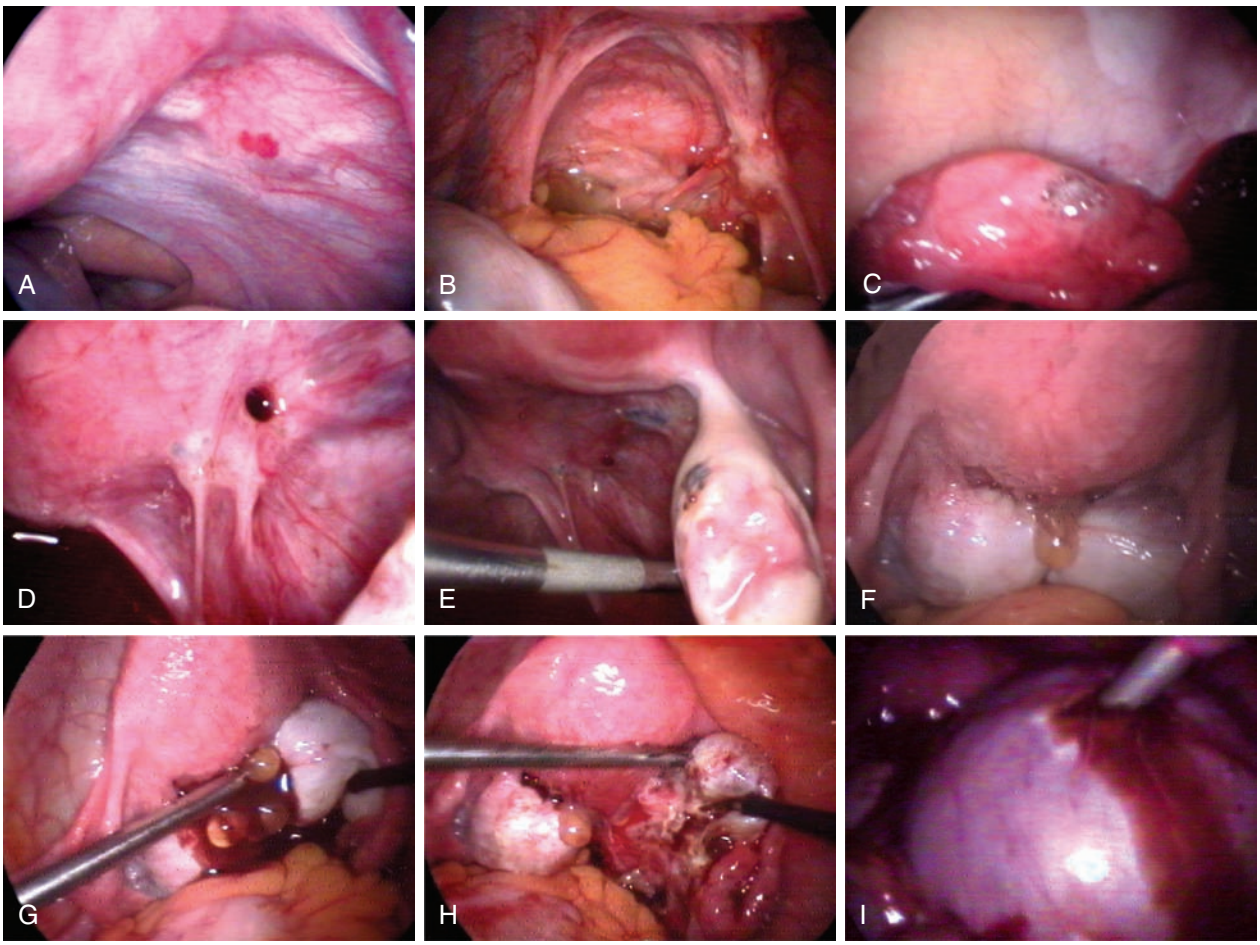

Figure 7.7 **(A)** to **(I)** Laparoscopic appearance of endometriosis—manifestations. **(A)** Superficial peritoneal flame-like patch. **(B)** Nodular uterosacral endometriosis with adhesions. **(C)** Endometriotic patch on anterior surface of the uterus. **(D)** Endometriotic nodule and powder burn marks in ovarian fossa. **(E)** Superficial endometriosis on ovarian surface and ovarian fossa. **(F)** Endometriotic adhesions binding down the ovaries into the pouch of Douglas 'Kissing-Ovaries'. **(G)** Chocolate material drained from small chocolate cyst. **(H)** Endometriotic adhesions posterior uterine surface and the ovaries. **(I)** Large chocolate cyst of the ovary (endometrioma) chocolate material drained.

can be studied in infertility. The laparoscopy decides the best treatment between tuboplasty and IVF (in vitro fertilization). Salpingoscopy through laparoscope studies the ampullary portion of the tube and extent of tubal damage.

Endometriosis. In about 20% of patients with infertility, endometriosis is present without any symptoms. It remains undetected until demonstrated at laparoscopy.

Chronic Pelvic Pain. In patients complaining of chronic pelvic pain, not responding to usual therapeutic measures, laparoscopy is indicated. Often unsuspected pathology is brought to light such as adhesions, cysts, chronic PID, tubal hydrosalpinx, endometriosis, pelvic congestion, window tears in the broad ligaments and varicosity of the pampiniform plexus of veins. Even a negative finding is valuable to reassure a patient that there is no pelvic pathology.

'Conscious pain mapping' helps to identify the organ which causes pain.

Ovarian Disorders. Most reproductive endocrine disorders of the ovaries do not need a diagnostic laparoscopy, ovarian surgery or biopsy. Ultrasonography and blood hormonal assays usually suffice in arriving at a diagnosis. However, in case of polycystic ovarian disease (PCOD) laparoscopy is useful to confirm the diagnosis, and to further investigate patient for other causes of infertility. The operation of ovarian drilling is performed to improve the results of ovulation induction therapy. Ovarian cyst, extent and spread of malignant tumour can be assessed by laparoscopy. Second-look surgery is now replaced mostly by ultrasound, MRI and tissue markers (Ch. 37).

Suspected Adnexal Masses. Ultrasonography, CT scan or MRI help in detecting adnexal masses and establishing their site of origin. However, it is not possible to identify a pedunculated fibroid from a solid ovarian tumour, and laparoscopy is necessary. Laparoscopy helps to distinguish a pelvic mass as uterine in origin, commonly a fibromyoma from an ovarian mass. An asymptomatic fibroid may require observation whereas an ovarian solid mass needs prompt surgical removal.

Suspected Ectopic Pregnancy. In a patient with abdominal pain, irregular menstruation and a positive pregnancy test, a laparoscope can detect an ectopic pregnancy even before it has ruptured and enable conservative surgery, thereby preserving her future reproductive potential.

Pelvic Inflammatory Disease. In PID, the diagnosis can be confirmed on laparoscopy. Peritoneal fluid or pus can be obtained for culture, and other causes such as acute appendicitis and pelvic tuberculosis considered in the differential diagnosis can be ruled out with certainty.

Ovarian Malignancy. In advanced ovarian malignancy, a laparoscopy is useful in staging the disease, in obtaining a biopsy from the affected tissue, which confirms the type of tumour and helps the oncologist to select chemotherapy or radiotherapy as the alternative therapy in an inoperable case.

Ascites. In ascites, laparoscopy helps to obtain ascitic fluid for cytology and biochemical analysis. It also helps to determine the cause of ascites as attributable to tumour, tuberculosis or hepatic cirrhosis. A biopsy from the tumour establishes the diagnosis. Ultrasonic-guided aspiration of fluid and biopsy is however a simpler procedure as compared to laparoscopy.

Tuberculosis. Genital tuberculosis accounts for 5% of patients of unexplained infertility in our country. The fallopian tube is the most commonly affected site. Presence of tubercles on the serosa, multiple constrictions, thick rigid tubes, presence of violin-string adhesions and tobacco-pouch appearance of the terminal parts of the tubes should arouse suspicion. Presence of tubercles on the bowel serosa or peritoneal surface can be biopsied to arrive at the diagnosis.

Uterine Abnormalities. Laparoscopy reveals uterine abnormalities:

- The Müllerian anomalies such as absent uterus as in cases of Rokitansky–Küster–Hauser (RKH) syndrome, bicornuate uterus, septate or presence of a rudimentary horn, testicular feminizing syndrome.
- Laparoscopy can distinguish between a septate uterus and a bicornuate uterus.
- An enlarged uterus due to fibromyomas or adenomyosis can be diagnosed.
- Adhesions to the uterus and its retroverted fixity.

Uterine perforation during MTP/D&C can be confirmed or refuted laparoscopically, and decision made regarding the need for laparotomy.

Inspection of the Pouch of Douglas. This can be inspected, often endometriosis is present at this site, so also adhesions to the rectum present. This can be a site of pelvic abscess and ovarian metastasis.

Operative Laparoscopy

Minimally invasive surgery is replacing conventional surgery as the procedure of choice in selective gynaecological surgeries.

General Indications. Pelvic adhesions. These adhesions are often postinflammatory, postsurgical or endometriotic in nature. Laparoscopic adhesiolysis restores the anatomy of pelvic organs, their mobility, and relieves pain and discomfort arising out of binding of the organs by adhesions. Pelvic endometriosis may affect many pelvic structures such as the ovaries, tubes, uterosacral ligaments, serosal surface of the uterus, pelvic peritoneum and the pouch of Douglas, as also the rectum, bladder and ureters. Adhesiolysis is done by ablation with cautery, laser or surgical excision of the lesions within the limits of safety and relieves symptoms.

Adhesiolysis is especially required in tubal infertility to restore the patency and mobility of the fallopian tubes and its fimbria.

Ovaries. The various MIS on ovaries are:

- PCOD. The medical hormonal therapy cures PCOD in many women. Those who fail to respond and in infertile women, laparoscopic puncture of cysts by cautery or laser improves the response to hormonal ovulation stimulation, avoids hyperstimulation syndrome and improves the fertility rate to 60–70%. However, because of possible subsequent adhesion formation and thereby impaired tubal fertility, women are advised to try conception in the first year of ovarian puncture.
- It is strongly recommended that no more than four cysts should be punctured in each ovary. More punctures may

increase the ovarian adhesions and ovarian destruction leading to premature menopause later.

- Ovarian cyst. A simple cyst less than 5 cm is usually a functional cyst, and it disappears in 3 months' time and needs only observation. A large benign cyst can be aspirated laparoscopically and fluid sent for cytology. The cyst wall is then peeled off by aqua suction and tissue sent for histopathology.
- Chocolate cyst. The chocolate cyst is incised, the content aspirated and the cyst wall cauterized or peeled off (Ch. 38). Pelvic endometriosis is also ablated.
- GIFT (gamete intrafallopian transfer) technique in assisted reproduction is performed laparoscopically by placing 2 ova and 50,000 sperms at each ampullary portion in an infertile woman with patent tubes.
- Second-look surgery laparoscopically is undertaken following primary surgery and a complete course of chemotherapy for ovarian cancer, before deciding if further chemotherapy or excision of residual tumour is required. Lately, however, tissue markers are relied upon and this procedure is avoided (Ch. 37).
- Pelvic lymphadenectomy is now performed laparoscopically in early cancer cervix and followed by vaginal hysterectomy or trachelectomy. This inflicts less surgical morbidity and allows quicker recovery especially in an obese woman.

Expert oncologists are now performing Wertheim's hysterectomy laparoscopically safely with equally good results.

The uterus. Operative procedures on the uterus include myomectomy, laparoscopy-assisted vaginal hysterectomy (LAVH), excision of a rudimentary horn, and Wertheim's radical abdominal hysterectomy for cancer cervix.

- Myomectomy is best planned for young women. Ideally it is rewarding in cases with not more than four fibroids, preferably subserous, and of moderate size not exceeding about 5.0 cm in size. After enucleating the myomas from their beds, the cavity is obliterated with interrupted apposing endosutures to achieve haemostasis and prevent adhesion formation. Large fibroids may be removed by morcellation or through a small suprapubic incision. Small myomas can be removed piecemeal after shredding (myelolysis) or by the vaginal route through the posterior colpotomy incision (Ch. 29).
- LAVH is performed in women in need of a hysterectomy for benign conditions (myomas, adenomyosis, menorrhagia and abnormal uterine bleeding [AUB]) and in situ cancer of the cervix in whom there is no descent of the uterus to facilitate vaginal surgery, and in women over the age of 45 years in whom concomitant removal of the ovaries is desirable. The purpose of LAVH is to convert an abdominal hysterectomy to vaginal hysterectomy or a difficult vaginal hysterectomy to an easy surgery. Realizing that LAVH carries a higher morbidity in terms of prolonged anaesthesia and restricted view, many laparoscopists now perform vaginal hysterectomy even on undescended uterus and are able to remove both the ovaries from below as well.

Other uterine surgeries done under laparoscopic guidance are excision of uterine septum and synechiae in Asherman syndrome. A rudimentary noncommunicating horn may be the site of a haematometra, ectopic pregnancy or torsion. Laparoscopic removal is feasible in such cases.

Oncologists now perform Wertheim's hysterectomy laparoscopically (radical abdominal hysterectomy and bilateral extraperitoneal dissection and excision of the iliac and pelvic lymph nodes for cancer of the cervix).

Fallopian tube. The most common operation performed on the tube is sterilization for family planning. The tubal blockage is achieved through occlusion with 'Falope rings' or 'Filshie clips'.

An early unruptured ectopic pregnancy can be treated effectively laparoscopically. The surgeon may attempt milking out the gestational sac, particularly so if it is close to the fimbrial end. An ampullary ectopic pregnancy can be treated by linear salpingostomy and enucleating the tubal gestational sac. An early unruptured ectopic pregnancy can be treated by local injection of methotrexate into the gestational sac. All these procedures are conservative measures aimed at preserving the woman's reproductive potential.

Hydrosalpinx of the tube can be treated by lateral salpingostomy and fimbrioplasty with eversion of the inverted fimbriae by fashioning a cuff. In blocked tubes, segmental resection and anastomosis has been successfully performed laparoscopically. Hydrosalpinx is also removed prior to IVF to improve the pregnancy rate (Ch. 17).

Other indications

Amongst the other operative procedures accomplished laparoscopically, the following deserve to be noted.

Genital prolapse. Conservative procedures for second-degree uterine prolapse such as abdomino-cervicopexy and uterine sling operation have been successfully performed laparoscopically. Vaginal vault prolapse is corrected by sacropexy.

Stress urinary incontinence. The operation of colposuspension has been successfully performed laparoscopically. Both the Marshall–Marchetti–Krantz procedure and the Burch operation can be undertaken laparoscopically.

Pelvic floor repair. This has been performed laparoscopically to restore the anatomy of the pelvic floor.

Dysmenorrhoea. Laparoscopic uterosacral nerve ablation (LUNA) aims at cautery and cutting of both the uterosacral ligaments close to their uterine attachment. The uterine pain-carrying nerve fibres travel along the uterosacral ligaments to reach the pelvic autonomic ganglia. Division of these ligaments interrupts the pain pathway and provides relief. However, there is risk of damaging the ureters, and in due course of time, the nerves regenerate, so that dysmenorrhoea often returns. The presacral nerve lies in front of the sacral promontory. Exposing the nerve bundles laparoscopically and dividing the same is possible. However, with the availability of efficient analgesic drugs, there is seldom any need to have recourse to such drastic surgical procedures except in endometriosis.

Others. Procedures such as repair of herniae, appendicectomy and pelvic lymph node biopsies, etc. are being performed laparoscopically.

Technique of Laparoscopy

Laparoscopy has become a safe MIS; therefore, it is employed more liberally than before, both for diagnostic and for certain therapeutic procedures. However, bearing in mind that a rare but a serious complication may develop during therapeutic procedures such as myomectomy, hysterectomy and ablation of endometriosis, certain preoperative preparations are required. These are:

- Fibroid. It is desirable to shrink a huge fibroid to reduce bleeding and make it easier to perform myomectomy. This is done by gonadotropin-releasing hormone (GnRH) injection administered monthly for 3 months (Ch. 27).
- Bowel preparation and intestinal antibiotics (metrogyl) are safe precautions in case bowel injury occurs.
- Bladder should remain empty throughout the procedure using a catheter.
- Systemic antibiotics should be started a day before surgery.
- Signature for open surgery should be obtained in the case of complication or inability to complete the procedure laparoscopically.

Procedure

- Whereas diagnostic procedure may be carried out under sedation and local anaesthesia, the therapeutic procedure always requires general anaesthesia because of prolonged time taken and intra-abdominal manipulations required.
- Position. Semilithotomy and slight Trendelenburg position.
- Pneumoperitoneum is created with a Veress needle using carbon dioxide (CO_2) gas through a small infraumbilical incision. Air and nitrous oxide (N_2O) should not be employed, because of the risk of air embolism in the former and combustion with N_2O if electrocautery is used. The proper pneumoperitoneum is confirmed by noting the uniform distension of the abdomen and Palmer test, which consists of injecting 5 mL of saline through Veress needle. Failure to aspirate saline indicates proper placement of the needle.

Continuous flow of CO_2 is maintained at the rate of 100 mL/min and pressure at 15–25 mm Hg. Trocar and laparoscope insertion follow, through the same skin incision. Under fibre optic illumination, the pelvic organs are inspected, and feasibility of the procedure under consideration confirmed.

- Bipolar cautery is safer than monopolar cautery as it does not spread the burn to the surrounding structures. Laser is even safer and does not form postoperative adhesions, but is expensive. Lately, harmonic scalpel is available and, though very expensive, is very safe and cuts the tissues well.

Additional portals and instruments are used in therapeutic procedures. Suction and irrigation are also provided to clear the blood and fluid from the abdominal cavity.

At the end of the procedure, after making sure haemostasis is secured and no gut injury has occurred, gas is expelled from the peritoneal cavity and the skin cuts sutured.

During the procedure, the uterus is manipulated in different directions by using uterine manipulator inserted transcervically before the start of the surgery.

Complications

Complications (0.5–1%) are observed in minor procedures, but the incidence as high as 5–15% is reported with major procedures. Death is reported in 0.08:10,000 cases.

Major complications are as follows:

- Cardiopulmonary arrest and gas embolism
- CO_2 causes acidosis, arrhythmia, cardiac arrest
- Haemorrhage
- Cautery burns to various viscera
- Sepsis
- Injury to the bowel, small intestine, blood vessels, bladder and ureter with the sharp instruments and burn injuries
- Failure to complete the procedure

Cardiopulmonary arrest is an anaesthetic complication. Embolism occurs with use of air, but excess CO_2 and accidental insertion of Veress needle into a blood vessel can also cause embolism. This mishap is avoidable if pneumoperitoneum is checked by Palmer test.

Haemorrhage. Injury to the epigastric vessel occurs during insertion of the Veress needle and trocar. Injury to the aorta, inferior vena cava, iliac vessels and mesenteric vessels mainly occurs with a sharp instrument such as a trocar. Prolonged surgery during myomectomy can also cause loss of blood.

Careful insertion of the trocar can avoid the injury. Uncontrolled haemorrhage requires laparotomy.

Cautery burns. Accidental burn to the surrounding structures occurs with unipolar cautery and sometimes with laser. The injury may go unnoticed during surgery and may not manifest clinically as peritonitis for 24 h or even more. The abdominal distension and vomiting are then the first indications of gut injury and peritonitis. The bowel injury requires laparotomy, resection of the bowel and end-to-end anastomosis.

Sepsis is avoided by preoperative antibiotics and aseptic precaution.

Traumatic injury to the viscera and ureter occurs with sharp instruments (bladder, ureter and intestines) or burn.

Other Complications

The other complications include surgical emphysema and haematoma.

- Postoperative peritoneal adhesions occur less commonly with laparoscopy than laparotomy, because the viscera

are not handled and are not exposed to air dryness as in open surgery.
- Hernia at the site of portals with omental protrusion rarely occurs. The uterine perforation with the uterine manipulator does not normally require laparotomy. Metastatic cancer has been reported at the portals.
- Emergency therapeutic procedures done laparoscopically for torsion and haemorrhage of ovarian cyst or rupture of endometrioma carry greater risk than planned surgery since preoperative preparation may not be adequate.
- Failed procedure. Due to adhesions, extensive pelvic lesions or uncontrolled haemorrhage, laparoscopic procedure needs to be abandoned and converted to laparotomy. The prior signature to this effect avoids medicolegal problems.

Contraindications to Laparoscopy

- Extreme obesity makes laparoscopic procedure and pneumoperitoneum difficult if not impossible. Alternatively, pneumoperitoneum can be created through posterior colpocentesis.
- Cardiac and respiratory diseases contraindicate Trendelenburg position and CO_2 pneumoperitoneum.
- Diaphragmatic hernia precludes Trendelenburg position.
- Umbilical hernia. The trocar can injure the bowel if the latter is adherent to the hernial sac.
- Previous abdominal scar also exposes the bowel to injury during trocar insertion.
- Acute pelvic infection can spread during laparoscopy.
- A large uterus (puerperal) and an abdominal tumour can be injured by the sharp instrument.

Advantages of Laparoscopy over Laparotomy

- Avoidance of abdominal scar, wound sepsis and scar hernia.
- Reduced pain and quick recovery.
- Short hospital stay.
- Less peritoneal adhesions postoperatively.

Lately robotic surgery is being attempted.

Hysteroscopy (Figure 7.8)

Hysteroscopy, which started first in 1869 with Pantaleoni as a means of inspecting the uterine cavity, is today functioning as an extended gynaecological armamentarium in various therapeutic procedures. Despite the initial poor light source and nonavailability of distending media, hysteroscopy was not abandoned, and its improvement developed into an important MIS and has led to a resurgence of interest worldwide in recent years.

Hysteroscope. Hysteroscope comprises a rigid 4-mm telescope with Hopkins rod lens optical system having a wide viewing angle and fibre optic illumination cable. Camera and television system enable video study and therapeutic procedures. The sheath is of 5 mm diameter, in the centre of which the telescope is fitted. The uterine cavity is distended with CO_2 at the rate of 70 mL/min and pressure less than 100 mmHg, or with saline, dextrose, Hyskon or glycine 1.5%. The scope is covered by inner sheath for inflow of distending medium, and outer sheath for its outflow.

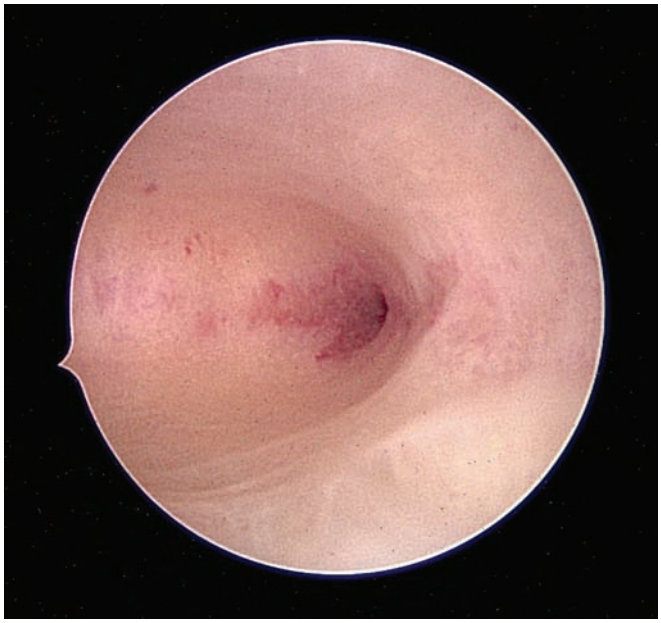

Figure 7.8 Hysteroscopic view of the patent cornual end. (Courtesy: Dr Vivek Marwah, New Delhi.)

Types of hysteroscopes

- Microhysteroscope provides magnification of 30–150 times.
- Contact hysteroscope is a diagnostic tool without distending medium.

Flexible hysteroscopy can be directed to all parts of the uterine cavity and extensive inspection is possible.

Technique

Hysteroscopy should be performed *in the preovulatory phase when the endometrium is thin and bleeding is less likely to occur*. In transcervical resection of endometrium (TCRE), shrinkage of endometrium is achieved with progestogen, danazol or GnRH given continuously for 6–8 weeks prior to surgery. Diagnostic hysteroscopy can be performed under local (paracervical) anaesthesia and sedation, but the therapeutic procedures mandate general anaesthesia (Figure 7.9). The cervical dilation is not always required.

In a postmenopausal woman, cervical or misoprostol vaginal tablet (prostaglandin E_1) will soften the cervix and cervical dilatation with the metal dilator made atraumatic as and when required.

The woman is placed in lithotomy position, and bimanual examination confirms the position and size of the uterus and also rules out adnexal mass. The cervix is dilated up to 4–5 mm. The hysteroscope is connected to the source of distending media. As the distension medium distends the cervical canal and uterine cavity, the telescope is

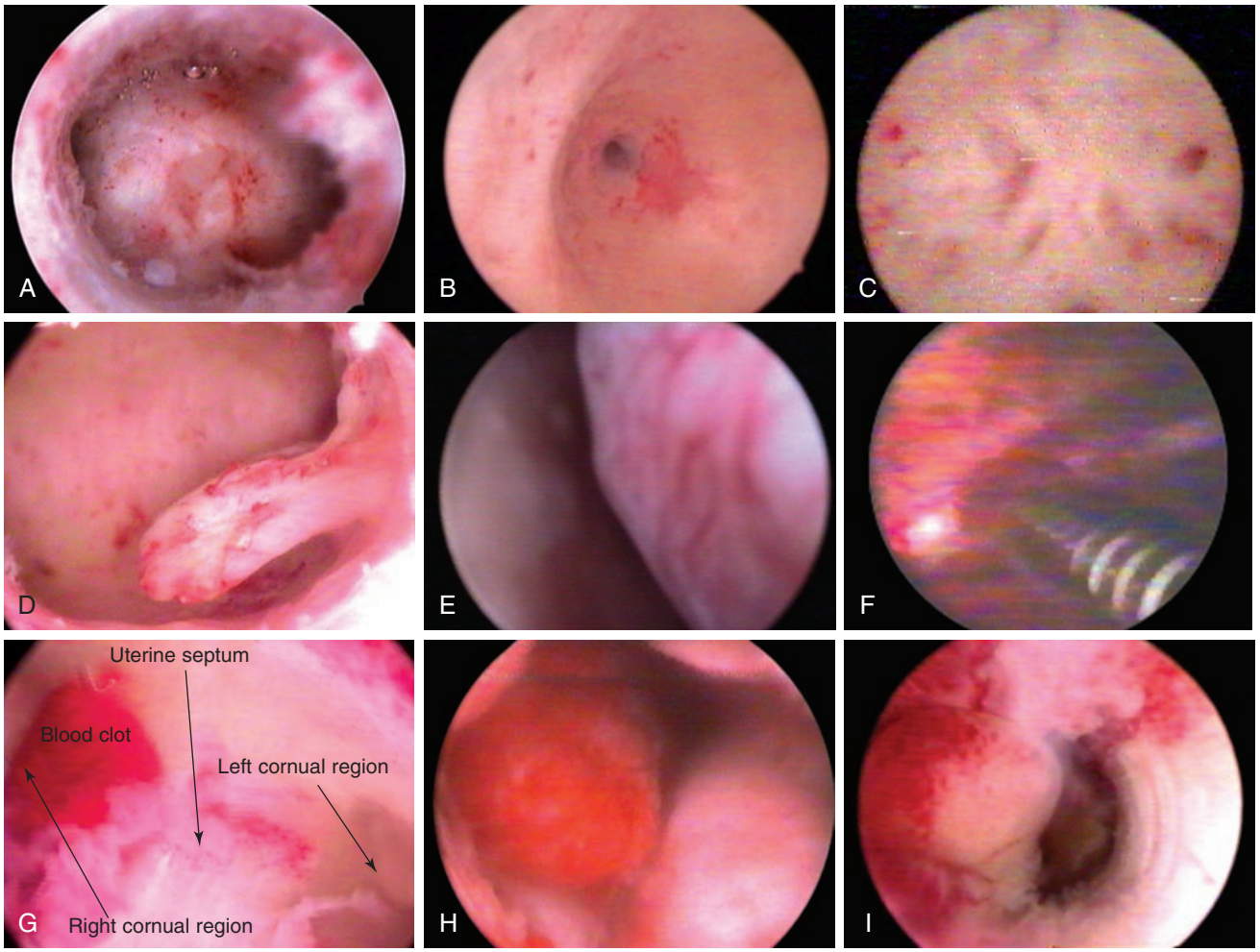

Figure 7.9 **(A)** to **(I)** Diagnostic hysteroscopy. **(A)** Panoramic view of uterine cavity. **(B)** Normal view of left tubal ostium. **(C)** Appearance of uterine wall in adenomyosis. **(D)** Endometrial polyp. **(E)** Submucous fibromyomatous polyp in uterine cavity. **(F)** IUCD-Cu-T in uterine cavity. **(G)** Müllerian anomaly, intrauterine septum. **(H)** Polyp protruding into the endocervical canal. **(I)** Polyp restricted to endocervix.

progressively advanced into the uterine cavity under direct vision. This precaution avoids perforation. The endocervical and uterine lining are studied, and both uterine ostia identified. Gas inflating machine used in laparoscopy should not be employed in hysteroscopy, since high pressure of the former can cause gas embolism.

The hysteroscope is provided with a cervical adaptor which fits snugly on to the cervix and prevents backflow of the uterine-distended medium.

Distending media

CO_2 obscures the vision in presence of blood and cannot be employed in presence of bleeding. Its use is therefore limited only to diagnostic hysteroscopy.

Five per cent glucose is cheap, and is miscible with blood.

Hyskon and glycine are used mostly nowadays. Hyskon (32% Dextrose) coalesces with blood into globules while the medium remains clear.

Normal Appearance of Endometrium

The appearance of endometrium changes with the phase of the menstrual cycle. During follicular phase, the endometrium looks thin and pale with a smooth surface and minimal vascularization; the glands are not easily seen. At ovulation, the endometrium appears oedematous, and the glands are seen. In the luteal phase, the increased vascularity causes oedema, and endometrium looks pink with glands seen. Postmenopausal endometrium is thin, pale in colour. The glands are hardly seen even with higher magnification.

Diagnostic Indications

1. **The study of endocervical mucosal lining.** Panoramic or contact hysteroscope allows inspection of endocervical epithelium in dysplasia and carcinoma in situ of the cervix, to trace the neoplastic process into endocervix and map the extent of neoplasm. A biopsy can be taken from the suspicious areas. Endocervical polyp can also be identified and removed. Staging of cancer of the cervix and endometrium is done by endocervical biopsy.
2. **Congenital malformation of the uterus.** Hysteroscopy combined with laparoscopy confirms whether the uterus is septate or bicornuate, enables the assessment of the capacity of each horn and also studies the depth

and thickness of the septum in planning corrective surgery. The presence of the fundus seen laparoscopically indicates it is a septate uterus. In a bicornuate uterus, the fundus is absent.

3. **Endometrial tuberculosis.** The presence of caseous areas, ulcers or tubercles on the endometrial lining suggests tuberculosis. Selective biopsies are required to confirm the diagnosis or curettage done.
4. **Asherman syndrome.** Hysteroscopy confirms uterine synechiae, type (flimsy or fibrous) and extent of adhesions.
5. **Misplaced IUCD.** Although ultrasound can locate a misplaced IUCD, hysteroscope determines if it is embedded in the endometrium and allows its safe retrieval under direct view.
6. **Endometrial lesions and abnormal uterine bleeding.** Endometrial and placental polyp, submucous fibroid polyp, endometrial hyperplasia and carcinoma can be identified by hysteroscopy. Five per cent acetic acid application renders abnormal endometrium an acetowhite appearance. Selective biopsy and downward extension of endometrial cancer can be assessed and staging done. In a suspected case of cancer, it may be prudent to perform contact hysteroscopy which avoids the risk of peritoneal spillage of cancer cells when distended medium is used. Negative findings for cancer can be very assuring to the woman.
7. **Polyp.** Endometrial polyp may be single or multiple, less than 1 cm in size, and its appearance is identical to the surrounding endometrium. It is usually sessile, immobile and is caused by folds of endometrium in hyperplasia. Therefore, the polyp disappears during follicular phase. On the other hand, a mucus polyp is often bigger than 1 cm, sessile or pedunculated, mobile and permanent. A fibroid polyp is firm, permanent and of various sizes, paler than a mucus polyp.
8. **Cornual tubal blockage.** When hysterosalpingography shows blockage of the corneal end of the tube, hysteroscope enables the falloscope to be inserted into the cornual end and study its patency and mucosa. The decision regarding the feasibility of tubal surgery can then be taken. Cannulation and adhesiolysis are also possible.

Therapeutic Indications

In therapeutic procedures, cervical dilation up to no. 10 may be required to insert the operating channel, and because of prolonged surgery, general anaesthesia is necessary.

Indications

- **Uterine septum** (Figure 7.10) is cut with scissors, cautery, laser or resectoscope. It is not necessary to excise the entire septum, as the fibrous tissue retracts and shrinks after cutting. Bleeding is minimal. Done under laparoscopic guidance, uterine perforation can be avoided. Seventy per cent pregnancy rate is observed following operation.
- **Asherman syndrome**. The adhesiolysis under laparoscopic view prevents uterine perforation. Insertion of IUCD for 3 months and oestrogen therapy prevent re-adhesions and helps to build up the endometrium. Lately, many omit the insertion of IUCD. Resectoscope, scissor, laser or cautery is used to break up adhesions.
- **Embedded IUCD** can be retrieved hysteroscopically.
- **Polypectomy**. The polyp can be grasped and twisted off with the grasping forceps. If the pedicle is broad, it can be ablated by cautery and polyp removed.
- **Submucous fibroid**. Type 0 fibroid (pedunculated) and type I fibroid with 50% intramural location can be morcellated or destroyed by coagulation. The leftover myometrial portion of the fibroid can be removed in the second stage when it protrudes further into the uterine cavity. Infection and bleeding are the risks of this operation.
- **Abnormal uterine bleeding** is now treated by TCRE in premenopausal women and hysterectomy is avoided. Prior to TCRE, malignancy and hyperplasia should be excluded. The endometrium is resected or ablated with cautery, laser or roller-ball coagulation. Sixty per cent become amenorrhoeic and 20% develop oligomenorrhoea at the end of 1 year. Recurrence of menorrhagia by the end of 3 years in 25% requires either repeat TCRE or hysterectomy. The details of TCRE and other ablative procedures are given in chapter on AUB. Partial TCRE is done to procure oligomenorrhoea.
- **New technique of tubal sterilization** using sclerosing agents, cautery or intratubal plugs is not universally accepted and not legalized in India, because of high failure rate, irreversibility of the procedures and complications.
- **Tubal blockage**. Tubal cannulation and breaking up of flimsy adhesions of the cornual end, removal of polyp and balloonoplasty is possible through hysteroscope.
- In IVF programme, it is now routine to perform diagnostic hysteroscope to study the endometrium prior to IVF.
- Intrafallopian insemination in infertility is practiced by a few.

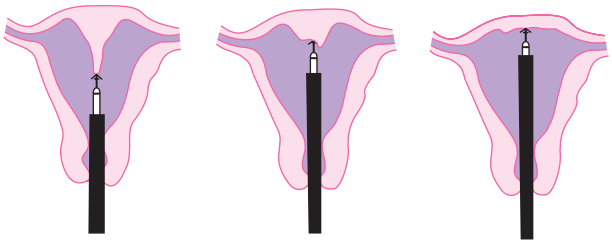

Figure 7.10 Hysteroscopic excision of uterine septum.

Indications of hysteroscopy are explained in Table 7.2

Contraindications

Contraindications to therapeutic procedures are as follows:

- Genital tract infection.
- Pregnancy.
- During menstruation, view is obscured and infection rate increases.
- Scarred uterus and enlarged uterus more than 12 weeks size form relative contraindications.
- Cervical stenosis can cause cervical tear and uterine perforation.

TABLE 7.2 Indications of hysteroscopy

Diagnostic	Therapeutic
• Endocervical study in suspected endocervical malignancy, preinvasive cancer and biopsy • Uterus—malformations endometrial TB Asherman syndrome misplaced IUCD menorrhagia, intermenstrual bleeding submucous fibroid, polyp • Falloscopy	• Endometrial polypectomy • Submucous fibroid • Septate uterus • Asherman syndrome • Removal IUCD • Tubal sterilization • Balloonoplasty • IVF Intrafallopian insemination

- Dysmenorrhoea can worsen following TCRE.
- Cardiopulmonary disorders—anaesthesia risks, fluid over blood and pulmonary oedema.

Distension Media in Hysteroscopy

Several distension media are in current usage for hysteroscopy. The choice of medium depends on its availability, safety, effectiveness and cost as well as whether cautery or laser is used. The media in common usage include carbon dioxide gas delivered through the hysteroflator at a maximum rate of 70 mL/min and pressure less than 100 mmHg. This gives a clear panoramic view of the interior of the uterine cavity, but flattens soft pedunculated polypi against the uterine lining as against those seen as floating objects when liquid media are used.

The popular liquid media used in practice include normal saline, 5% dextrose and Ringer's lactate solutions. To provide adequate uterine distension, the intrauterine pressure needs to be 40–50 mm of Hg. More sophisticated pressure systems are available for use during prolonged hysteroscopic operative procedures such as myomectomy, septum cutting or endometrial ablation where continuous flow of fluid is essential. In the above-mentioned procedures, the use of electrocautery is necessary. In such cases, the distension medium must be nonionic (not normal saline) to prevent spread of electrical energy; also, the medium should not get admixed with blood as this would interfere with proper visualization of the ongoing operative procedure. The distending media in common use are Hyskon and glycine. Hyskon 1.5% is very thick and sticky; hence, immediately after the operation, the hysteroscope and its sheath must be thoroughly cleaned and the sheath scrupulously brushed of all traces of the medium. Delay may lead to jamming of the instrument. Hyskon is a concentrated dextran solution (32% dextrose), not miscible with blood and with good optical qualities. It can cause anaphylactic reaction and infection. Glycine is absorbed from the uterine cavity and peritoneum. Excess glycine can lead to problems of fluid overload and electrolyte disturbances. Hence, it cannot be overemphasized *that strict monitoring of the amount of glycine used, its input and output must be accurately documented. Also a record of the electrolyte readings before commencement of surgery and at the end of the same must be documented as safety precautions.*

Contact Hysteroscopy

This 6-mm contact hysteroscope (Hamou type) can be inserted into the uterine cavity without prior dilatation. On light contact with the endometrial surface, and systematic examination of all the uterine walls and the fundus, it enables assessment of the normality of the endometrial tissue lining, and helps to diagnose any early neoplastic change.

Complications of Hysteroscopy

The following complications are reported during hysteroscopic surgery. These are:

- Anaesthesia complication, more with CO_2 used as a distending medium. Gas embolism can occur.
- Uterine perforation. Uterine perforation occurs in 1–10% mostly during insertion of the hysteroscope through the cervix and during operative procedures. This can be avoided by introducing the telescope under direct vision and performing surgery under laparoscopic guidance. Perforation is suspected when the distending medium escapes into the peritoneal cavity and uterine walls collapse with poor vision and fall in the intrauterine pressure. The perforation is managed by observation, laparoscopic coagulation of the bleeder or laparotomy.
- Organ injury to the bowel and intestine is rare.
- Thermal injury to the bowel occurs with cautery and laser. The injury is not diagnosed at the time of surgery unless perforation also occurs. Delayed diagnosis increases the morbidity. Bipolar cautery is safe from this point of view.
- Bleeding occurs in 1–2%. Bleeding can be minimized by performing the surgery in the preovulatory phase and thinning the endometrium by hormones prior to TCRE. The bleeding normally occurs as the medium is released and intrauterine pressure drops. The bleeding can be controlled by inserting the Foley catheter, distending its balloon with 30 mL saline and leaving it in the uterine cavity for 24 h for haemostasis.
- Sepsis occurs usually with myomectomy.
- Embolism with CO_2 can be avoided by using the proper instrument, not increasing the flow to more than 70 mL/min and pressure less than 100 mm Hg. Avoiding head-low position also reduces the morbidity when embolism occurs.
- Distending media cause complications in 4% cases. While allowing proper view and surgical procedures, the various distending media can increase the procedure morbidity.
- Allergic reaction is noted with dextran and glycine.
- Fluid overload occurs in 4% cases, and leads to pulmonary oedema if deficit of fluid is more than 1000 mL and electrolyte imbalance occurs. Diuretics are required. Saline and dextrose cause hyponatraemia, hypokalaemia, haemolysis and encephalopathy. Hyskon

causes anaphylactic reaction, pulmonary oedema and encephalopathy, brain herniation and temporary blindness. Fluid overload occurs when the intrauterine pressure exceeds 100 mm Hg. Cerebral oedema and cardiac failure may occur.
- Failure to perform therapeutic procedure.

Late Complications

- Haematometra following cervical stenosis.
- Unwanted pregnancy following TCRE.
- Cancer endometrium may go unnoticed for a long time. Delayed diagnosis worsens the prognosis.
- Infection may lead to PID.
- Dysmenorrhoea following TCRE requires hysterectomy.
- Amenorrhoea following TCRE may not be desirable in some women.
- Treatment failure.
- Repeat surgery for treatment failure is seen in 12% at the end of 1 year and 25% following TCRE at the end of 3 years. Either repeat TCRE or hysterectomy is indicated.
- Uterine rupture during pregnancy and late diagnosis of endometrial pathology are other complications.

Salpingoscopy and Falloscopy

In salpingoscopy, a fine salpingoscope 1 mm in diameter is introduced through the fimbrial end of the fallopian tube via the laparoscope, and ampullary portion studied after distending its lumen with saline. Flattening of mucosa, adhesions and mucus polyp can be recognized, and feasibility of tuboplasty considered. Hysteroscopic falloscopy reveals the tubal pathology of the cornual and interstitial end of the fallopian tube. The risks of these endoscopes are perforation, damage to the tubal mucosa, infection and difficulty in inserting the catheters.

Colposcopy

Colposcopy, first introduced by Hinselmann in 1927, enjoys a universal place and its value is recognized in the integrated screening programme of cervical cancer world over (Figure 7.11).

The colposcope is a binocular instrument providing a magnification of 10–20 times and colpomicroscope 100–300 times using external light source. The purpose of the colposcope is to map the abnormal areas on the cervix so that selective biopsy can be obtained under magnification. Colposcopy is not needed routinely in all patients, or patients with obvious lesions. Only those with positive cervical cytology for malignant cells or suspicious cells but clinically normal-looking cervix need colposcopic study. No vaginal examination should be done prior to colposcopy, as with Pap smear, to avoid denuding the epithelium which will yield false-negative findings. A green filter helps to study the vascular pattern. The blood vessels appear black.

Figure 7.11 The Carl Zeiss colposcope. (Source: Used with permission from PEE BEE INDIA endoscopy, www.peebeeindia.com)

Indications

Diagnostic screening procedures are:

- Abnormal Pap smear of the cervix. Even persisting CIN-I (especially those with positive HPV [human papillomavirus] infection) should be screened, because as much as 50% of persistent CIN-I reveal CIN-II and CIN-III on colposcopy and on subsequent histology.
- Abnormal areas on the vagina and preoperative assessment in early stages of cancer cervix.
- Abnormal vulval area.
- Locate the abnormal areas and biopsy.

Therapeutic Indications

- Precise conservative treatment with cautery or laser and cone biopsy can be performed in CIN (cervical intraepithelial neoplasia) lesions under colposcopic guidance using micromanipulator which delineates the area and destroys the entire lesion. Depth of destruction of 4–5 mm is adequate in CIN lesions. Depth up to 1 cm may sometimes be required (Figure 7.12).
- Lifelong follow-up of conservative treatment for preinvasive cancer cervix.

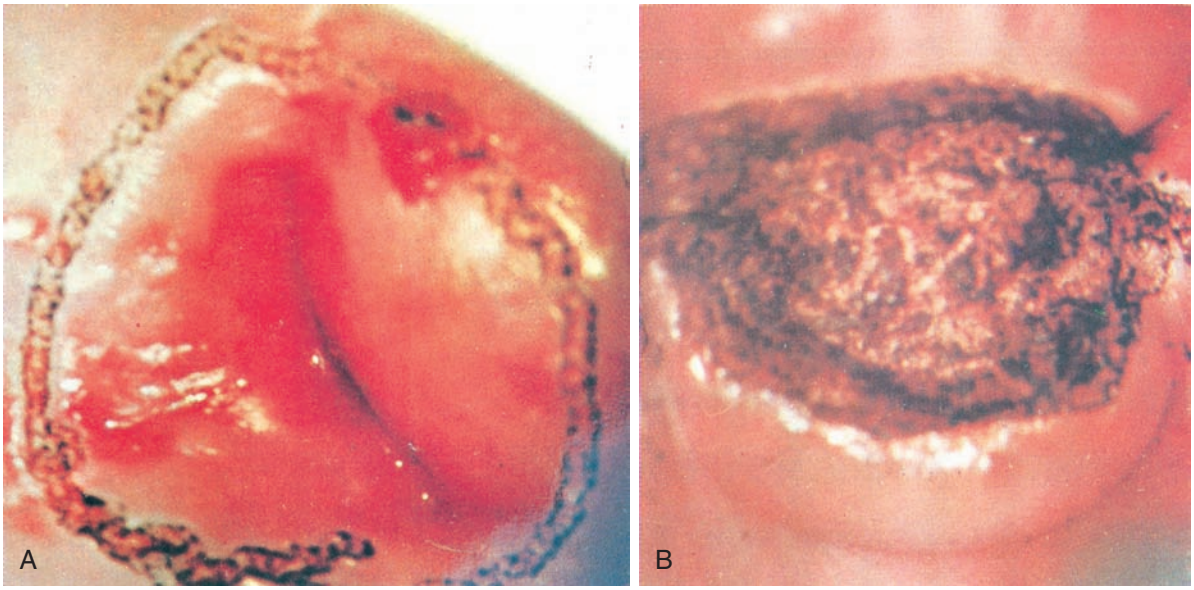

Figure 7.12 **(A)** Cervical lesion outlined by laser beam. **(B)** Completely ablated cervical lesion.

Technique

Colposcopy is best performed during the proliferative phase for optimal findings, though it can be performed any day of the cycle (but not during menstruation). The cervix is moist with mucus and the external os slightly patulous in the proliferative phase and exposes the squamocolumnar junction adequately.

The patient is placed in lithotomy position, the cervix is exposed with a bivalve speculum and the colposcope focused on the external os at a distance of about 20 cm. For a general view of the cervix, the lower magnification is used. The cervix is gently swabbed and cleaned with saline to remove mucus, taking care not to provoke bleeding. The squamocolumnar junction is brought into view and inspected before and after applying 3–5% aqueous acetic acid solution. Three per cent acetic acid is applied to a thin epithelium, but it takes more time to turn acetowhite. Acetic acid precipitates protein, and abnormal epithelium appears white. Wait for at least one minute for the colour change. Viewing the acetowhite areas after interposing a green-light filter permits a more clear assessment of the vascular architecture. Finally the cervix is painted with Schiller's iodine which differentiates the darker glycogen-laden cells from the paler glycogen-free cells which are abnormal.

In a postmenopausal woman, it is desirable to administer oestrogen daily for 1–2 weeks to improve colposcopic findings and allow squamocolumnar junction to pout out of external os. Vaginal misoprostol (prostaglandin) 3 h before colposcopy can also dilate the cervix and allow endocervical visualization. Transformation of columnar epithelium to squamous cells is known as metaplasia, which occurs at transformation zone (TZ) or also known as squamocolumnar junction. Metaplasia is benign but atypical metaplasia developing under the adverse environment such as pH, hormonal influence (oestrogen), virus and mutagens become precursors of cancer cervix.

Colposcopic Findings (Figures 7.13–7.15) (Table 7.3)

Interpretations of findings are based on the following:

- Response to acetic acid
- Response to Lugol's iodine
- Surface, contour and margins
- Punctations, mosaics, inter capillary distance
- Atypical vessels

Invasive—more of high-grade squamous intraepithelial lesion (HSIL), comma-shaped or cork-screw-shaped vessels.

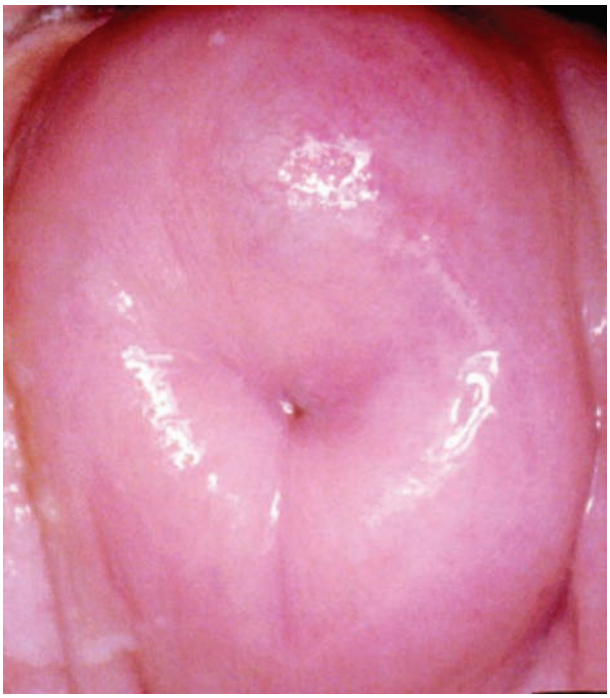

Figure 7.13 Colposcopic view of transformation zone. (From Plate 7-18, Barbara S Apgar, Gregory L Brotzman, Mark Spitzer. Colposcopy: Principles and Practice, 2nd Ed. Saunders: Elsevier, 2008.)

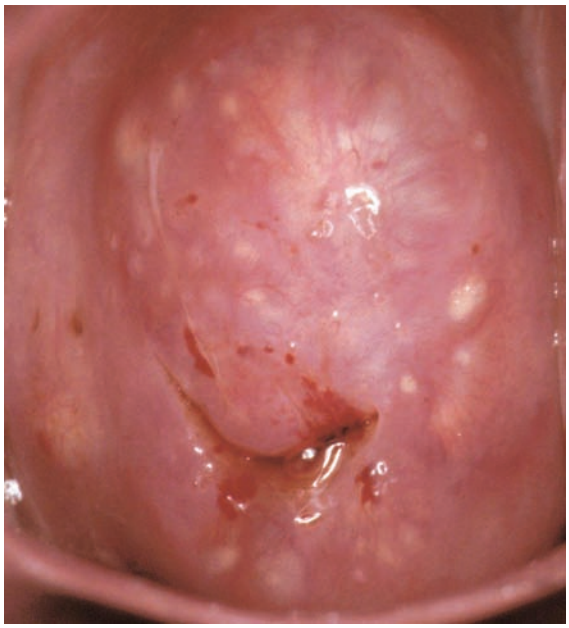

Figure 7.14 Colposcopic view of normal, large transformation zone with multiple nabothian cysts present. (From Figure 9-1, Barbara S Apgar, Gregory L Brotzman, Mark Spitzer. Colposcopy: Principles and Practice, 2nd Ed. Saunders: Elsevier, 2008.)

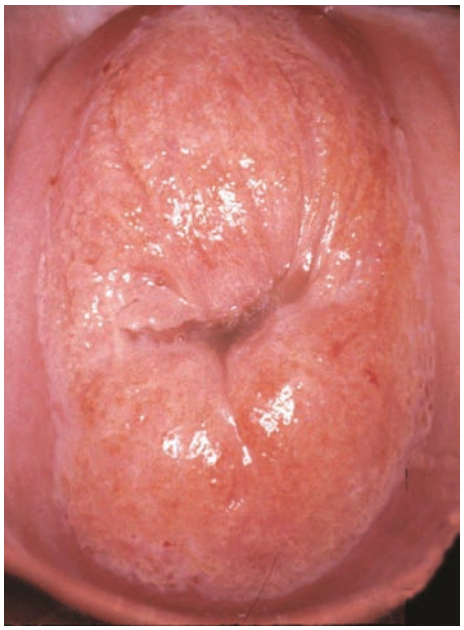

Figure 7.15 Colposcopic view of a large ectropion. (From Figure 7-13, Barbara S Apgar, Gregory L Brotzman, Mark Spitzer. Colposcopy: Principles and Practice, 2nd Ed. Saunders: Elsevier, 2008.)

Aceto-white areas also appear in inflammation, HPV infection, metaplasia and during regeneration of tissue.

Indications of Colposcopy

Diagnostic

- Abnormal Pap smear
- Cervical lesion
- Vaginal lesion
- Vulval lesion
- Follow-up of ablation therapy

TABLE 7.3 Colposcopy reporting

1. Satisfactory colposcopic examination
   Columnar epithelium, squamous and squamocolumnar junction seen
2. Unsatisfactory—squamocolumnar junction not completely seen
3. Abnormal findings
   - Mosaics, punctuations
   - Acetowhite area, keratosis
   - Atypical vessels
   - Iodine negative area
   - Raised area

Therapeutic

- CIN II and III—ablative therapy
- Conization

Colposcopic examination is considered satisfactory when the entire squamocolumnar junction is visible and the lower portion of the endocervical columnar epithelium is seen.

Normal columnar epithelium looks like red grape-like structures with furrows. Squamous epithelium looks homogenous grey.

Abnormal findings (Figures 7.16–7.20)

Abnormal area turns acetowhite with acetic acid. The faster this appears and longer it lasts, the higher is the grade of lesion. Acetowhite area shows sharp margins and coarse mosaic pattern with irregular mosaic formed by the vessels running parallel to the surface. The vessels running perpendicular to the surface show up as irregular, large punctuate red spots. The acetowhite area is irregular with raised papillae. Invasive cancer shows comma-shaped or cork-screw shaped vessels with wide, irregular mosaics (Figure 7.21). The abnormal areas do not take up iodine

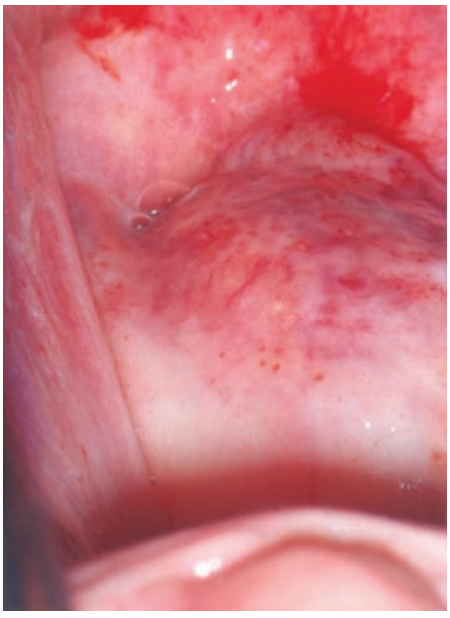

Figure 7.16 Abnormal vessels and punctuation on anterior lip.

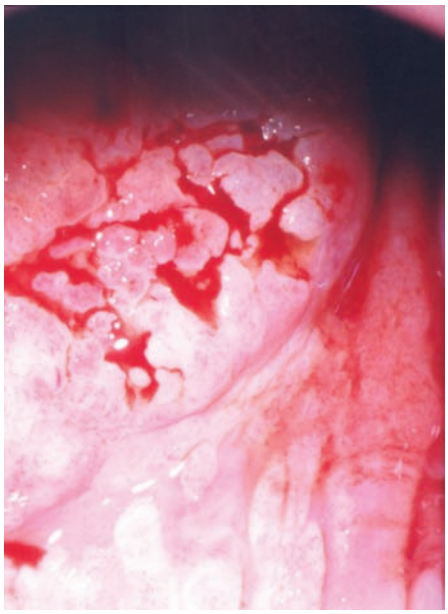

Figure 7.17 Colposcopy coarse acetowhite epithelium showing abnormal vessels and few mosaics.

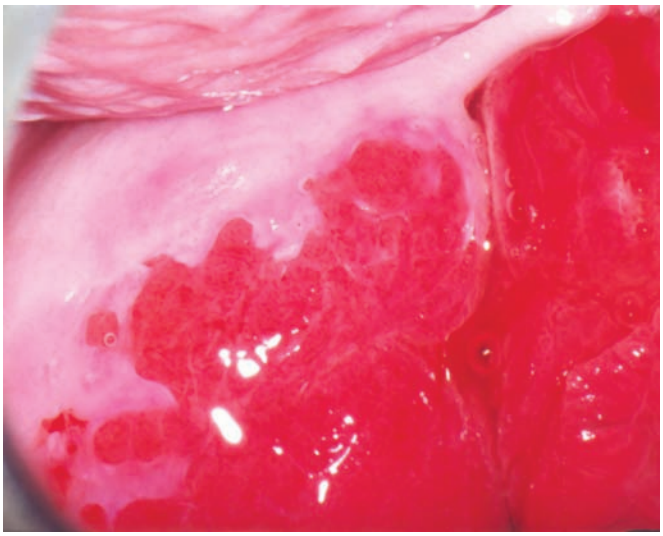

Figure 7.18 Mosaic pattern; colposcopic view.

and do not show mahogany brown stain, the vessels are dilated.

The first change in precancerous lesion is seen in punctuation. Thereafter abnormal mosaics appear followed by acetowhite lesions. Lastly atypical cells make their appearance. Keratosis is visible on naked eye examination.

Low-grade squamous intraepithelial lesion (LSIL) shows smooth surface, irregular outer borders and mild acetowhite change which disappears quickly. Fine punctuation and mosaics are present.

HSIL—has sharp borders, dense acetowhite lesions, coarse punctuations and irregular mosaics, atypical vessels..

Endocervical curettage is required if the squamocolumnar junction is not entirely visible.

During pregnancy, intense white appearance with coarse mosaics may be present, but the vessels are normal. One

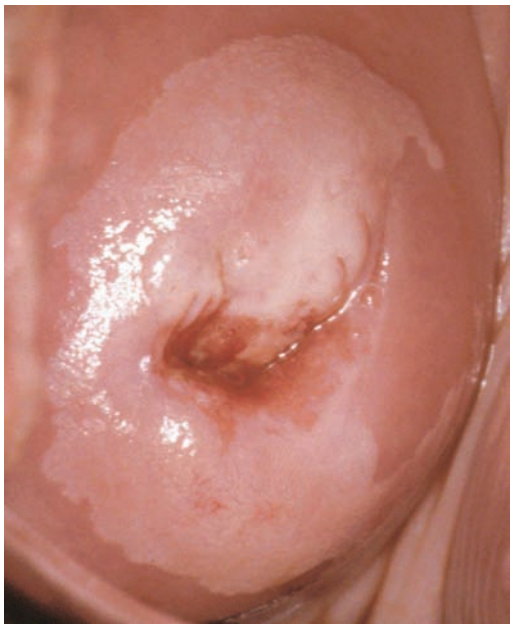

Figure 7.19 Colposcopic view of peripheral low-grade lesion and a central denser acetowhite epithelium of a high-grade lesion at 12 o'clock, with an internal margin noted. (From Figure 9-8, Barbara S Apgar, Gregory L Brotzman, Mark Spitzer. Colposcopy: Principles and Practice, 2nd Ed. Saunders: Elsevier, 2008.)

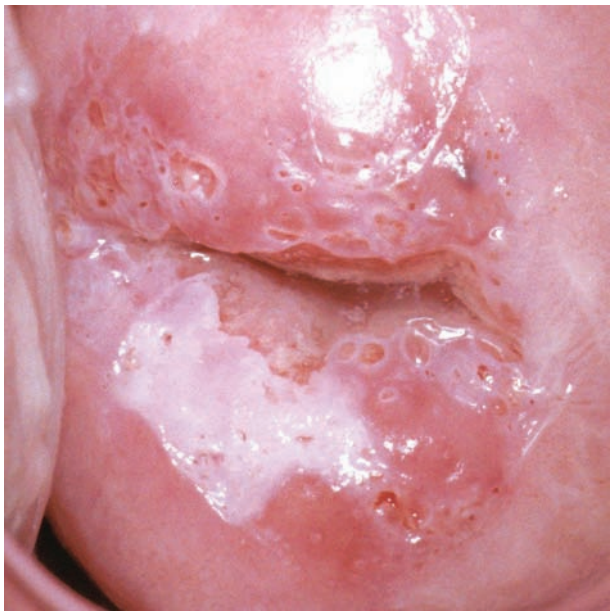

Figure 7.20 Colposcopic view of example of a high-grade lesion with dense acetowhite epithelium on the posterior lip of the cervix and no abnormal vessels present. (From Figure 9-14, Barbara S Apgar, Gregory L Brotzman, Mark Spitzer. Colposcopy: Principles and Practice, 2nd Ed. Saunders: Elsevier, 2008.)

should not use endocervical brush, because it can cause premature rupture of membranes and bleeding may endue. Use instead, wet cotton-tipped application for endocervical tissue.

Colposcopy can:

- Avoid unnecessary biopsy if the findings are normal
- Avoid cone biopsy

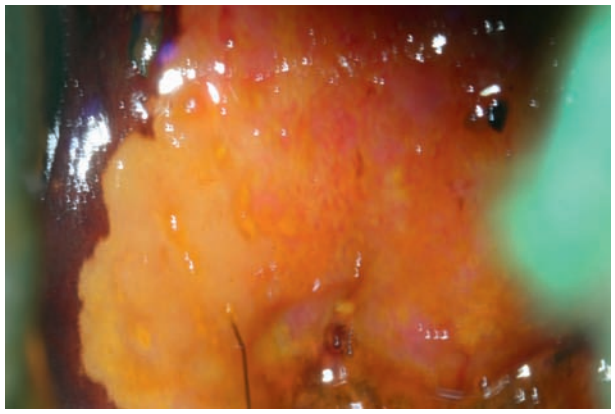

Figure 7.21 After application of Lugol's iodine, acetowhite areas, coarse mosaic and punctuations show significant iodine negativity. The squamous epithelium is stained mahogany brown. HPV and carcinoma in situ do not take up the stain.

- Select the appropriate site of biopsy
- Reduce the size of biopsy and conization

Therapeutic application of colposcopy. Colposcopic ablative techniques have been successfully employed in preinvasive cancer of the cervix and vagina. The details are mentioned in the chapter on cancer cervix.

Colposcopy should be preferably restricted to first-trimester pregnancy, as it can cause bleeding, besides causing discomfort once fetal head enters the pelvis.

Colposcopy of the vagina is indicated in the following conditions:

- To evaluate vagina with abnormal Pap smear but normal colposcopic findings of the cervix.
- Rule out extension of CIN.
- Women with HPV viral infection.
- Gross lesion present.
- Follow-up of hysterectomy or conservative therapy performed for CIN disease.

Because of multifocal lesions, wide vaginal wall and viewing at an angle, colposcopic examination of the vagina is difficult. Use Lugol's iodine to identify abnormal epithelium.

Colposcopy of the vulva is not always informative because of keratinization and deep-seated vessels (Figure 7.22) and multiple lesions. Toluidine blue shows heavy staining but does not give clue to the underlying pathology. Biopsy is required.

Colpomicroscopy

Unlike colposcopy which looks at the tissue patterns, colpomicroscopy looks at the structures at the cellular level. The magnification is 100–300 times. Interpretation is not very easy, hence lacks popularity. Confocal endomicroscopy studies the depth of tissue up to dermis, and is recently employed as an adjuvant to colposcopy.

Extragenital Endoscopy

Endoscopic examination of other pelvic viscera of interest to the gynaecologist includes the urethra, urinary bladder, anal canal, rectum and the sigmoid colon. Seeking this information is useful in gynaecological malignancy, genital fistulae, stress urinary incontinence, and in cases of developmental anomalies such as the presence of double ureters or ectopic ureter. Preoperative ureteric catheterization in gynaecological malignancy or difficult operations involving large fibroids, broad ligament pathology, advanced endometriosis or anticipating dense pelvic adhesions and disturbed tissue plains safeguards against accidental ureteric injuries. Teaming up with a urologist and a proctologist can be mutually beneficial when treating a high-risk patient suffering from advanced pelvic pathology.

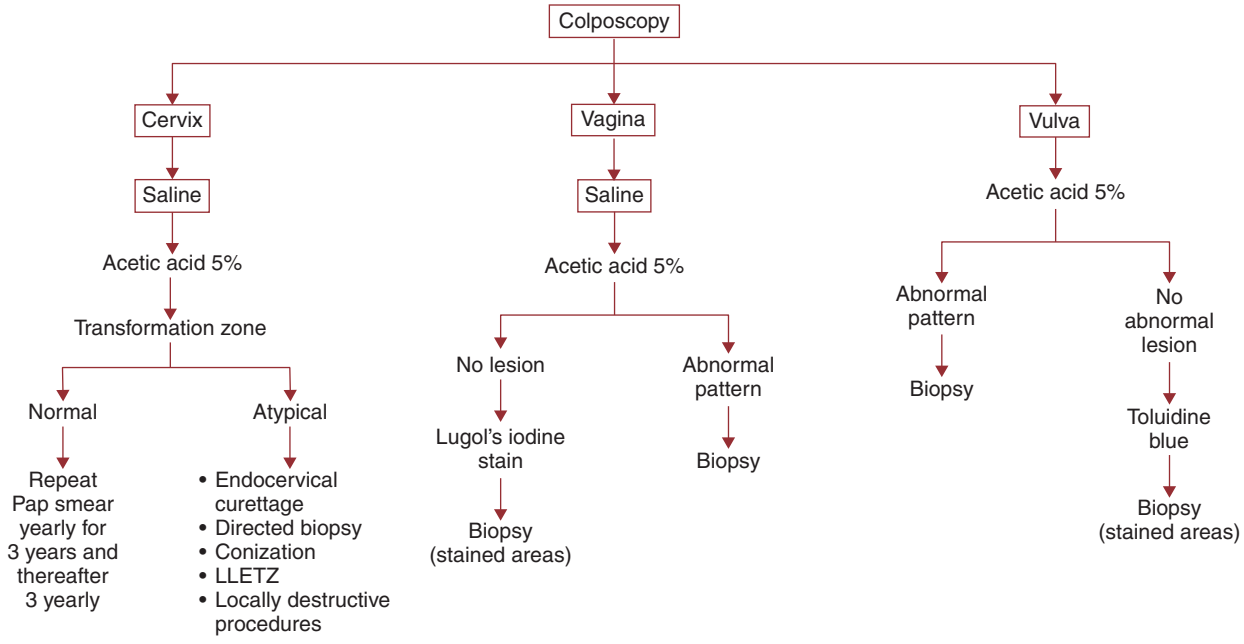

Figure 7.22 Applications of colposcopy in clinical practice.

Culdoscopy

When laparoscope and ultrasound had not developed, culdoscopy enjoyed the privilege of diagnostic and therapeutic procedures. It was used to visualize the pelvic organs and test the potency of fallopian tubes. Therapeutically, it was performed for tubal sterilization, removal of ectopic pregnancy and adnexal mass.

Once laparoscope came into use, culdoscopy took a back seat, and was abandoned. With certain limitations and contraindications to laparoscopy being understood, culdoscopy is now occasionally employed (obesity and pelvic and abdominal scar adhesions contraindicate laparoscopy). It requires only 2 cm incision in the posterior fornix, so trocar is not needed. Culdoscope is 4–8 mm in size.

Contraindications

- Pelvic adhesions and obliteration of pouch of Douglas.
- Pelvic endometriosis suspected.
- Vaginal infection.

Key Points

- Various endoscopic telescopes have been designed to enable the visualization of body cavities. Of particular use in the practice of gynaecology are the colposcope, the laparoscope and the hysteroscope.
- The laparoscope has been very useful in the diagnosis of uterine, tubal, ovarian and generalized diseases affecting the pelvic organs such as endometriosis, chronic PID, genital tuberculosis and in staging of genital cancers chronic pelvic pain.
- The role of the laparoscope in the evaluation of infertility is undisputed. It is now a common practice to combine laparoscopy with hysteroscopy in its evaluation.
- Operative laparoscopy has made great inroads into clinical practice, making minimally invasive surgery a valid and safe therapeutic option in many situations.
- Diagnostic hysteroscopy helps in the evaluation of a patient presenting with the menstrual disturbances, endometrial polyps, submucous fibromyomatous polyps, a misplaced IUCD and endometrial malignant growth. The indications have expanded in therapeutic procedures.
- Operative hysteroscopy is also performed effectively to correct several menstrual problems, mainly abnormal uterine bleeding.
- Colposcopy complements the results of Pap tests. It helps in delineating suspicious areas in the squamocolumnar junction suggestive of preinvasive and invasive cancer of the cervix, and guides the clinician in planning out selective or a cone biopsy of the cervix in suspicious cases.
- Colposcopy is also useful in conservative therapy in CIN diseases. Lifelong follow-up of women undergoing conservative treatment is important with colposcope.
- Colposcopy is not competitive, but complimentary to Pap smear.
- Culdoscopy is now reintroduced in selective cases when laparoscopy is contraindicated or difficult.

Self-Assessment

1. Discuss the diagnostic indications of laparoscopy in gynaecology.
2. Discuss the therapeutic procedures done laparoscopically.
3. Discuss the contraindications and complications of laparoscopy surgery.
4. What are the diagnostic indications of hysteroscopy?
5. Discuss the therapeutic role of hysteroscopy.
6. Mention the complications and contraindications of hysteroscopy.
7. Discuss the role of colposcopy in gynaecological oncology.

Suggested Reading

Advances in laparoscopy and minimal invasive surgery. Obstet Gynaecol Clin N Am 2011; 38.
Studd J (ed). Progress in Obstetric Gynaecology Vol 7, Edinburgh: Elsevier.
Studd J (ed). Progress in Obstetric Gynaecology Vol. 16, London: Elsevier, 2005.

Chapter

8

Imaging Modalities in Gynaecology

CHAPTER OUTLINE

Plain Radiography

Plain radiographs have a minor role in present-day gynaecological practice. An abdominal radiograph is not used in the diagnosis of pelvic pathology. However, an incidental radiograph taken for other medical or surgical conditions may reveal unsuspected pelvic pathology such as presence of a tooth in a dermoid cyst or a calcified fibroid (Figure 8.1).

A plain radiograph of the pelvis in AP and lateral views taken after placing a uterine sound in the uterine cavity help to locate an intrauterine contraceptive device (IUCD; commonly a Cu-T in present times) that has perforated the uterus and is located outside (Figure 8.2).

A plain radiograph of the chest is required in suspected tuberculosis, to determine presence of metastasis in gynaecologic malignancies, and finally, as a part of the work-up prior to undertaking any major gynaecological surgery.

Hysterosalpingography

Hysterosalpingography (HSG) is employed for the following:

- To study the patency of the fallopian tubes in infertility and postoperative tuboplasty (Figure 8.3 A–E).
- To assess the feasibility of tuboplasty by studying the location and extent of tubal pathology.
- To study uterine anomaly such as septate and cornuate uterus.
- To detect uterine synechiae.
- To detect uterine polyp.
- To study incompetence of internal OS. HSG has also been described in Chapter 19.

Technique

- It is done as an outpatient procedure, without any anaesthesia, in the Department of Radiology.
- Premedication with atropine and analgesia may be required in an apprehensive woman to prevent tubal spasm.
- The woman is asked to empty her bladder.
- She is placed in the lithotomy position, perineal area cleaned with Betadine and draped.
- Bimanual examination is done to note the size and position of the uterus.
- The cervix is exposed and held with an Allis forceps.
- Rubin's cannula, Leech Wilkinson cannula or Foley catheter No. 14 is introduced gently into the uterine cavity beyond the internal os (bulb of the catheter distended to prevent leakage). The cone of Rubin's cannula snugly fits into the external os.
- The radio-opaque dye (usually water soluble, rarely oil based), 10–15 mL, is gently injected by attaching the loaded syringe to the cannula or Foley catheter.
- The uterine cavity and fallopian tubes are visualized as the dye passes through them during fluoroscopy.
- At a specific time desired, X-rays are taken for a permanent record.
- The instruments are withdrawn, and the woman is observed for half an hour.

Contraindications

- Presence of genital tract infection and bleeding.
- Premenstrual phase. If by chance pregnancy has occurred, it may be dislodged. Embolism is also possible. Thick endometrium may prevent smooth flow of the dye

Figure 8.1 X-ray of pelvis showing teeth in an ovarian dermoid cyst.

at the cornual end. The risk of endometriosis also precludes doing HSG in the premenstrual phase.
- Suspected pregnancy.
- Allergy to the dye.
- Genital tuberculosis suspected. Risk of spread of infection.

Complications

HSG is a safe procedure.

The following are the complications:

- Ascending infection, spread of tubercular infection.
- Pelvic irritation and pain due to dye (chemical peritonitis).
- Allergic reaction to the dye.
- Pelvic endometriosis if done premenstrually or while the woman is bleeding.

Advantages

- Provides a permanent record.
- Shows the pelvic pathology and the exact site of tubal blockage.
- Dye dislodges the mucus plug and clears the tubal blockage, providing salvage rate of 30%.

Sonosalpingography

Sonosalpingography is described in Chapter 19. It is of particular use in the diagnosis of uterine polyp.

Intravenous Urography

Urography outlines the urinary tract following the administration of an intravenous iodinated contrast medium.

Indications

Intravenous urography (IVU) is useful in the following indications:

- Gynaecologic malignancy to determine the normality of the urinary tract. In advanced cancer cervix, the ureters may get involved leading to partial or complete obstruction. Advanced cancer of the cervix involving the parametrium constricts the ureter in its passage through the ureteric tunnel causing obstruction, and back pressure initially leading to hydroureter and hydronephrosis and finally renal atrophy.
- In ovarian cancers and in the presence of other pelvic masses such as broad ligament fibroids, the ureters

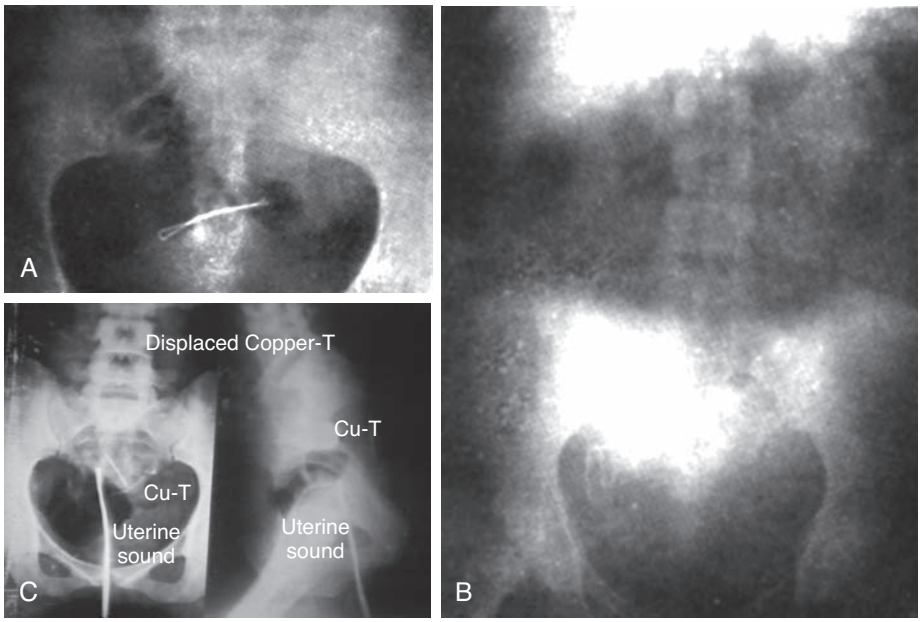

Figure 8.2 **(A)** and **(B)** showing presence of foreign body, and **(C)** shows a migrated Cu-T outside uterus. An anteroposterior (AP) and lateral view of the pelvis with a uterine sound in situ confirm the extrauterine location of the IUCD.

may get displaced and are prone to injury during pelvic surgery.
- Rarely, an unidentified pelvic mass turns out to be a solitary pelvic kidney. Instances of removal of such kidneys by the unsuspecting surgeon leading to disastrous consequences have been reported.
- In suspected ureteric injury during difficult pelvic surgery, a descending pyelography may help to confirm or refute the injury (Figure 8.4).
- Renal tract anomalies often coexist with Müllerian duct anomalies; hence, in every case of congenital malformation of the genital tract, it is wise to perform IVU to exclude urinary tract abnormalities. Today, this is diagnosed by noninvasive ultrasound.
- Urinary incontinence in young girls may be due to an ectopic ureter: this can be demonstrated on urography.
- In genitourinary fistulae, the relationship of the ureteric orifice to the site of fistula is important in planning any surgical repair.
- To study the anatomy of the ureter in a difficult pelvic surgery.

Precautions and Contraindications

- IVU is contraindicated in women with iodine sensitivity.
- It should be undertaken with caution in women with impaired renal functions. Renal function should be assessed prior to undertaking IVU.

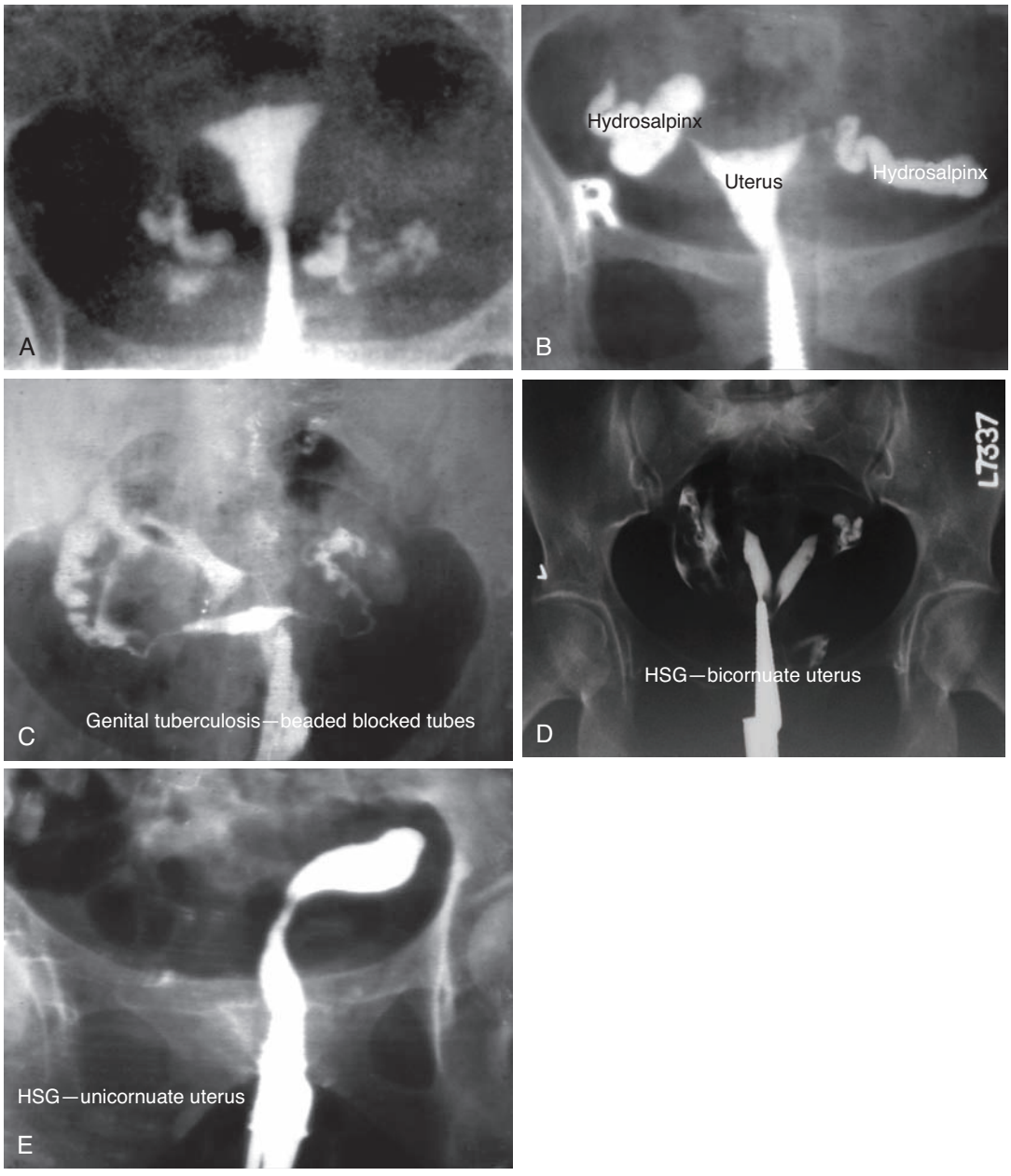

Figure 8.3 **(A)** HSG showing patent fallopian tubes with free peritoneal spill. (Courtesy: Dr Ajit M Virkud, Mumbai.) **(B)** HSG showing bilateral hydrosalpinx. **(C)** HSG showing genital tuberculosis—typically beaded blocked tubes seen. **(D)** HSG showing bicornuate unicollis uterus with normal corresponding fallopian tubes and free peritoneal spill. (Courtesy: Dr K K Saxena, New Delhi.) **(E)** HSG showing unicornuate uterus.

Continued

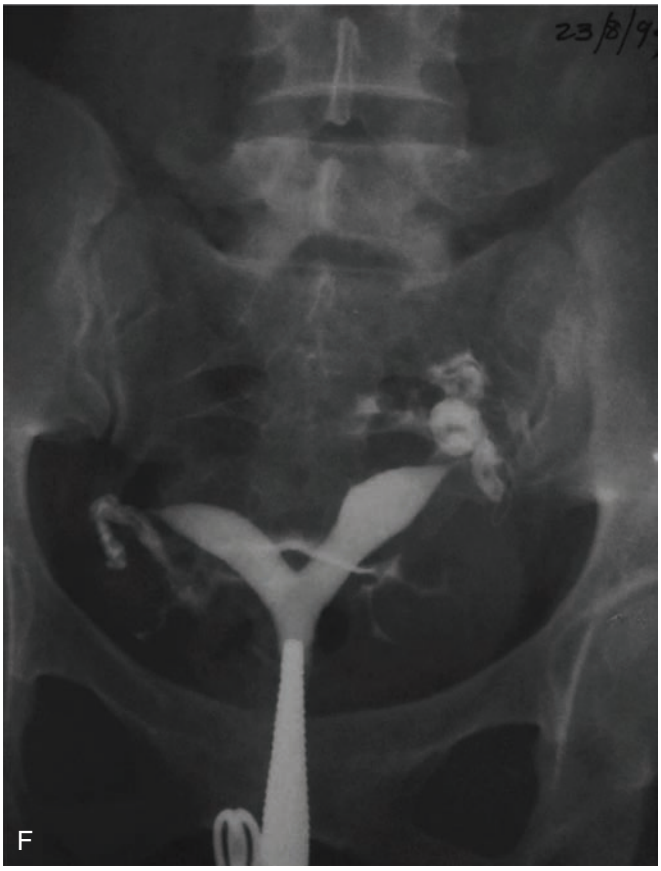

Figure 8.3, cont'd (F) HSG showing deep septate uterus. Both fallopian tubes are normal and show free peritoneal spill. (Courtesy: Dr K K Saxena, New Delhi.)

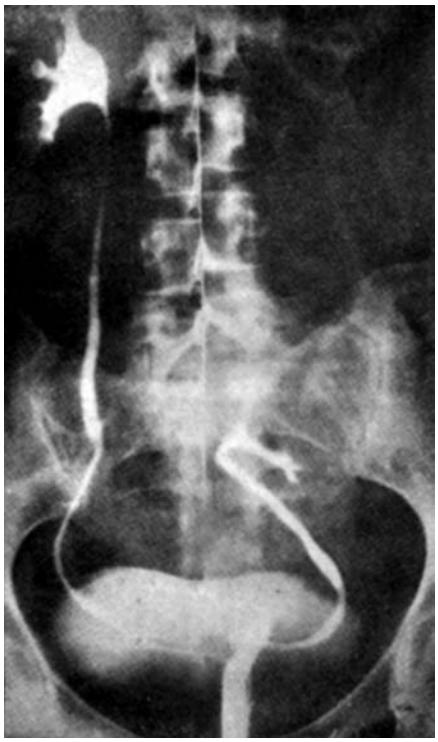

Figure 8.4 Composite X-ray showing ectopic pelvic left kidney demonstrated by retrograde pyelography (clinically diagnosed as left ovarian tumour).

- Exercise caution prior to the test in women with allergic diathesis, asthmatics and diabetics on metformin. It is mandatory to perform a sensitivity test prior to the investigation.
- Suspicion of pregnancy. Radiation is harmful to the fetus.

Cystography and Urethrography

Cystourethrography is useful in the investigation of urinary incontinence (Figure 8.5). Most information is obtained by combining video studies and pressure studies (simultaneous video cystometrography). This investigation permits the evaluation of the anatomical disorders of bladder neck and proximal urethral displacement and inappropriate detrusor contraction in a patient with incontinence of urine.

Gastrointestinal Studies

Barium Meal and Follow Through

This examination and gastroscopy are useful in suspected ovarian metastatic disease. Stomach cancer is often the primary site. Visualization of the ileocaecal region may help to differentiate a pelvic mass due to ileocaecal tuberculosis from an adnexal mass.

Barium Enema

This examination allows the visualization of the colon. Many gynaecological conditions such as ovarian malignancy, pelvic endometriosis, pelvic inflammatory disease (PID), genital and abdominal tuberculosis and previous radiotherapy may all be associated with small and large bowel disturbances. Large bowel inflammation, Crohn's disease, chronic amoebiasis, worms and diverticulitis can all confuse the clinical picture and complicate gynaecological procedures.

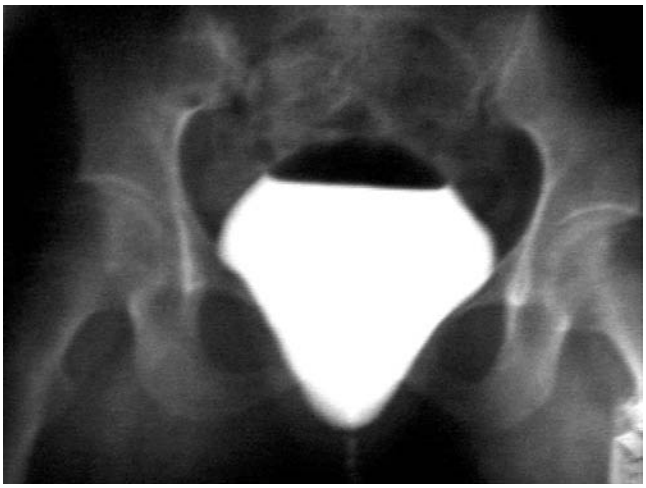

Figure 8.5 Cystography showing altered shape of the full bladder in case of a large cystocoele. Note the descent of the bladder neck and proximal urethra which predisposes to stress incontinence.

Arteriography and Arterial Embolization

The arterial supply of the uterus and appendages can be demonstrated by aortography or internal iliac arteriography. In modern-day practice, the use of ultrasonography, computed tomography (CT) scan, magnetic resonance imaging (MRI) and Doppler blood flow studies have minimized the need for arteriography. However, arteriography can establish the cause of heavy abnormal uterine bleeding not responding to conventional therapy to an arteriovenous aneurysm, or varicose veins. Selective embolization of the same can result in cure.

Embolization of the anterior division of internal iliac artery has been successfully used in the treatment of bleeding from advanced cervical cancer, secondary haemorrhage after a hysterectomy, cervical ectopic pregnancy and for embolization of uterine artery in menorrhagia and in fibroids.

Ultrasonography (Figures 8.6–8.15)

This imaging modality was first pioneered by Ian Donald (1974) in gynaecology and obstetrics. Sonography is generally the first and often the only imaging modality used to demonstrate pelvic anatomy and to document physiological

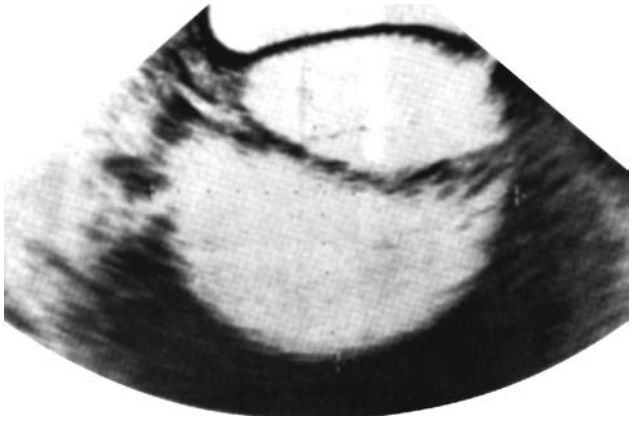

Figure 8.6 USG showing a septate ovarian serous cystadenoma. (Courtesy: Diwan Chand Satyapal Aggarwal Imaging Research Center, New Delhi.)

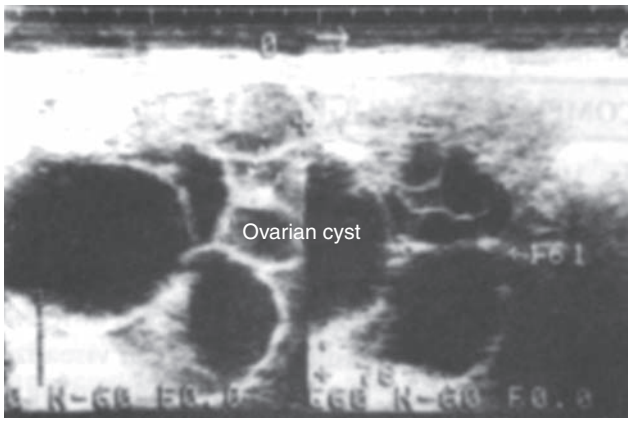

Figure 8.7 USG showing a multiloculated ovarian cyst.

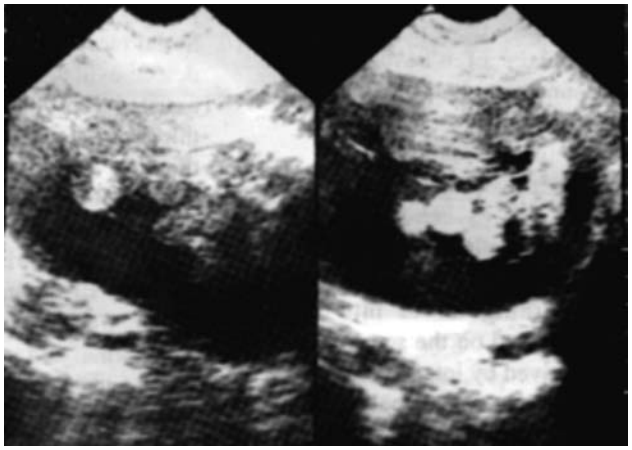

Figure 8.8 USG showing dermoid cyst of the ovary. (Courtesy: Diwan Chand Satyapal Aggarwal Imaging Research Center, New Delhi.)

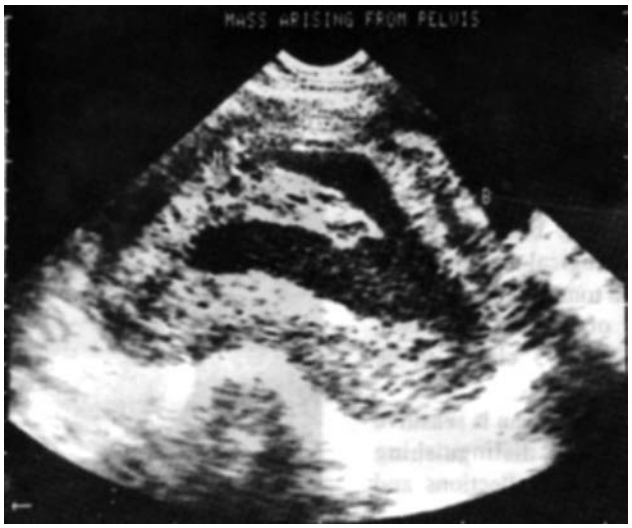

Figure 8.9 USG showing ovarian carcinoma. (Courtesy: Diwan Chand Satyapal Aggarwal Imaging Research Center, New Delhi.)

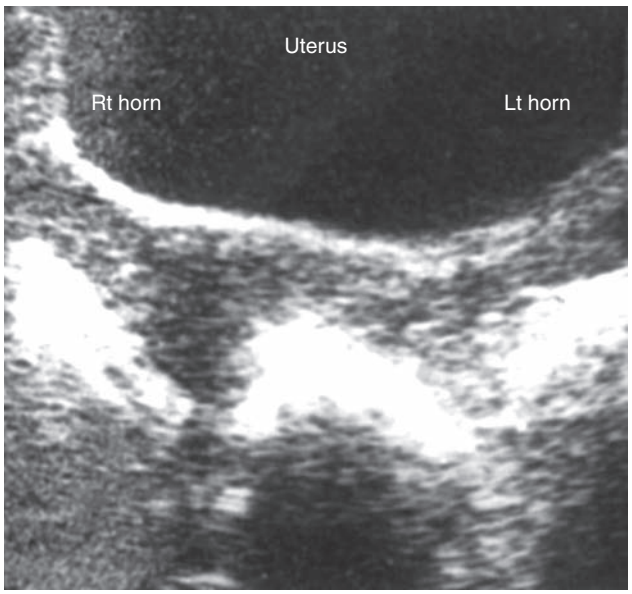

Figure 8.10 USG showing a bicornuate uterus. (Courtesy: Dr Ashok Khurana, New Delhi.)

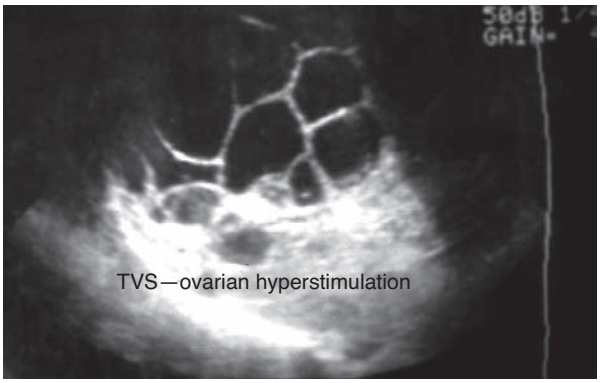

Figure 8.11 Ovarian hyperstimulation.

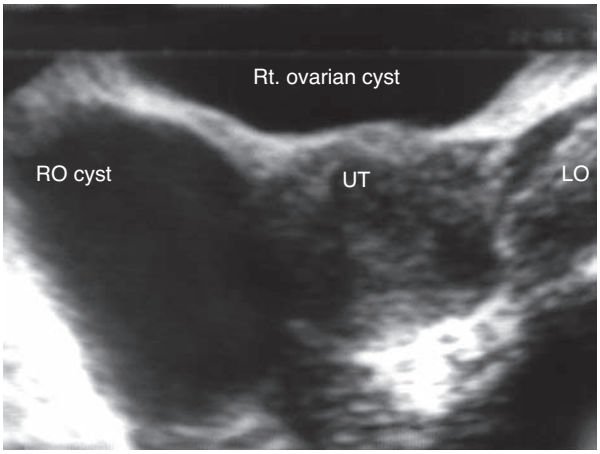

Figure 8.12 Ovarian cyst.

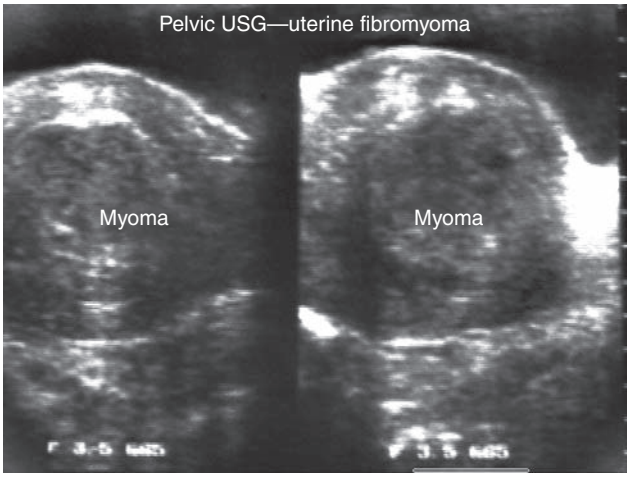

Figure 8.13 Uterine fibromyoma.

(ovulation monitoring) and pathological changes. Ultrasound examination may be performed by the transabdominal/transvaginal/transrectal or transperineal approach. *The vaginal probe is considered a natural extension of bimanual examination with better precise pelvic findings.*

Advantages of ultrasound are:

- Noninvasive technique.
- Soft tissue imaging possible unlike X-rays.
- No ionizing radiation, so it can be repeated.

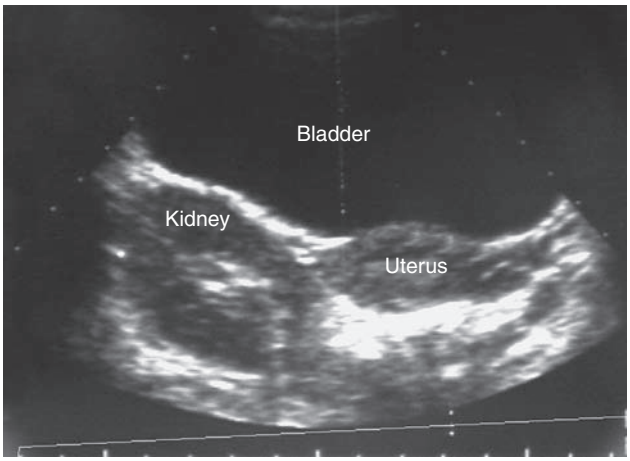

Figure 8.14 Ectopic pelvic kidney.

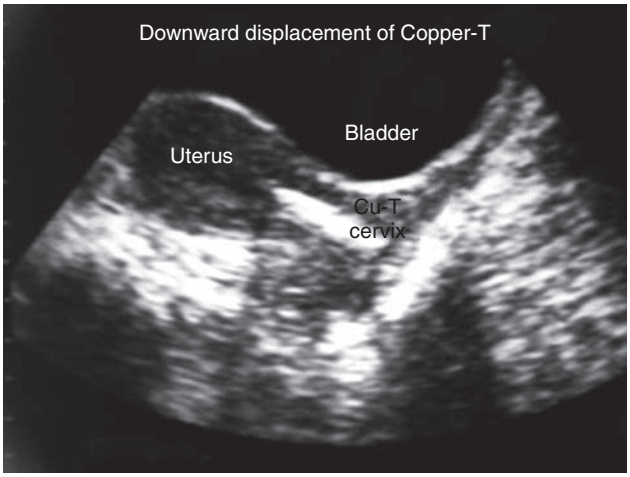

Figure 8.15 Downward displacement of Cu-T.

Standard examination of the female pelvis is performed by traditional transabdominal approach (TAS) and by the transvaginal route (TVS). TAS is performed with 3.5 MHz convex transducer through the full urinary bladder, which provides an acoustic window as well as displaces the bowel loops away from the path of the ultrasonic beam. The structures superficial and remote from the vagina are better assessed via TAS approach.

Transvaginal sonogram is performed with high-frequency 7.5 MHz which demonstrates better anatomic details of the pelvic organs as compared to TAS. The proximity with which the high-frequency TV probe can be placed on the pelvic contents produces vastly superior resolution. In addition, demonstration of local tenderness and organ mobility yields information equivalent to a gynaecological examination (pain mapping).

The ultrasonic scan should be initiated with TAS and then followed up with TVS after the woman empties her bladder. This also gives the information of residual urine in investigation of urinary dysfunction. TVS should not be performed in virgins, or when TVS is refused by the woman. It is also difficult in a menopausal woman and in stenosed vagina.

Lately, perineal and anal ultrasound are being employed in faecal incontinence and when TVS is not possible. They are also useful in studying the pelvic floor muscles and plan surgery in genital prolapse. The ultrasound shows breaks in the pelvic floor muscles, and helps to determine appropriate surgical approach.

Advantages of TVS over TAS are as follows:

- Full bladder is not required.
- Better resolution and image of pelvic organs.
- In obese women, sound waves are attenuated by subcutaneous fat, and TAS gives a poor image.
- Sonography is the diagnostic modality of choice in pelvic imaging to determine and confirm the presence or absence of pelvic pathology, determine the size, texture and contour of the lesion, and to establish the origin and anatomic relationship of the lesion with other pelvic structures. It also helps to determine the presence or absence of abnormalities associated with malignant diseases such as ascites or metastasis. It also provides guidance to the gynaecologist in performing aspiration and biopsy under sonographic control, and selective therapeutic procedures.

Colour flow Doppler studies with spectrum are added to the examination depending upon the clinical situation and pathology demonstrated on grey scale.

- Three-dimensional (3D) ultrasound accurately measures the uterine and ovarian volume and blood supply.

Normal Ultrasonic Findings

The mean dimensions of the uterus of reproductive age are 7 cm in length and 4 cm in width in a nulliparous woman. It is 8.5 cm in length and 5.5 cm in width in a multiparous woman. After menopause, reduction in the uterus occurs proportionate to the duration of menopause. The location of the uterus is used as a road map in locating adnexal structures.

Ovaries are oval shaped measuring $3.0 \times 2.0 \times 1.0$ cm located laterally in the pelvis. Visualization of the ovary improves the detection of follicles within.

Since the ovaries have marked variation in size and shape, ovarian volume is considered the most reproducible parameter (Campbell et al. 1982). Mean ovarian volume in reproductive age is 9.5 ± 5.0 mL.

Mean ovarian volume in perimenopausal age is 6.8–9 mL. In postmenopausal woman, it diminishes from 8 mL to 2 mL with advancing age.

A dominant follicle that ovulates is 20 or more millimetres.

Corpus luteum is recognized in the postovulatory phase and a small haemorrhage may be recognized. Corpus luteal cyst is absent in anovulatory cycles.

Endometrial changes: These vary according to the different phases of the menstrual cycle.

Proliferative phase: It is thin and starts growing up to 6 mm before ovulation.

Secretory phase: The endometrium grows up to 10 mm in the late secretory endometrium. The glands have a cork-screw appearance and the vascularity increases. In endometrial hyperplasia, the endometrium grows beyond 10 mm, shows irregular margins with folds projecting into the uterine cavity as a sessile single or multiple polyp of same echogenicity.

After menopause, the endometrium atrophies and shrinks to less than 4 mm. The endometrial thickness of more than 4 mm, irrespective of postmenopausal bleeding, is considered abnormal, and requires investigations.

Subendometrial halo is demonstrated in late proliferative phase and its infiltration by endometrial tissue suggests adenomyosis or cancer of the uterus.

Diagnostic Indications

- Congenital anomalies of uterus.
- To diagnose haematocolpos, haematometra.
- To diagnose ectopic pregnancy. In an *intrauterine pregnancy*–the gestation sac is generally eccentric in location. It grows and grows 1.0 mm/day. In an ectopic pregnancy, the pseudosac is centrally located.
- To diagnose adnexal mass.
- To diagnose uterine pathology—fibroids, adenomyosis, uterine synechiae.
- To monitor ovulation.
- In abnormal uterine bleeding— to study the endometrial pattern.
- To study endometrial lining in postmenopausal bleeding and its vascular pattern.
- To study ovarian pathology, i.e. PCOD, ovarian cyst, ovarian tumour.
- Location of misplaced IUCD.
- Infertility—sonosalpingography to study patency of the fallopian tubes, detect submucous polypus.
- Endometriosis.
- Fine-needle aspiration cytology (FNAC) in gynaecological malignancy.
- Falloscopy to study the medial end of fallopian tube.
- In a male, to detect varicocele by Doppler.

Details have been described in respective chapters. Therapeutic applications of ultrasound in clinical practice are:

- Oocyte retrieval in IVF programme.
- Drainage of chocolate cyst/simple benign cyst of the ovary. Laparoscopic surgery is superior to ultrasonic guided procedure, though more invasive.
- Drainage of pelvic abscess.
- To break uterine synechiae in Asherman syndrome.
- Evacuation of molar pregnancy, and MTP under ultrasound guidance. This avoids uterine perforation.
- Transcervical cannulation and sperm injection into the fallopian tube in infertility.
- Retrieval of embedded IUCD
- Injection of methotrexate into the ectopic gestational sac in unruptured ectopic pregnancy. Now, IM injection is preferred as it is noninvasive and equally effective.

Colour Doppler ultrasound is useful in suspected malignant ovarian tumour and endometrial carcinoma. Neovascularization and decreased resistance index (<0.4) suggest malignancy. Doppler ultrasound is useful to diagnose a rare case

of arteriovenous malformation causing menorrhagia. Red blood flow indicates blood flow towards the transducer, and blue colour away from it.

3D and 4D ultrasound provide multiplanar image used mainly to detect fetal anomalies. In gynaecology, these ultrasounds are used for effective therapeutic procedures.

Some descriptions are mentioned below:

1. **Congenital Müllerian malformations** (American Fertility Society Classification System)
   - Class I (agenesis, hypoplasia). Uterus is absent in total agenesis. Partial agenesis is identified as unicornuate uterus. In hypoplasia, the endometrial cavity is small with reduced intercornual distance of less than 2 cm.
   - Class II (unicornuate uterus) appears banana-shaped without the rounded fundus and triangular-shaped uterine cavity. If present, rudimentary horn presents as a soft tissue mass with similar myometrial echogenicity. Obstruction in the rudimentary horn is recognized as haematometra on one side.
   - Class III (uterus didelphys). The two horns are widely separated, but vaginal septum is difficult to identify.
   - Class IV (bicornuate uterus) shows two uterine cavities, with concave fundus, with fundal cleft greater than 1 cm, and this differentiates between the bicornuate and the septate uterus. The intercornual distance is more than 4 cm.
   - Class V (septate uterus) shows a convex or flattened fundus. The intercornual distance is normal (<4 cm) and each cavity is small.
   - Class VI (arcuate uterus) with no fundus is of no clinical importance.
2. **Uterine polyp.** Endometrial polyp is sessile, single or multiple, less than 1 cm in size and homogenous with the surrounding endometrium, as it is formed by folding in of endometrial hyperplasia. Submucus polyp on the other hand is larger than 1 cm, sessile or often pedunculated, mobile. It has a different texture as compared to the endometrium. Sonosalpingography reveals a polyp, but cannot differentiate between submucus and endometrial polyp. TVS yields better image than TAS.
3. **Endometrial cancer.** Apart from endometrial thickness, endometrial irregularity, increased blood flow by Doppler and disruption or absence of subendometrial halo suggest myometrial invasion best seen on TVS.
4. **Uterine fibroids.** It is not only important to confirm clinical diagnosis of uterine fibroid, but it is necessary to assess the number, size and location to plan the management and decide on the type of surgery required. A rapid increase in the size of the fibroid in a menopausal woman suggests sarcomatous change in a fibroid.
5. **Ovaries.** The ovaries contain heterogenous morphology and several pathological changes can be identified by ultrasound.
   - Functional cyst. It is the most common ovarian finding in the reproductive age group. A follicular cyst may be persistent at times, but never grows more than 5 cm and spontaneously resolves within a month or so. A Graafian follicle starts growing soon after menstruation, and grows by 1–2 mm near ovulation, reaching about 20 mm in size or little larger. Ovulation is recognized by its disappearance at ovulation and presence of free fluid in the pouch of Douglas. This is followed by growth of corpus luteum. The corpus luteum cyst has a thick, hypoechoic, sometimes irregular wall and has echogenic content. Haemorrhage in the cyst reveals as internal low-level echoes. A functional cyst may be persistent at times, but never grows more than 5 cm and spontaneously resolves within a month or so.
   - **Ovarian hormonal hyperstimulation syndrome (OHSS)** has been described in Chapter 43.
   - PCOD is characterized by more than 12 small follicles, 2–9 mm in size placed peripherally giving a necklace appearance
   - Endometriosis. Ultrasound shows varied appearance ranging from an anechoic cyst, with low echoes with or without solid components to a solid-appearing mass, resembling dermoid cyst, benign neoplasm and fibroid.
6. **Fallopian tubes (PID).** Ultrasound shows one or more of the following features:
   - Thickening of the tube wall of more than 5 mm.
   - 'Cogwheel' sign, defined as cogwheel-shaped structure visible in cross-section of the tube with thick walls in acute salpingitis.
   - Incomplete septa with dilated tube, which is sonolucent or contains low-level echoes.
   - Beaded appearances measuring 2–3 mm seen in a fluid distended structure. Cul-de-sac may show presence of free fluid in the pouch of Douglas in acute infection.
   - Hydrosalpinx appears as a retort-shaped or tubular cyst showing incomplete septa and the ovary in the vicinity of the lesion.
7. **Infertility.** Ultrasound has a vast role in the infertility work-up. It is used for:
   - Sonosalpingography which delineates the uterine cavity and studies the patency of the fallopian tube.
   - Detecting unsuspected endometriosis.
   - IVF—To monitor ovulation, to retrieve ova and embryo transfer under ultrasound guidance.
   - In a male, to detect varicocoele.

To decrease the cost and invasiveness of gamete intrafallopian transfer technique (GIFT), some employ transvaginal ultrasound to retrieve ova and transfer oocytes and sperms into the fallopian tube from below by ultrasound-guided catheterization.

Sometimes, the abnormal findings on ultrasound are incidental and have no bearing on a woman's symptoms and clinical features. It is important therefore, to correlate these findings with clinical features. The role of ultrasound is discussed in Table 8.1.

TABLE 8.1 Role of ultrasound

Diagnostic	Therapeutic
• Endometrial study—endometrial thickness irregularity, polyp, endometrial biopsy, haematocele, haematometra • Uterus—fibroid, adenomyosis misplaced IUCD, Asherman syndrome, endometrial tuberculosis, intermenstrual bleeding, postmenopausal bleeding, menorrhagia, biopsy, uterine abnormality, absent uterus • Falloposcopy • Tubal ectopic pregnancy • Tubo-ovarian mass • PID, ovary: PCOD ovarian cyst differentiate between benign and malignant ovarian tumour • Ovarian monitoring • Pelvic endometriosis • Chronic pelvic pain • Infertility—saline salpingography • Varicocele in male	• IVF—ova retrieval • Drainage of pelvic abscess • During falloposcopy • Retrieval of IUCD • Injection of methotrexate, KCl in ectopic pregnancy • MTP under ultrasound guidance • Evacuation of a molar pregnancy • Drainage of a simple ovarian cyst

Computed Tomography Scan

In gynaecology, CT supplements information obtained on ultrasound examination. The advantage of CT is its easy availability and the ability to survey the whole abdomen and pelvis accurately and rapidly in one sitting. CT is accurate in assessing local tumour invasion and enables accurate localization for biopsy. CT can also demonstrate other masses (Figure 8.16) and abnormalities of extragenital origin. However, both CT and the MRI cannot detect small peritoneal metastatic implants and lymph nodes in cancers of less than 1 cm in size.

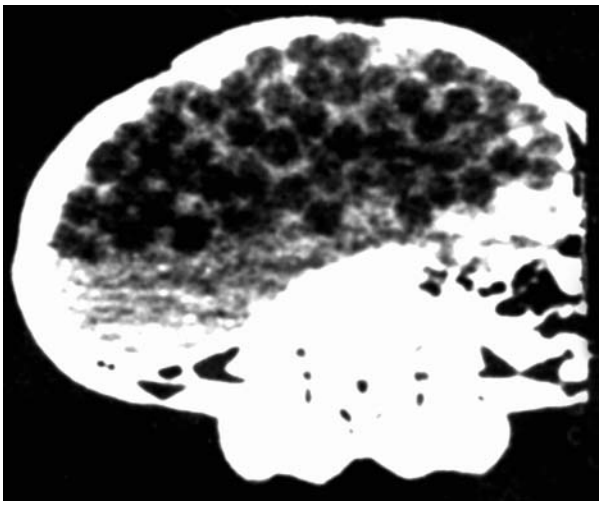

Figure 8.16 CT scan showing dermoid cyst. (Courtesy: Diwan Chand Satyapal Aggarwal Imaging Research Center, New Delhi.)

Recently, *spiral CT* has been introduced into clinical practice. This enables continuous volumetric data acquisition in a single breath-hold. This potentially offers improved lesion detection, optimization of contrast media enhancement and multiplanar or 3D image information.

Technique

Before undertaking a CT scan, exclude the possibility of pregnancy. The patient is required to have a full bladder. The patient is given 600–800 mL of a dilute oral contrast medium about 1 h prior to commencement of the procedure. Just before starting, a vaginal tampon is inserted to help delineate the position of the vaginal vault and cervix, and a rectal contrast medium given. The oral and rectal contrast media help to differentiate bowel loops from other pelvic organs. The patient is scanned in supine position. In gynaecologic malignancies, intravenous injection of iodinated contrast medium is recommended to improve tumour delineation, characterization, assess vascularity and lymph node identification.

Advantages of CT are as follows:

- It is useful in the diagnosis of intra-abdominal abscess.
- It is useful to diagnose pelvic vein thrombophlebitis.

Disadvantages of CT are as follows:

- It is expensive.
- Radiation up to 2–10 cGy does not permit its use in obstetrics.
- CT scan does not pick up lymph nodes less then 1.0 cm in size.

Indications

In cancer cervix, local recurrence, parametrial infiltration and lymph nodes more than 1 cm can be identified. However, it cannot differentiate between malignant infiltration and fibrosis.

- Endometrial cancer—myometrial invasion can be studied.
- In ovarian cancer, intrahepatic metastasis and paraaortic lymph nodes can be identified. It is also useful to detect pituitary tumour and brain metastasis in choriocarcinoma, hyperprolactinaemia and amenorrhoea.
- To diagnose intra-abdominal abscess, pelvic vein thrombosis.

Magnetic Resonance Imaging

MRI is the well- established cross-sectional imaging modality. It provides multiplanar imaging capability with high soft tissue contrast resolution without interference from air or bone. There is no need for administration of oral contrast or for injection of intravenous dye for vascular contrast. MRI, unlike CT, has no adverse effects on pregnancy, embryo, fetus or future reproductive potential of the ovary

as it has no radiation effect. The major limitations are availability, time and expenses involved.

Indications

- To assess pelvic anatomy and endometriosis.
- To evaluate Müllerian anomalies.
- Localize the position and size of the fibroids (Figure 8.17A and B) and sarcomatous change.
- Staging and assessment of pelvic neoplastic diseases—in cancer cervix and uterus.
- Assess adnexal pathology, endometriosis and chocolate cyst.
- To assess depth of myometrial invasion in case of endometrial carcinoma.
- Staging of cervical cancer and detection of recurrence.
- Assess recurrent pelvic disease and metastasis.
- In obstetrics, it can pick up fetal anomalies.
- Detection of lymph nodes metastasis.
- MRI-guided therapeutic procedures used in fibromyomas and adenomyosis.

Contraindications

- Patients with a pacemaker or cochlear implant.
- Metallic foreign body in the eye.
- Paramagnetic aneurysm clips.
- Overanxious patients need prior sedation.
- Those who suffer from claustrophobia may not stand the procedure well. However, newer open machines are now available which overcome this disadvantage.
- Epileptic and women with atrial fibrillation because electroconvulsions can occur.

Indications of CT and MRI are discussed in Table 8.2.

Radionuclide Imaging

This form of imaging in gynaecology is used for specific clinical situations. Bone scans using *technetium*-99 m diphosphonate are used to detect bone metastasis in patients with malignancies. *Ventilation perfusion scans* are used for detecting pulmonary emboli. *Radio-labelled white cell* scans can be used for locating abscesses.

Dual Photon Densitometry

The use of this imaging technique is becoming increasingly popular in determining the risk of osteoporosis in postmenopausal women. It is recommended in women who suffer from early menopause or who undergo oophorectomy. The lumbar spines and hip are scanned with a dual photon densitometer, which produces computerized graphs and measurements of bone density and relates them to age-related normal values.

Positron emission tomography (PET) is a functional diagnostic imaging technique, taking note of the fact that malignant cells have a greater glycolysis as compared to normal tissue. It helps in initial staging, management and follow-up of cancer growths. PET-CT combines the anatomical details with metabolic status of the lesion.

[F-18]-fluoro-2 deoxy-D-glucose (FDG) is used as radiopharmacological agent which is an analogue of glucose. Glucose uptake by malignant cells is higher than that of normal cells. PET maps the tissue spread. It also helps to distinguish cell death following radiotherapy from tumour recurrence, and helps in post-treatment management.

Positron emission tomography (PET) scan is a nuclear biological modality and functional diagnostic image technology using radioactive material given orally, injected into the body or inhaled. It is now used in the diagnosis of cancer in its early stage, detect its extent and severity and also assess the patient's response to therapeutic interventions by studying the molecular activity in the tissues. It is noninvasive. PET scan measures the blood flow to the organ, oxygen consumption and glucose metabolism, which is high in the cancer cells.

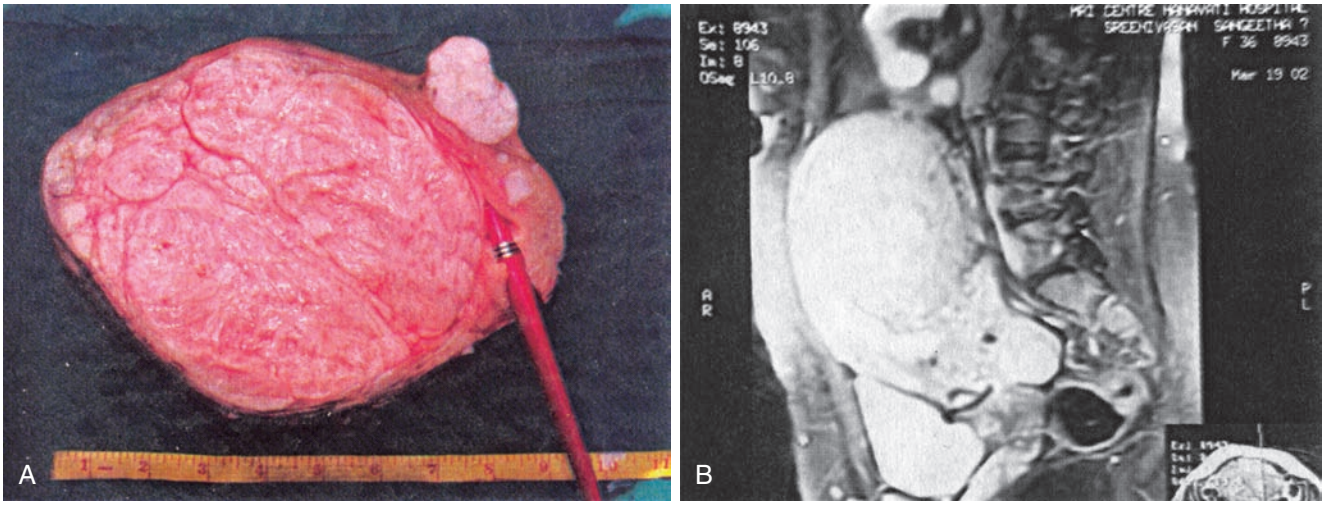

Figure 8.17 **(A)** Mirror image of fibroid seen on MRI. **(B)** MRI showing fibroid uterus.

TABLE 8.2 Indications of CT and MRI

CT	MRI

Diagnostic
• Endometrial cancer staging, lymph node assessment, recurrence
• Cancer cervix extension, lymph node involvement recurrence
• Ovarian cancer staging, lymph node involvement, recurrence
• Pituitary tumour
  ◦ Hyperprolactinaemia
  ◦ Amenorrhoea
  ◦ Cerebral metastasis
• Abdominal abscess
• Pelvic vein thrombosis
Contraindicated in obstetrics—radiation
	• Endometrial cancer—same as CT
	• Müllerian anomalies
	• Endometriosis
	• Fibroid, sarcoma
	• Cancer cervix—same as CT
	• Ovarian cancer
	• Obstetrics to detect fetal anomalies
	Therapeutic
	MRI-guided procedures in uterine fibroids and adenomyosis

Combining with CT, which provides anatomical details and PET showing metabolic status, it improves the accuracy of the tests.

'Hot-spots' are detected where large amounts of radiotracer have accumulated, and these spots are mapped in planning therapy.

Preparation:

The woman should not eat food for a few hours as this causes misinterpretation of the test, but take plenty of oral fluids. PET takes 30 min to perform, and CT about 2 min.

PET is contraindicated in the following:

- Pregnancy and lactation, because of radiotracer.
- Diabetes—one should be careful, as tissue blood sugar is usually high.
- An obese woman as she may not fit into the narrow machine.
- All metals, i.e. hairpins, jewellery and metal implants should be removed.

Sensitivity of PET is 80–90%. The role of PET is well established in cancer of the cervix, but more study is required to know its usefulness in endometrial and ovarian cancer.

Key Points

- Several newer imaging modalities have come into vogue for a more accurate assessment of the clinical problems under review.
- A plain radiograph in gynaecological practice involves a PA view of the chest as part of the preoperative work-up of patients undergoing surgery. X-ray chest is required in suspected lung metastasis in choriocarcinoma and endometrial cancer.
- A hysterosalpingogram is performed to test tubal patency in infertility, intracavitary uterine lesion and to demonstrate Müllerian anomalies of the uterus.
- Ultrasonography has now become the first line of imaging investigation in the management of gynaecological problems because of its wide availability and low cost. It is an excellent first-line investigation to determine the location and nature of the pelvic pathology. Ultrasound is noninvasive and the report is available on the spot.
- CT scan and MRI are used as additional tools to define the limits of the neoplasms and to determine spread to adjacent structures and lymph nodes. These have a great role to play in staging of genital cancers.
- A Doppler examination helps to determine the pattern of blood flow in the organ, identify an ectopic pregnancy and detect suspicious malignant tumours.
- Sonosalpingography is superior to hysterosalpingogram to identify intrauterine growth and polypus.
- PET is the latest technology which studies the metabolic status of the tumour, and when combined with CT gives anatomical details also.

Self-Assessment

1. What is the role of hysterosalpingography in the practice of gynaecology?
2. Discuss the importance of ultrasonography as an imaging modality in obstetric practice.
3. What is the role of TAS and TVS in gynaecological practice?
4. Write short notes on (a) Colour Doppler and (b) Role of CT and MRI scans in gynaecology.
5. What is the role of dual-photon bone densitometry in gynaecological practice?

Suggested Reading

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Chapter 9

Malformations of the Female Generative Organs

CHAPTER OUTLINE

Development of the Female Generative Organs

There is a close relation between the genital glands, the urinary organs and the uterus with its appendages during early intrauterine life (IUL). Congenital anomalies of the urinary and genital tract cause long-term effects on continence, sexual and reproductive functions. If a transverse section is cut through the upper part of the coelomic cavity of an embryo of 8 weeks' development, the primitive mesentery is seen to project into the coelomic cavity posteriorly near the midline. On each side of the primitive mesentery another projection, the intermediate cell mass can be distinguished. On the inner side of the *intermediate cell mass,* by the end of the eighth week, a ridge has appeared—the genital ridge. The *Wolffian body* with primitive tubules and primitive glomeruli occupies the rest of the intermediate mass (Figures 9.1 and 9.2).

The *primitive urinary system* consists of the pronephros, the mesonephros or Wolffian body and the metanephros, which gives rise to the permanent kidney. Each of these systems is derived from the urogenital plates of the primitive somites. The pronephros corresponds to the hinder cervical, the Wolffian body to the dorsal and lumbar while the metanephros is sacral in origin. Each system consists of a series of tubules and a collecting tubule or duct. In the human female the pronephros disappears, and the Wolffian body is represented by the straight tubules of the epoophoron, or organ of Rosenmüller, found in the mesosalpinx of the adult while the tubules of the paroophoron represent the relics of the renal tubules of the Wolffian system, and the Gartner's duct represents the Wolffian duct (Figure 9.3). The metanephros gives rise to the tubules of the permanent kidney while the ureter and renal pelvis are formed from a diverticulum from the lower end of the Wolffian duct. In an embryo, two ridges appear between fifth and eighth week, mesonephric (Wolffian) and paramesonephric ducts. The former disappears in a female, and paramesonephric duct (Müllerian) develops into female genital organs. The uterus, fallopian tubes and most of the vagina are derived from the Müllerian duct in the absence of Y chromosome. The Müllerian duct is formed as a result of invagination of the mesothelium of the coelomic cavity on the ventral part of the intermediate cell mass. The invagination extends from the pronephros region above to the sacral region below, and both ducts terminate in the primitive cloaca. The position of the Müllerian duct is of importance, for it lies ventral to the Wolffian duct on the outer surface of the intermediate cell mass. In the human embryo, the caudal parts of the two Müllerian ducts fuse to form the uterus while the upper parts remain as the fallopian tubes (Figure 9.3).

The uterus itself can be identified as early as the end of the third month. The upper end of the Müllerian duct becomes the abdominal ostium of the fallopian tube, and it is not uncommon for small accessory ostia to be found (Figure 9.4). *Thus, the normal development of Müllerian system comprises organogenesis, fusion and later septal resorption.*

In its early stages of development the uterus is bicornuate, corresponding in form to the uterus of lower Mammalia. Later, as the result of fusion of the two Müllerian ducts, a single uterus with a midline septum remains. During the fifth month of IUL the septum disappears and all that is left of it in the adult uterus is the anterior and posterior columns of the mucous membrane of the cervical canal. The muscle wall of the uterus is differentiated from mesoblastic tissues, and during the fifth month a circular layer of muscle can be distinguished. The longitudinal muscles of the

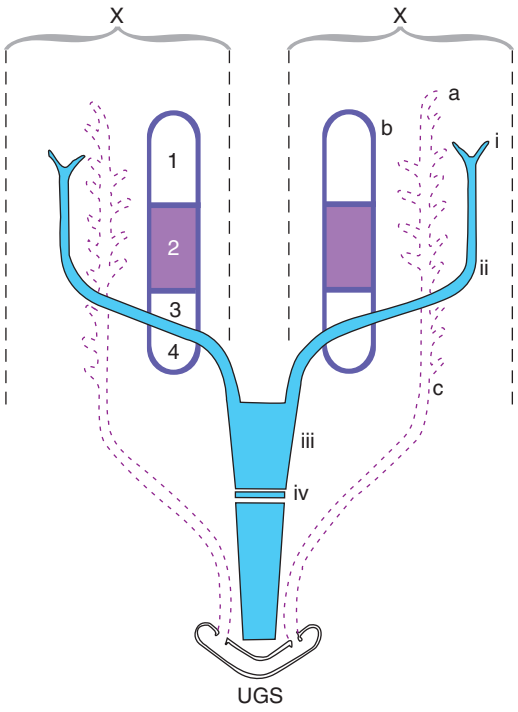

Figure 9.1 Diagram of urogenital system: X—intermediate cell mass—shaded areas is the genital ridge. (1) Infundibulopelvic ligament, (2) ovary, (3) ovarian ligament, (4) round ligament. Dotted outline is Wolffian duct (Gartner's duct). (a) Pronephros, (b) epoophoron, (c) mesonephros. Solid block is Müllerian ducts. (i) Fimbria, (ii) fallopian tube, (iii) uterus, (iv) upper three-fourth of the vagina. UGS—urogenital sinus.

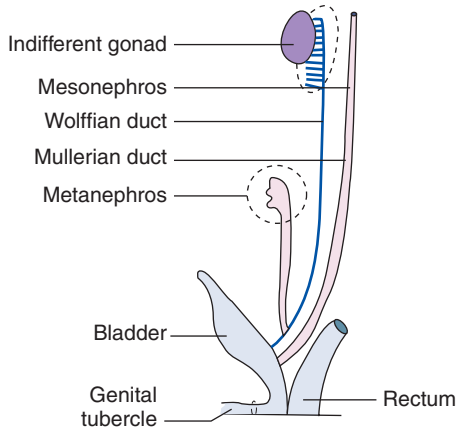

Figure 9.3 Development of genital tract—undifferentiated stage.

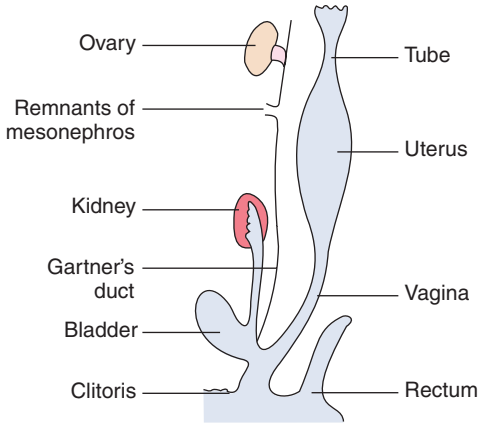

Figure 9.4 Female genital tract development.

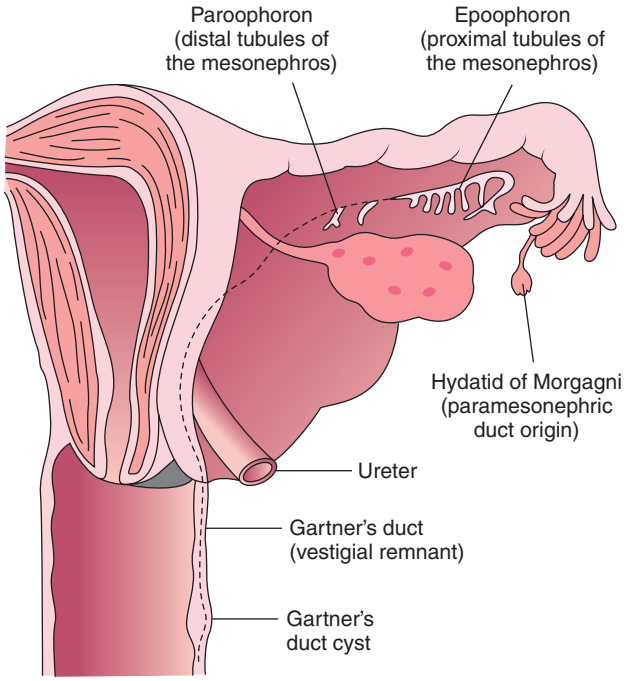

Figure 9.2 Remnants of the mesonephric (Wolffian) ducts that may persist in the anterolateral vagina or adjacent to the uterus within the broad ligament or mesosalpinx.

uterus can be recognized during the seventh month, and this muscle layer is continuous morphologically with the plain muscle tissue of the ovarian ligament, the round ligament and the muscle fibres found in the uterosacral ligaments (Figure 9.5).

The *primitive cloaca* is divided by the formation of the urorectal septum into a ventral part, the urogenital sinus, and a dorsal part, the rectum. The urorectal septum ultimately develops into the perineal body. The lower ends of the Müllerian ducts terminate in the urogenital sinus, into the posterior part of which they project as a solid Müllerian tubercle. Around this Müllerian tubercle, there is a solid proliferation of the urogenital sinus on each side, called the sinovaginal bulbs. *By canalization of the sinovaginal bulbs, the lower quarter to one-third of the vagina is formed and the hymen represents the remnants of the sinovaginal bulb*. Incomplete breakdown is one cause of congenital vaginal atresia or vaginal septum.

The vagina is therefore developed in its upper three-quarters from the fused Müllerian ducts and represented at its lower end by the solid Müllerian tubercle, which subsequently becomes canalized. The lower quarter of the vagina is developed from the sinovaginal bulbs of the urogenital sinus, which also becomes canalized. The epithelium of the vagina and the portio vaginalis of the cervix, since it is

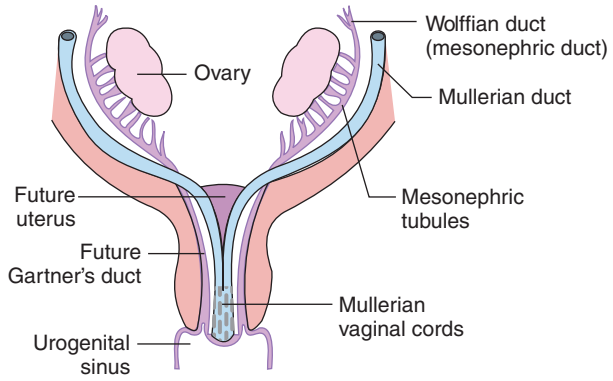

Figure 9.5 Müllerian and Wolffian system.

stratified, are derived from an upgrowth of the epithelium of the urogenital sinus. This is comparable to the stratified epithelium of the anal canal. The vertical fusion between the Müllerian systems and the sinovaginal bulb results in the formation of the vaginal canal.

In the early stage of the development, the cervix of the uterus is longer and thicker than the body, and this proportion persists until puberty. The proportion may persist in adult life, when the uterus is described as infantile in type. The cervical glands can be recognized in the sixth month while the glands of the body of the uterus develop only during the last month of IUL though primitive glands are present at the fourth month.

The Urogenital Sinus and the External Genital Organs (Figures 9.6 and 9.7)

The cloaca becomes divided into two parts by the development of the urorectal septum, which originally consists of two folds which project on each side and then fuse caudally to divide the cloaca into a dorsal part, the rectum, and a ventral portion, the urogenital sinus. The primitive cloaca is closed by the cloacal membrane, which can be recognized very early in the development of the embryo and from which the vessels of the allantois are developed. The primitive intestines enter the dorsal part of the cloaca. Both Wolffian ducts, both Müllerian ducts and the allantois, from

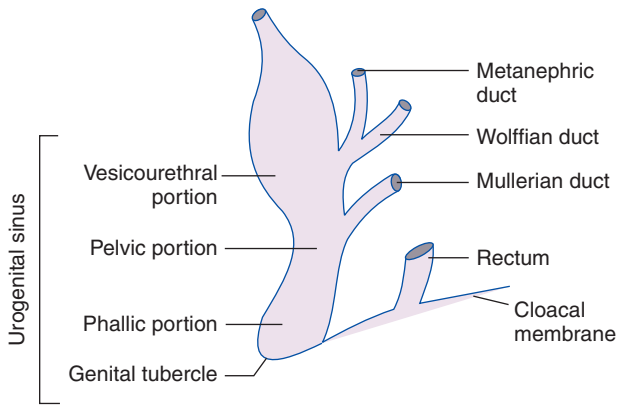

Figure 9.6 Development of the lower genital organs.

which the bladder and the urethra are differentiated, enter the urogenital sinus. Originally, the ureter arises from the lower end of the Wolffian duct near the opening of the duct into the urogenital sinus. Subsequently, as a result of the growth of the surrounding mesoblastic tissues, the ureter is displaced cranially so that it enters the urogenital sinus independently of the Wolffian duct. This displacement of the ureter explains the aberrant type of ureter which is sometimes encountered in gynaecological surgery. The part of the urogenital sinus which lies ventral to the mouths of the Wolffian ducts becomes differentiated into the bladder while the allantois is represented by the urachus passing upwards from the apex of the bladder to the umbilicus. Prior to ninth week, it is not possible to recognize the fetal sex by external genitalia. In a male, the genital tubercle elongates to form a phallus, and by 12th week, urethral opening is located in the phallus.

The clitoris is developed from the genital tubercle, which appears about the fifth week and is originally a bilateral structure derived from mesoderm. From the region of the genital tubercle, a genital fold passes backwards lateral to the urogenital sinus to form the labium majus (scrotum in the male). Between the genital folds lies the urogenital or anterior part of the cloacal membrane which breaks down to form the labia minora (sixth week). The vestibule and urethra are thus derived from the anterior part of the urogenital sinus, and Bartholin's glands and Skene's paraurethral glands are developed from downgrowths of the urogenital sinus. The female urethra represents the upper part of the male urethra, and the para- and periurethral glands are homologous of the male prostate. The external genitalia (Figure 9.8) is recognizable by the 12th week of IUL. In a female, urethral groove remains open to form the vestibule.

Development of the Ovary

Ovary starts to develop by the fifth week. The ovarian differentiation is determined by the presence of a determinant located on the gene of the short arm of X-sex chromosome though the autosomes are also involved in the ovarian development. Two intact sex chromosomes (XX) are necessary for the development of the ovaries.

The genital ridge extends from the pronephric region above to the sacral region below and, in its earliest form, is represented by an elongated vertical prominence. Very soon it develops a mesentery of its own, the mesovarium, by which it is attached to the intermediate cell mass. The infundibulopelvic fold passes upwards from the upper pole of the ovary and contains the ovarian vessels. The ovarian vessels of the adult, arising from the abdominal aorta, illustrate the original lumbar position of the upper part of the genital ridge. The genital fold of peritoneum passes downwards from the lower pole of the ovary to the region of the internal abdominal ring. The Müllerian duct originally lies on the outer aspect of the genital ridge, but it crosses the genital fold below. As the Müllerian duct crosses the genital fold, the two structures fuse, and after muscle

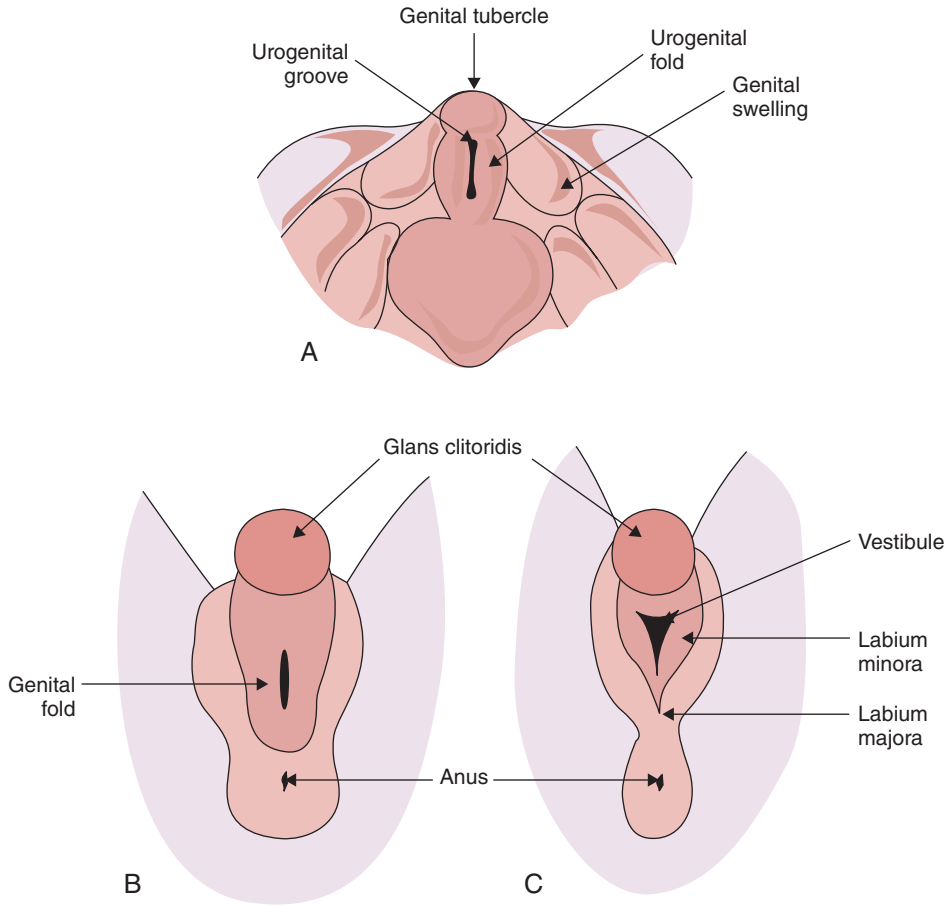

Figure 9.7 Development of the external genitalia.

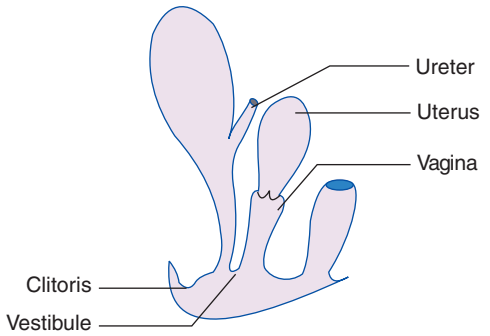

Figure 9.8 **(A)** Development of the lower genital tract in female.

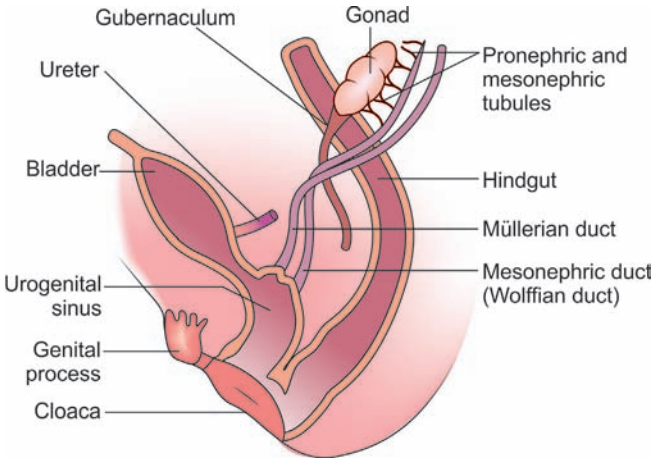

Figure 9.8 **(B)** Undifferentiated stage 12–14 mm embryo.

tissue has formed around the Müllerian duct, it passes into the tissues of the genital fold. The part of the genital fold lying proximal to its point of intersection with the Müllerian duct becomes the ovarian ligament while the distal portion becomes the round ligament (Figure 9.1). This corresponds to the gubernaculum of the male. The ovaries are developed by the 12th week.

Undescended ovaries. At birth, the ovaries are located at the pelvic brim. They gradually descend to the pelvis by puberty. Undescended ovaries (rare) are associated with absent Müllerian system or unicornuate uterus and can confuse the ultrasound scanning. The undescended ovaries are at risk of malignancy as with undescended testes.

The undescended ovaries are seen in the absence of bilateral Müllerian duct in as much as 40% cases and unicornuate uterus in 20% cases. The ovaries can be located by ultrasound scanning, computed tomography (CT) and magnetic resonance imaging (MRI).

The significance of undescended ovaries is as follows:

- They are associated with Müllerian duct anomalies and may adversely influence the menstrual and reproductive functions.
- Ovulation monitoring may be difficult.
- Ovarian pain may be misinterpreted as appendicitis or intestinal pain.

- Ovarian tumour may be misinterpreted as other abdominal tumour.
- Risk of malignancy.

Since these abnormally located ovaries may develop malignancy, it may be advisable to remove them and put the woman on hormonal replacement therapy. In vitro fertilization with donor egg may be possible if the uterus is present.

The ovary descends from its original lumbar position so that at term it lies at the level of the pelvic brim with its long axis directed vertically.

The sex germ cells first appear in the genital ridge. It is accepted at the present day that the germ cells originate in the endodermal cells of the yolk sac by the fourth week from the hind gut of the embryo and migrate along the dorsal mesentery to the genital ridge. At first, the sex cells are arranged in columns perpendicular to the surface by the sixth week. These columns are called primary sex cords and they lie deeply in the substance of the genital ridge. At a later date, secondary cords develop nearer to the surface epithelium. Both primary and secondary cords consist of cells derived, in the main, from the local stroma of the genital ridge. The egg cells or primordial ova are distinguished by their large size and peculiar mitochondria. It is believed that the sex cells act as organizers to the adjacent stroma cells, which then become converted into granulosa cells. In the male, the cells of the primary cords predominate while in the ovary the secondary cords are most marked. Nevertheless, relics of the primary cords may persist under exceptional conditions in the hilum of the ovary. One theory of the aetiology of the virilizing ovarian tumours is that such tumours are derived from these rudiments. In the ovary, the cortex enlarges, but the medulla shrinks. The reverse occurs in the testes.

Urogenital differentiation in the embryo is a rather complex process involving genetic, hormonal and environmental influences. Since the genital and urinary systems develop in close relationship, developmental errors in both these systems often coexist. Some anomalies are obvious at birth, but most come to light only at puberty, when the girl fails to menstruate. Modern technologies in reconstructive surgery for congenital anomalies have yielded good results and enabled the patient to be satisfactorily rehabilitated. Such abnormalities account for less than 1% of all gynaecological cases, but they can contribute to failure of consummation of marriage, infertility, pregnancy losses and other gynaecological problems requiring surgical rectification.

Gonad

The chromosomal sex of the fertilized ovum determines the development of the embryonic gonad into the ovary or the testis, and this in turn directs the further differentiation and development of the internal and external genital organs. The gonads remain undifferentiated until sixth week.

About the sixth week of IUL, a genital ridge appears (crown-rump length of 5 mm) (Figures 9.1–9.5) on the dorsal aspect of the embryo, on either side of the midline. It consists of proliferation and thickening of the coelomic epithelium overlying some mesenchymal tissue near the developing kidney. In the female embryo, germ cells originate in the endoderm of the yolk sac near the developing hindgut; they migrate along the root of the dorsal mesentery to enter the developing gonad. Columns of coelomic epithelial cells designated as sex cords invade the cortex of the developing gonad and surround the germ cells, thus forming the primitive primordial follicles. The primordial follicles are recognizable by 20th week of IUL. These proliferate to reach about 7 million at the seventh month of fetal life. However, as the gonadal stroma proliferates, many of these follicles degenerate, so that the ovaries at birth contain about 2 million follicles. Of these, only 300–400 will ever ovulate.

The first meiotic division begins in the oocyte by 20th week in the embryo, but remains dormant in the prophase until ovulation occurs at puberty. The second meiotic division occurs only at fertilization when the sperm penetrates the zona pellucida. The ovary plays no role in the development of internal genital organs.

By the 10th week of IUL, the female gonad assumes histological characteristics of the ovary. The basic sexual pattern is female in all embryos. It is the androgen of testicular origin in the male embryo which causes the male elements to grow. Its absence in the female embryo permits development along the female line. In the male embryo, the fetal testis elaborates two substances: (i) a Müllerian suppression substance which inhibits the development of the Müllerian ducts, Müllerian-inhibiting factor (MIF) glycoprotein secreted by the Sertoli cells of the testes, and (ii) testosterone derived from Leydig cells, which is responsible for completing the development of the Wolffian structures, and fusion of the labioscrotal folds and development of the phallus, so that the external genitalia develop along the male line. In the absence of androgen, the genital organs develop along the female line. The male external genitalia develop in response to dihydrotestosterone derived by conversion of testosterone by enzyme 5 α-reductase.

If the early embryonic state of bisexuality persists into adult life, it results in the rare state of the true hermaphrodite wherein masculine and feminine elements are observed in the gonad as well as the external and internal genitalia.

In the female pseudohermaphrodite, the gonad and Müllerian system are normal, though perhaps underdeveloped as far as the level of the urogenital sinus. The Wolffian vestigia persist as usual, but the phallus (clitoris) is hypertrophic, the labia appear fused in the midline and the urogenital sinus opens at the base of the phallus. Such females may be regarded as males with a hypospadias. The source of the androgen responsible for the altered development of the external genitalia is commonly the adrenal gland. The underlying adrenal hyperplasia may cause electrolyte imbalance, with feeding difficulties at birth, often leading to death in early life. Knowledge of the nuclear sex at birth is essential to decide the proper sex of rearing.

If the female embryo in utero is exposed to androgen secreted by maternal ovarian or adrenal neoplasms (arrhenoblastoma or hilar cell tumour), or to progestogens which are mildly androgenic, then such altered hormonal influence can lead to varying degrees of masculinization of the female fetus.

Complete aplasia of ovary is rare, but agenesis appears as a streak ovary in Turner's syndrome. The streak ovary contains undifferentiated stroma devoid of germ cells. This happens if the chromosome pattern is 45/XO, when the germ cells fail to migrate along the dorsal mesentery into the gonad.

Müllerian Ducts

It is desirable to recapitulate the development of the Müllerian ducts.

In the seventh week of IUL of the embryo, an invagination of coelomic mesothelium occurs close to the primitive gonad, in the upper lateral portion of the intermediate cell mass; this is called the Müllerian duct (paramesonephric duct). As the two Müllerian ducts, one on either side, develop and grow caudally, they approach each other in the midline after crossing the Wolffian duct (mesonephric duct) and fuse (Figures 9.1 and 9.9). The caudal tip of the fused Müllerian ducts called the Müllerian tubercle consists of a solid band of cells. It projects into the urogenital sinus; the intervening portion is filled up by a proliferation of cells called the sinovaginal bulbs. These bulbs later canalize to form the lower part of the vagina. The hymen represents the junction between the sinovaginal bulbs and the urogenital sinus. The cranial free parts of the Müllerian ducts develop into the fallopian tubes. The middle fused portion goes to form the uterus and cervix, and the caudal fused portion forms the upper three-quarter of the vagina. Initially, when the two Müllerian ducts fuse, the intervening septum is present, but later it disappears so that the uterovaginal canal appears as a single continuous passage. Myometrium and endometrial stroma are derived from adjacent mesenchyma, but the glandular epithelium of the uterus and cervix develops from the Müllerian duct. Arrest in the normal development of the Müllerian ducts can cause several anomalies as listed below (Jones' classification).

1. *Aplasia,* in which the organs fail to develop.
2. *Hypoplasia,* in which the organs are rudimentary.
3. *Atresia,* in which there is partial or complete failure of canalization of these ducts leading to varying degrees of gynatresia.

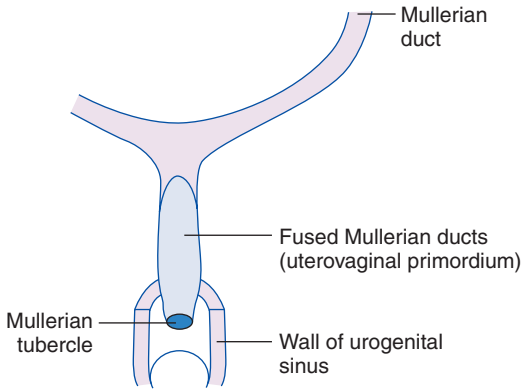

Figure 9.9 Diagrammatic representation of the embryology of the Müllerian duct system.

4. *Müllerian duct anomalies,* like asymmetric development, may lead to a unicornuate uterus, with or without a rudimentary horn. Failure of fusion in part or its entirety may lead to duplication of the genital tract, and failure of disappearance of the intervening septum may lead to a septate or subseptate uterus, which may coexist with a septate vagina.
5. *Hermaphroditism and pseudohermaphroditism* may be the result of abnormalities of development of the gonads, sex ducts and external genitalia.
6. *Developmental defects* of the urogenital sinus may manifest in the form of defective development of the urinary bladder, hymen and the perineum.

Structural homologues in males and females are discussed in Table 9.1.

Müllerian duct anomalies: Some anomalies are detected at birth, i.e. external genital organs. Primary amenorrhoea detects absent uterus. Some are revealed during investigations of infertility and repeated pregnancy losses. Although a great number of anomalies of the uterus have been described, these can be broadly grouped as follows:

1. ***Agenesis***
2. ***Anomalies arising out of defects in vertical fusion (Figures 9.10 and 9.21A)*** between the down growing fused Müllerian ducts and the up growing derivative from the urogenital sinus. These may manifest as (a) obstructive lesions or (b) nonobstructive lesions.
3. ***Anomalies arising out of defects of lateral fusion or resorption*** resulting in duplication defects. These may manifest as (a) obstructive lesions or (b) nonobstructive lesions.

The Müllerian ducts form the uterus and cervix, fallopian tubes and the upper 4/5th of the vagina. Where these ducts originate, these ducts are open or canalized. The ducts grow, descending caudally and medially by progressive development of a solid bud that canalizes simultaneously with its downward growth. By the 8th week of development, they have fused in the midline with the urogenital sinus, forming a solid mass termed as Müllerian tubercle. Next, fusion of the median septum of the Müllerian ducts proceeds cephalad from the Müllerian tubercle up to the junction of the future round ligaments. Shortly thereafter, the intervening septum between the ducts gets resorbed.

Congenital defects can occur because of the following:

(a) Failure of initial descent—agenesis.
(b) Failure of vertical fusion—transverse vaginal septum, imperforate hymen.
(c) Failure of lateral fusion—this may result in complete or partial duplication, which may be either symmetrical or asymmetrical. Symmetrical fusion defects would lead to bicornuate uterus or uterus didelphys while the asymmetrical fusion defects would result in one well-developed uterine horn with the other being rudimentary. Noncommunicating horn of the uterus is an example of obstructive defect.
(d) Defects in the resorption of the septum—example septate uterus.

TABLE 9.1 Structural homologues in males and females

	Male	Female	Determining Factor
Gonadal			
Germ cells	Spermatozoa	Oogonia	Sex chromosomes
Coelomic epithelium	Sertoli cells	Granulosa cells	
Mesenchyme	Leydig cells	Theca cells rete ovarii	
Ductal			
Paramesonephric duct (Müllerian)	Hydatid testis	Fallopian tubes, uterus and upper three-fourths of vagina	Absence of Y chromosome
Mesonephric duct (Wolffian)	Vas deferens seminal vesicles epididymis	Epoophoron Paroophoron Gartner's duct	Testosterone MIF
External genitalia			
Urogenital sinus	Prostrate Cowper's glands	Lower vagina Skene's tubercles Bartholin's gland	Presence or absence of testosterone and dihydrotestosterone
Genital tubercle	Penis	Clitoris	
Urogenital folds	Corpora spongiosa	Labia minora	
Genital folds	Scrotum	Labia majora	
Urogenital sinus	Bladder, urethra prostrate, bulbourethral glands	Lower portion of vagina, Bartholin gland, paraurethral gland, urinary bladder, urethra	

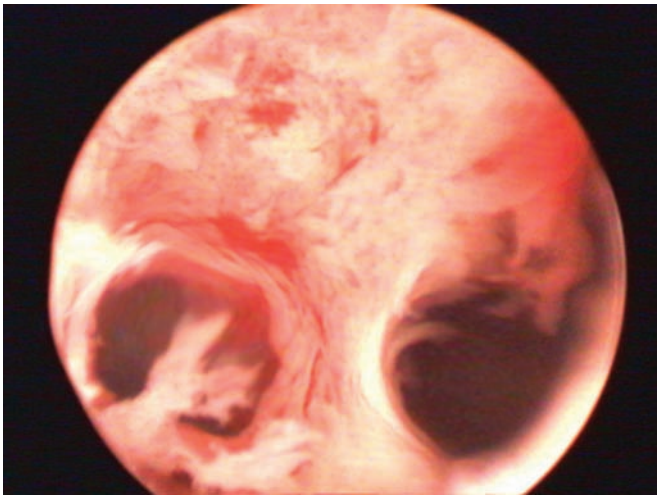

Figure 9.10 Hysteroscopy showing septum in the uterus dividing the uterine cavity. Laparoscopy revealed a single uterus. (Courtesy: Dr Shyam Desai, Mumbai.)

Detailed Consideration of Müllerian Defects

(a) Vertical fusion defects

1. *Vaginal Atresia:* Simpson (1976) stated that vaginal atresia is a condition in which the lower portion of the vagina is represented merely by fibrous tissue while the contiguous superior structures (uterus) are well differentiated.

2. *Transverse vaginal septum:* It occurs in upper portion of vagina in 50%, middle portion in 30–40% and lower portion in 10% cases.

(a) Imperforate hymen—this is entirely of urogenital origin. Failure of canalization may lead to formation of a mucocolpos, this may be recognized in early infancy and get treated. However, the anomaly often continues unrecognized until puberty, when amenorrhoea in the presence of secondary sexual characters, cyclic abdominal discomfort, urinary symptoms (retention of urine) and often the palpation of a midline hypogastric lump leads to the examination of the external genitalis, parting of the labia reveals the presence of a tell tale bluish bulging membrane in the region of the hymen that points to the diagnosis of haematocolpos. A simple cruciate incision followed by excision of the tags of hymen allows drainage of the retained menstrual blood. The operation should be performed under aseptic conditions and under an adequate antibiotic cover to avoid any ascending infection. The vagina regains its tone very quickly (Figures 9.11–9.16).

(b) Congenital absence of vagina—Müllerian agenesis (absent vagina)

Introduction

The common synonyms in clinical usage include Müllerian agenesis (MA), Mayer–Rokitansky–Kuster–Hauser (MRKH) syndrome and vaginal agenesis.

Defining Features

Clinically identified by absence of structures derived from Müllerian ducts, namely the uterus, cervix and upper vagina, 25% patients may have a short vaginal pouch. Rudimentary tubes are often present. The gonads are ovaries. The karyotype is XX, the disorder seems to be an accident of development. In clinical practice, the working diagnosis for any individual presenting with primary amenorrhoea, feminine secondary sexual characteristics and an absent vagina is MRKH syndrome (Griffin et al.

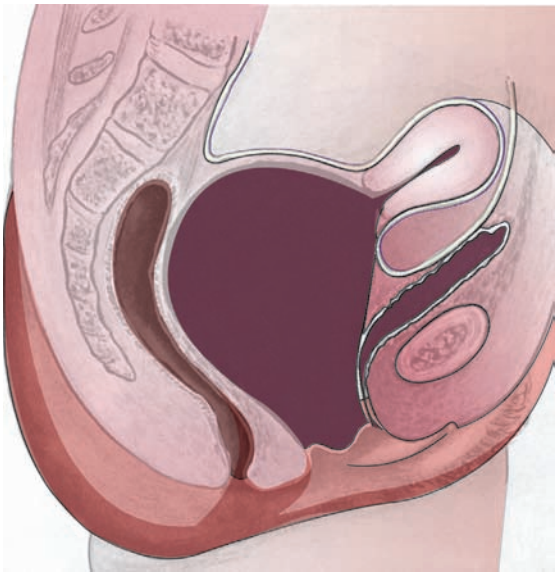

Figure 9.11 Haematocolpos. The illustration shows the distended vagina filled with blood.

Figure 9.12 Suprapubic bulge caused by haematocolpos.

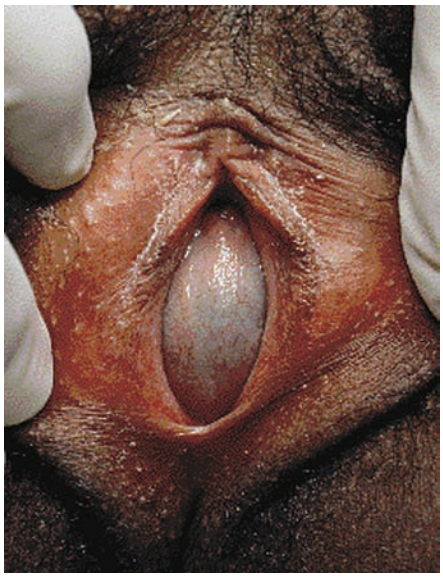

Figure 9.13 Vaginal introitus showing the bulging membrane caused by haematocolpos. (Source: Textbook of Gynaecology, India: Elsevier, 2008.)

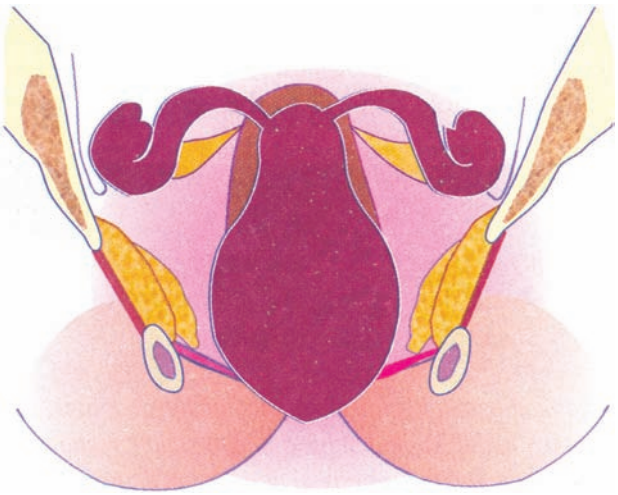

Figure 9.14 Imperforate hymen causing haematocolpos, haematometra and haematosalpinx.

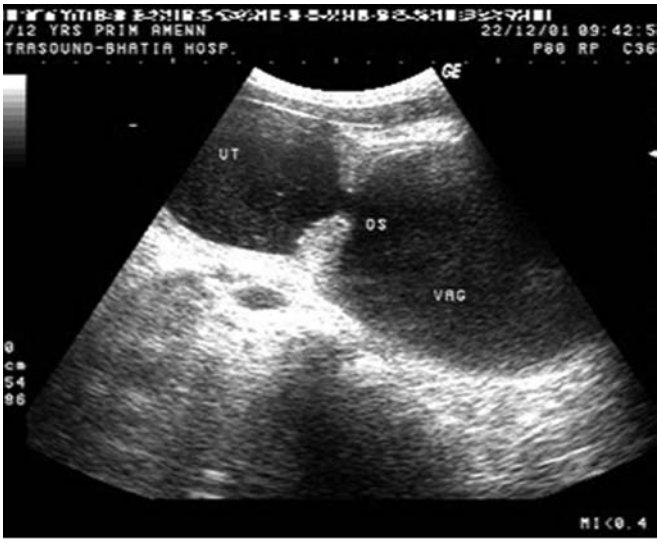

Figure 9.15 Imperforate hymen—ultrasonography showing haematocolpos (distended vagina) and haematometra (distended uterus). (Courtesy: Dr Rajeev H Kothari, Mumbai.)

1976) with a familial tendency in uterus is present in only 7–8% cases.

Clinical features:

- Ovaries present and functional
- Patients present with amenorrhoea
- Normal female external genitalia
- Secondary sexual characteristics—feminine
- Regression of Müllerian derivatives (tubes, uterus, cervix and upper vagina), incomplete regression may occur when rudimentary structures may persist
- Absent or short vagina
- Karyotype 46, XX
- Uterus not felt on rectal examination—not revealed on ultrasound

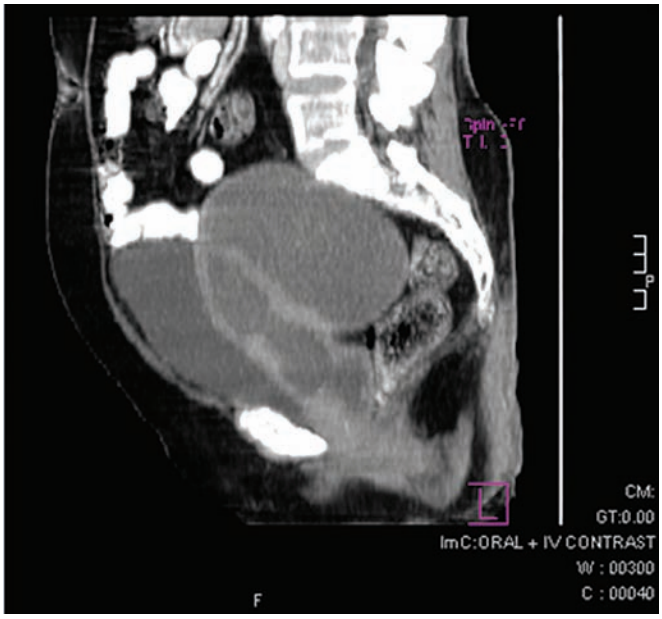

Figure 9.16 CT showing haematometra and haematocolpos. (Courtesy: Dr Parveen Gulati, New Delhi.)

- Skeletal and spine abnormalities often present (20–30%)
- Wolffian abnormalities known to occur, malrotation of kidney, ectopic kidney, (horseshoe kidney, pelvic kidney) and anomalies of urinary collecting system need to be investigated for—by intravenous pyelogram or ultrasound (40%)

Differential Diagnosis

- Imperforate hymen
- Transverse vaginal septum
- Complete androgen insensitivity syndrome (testicular feminization syndrome)

Imperforate hymen can be detected by observing the vaginal outlet. On performing the Valsalva manoeuvre, the membrane bulges. Pelvic sonography reveals presence of haematocolpos and presence of internal genitalia. Transverse septum reveals presence of a short vagina, absence of bulging on Valsalva manoeuvre. Testicular feminization or androgen insensitivity syndrome closely mimic one another, and efforts to differentiate between the two has therapeutic bearings. Differences between these two conditions have been tabulated below for quick reference.

Investigations

- Pelvis and abdomen ultrasound—pelvic organs and kidneys.
- MRI gives more precise definition of pelvic viscera.
- Karyotype.
- Laparoscopy (invasive procedure) may be avoided, extirpation of the Müllerian remnants is not necessary, unless it is causing problems such as fibroids, haematometra, endometriosis or symptomatic herniation into the inguinal canal.
- Radiology—descending pyelography to delineate urinary tract anomalies.

Müllerian Inhibiting Substance—MIS (Müllerian Inhibiting Factor—MIF)

- Derived from Sertoli cells (SC) and granulosa cells after puberty.
- Its likely mode of action is via the mesenchyme.
- Glycoprotein cleaved into two different protein products—the larger MIS secreted by the Sertoli cells of the embryonic testis and a smaller MIS derived from granulosa cells of postnatal ovary. Target cells may have the affinity to the MIS precursor molecule. The MIS receptor cells are present in Sertoli cells (embryonic testis), fetal and postnatal granulosa cells and the mesenchyme around the Müllerian ducts.
- The effects of MIS are dominant between 8–10 weeks of IUL.
- In *males,* the small MIS is elevated for several years after birth reaching very low levels during puberty. In *females,* MIS (small and large) below levels of assay sensitivity until puberty, later possibly play a role in ovarian gametogenesis.

Management

- Nonsurgical methods and surgical vaginoplasty for creation of neovagina should be ideally delayed until the patient becomes sexually active.
- Frank's nonsurgical method of using graduated vaginal dilators of 0.5–1.0 inch diameter and 4–5 inches in length is used to apply constant pressure to the vaginal dimple for 20 min t.i.d. for 6–8 weeks to achieve clinically acceptable results. Normal sexual function is possible in over 75% individuals. To maintain patency, vaginal dilator use should be continued until regular sexual intercourse begins. Other modifications of Frank's artificial vagina include Ingram's bicycle seat stool used for 2 h daily to maintain constant perineal pressure, Jaffe successfully modified Frank's dilation technique by using increasing sizes of syringe containers. Oestrogen creams help in vaginal epithelial transformation.
- Surgical method of vaginoplasty—the McIndoe operation of vaginoplasty using split-thickness skin graft spread over a mould and held in place in an artificial space created between the bladder in front and the rectum behind has been successfully performed and served functional use. Surgeons have also successfully used fresh amniotic membrane graft to line the vaginal space. HIV testing of the donor is required. Another surgical procedure which is simple to perform has been devised by Williams using labial skin. However, the axis of the artificial vagina points directly backwards.
- Tissue expansion vaginoplasty using tissue expander has also been tried with success.
- Shirodkar used a section of the sigmoid colon to prepare an artificial vagina, but this method was technically

difficult to perform, and the mucus secretion caused discomfort, hence this method is not currently practiced.

This condition, though commonly referred to as *congenital absence of the vagina*—a misnomer, is truly a developmental defect of the Müllerian ducts resulting in the condition described as the *Mayer–Rokitansky–Kuster–Hauser (MRHK) syndrome.* The MRHK syndrome occurs in 1:5000–1:20,000 women at birth, and is diagnosed in approximately 1:1500 gynaecologic admissions. The clinical features include primary amenorrhoea, partial or complete absence of vagina, a wide array of uterine abnormalities, skeletal/renal and other associated abnormalities, a normal female appearance and secondary sexual characteristics and a normal 46 XX karyotype. The ovaries are anatomically and functionally normal. These patients seek medical consultation because of primary amenorrhoea or in case of presence of functional uterus (1:10 cases)—because of cyclic abdominal pain occurring as a result of occult menstruation. Pelvic ultrasonography/MRI and laparoscopy help to establish the diagnosis.

Müllerian duct agenesis may result in the uterus represented by a nodule (rudimentary uterus) with hypoplastic or dimple vagina.

Surgery for creation of an artificial vagina must be undertaken only when the patient contemplates marriage. In presence of a functioning uterus, an artificial vagina communicating with the uterine cavity cranially can be performed to provide an outflow tract, successful pregnancies have been recorded.

Transverse vaginal septum can be very easily mistaken for congenital absence of the vagina. It is a rare condition having an incidence of 1:84,000 gynaecologic visits. The clinical symptoms will depend entirely on whether the septum is imperforate or otherwise. In case of a perforated septum, menstruation occurs and no difficulty is suspected until the time of marriage when apareunia may lead the patient to seek consultation, or at the time of pregnancy. If the septum is imperforate, the symptoms of amenorrhoea, and those resulting from mucocolpometra may call for attention. Ultrasonography helps to arrive at the diagnosis. The commonest site for the occurrence of a transverse septum is the junction of the upper and middle third of the vagina. Treatment consists of either manual dilatation from the microperforation or surgical excision of the septum. If the septum is thick and wide, reanastomosis of the upper and lower vagina may be difficult; it may require skin grafting to cover the intervening raw area.

Androgenic insensitivity syndrome—originally described as testicular feminization syndrome—needs to be differentiated from the Müllerian duct anomaly causing MRHK syndrome, which also presents with amenorrhoea and absent uterus. Androgen insensitivity syndrome is a genetically transmitted androgen receptor defect in a 46 XY individual with testes and normal testosterone levels. These individuals present with amenorrhoea, they have no internal male or female internal genitalia (absent uterus), normal female external genitalia, an absent or shallow vagina, a normal female phenotype with well-developed breasts, and scanty body hair. Ultrasound/MRI examination coupled with a karyotype XY helps to settle the diagnosis. Since the abnormal gonads are prone to malignancy, these should be surgically removed at an early date, soon after sexual maturity has been achieved.

(b) Lateral fusion defects—these include partial or complete duplication:

1. *Double or septate vagina*—this may occur with an entirely normal fallopian tubes uterus and cervix, or with duplication of the uterus. The longitudinal antero-posterior septum may be partial or complete extending right down to the vaginal outlet. Generally, both sides are patent, but in rare instances the septum may deviate from the centre and fuse with one lateral vaginal wall, so that one side of the vagina and uterus are obstructed and there is unilateral haematocolpos. The asymptomatic longitudinal septum may only come to light when the patient complains of soiling her clothes in spite of using a tampon during menses. Examination may reveal a septum with Müllerian duplication, wherein her placement of the tampon in one vagina cannot prevent egress from the other side, or it may be detected after marriage when it may be a cause of dyspareunia, or become apparent only at the time of labour. Symptomatic septum requires excision. A thick septum can be very vascular.

Complete nonfusion of the Müllerian ducts results in duplication of the genital tract.

2. *Duplication of the uterus*—defects in lateral fusion of the Müllerian ducts may result in partial or complete duplication, the two halves may be symmetrically developed or asymmetrically formed. These may result in obstructive or nonobstructive malformations. Symmetrical malformations include uterus didelphys, bicornuate uterus with double or single cervix, or an arcuate uterus depending on the extent of nonfusion. Asymmetric malformations include uterine duplication in which one uterine horn is fully developed and represented by a hemi uterus, and the other exhibits varying degrees of rudimentary development or may even be totally absent, clinically presenting as a rudimentary uterine horn communicating with the main well-developed horn, a noncommunicating rudimentary functional horn, a nonfunctioning rudimentary horn with considerable disproportion between the two horns or a unicornuate uterus. Wolffian duct anomalies often coexist with Müllerian duct anomalies, hence the importance in clinical practice to undertake an intravenous pyelography or ultrasound in all cases of Müllerian duct anomalies to detect presence of any coexisting urinary tract anomalies.

Detailed consideration of relevant anomalies of the Müllerian ducts

Classification. The following classification was proposed by Buttram and Gibbons in 1979. It was endorsed in 1988 by American Society of Reproductive Medicine.

Class I—Müllerian agenesis or hypoplasia.
Class II—Unicornuate uterus, with absent or defective development of one Müllerian duct.
Class III—uterus didelphys.
Class IV—bicornuate uterus.

Class V—septate uterus.
Class VI—arcuate uterus.

(a) Absent uterus: In an otherwise normal female, absence of the uterus with a normal vagina is unheard of, generally some degree of absence of vagina is known to occur. This is evident in the commonly encountered MRKH syndrome (Figures 9.17 and 9.18).

(b) Unicornuate uterus: Developmental arrest of one Müllerian duct results in the formation of the uterus and fallopian tube entirely from the other Müllerian duct. Often a solid nonfunctioning horn is present but remains undiagnosed, and renal anomalies frequently coexist on the side of the absent horn. It accounts for 1–2% of all uterovaginal anomalies and is often associated with a poor reproductive performance. Spontaneous abortion rates are high, as also the incidence of prematurity. A third of these patients have breech presentations, a high incidence of severe intrauterine growth restriction (IUGR) has been recorded. It is worth noting that fetal survival has been recorded in only 40% of women with unicornuate uteri. The incidence of caesarean sections is high in this sub-group of women.

(c) Rudimentary uterine horn: When the development of the Müllerian duct is normal on one side, but imperfect on the other side, a lateral fusion defect often with obstruction described as rudimentary horn is produced. Most rudimentary horns are noncommunicating and attached to the functioning contralateral horn by means of fibrous bands. Sometimes, the endometrium lining the cavity of the noncommunicating rudimentary horn is nonfunctional so that no clinical symptoms arise; however, if the endometrium is functional, retention of menstrual blood causes cyclic abdominal pain and the spillage of blood into the coelomic cavity via the tubal ostium may lead to endometriosis. Sometimes a narrow communicating channel exists between the rudimentary horn and the opposite uterine cavity. Under these circumstances, pregnancy is possible, most of these patients present with symptoms suggestive of an ectopic pregnancy including uterine rupture causing catastrophic bleeding and circulatory collapse. A high index of clinical suspicion coupled with the use of ultrasonography may enable a diagnosis before rupture occurs. If the diagnosis is made prior to occurrence of pregnancy on hysterosalpingography/laparoscopy, the more rational approach would be to undertake surgical excision of the horn and to investigate the patient with intravenous pyelography to detect urinary tract anomalies. These are generally present on the side where the Müllerian abnormality is most pronounced. Renal agenesis may be present or the kidney may be malrotated, low lying or pelvic in location.

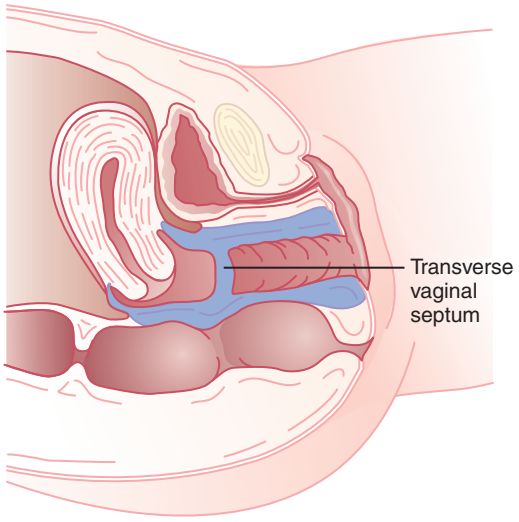

Figure 9.17 Transverse vaginal septum. (Source: Hacker NF, Gambone JC, Hobel CJ, Hacker and Moore's Essentials of Obstetrics and Gynecology, 5th ed. Philadelphia: Elsevier, 2010.)

(d) Blind uterine horn: When the two Müllerian ducts develop equally, but one fails to communicate with the other or exteriorly, a blind horn results. These patients present with increasing dysmenorrhoea and the presence of a lump in the lower abdomen and vagina lateral to the cervix. It may be possible to join the blind horn to the opposite side.

(e) Symmetrical double uterus: A symmetric lateral fusion defect results in each Müllerian duct developing independently side by side without communication leading to the formation of double uterus. Each duct forms one cervix, one uterus and one fallopian tube on either side. The duplication may go right down the vagina (part derived from Müllerian ducts) as well. Such complete duplication of the uterus is often referred to as 'uterus didelphys' (Figure 9.19).

(f) Partial reduplication of the uterus: Most often the reduplication is only partial giving rise to a bicornuate uterus with a single cervix and a single vagina. If the condition is minimal, it results in an arcuate uterus. Sometimes the external configuration of the uterus is normal, and the malfusion is represented only by the presence of a septum. These various degrees of reduplication are often associated with reproductive failure in about 25% of affected women. These women often suffer from miscarriages, preterm births, IUGR, abnormal fetal presentations like breech and oblique presentations. Incidence of dystocia during labour is high, and 3rd stage complications like adherent placenta and postpartum haemorrhage is more frequent. Unification surgical procedures undertaken at laparotomy (Strassman operation, Tompkins operation or Jones' wedge metroplasty operation) or hysteroscopic resection of uterine septum help to improve obstetric performance in 60–85% cases.

(g) Intrauterine vertical septum: This may be partial, complete, thick or thin. It is associated with higher incidence of pregnancy wastage. Septate uterus is a variant of vertical Müllerian fusion defects which has an important bearing on reproductive performance.

Prevalence

- About 1.0% in normal fertile and subfertile women
- About 3.3% in cases of recurrent pregnancy loss

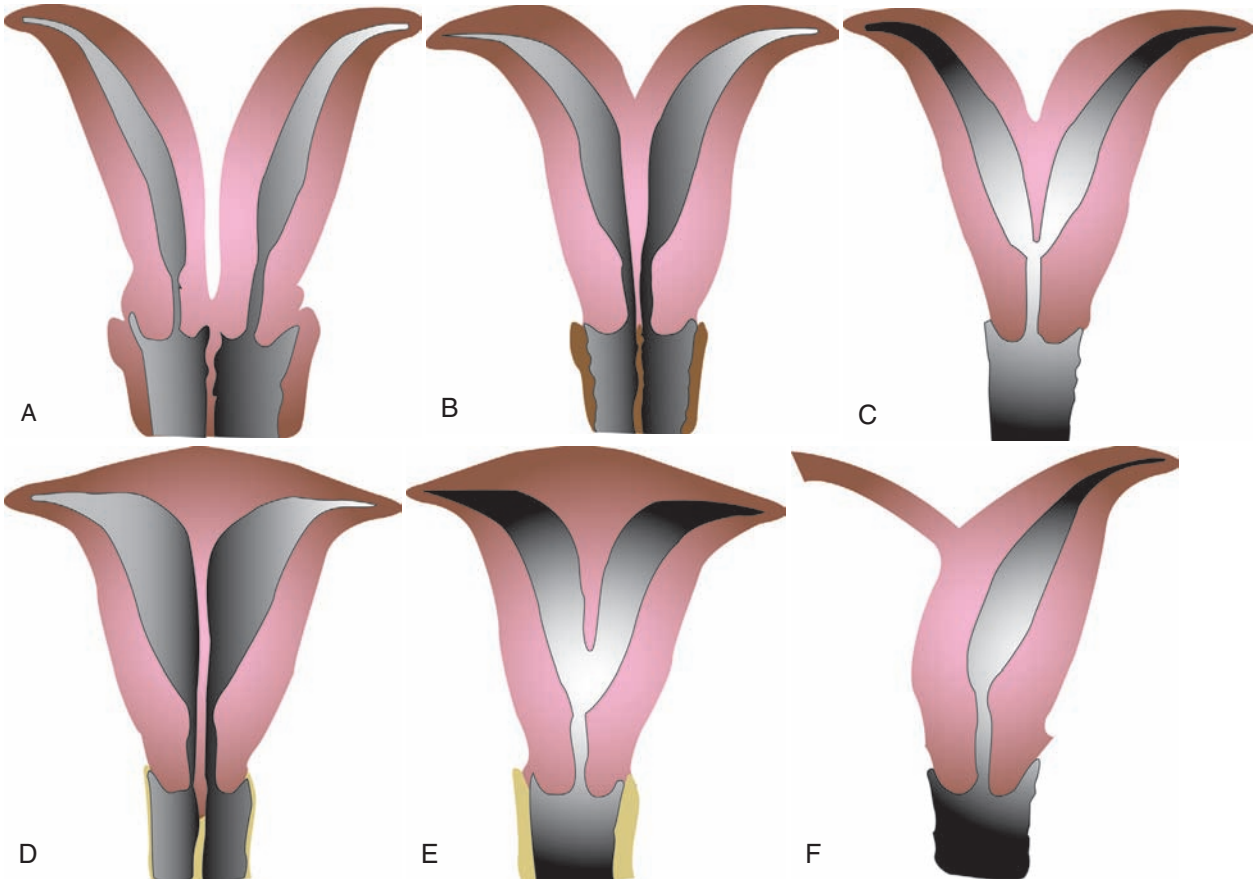

Figure 9.18 Common lateral fusion defects affecting the development of the uterus. **(A)** Uterus didelphys. **(B)** Uterus bicornis with septate vagina. **(C)** Uterus bicornis unicollis. **(D)** Uterus septus. **(E)** Uterus subseptus. **(F)** Uterus unicornis with a rudimentary horn.

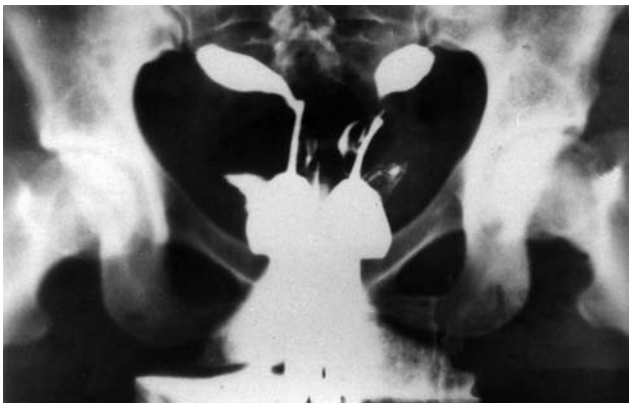

Figure 9.19 (A) Uterus didelphys established using two Rubin's cannula inserted in either half prior to injecting radio-opaque dye during hysterosalpingography. (Courtesy: Dr Ajit M Virkud, Mumbai.)

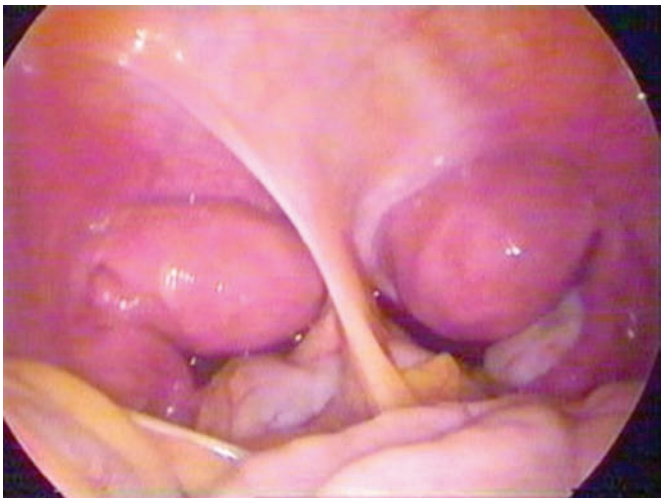

Figure 9.19 (B) Laparoscopy showing well-developed double uterus with a vesico-rectal fold in between. (Courtesy: Dr Shyam Desai, Mumbai.)

Background

- Congenital uterine anomalies resulting from Müllerian duct fusion defects are the commonest malformations encountered in clinical practice.
- Septate uterus is most common. About 25% incidence of spontaneous first trimester abortions, 6% second trimester abortions.
- Implantation into a poorly vascularized fibrous septum might be a contributory factor (Fedele et al. 1996).
- Bicornuate uterus is not generally associated with recurrent pregnancy losses (Proctor et al. 2003).

Diagnosis:

- *Combined hysteroscopy and laparoscopy* help to differentiate between bicornuate uterus and septate uterus.

The presence of the uterine fundus suggests a septate uterus.

- *Ultrasonography*—septate uterus appears as two cavities without sagittal notching and the intercornual distance <4.0 cm. Diagnosis of bicornuate uterus is favoured, if the fundal midpoint indentation is >5 mm above the inter-ostial line.
- *Hysterosalpingography (HSG)*—cannot reliably differentiate between septate and a bicornuate/arcuate uterus. If the angle of divergence between the two uterine cavities is ≤75°, the defect is most likely to be septate uterus. If the angle of divergence is >75° but <105° a diagnosis cannot be made.
- *Magnetic resonance imaging (MRI)*—it is an accurate and noninvasive investigation to make a diagnosis of septate uterus. If the septum extends to ≥30% of the septal cavity, surgical resection is indicated.

Adverse Obstetric Outcomes. The following adverse obstetric events have been associated with septate uterus:

- First and second trimester pregnancy losses: (between 8–16 weeks gestation) spontaneous abortions—25%, preterm delivery—14.5% and live births—62%.
- About two-thirds of abortions occur in the first trimester.
- It constitutes an important cause of repeated pregnancy losses.
- Other adverse obstetric outcomes include abnormal presentation, IUGR.

Surgical Resection of the Intrauterine Septum (Metroplasty): *Today hysteroscopic resection is considered best as it avoids a uterine scar and need for elective caesarean section. The septum is resected with resectoscope or scissors.*

Indication: Presence of uterine septum in association of adverse reproductive outcome.

Postoperative management: Oral oestrogen for 3 months after completion of surgery has been the accepted practice. Insertion of a Foley catheter with its bulb distended with 4–8 mL of sterile water has been used for 5–7 days to keep the uterine cavity open and prevent intrauterine adhesions. This is coupled with the administration of antibiotics (doxycycline 100 mg b.i.d. for 5–7 days) and nonsteroidal anti-inflammatory drugs (NSAID) to control pain and prevent adhesions are recommended. Asherman syndrome with uterine adhesions and adherent placenta are the late complications.

Amongst the uterine anomalies, bicornuate uterus is seen in 35–40%, arcuate uterus in 15%, uterus didelphys in 10% and uterine septum in 5–10%.

Diagnosis of Müllerian anomalies: This is based on the following information.

1. Clinical Data—family history, menstrual history, past obstetric history and detailed pelvic examination.
2. Imaging sciences—hysterosalpingography, ultrasonography, MRI imaging.
3. Endoscopic examination—laparoscopy and hysteroscopy.

Arterio-venous anastomosis causing menorrhagia not responding to medical therapy and occasional rupture with internal haemorrhage is known. It responds to embolization of uterine arteries. The diagnosis is made by Doppler ultrasound.

Hermaphroditism and Pseudohermaphroditism

In true hermaphroditism, the glands of both the sexes must be present in the same individual. Such cases are very rare. In most cases the accessory sex gland is atrophic and shows no evidence of functional activity. In other cases, the sex gland consists partly of ovarian and partly of testicular tissue.

In pseudohermaphroditism, the sex glands are of one sex while the external genitalia are of the opposite sex. The ovaries may descend within the inguinal canal to lie in the labia majora, and if the clitoris is hypertrophied, it may at first glance resemble the penis, and the fused labioscrotal folds resemble a rudimentary scrotum. This condition is best termed female pseudohermaphroditism. In the opposite (male pseudohermaphroditism) type, the testis fails to descend into the scrotum, the penis is ill developed, and as a result of extreme hypospadias, the external genitalia resemble those of the female. Many individuals are reared in the role of the mistaken opposite sex and have developed attitudes and psyche according to their sex of rearing. It is best to undertake cosmetic corrections and treatment measures to rehabilitate these individuals in the gender roles as per their sex of rearing.

Details of intersex are described in Chapter 10.

Developmental Defects of the Urogenital Sinus

Epispadias is a rare anomaly, often presenting as a case of genital prolapse, with urinary incontinence and a split pelvis.

Ectopia vesicae is the result of defective development of the lower abdominal wall and the anterior wall of the urinary bladder. The symphysis pubis also fails to develop as does the anterior wall of the urethra. The red mucous membrane of the interior of the bladder lies exposed, and the two ureteric orifices are visible. Treatment consists of transplanting the ureters into the sigmoid colon and attempting to close the bladder and the anterior abdominal wall.

Hypospadias probably never occurs in the female.

Malformations of the Rectum and Anal Canal

Imperforate Anus

Imperforate anus results from the failure or breakdown of the cloacal membrane between the anal depression and

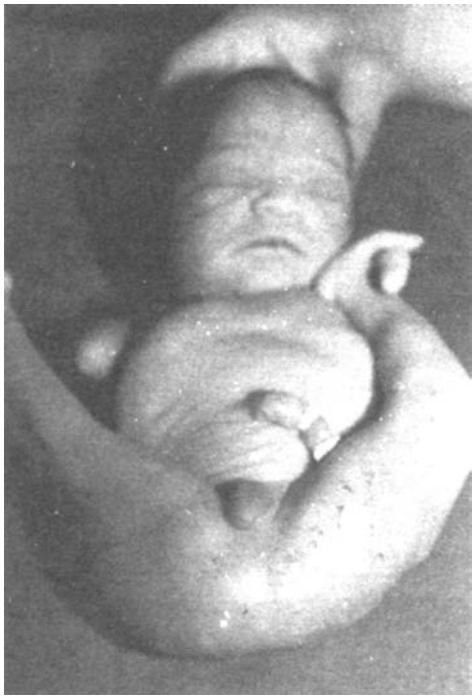

Figure 9.20 Imperforate anus.

the terminal intestine (Figure 9.20). The diagnosis is made at birth when corrective surgery is required forthwith.

Atresia Recti

Atresia recti is a condition in which the lower part of the rectum fails to develop. This is a much more serious situation than an imperforate anus. Major surgical intervention is called for, and the prognosis is guarded.

Congenital Rectovaginal Fistula

Various types have been described; these result from the imperfect separation of the rectum from the urogenital sinus. In some cases the anus is represented by a depression in the expected normal position, but the rectum opens on to the exterior somewhere else on the perineum. It is called a perineal anus, or it opens partly by way of an anal canal and partly as a fistula in the location of the perineal body, or it opens through the lower part of the posterior vaginal wall into the navicular fossa just within the fourchette. This is often termed the vaginal anus. It is surprising how many women with an ectopic anus suffer little inconvenience and acquire satisfactory bowel control. During childbirth, however, there is a danger of severe and complicated third-degree perineal tear; hence, these patients are best delivered by caesarean section. It should be remembered that if surgical correction of an ectopic anus is undertaken, the sphincteric control of the transplanted anal canal may not be as satisfactory as in the previous situation.

Wolffian Duct Anomalies

The upper portion of the Wolffian duct may at times dilate to form a paraovarian cyst, and the lower portion forms a Gartner cyst (Figure 9.21). The paraovarian cyst may appear like an ovarian cyst. Its true nature is revealed at laparotomy when the ovary is normal, and the cyst lies in the broad ligament. During its removal, one should look for the ureter, and not injure it. A small Gartner cyst can be left alone but will require marsupialization or excision if it causes dyspareunia.

Renal Tract Abnormalities

A double ureter is rarely encountered. Its recognition at laparotomy is necessary if injury to it is to be avoided.

An ectopic ureter sometimes communicates with the vagina, and the diagnosis is made by pyridium test and intravenous pyelography (IVP). It is dealt with by the urosurgeon.

In the fetus, the kidneys initially develop in the pelvis. They migrate upwards as the ureter starts growing cranially. In a rare instance, the kidneys remain in the pelvis and are mistaken for a retroperitoneal tumour. IVP should be done before surgery is planned in the removal of a retroperitoneal tumour.

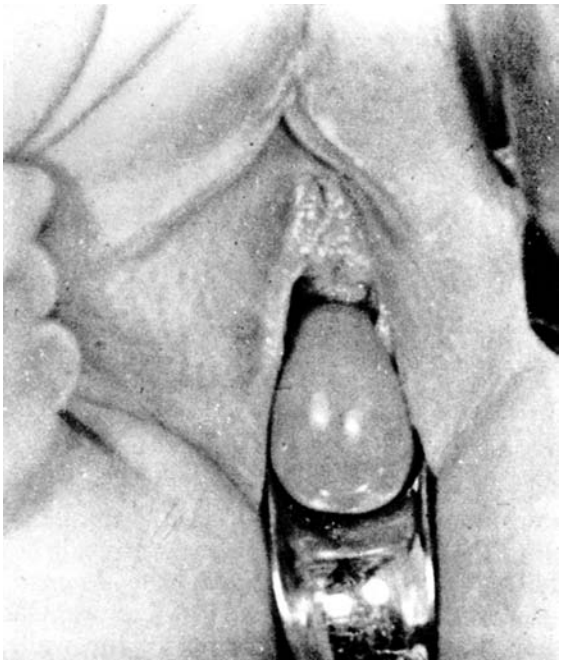

Figure 9.21 Gartner's duct cyst. (Source: Novak Emil and Novak Edmund, Gynecologic and Obstetric Pathology, 4th ed., Philadelphia and London: WB Saunders, 1958.)

Key Points

- A close developmental association of Müllerian system with urinary tract mandates investigations of both, if a malformation is detected in one system.
- Whereas genital tract abnormalities are encountered in only 1% of gynaecological patients, all varieties starting from aplasia, hypoplasia, atresia and nonfusion have been described.
- Hysterosalpingography, hysteroscopy and laparoscopy are required to confirm and assess the degree of uterine malformation.
- Ultrasound, besides diagnosing genital tract malformation, can detect associated renal anomalies.
- Some abnormalities do not require correction, if the woman is asymptomatic. Some are not amenable to correction. Some need plastic surgery to improve fertility, avoid pregnancy loss and solve gynaecological problems like haematocolpos and haematometra.
- Vaginoplasty to create an artificial vagina requires surgical expertise. It restores sexual function.
- Undescended or ectopic ovaries are lately diagnosed on ultrasound scanning and MRI. Their significance lies in the diagnosis of ovarian pain, ovulation monitoring and their potential for malignancy as in undescended testes.
- A rare condition of arterio-venous anastomosis causing menorrhagia responds well to embolization of uterine arteries. It is diagnosed by Doppler ultrasound when excessive menstrual bleeding does not respond to medical treatment.

Self-Assessment

1. Describe anomalies arising from fusion defects of the Müllerian Ducts.
2. Elucidate the pregnancy outcome associated with Müllerian anomalies.
3. How would you differentiate between Müllerian agenesis and testicular feminization syndrome (androgen insensitivity) as the cause of absent vagina?
4. Describe the operations of vaginoplasty.
5. Describe the investigations that assist in establishing the diagnosis of Müllerian anomalies, their limitations and comparative usefulness.

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Chapter

10

Sexual Development and Development Disorders

CHAPTER OUTLINE

Sex differentiation is a complex process comprising a cascade of events that begin with the undifferentiated (potentially bisexual) gonad up to the sixth week of intrauterine life and end up with the development of the specific gonads and their corresponding internal and external genital organs. *Genetic and hormonal influences are the main determinants in the development of sex, although other factors may modify its development.* The environmental and teratogenic factors are ionizing radiation, viral infection, chemical agents, immunological disturbances, hormones and nutritional deficiencies.

New insights into the biology of sexual development and advances in chromosome analysis have encouraged clinicians to determine sex of the individual at an early age and institute prompt treatment of the intersexual state to enable the individual to lead a more normal life.

The expanding knowledge and recognition of intersexual states have helped to develop a classification of abnormal sexual development based on gonadal and genital anatomy, chromosomal findings and specific identifiable genetic/metabolic defects.

The benefits of this classification are the presentation of the spectrum of intersexual variants in a comprehensive manner and identifying the group vulnerable to gonadal neoplasia.

The knowledge of embryology is necessary to understand how congenital malformations occur in 1% of female population.

Principles of Sexual Development (Figure 10.1)

The development of normal male and female genital organs and tracts is determined by several factors, all of which are time specific during embryogenesis. The critical period for gonadal development is at 6–7 weeks of embryogenesis when Y chromosome promotes male gonadal development. The external genital organs (phenotype) start developing at 10th week and reach completion by 16th week.

The genetic sex is determined at fertilization, but the gonads remain undifferentiated until 6 weeks of intrauterine life. First, the sex chromosomes determine whether the indifferent gonad (urogenital ridge) will differentiate into a testis or ovary. Y chromosome develops a male gonad and absence of Y and presence of XX chromosome ovaries. If the gonad is male, genes associated with the Y chromosome interact with other components of the somatic cells in the primitive gonad and initiate development along the male lines. The

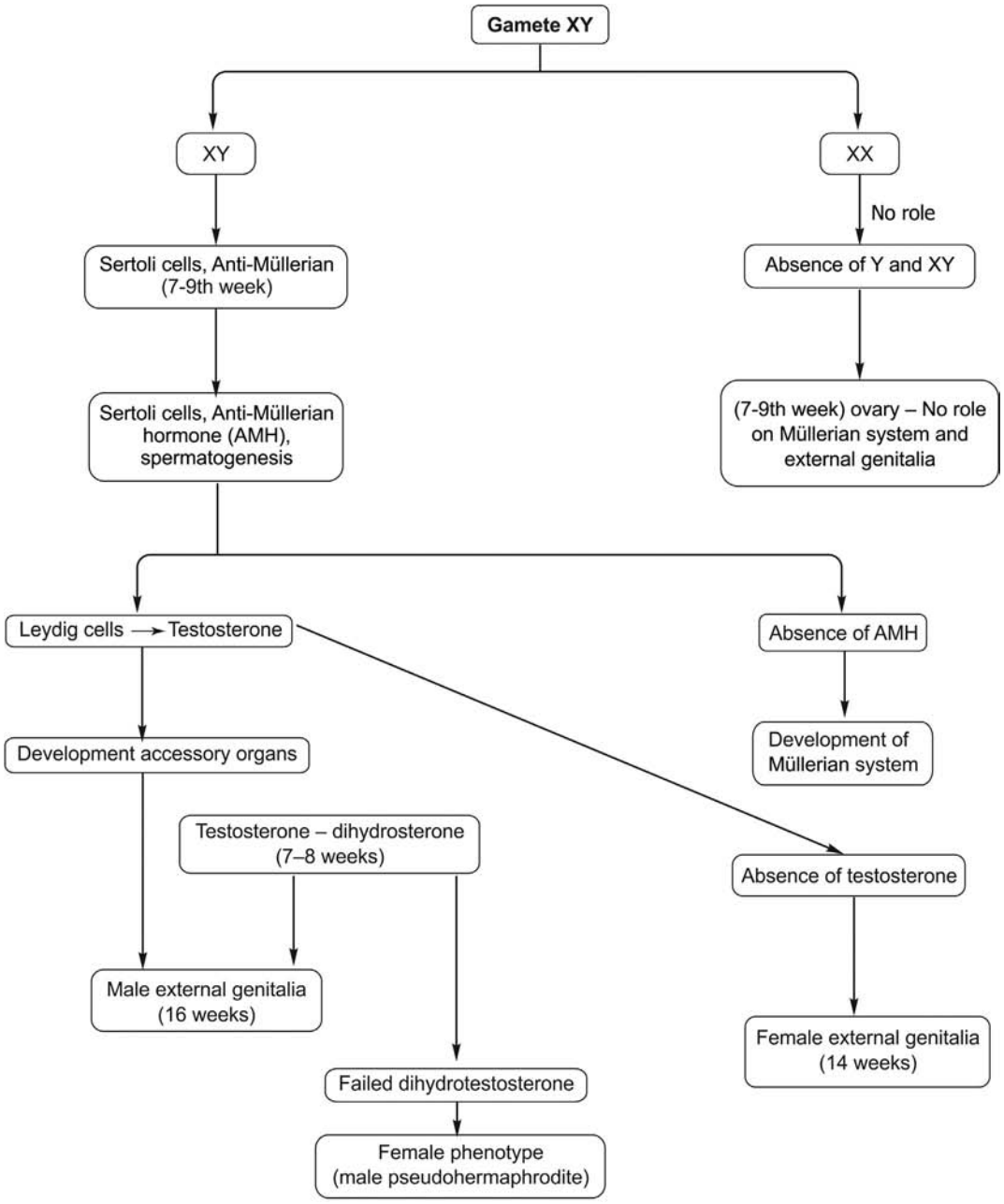


Figure 10.1 Development of male and female reproductive organs.

elaboration of the H–Y antigen complex in the short arm of Y chromosome known as sex-determining region Y (SRY) induces testicular development. The Sertoli cells in the developing testis produce Müllerian-inhibiting substance (MIS) that causes regression of the Müllerian (paramesonephric) ducts. In the absence of MIS, Müllerian ducts develop passively to form the fallopian tubes, uterus and upper vagina. Female internal organs and external genitalia develop partially without the need for ovarian hormones and differentiate even in the absence of the gonads, unless interrupted by the regressive influence of MIS. Differentiation of the Müllerian ducts proceeds cephalocaudally to form the female internal genital organs. In the absence of the masculinizing effects of dihydrotestosterone (DHT) of testicular origin, the undifferentiated external genital anlage develops along feminine lines (vulva). The genital tubercle develops into the clitoris and the genital folds into the labia majora. Only if the female fetus is exposed to elevated levels of androgen prior to the 10th to 12th week of gestation, does any degree of masculine developments occur. In such situations, the external genitalia may appear ambiguous. If the androgens are not elevated until after the 20th week, by that time the external genitalia have fully formed; the only masculine effect is an enlarged clitoris. In a male, testosterone is converted to DHT that promotes formation of male phenotype (external genitalia).

Summary of Sex Organs Development

Gonads

1. Formation of a testis occurs in the presence of Y chromosome (46 XY).
2. Formation of ovary occurs in the absence of Y chromosome and in the presence of second X chromosome. XX chromosomes are required for ovarian development. One X causes ovarian dysgenesis or Turner's syndrome.
3. Development of the gonads begins between 6 and 7 weeks of gestation.

Testicular determinants: SRY on the short arm (p) of the Y chromosome is the gene involved in testis determination. At first, the germ cells appear followed by Sertoli cells that secrete MIF and prevent development of female genital tract.

Sertoli cells also secrete testosterone-binding protein that binds to testosterone, as a result testosterone concentration in the testis is higher than the serum level, and this is necessary for spermatogenesis from primitive germ cells.

A week later (eighth week), Leydig cells start secreting testosterone by human chorionic gonadotropin (hCG) and develop accessory organs (Wolffian duct).

Peripheral conversion of testosterone to DHT is responsible for male external genitalia (male phenotype); clitoris enlarges to form penis by twentieth week.

Ovarian determinants: Unless SRY is expressed, ovarian development ensues in the presence of XX karyotype. The ovary has no role in the development of Müllerian system and external genital organs.

Internal Genitalia

Wolffian ducts under the influence of testosterone (testis) form epididymis, vas deferens and seminal vesicles (male internal genitalia). MIS from the Sertoli cells suppresses the development of female internal genitalia from the Müllerian ducts. Müllerian ducts in the absence of MIS form fallopian tubes, uterus and upper vagina (female internal genitalia).

Müllerian and Wolffian development begins at the same period of embryogenesis; these are local phenomena occurring ipsilaterally depending on the presence or absence of testosterone and MIS.

External Genitalia

DHT determines the development of male external genitalia. It is produced in adequate amounts from 7–8 weeks of gestation until term. hCG stimulates Leydig cells of the fetal testis to produce increasing amounts of testosterone, which develops male organs such as vas deferens, epididymis and seminal vesicles. Feminization of the external genitalia is completed by 14 weeks of gestation, whereas masculinization is completed by 16 weeks of gestation. Descent of the testis is mediated by testosterone, insulin-like 3 ligand and its receptor. Masculinization of cloaca occurs only if testosterone is converted via 5 alpha-reductase to DHT. In the absence of this enzyme, Wolffian system develops normally, but external genitalia will be of female phenotype. Similarly, exposure to androgen in utero causes masculinization of external genitalia in a female, but Müllerian system develops normally.

Facets of Sexual Differentiation

These can be broadly classified as follows:

1. Gonadal development
2. Genital differentiation
3. External genitalia – phenotype.
4. Behavioural differentiation: Sexual/gender identity as male or female is consciously appreciated by the individual by the age of 2–3 years, derived through internalization of cues based on external genitalia. Patients with 5 alpha-reductase deficiency or 17 beta-hydroxysteroid dehydrogenase deficiency may change from male to female gender identity at puberty, suggesting a hormonal role in sexualization. Sexuality is influenced by libido driven by testosterone and intimacy driven by oestradiol (Table 10.1).

Classification of Intersex

Gender Identity Disorders Associated with Normal Sex Chromosome Constitutions

Female pseudohermaphroditism:

- Adrenogenital syndrome (testosterone overproduction due to adrenocorticoid insufficiency)
- 21 alpha-hydroxylase deficiency
- 11 beta-hydroxylase deficiency
- Treatment of mother with progestins or androgens
- Ovarian virilizing tumour

Male pseudohermaphroditism:

- Primary gonadal defect
- Testicular regression syndrome
- Leydig cell agenesis
  - Defective hCG–luteinizing hormone (LH) receptor
- Defect in testosterone synthesis
  - 20,22-desmolase deficiency
  - 3 beta-hydroxylase dehydrogenase deficiency
  - 17 alpha-hydroxylase deficiency
- Male pseudohermaphroditism (testosterone insufficiency only)
  - 17,20-desmolase deficiency
  - 17 beta-hydroxysteroid (17 ketosteroid reductase) dehydrogenase deficiency
- Defect in Müllerian-inhibiting system

End-organ defect:

- Disordered androgen action (cytosol androgen receptor-binding defect)
  - Androgen insensitivity syndrome (testicular feminization)
  - Incomplete androgen insensitivity syndrome (Reifenstein syndrome)
- Disorders of testosterone metabolism
  - 5 alpha-reductase deficiency

TABLE 10.1 Chronological order of sexual development

Time in Weeks	Organ	Male	Female
At fertilization	Genetic determinant (XX or XY)	XY and SRY antigen in the short arm of Y chromosome induce testicular development	XX or absence of Y chromosome induces ovarian development
7–8 weeks	Gonads are formed	Testes seminiferous tubules	Ovarian cortex medulla-rete ovarii
10–12 weeks	Internal and external genitalia	Wolffian duct develops vas, epididymis, seminal vesicles and external genitalia	Müllerian duct develops into fallopian tube, uterus, cervix and upper three-fourths of vagina. External genitalia
At birth		Appropriate external genitalia	Appropriate external genitalia
Puberty		Continuous GnRH releases testosterone secretion and development of male secondary sex characters	Pulsatile secretion of GnRH releases FSH, LH and ovarian hormones Development of secondary sex characters

Gender Identity Disorders Associated with Abnormal Sex Chromosome Constitutions

Sexual ambiguity infrequent:

- Klinefelter syndrome (XXY)
- Turner's syndrome (XO)
- XX male
- Pure gonadal dysgenesis (some forms)

Sexual ambiguity:

- Mixed gonadal dysgenesis (MGD) including
  - Some forms of pure gonadal dysgenesis
  - Dysgenetic male pseudohermaphroditism
- True hermaphroditism

Components Contributing to Determination of Sex

Genetic Sex

In each individual, the nuclei of humans contain a diploid number of chromosomes, 22 pairs of autosomes and 1 pair of sex chromosomes, making a total of 46. During maturation, a reduction division results in each ovum or spermatozoon containing only the haploid number of 22 unpaired autosomes and 1 sex chromosome. In the ovum, the sex chromosome is always X, but in the sperm, it is either X or Y.

The relative number of X- and Y-carrying spermatozoa is equal. As the spermatozoon carries either an X or a Y chromosome, fertilization results in a 46-chromosome pattern carrying either an XX or XY – a genetic female or a genetic male, respectively. Thus, the original diploid number of chromosomes is restored (22 pairs of autosomes plus the paired sex chromosomes – 46 in all).

The genetic sex of an individual is determined at fertilization. In the fertilized egg, the Y chromosome directs the development of the undifferentiated gonads into testes and absence of Y into ovaries 2 weeks later. The ovaries do not participate in sexual development. Y chromosome contains on its short arm H–Y antigen (surface SRY cell antigen), which is responsible for the development of testes. The autosomes also take part. This Y chromosome has no further influence beyond the development of the gonads.

The germ cells arise in the endodermal wall of the primitive gut near the yolk sac from where they migrate along the dorsal mesentery into the gonadal site. The Leydig cells (interstitial cells) produce testosterone that develops the Wolffian duct and urogenital sinus into male genital organs and external genitalia. The Sertoli cells of the testes also secrete a nonsteroidal substance known as the MIF, which is responsible for inhibiting the growth of the Müllerian system in a male.

The embryo bearing XX chromosome develops along the female line and turns the undifferentiated gonad into ovaries. The absence of testosterone will cause atrophy of the Wolffian duct, and the absence of MIF will permit the growth of the Müllerian system along the female line.

It must be emphasized that it is the absence of Y chromosome with its H–Y antigen that directs the gonads and the Müllerian system into the feminine pattern. Recently, it has been reported that it is the sex-determining region located on the short arm of Y chromosome (SRY), which controls the development of testes. Its absence leads to the development of female gonads. In a rare case when the Sertoli cells fail to secrete MIF, the individual will develop Müllerian structures in addition to the Wolffian derivatives and grow as a hermaphrodite.

Similarly, castration of male gonads in early embryos will cause atrophy of the Wolffian duct but will permit growth of the Müllerian system along the female lines. Unilateral castration has enabled one-sided growth of the Wolffian system and growth of the Müllerian duct on the castrated side.

The testicular differentiation starts at the sixth week of intrauterine life. First, the Sertoli cells appear followed by the seminiferous tubules. Under hCG influence, Leydig cells secrete testosterone (peak level at 15–18 weeks). In absence of Y chromosome, the ovary develops 2 weeks later.

Chromosomal sex can be determined by the study of the leucocytes or by simply taking a smear from the buccal mucosa (Figure 10.2). The nuclei of the chromosomal female contain a small stainable body called the sex chromatin; hence, female

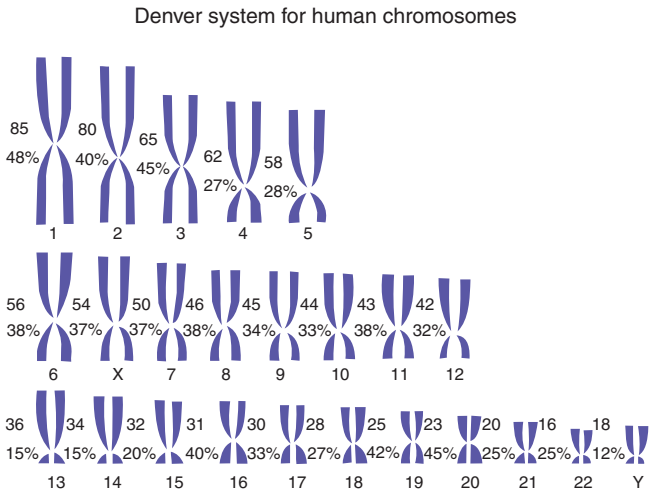


Figure 10.2 An idealized chromosome set, numbered according to the internationally agreed Denver system. Note that only one of each pair is represented. The small figures besides each chromosome indicate approximately the relative length of the whole chromosome and the proportion of the total length occupied by the short-term arm (By permission of Dr Bernard Lennox and the *Lancet*).

cells are termed as chromatin positive. In epithelial cell nuclei this small, peripherally situated, darkly staining nodule is called the 'Barr body'. Male cell nuclei lack this body and are therefore termed chromatin negative. This chromatin nodule has been shown to consist of deoxyribonucleic acid (DNA). It measures 1 μm in diameter and is present in approximately 75% of the female cells. A distinctive and similar type of nuclear appendage shaped like a drumstick is seen attached to the nuclear substance of female neutrophils. It is also possible to sex eosinophils. The culture of the fetal cells allows the chromosomal pattern study (Figure 10.3). The sex of the fetus can be determined in utero by examining fetal desquamated epithelium in the liquor amnii. Chorionic villus biopsy (CVB) either through cervical route in early pregnancy or transabdominally in the second trimester has recently become the well-established technique of determining the fetal sex.

The latest noninvasive technique of studying fetal sex is polymerase chain reaction (PCR) staining of fetal cell-free nuclei in the maternal blood of a pregnant woman.

External Anatomical Sex

The shape of the body contours, the development of the musculature, the characteristics of the bones (notably the pelvis), the distribution of hair on the face and body, breast development and the external genitalia are strong presumptive evidence of either sex.

Internal Anatomical Sex

The presence of a recognizable uterus, fallopian tubes and ovaries is the evidence that the individual is a female. The rare exception is the true hermaphrodite.

Gonadal Sex

Gonadal sex depends on the histological appearance of the gonad from the study of a biopsy or the removal of the organs. It is not entirely diagnostic such as in the case of an

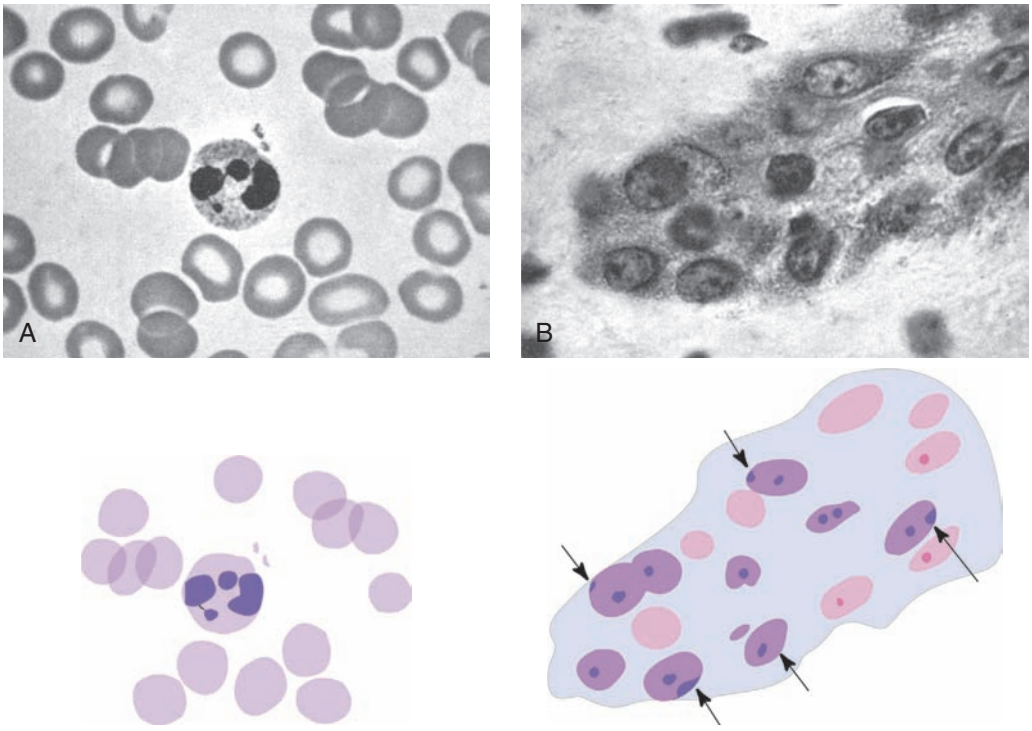


Figure 10.3 **(A)** The typical chromatin nodule in a neutrophil leucocyte in the female. The nodule is 1.4 μm and red cells measure 7.3 μm. **(B)** Typical nodules in the nuclei of the epithelial cells of the skin. The nucleus is 1.6 × 0.9 μm.

ovotestis in which both female and male elements are histologically demonstrated. Also, it is possible to have a rudimentary testis on one side and a rudimentary ovary on the other. Such findings are, however, so rare that the sex of the gonad is a reasonably reliable guide to the true sex of an individual.

Hormonal Influences

In the female pseudohermaphrodite, an excess production of androgenic hormone by adrenal cortical hyperplasia can modify the external genitalia of a genetic female. Hypertrophy of the phallus and fusion of the labia majora may cause the parents to consider their child to be a male. The virilizing tumours of the ovary, such as arrhenoblastoma, can cause hirsutism, hypertrophy of the clitoris, deepening of the voice, masculine body contours and amenorrhoea. The presence of oestrogen in the male can cause gynaecomastia (Figure 10.4). These are all examples of how hormones, natural or exogenous, can modify the sexual organs and secondary sexual characteristics.

Psychological Sex

Many men and women are psychologically dominated towards sexual inversion, a persistence of the childhood tendency. Behaviour, speech, dress and sexual inclination proclaim this fact. Transvestism and effeminate behaviour are the most obvious and complete examples where men dress in women's clothes and assume that gender role and vice versa.

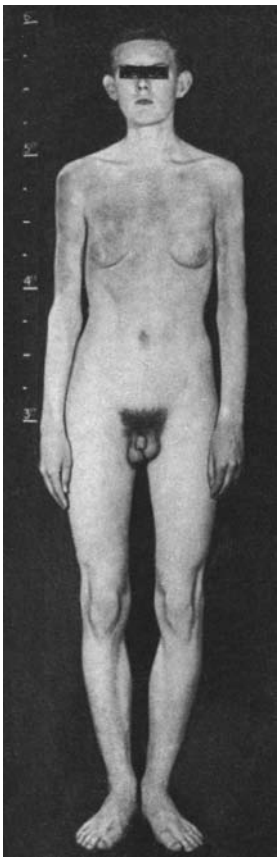


Figure 10.4 Gynaecomastia in an otherwise obvious male.

Environment and Upbringing

Environment and upbringing decide the sex of rearing. There are many examples of genetic males and females being reared by their parents in the mistaken sexual category, and who have acquired over the years the habits and mental inclination of the opposite sex to a sufficient degree to pass off as members of the opposite sex. Figure 10.5 shows the development of gonads and genital organs.

Clinical Diagnosis of Sex

Some of the abnormalities are seen at birth, but most are discovered at puberty.

External Appearance

Most men look like men and women like women because of their so-called secondary sexual characteristics. A man is broad shouldered, he is more hirsute especially about the face and chin, his scalp hair is coarser, his nature is more aggressive and robust, his voice deep and his sexual instincts inclined to the heterosexual. A woman has narrow shoulders, broad hips, is rarely hirsute, has fine abundant scalp hair, more delicately modelled features, and a typical pattern of pubic hair, triangular, with the apex downwards and a flat base at the upper level of the mons, her voice is softer, her nature is supposed to be less self-assertive and aggressive than the male and her sexual instincts are heterosexual; a well-developed breast is probably the strongest external evidence of femininity.

External Genitalia

In the male, the phallus is well developed from genital tubercle, the urethra opens in the glans by 12th week, the scrotum is rugose from the presence of the dartos muscle – an almost exclusively male possession – and the testicles are in the scrotum. In the female, the phallus (clitoris) is rudimentary, the urethra opens into the vestibule, the labia majora are smooth and bifid and do not possess a dartos muscle, and a vagina is present.

Internal Genitalia

Bimanual examination discloses the presence of a uterus and appendages in the female.

Signs of Feminism in the Male

External Appearance

Feminine figure, poor musculature, a tendency to obesity, high-pitched voice, absence of hirsutism, feminine personality and sexual inclinations, and gynaecomastia (Figure 10.4).

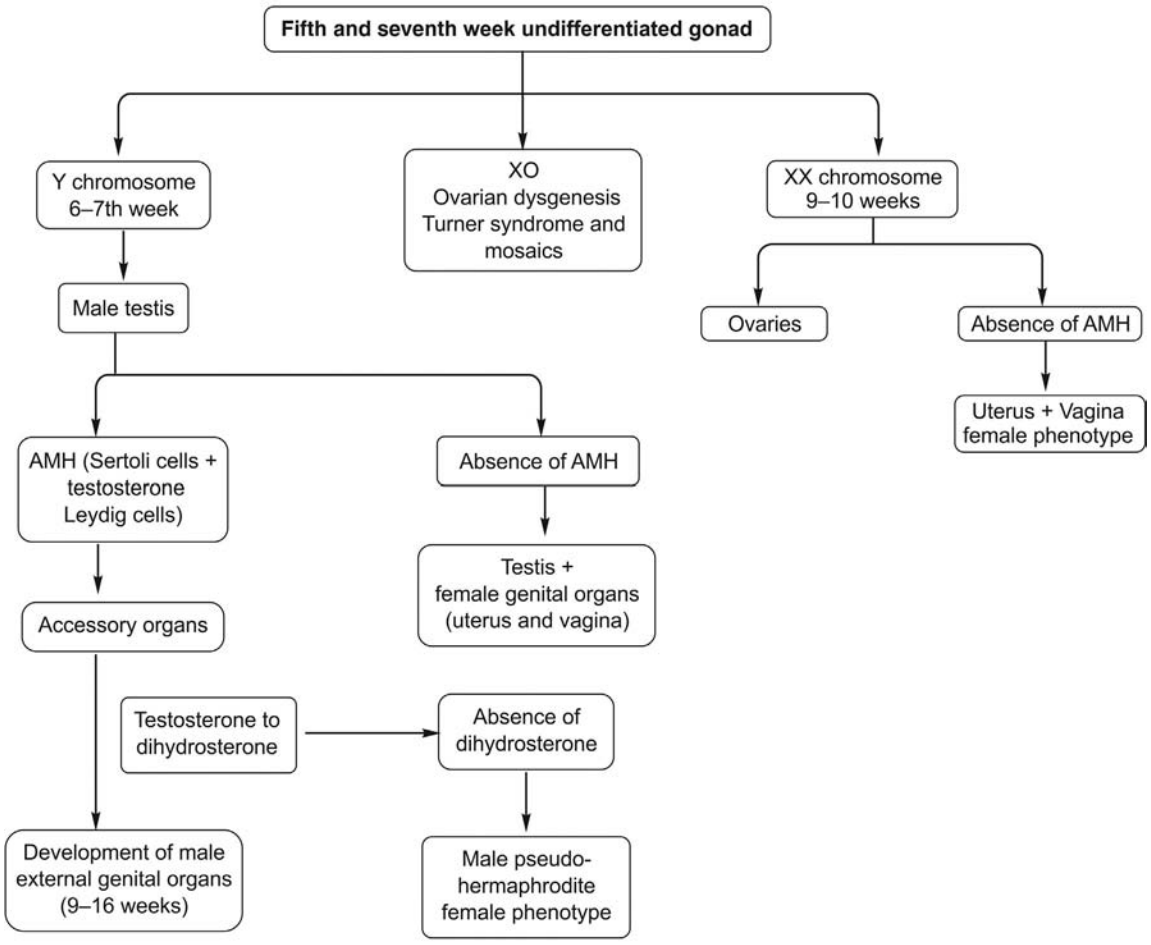


Figure 10.5 Development of gonads and genital organs.

External Genitalia

Hypospadias (urethra opening below the phallus), underdevelopment of the phallus, a split scrotum and undescended testicles.

The grey areas exist in the biological spectrum ranging from pure masculine to pure feminism.

Clinical Examples

Intersex is classified as

- Chromosomal abnormalities
- Gonadal
- Masculinization of female
- Partial or incomplete masculinization in a male

Feminism

Swyer's Syndrome

This syndrome is a male pseudohermaphrodite, a pure 46 XY gonadal dysgenesis with presence of uterus and the cervix but with hypo-oestrogenism and poorly developed breasts. Undeveloped testes do not secrete testosterone and MIF resulting in the development of female genital organs and female phenotype. The woman presents with primary amenorrhoea, absence of secondary sex characters and female external genitalia. Cyclical oestrogen and progestogen can induce menstruation. Conception with in vitro fertilization (IVF) using donor eggs is a possibility. The gonads (testis) have 30% risk to undergo malignancy and should be removed.

Turner's Syndrome

In this syndrome, either the short arm of X chromosome is deleted or the nucleus possesses only 45 chromosomes, i.e. 22 pairs of autosomes plus a sex chromosome XO. The absence of Y chromosome resembles the female, but these patients are, like males, chromatin negative, i.e. their nuclei contain no nuclear satellite body and no drumsticks in the neutrophils. It should be explained here that the presence of a Barr body is dependent on the presence of the second X chromosome and if the chromosome pattern is XXX or XXXY the extra X complement tenders the eccentric chromatin nodule either larger in size or in number.

Turner's syndrome has also been called ovarian agenesis or gonadal dysgenesis because at laparotomy the gonad is found to consist of undifferentiated stroma with absence of sex cells, a mere strip of fibrous tissue attached to the back of the broad ligament like a pale strip, the so-called streak gonad. The follicles grow up to 20th week of fetal life but become atretic due to absence of one X sex chromosome. In some, germ cells fail to migrate to the genital ridge from the yolk sac. These ovaries do not contain Graafian follicles, so oestrogen is not produced. The patients are clinically of short stature though not actual dwarfs, the trunk is muscular, the neck is short and webbed, cubitus valgus is notable. The breasts are not developed and pubic, and axillary hair is scanty or absent (Figures 10.6 and 10.7). Exaggerated epicanthic folds may be present, one of the obvious defects first noticeable on examining the patient. The vagina and uterus, if present, are underdeveloped. Other gross congenital abnormalities are present such as coarctation of the aorta. Deformities of the digits are also seen. Other stigma of Turner's syndromes includes shield chest, high palate, low-set ears, lymphoedema of the extremities at birth and deafness. The stigma is due to chromosomal deficiency in the short arm of X chromosome and is not always present (seen in 20%–30%), and the percentage of stigma depends on the percentage of abnormal X chromosome.

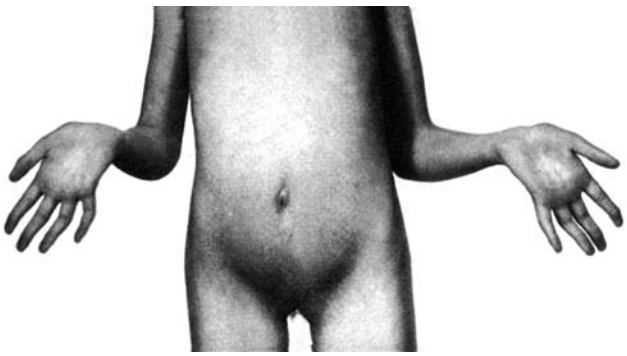


Figure 10.6 Turner's syndrome. Note the marked cubitus valgus.

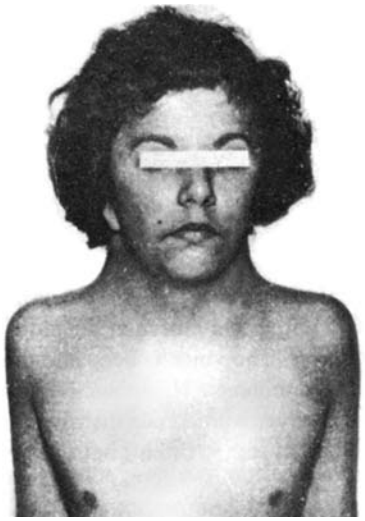


Figure 10.7 Turner's syndrome. Note the webbing of the neck and aplasia of breasts.

The classical picture of Turner's syndrome as described should have a chromosomal pattern of XO. However, there are variants in which mosaicism of XO/XX or even XO/XY produce less clear-cut syndromes, e.g. a normal-appearing female apart from gonadal dysgenesis. The young girl with Turner's syndrome presents with primary amenorrhoea. Serum follicle-stimulating hormone (FSH) is above 40 mIU/mL and E_2 is below 25 pg/mL. Oestrogen therapy with intermittent progesterone is advised to prevent osteoporosis. Artificial vagina may be needed at a later date for sexual function. Administration of growth hormone 0.05 mg daily for 5 years near puberty will improve the height. A pregnancy can occur with the donor egg in IVF programme if the uterus is present. If few follicles persist after puberty, menstruation and pregnancy is possible (15%). Incidence of Turner's syndrome is 1:2000 to 1:5000 live born girls. About 70%–90% of pregnancies with XO chromosome abort in early weeks of gestation.

Superfemale (Triple X Chromosome)

The possession of an extra X is not excessively rare since it is quite compatible with complete feminine normality. There is however a well-recognized triple X syndrome in which the patient, who is often mentally subnormal, suffers from scanty or irregular menstruation and infertility. Clinical examination may reveal hypoplasia of the genital tract. The importance of chromosomal studies in such a patient is obvious, and its determination plays an important role in the investigations.

Male Pseudohermaphrodite

Testicular feminizing syndrome, as initially described by Norris in 1953, is now correctly designated as either complete androgen insensitive syndrome (CAIS) or partial androgen insensitive syndrome (PAIS), and this reflects the aetiology. Incidence is 1:2000 to 1:60,000.

Aetiology

The peripheral receptors for testosterone are absent or scanty or they fail to respond to testosterone. The external genitalia are of female phenotype. Chromosome is XY, and the testes are located along its line of descent in the abdominal cavity or in inguinal canal and are maldeveloped. The Wolffian duct fails to develop because of absence of testosterone receptors. Testes produce MIF, so the Müllerian system fails to develop. However, the lower portion of the vagina derived from sinovaginal bulb appears as a dimple of 1–2 cm in length. There is often a strong familial tendency to this disorder, and several cases may appear in the same family and in different generations, and the condition is attributed to X-linked recessive gene.

Unless there is a family history, or childhood inguinal hernia discovers the testes, the condition is not revealed until

puberty. The girl is typically feminine and tall. The pubic and axillary hair are scanty, but the breasts are developed because of oestrogen derived from peripheral conversion of androstenedione. The girl presents with primary amenorrhoea. The ovaries and the uterus are absent.

Ultrasound reveals absence of ovaries and the uterus. Testosterone is present (>200 ng/mL). LH is raised, but FSH is normal. Chromosome study reveals XY chromosomes (Figure 10.8).

Management

- Once diagnosed, it is important to trace the location of the testes and perform gonadectomy, because testes are liable to undergo malignancy in 10%–30% cases. The controversial point is as to when to perform gonadectomy. It is preferred to remove the testes in puberty when the correct diagnosis is made (16–18 years).
- The girl will require oestrogen therapy for the development of the breasts as well as to prevent osteoporosis.
- If she plans to marry, vaginoplasty should be done. If sufficient length of vagina prevails, vaginal dilators may be effective in stretching its length.

The reproductive function is not possible with absent ovaries and the uterus.

Partial Androgen Insensitivity Syndrome

In PAIS, few receptors respond to testosterone, and the clinical features are variable. Some present at birth with ambiguous genitalia, and chromosome study reveals XY chromosomes.

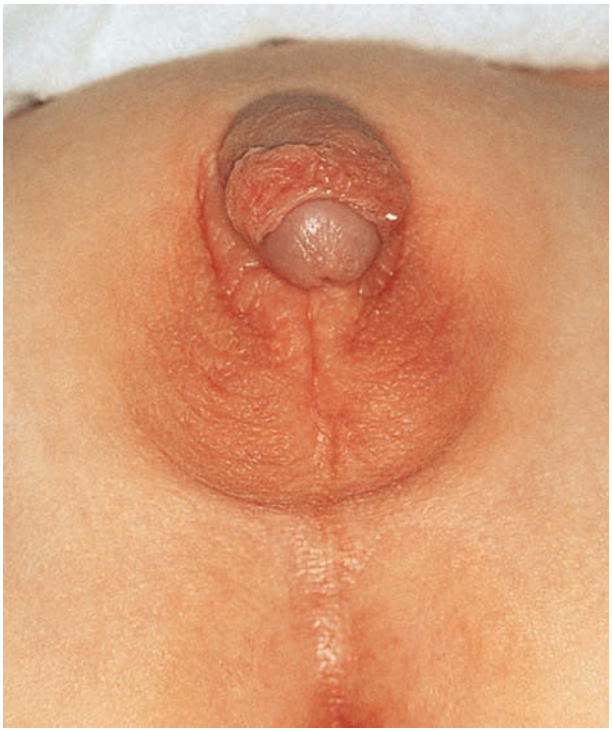


Figure 10.8 Ambiguous genitalia in a child with an XY karyotype and partial androgen insensitivity. (Source: Hacker NF, Gambone JC, Hobel CJ, Hacker and Moore's Essentials of Obstetrics and Gynecology, 5th ed. Philadelphia: Elsevier, 2010.)

Others present at puberty with lack of virilization in a boy or signs of virilization in a girl with primary amenorrhoea.

The treatment is based on the sex in which the child is reared, psychological behaviour and the amount of virilization. If the child is reared as female, it is best to perform gonadectomy in childhood to avoid virilization. In a boy, testosterone will help. The reproductive function remains poor.

Enzyme Errors in Androgen Production

The production of testosterone from the testes requires enzymes, the most important of which is 5 alpha-reductase. This enzyme converts testosterone into DHT, which is capable of acting on peripheral target tissues to produce male phenotype. Absence of this enzyme results in female phenotype and male pseudohermaphroditism.

Masculinism

Klinefelter Syndrome

Klinefelter syndrome is seen in 1:500 males. The patient with this rare disorder externally resembles a male in general body conformity, the penis is small or normal in size, the testes are small, but as a rule are normally placed. Sterility is common, gynaecomastia is frequently present (Figure 10.4), the voice may be high pitched, and the appearance may be eunuchoid. The patient is often mentally defective or delinquent. Most of these individuals are sex chromatin positive like females because of the extra X chromosome. Genetic analysis reveals their karyotype to be 47 XXY. Testicular biopsy usually reveals hyaline degeneration of the seminiferous tubules and overgrowth of Leydig cells as a result of which sterility is so often the presenting symptom (Figure 10.9). Sole-to-pubic length is more than normal. The person should be bred as male and should not be told about chromosomal abnormality. Testosterone may help. The breasts may need surgical excision.

Virilism

Virilism is characterized by hirsutism and some of the male appearances, atrophy of the breasts.

In patients exhibiting virilism, the chromosomal and gonadal sex is female and the accessory sex organs of Müllerian origin are also feminine. The external genitalia, however, resemble the male.

Clinical Features

The body conformity is largely male with good muscular development and broad shoulders. The voice is deep and the thyroid cartilage is prominent. Hirsutism is present to a remarkable degree, with a male distribution of hair. The psychological sex is often, but not invariably, male.

The external genitalia shows hypertrophy of the clitoris and fusion of the labia majora due to failure of the cloacal

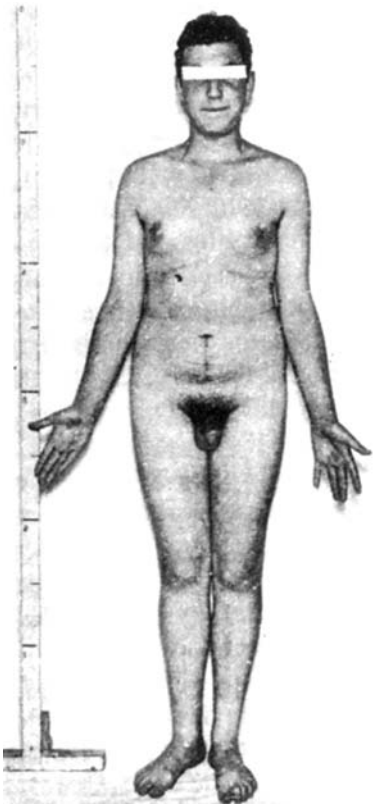


Figure 10.9 Klinefelter syndrome. Note the superficially normal male genitalia, gynaecomastia and feminine distribution of the pubic hair.

membrane to divide in congenital variety. The vagina is often absent if the cause is congenital (Figures 10.10 and 10.11). The breasts are underdeveloped. Other signs are frontal, temporal and vertex baldness, hoarseness of voice, diminished size of breasts, hirsutism, clitoral enlargement, acne and amenorrhoea.

Clinical Varieties

Adrenogenital Syndrome

Adrenogenital syndrome occurs due to hyperplasia of the adrenal cortex and there are two types:

Congenital or Intrauterine Adrenogenital Syndrome. Congenital or intrauterine adrenogenital syndrome (CAS) in which the primary defect is a block in the conversion of 17-hydroxyprogesterone into hydrocortisone due to enzyme failure of 21 hydroxylase. The normal adrenal cortex produces three C21 compounds: hydrocortisone, corticosterone and aldosterone and in addition certain androgens C19 compounds. The production of 17-hydroxyprogesterone, which is mildly androgenic in action, is controlled by adrenocorticotropic hormone (ACTH), and this in turn is controlled by the reciprocal action of hydrocortisone. If, therefore, the hydrocortisone–ACTH interaction is upset by a deficiency of hydrocortisone, the pituitary produces an excess of ACTH, which in turn leads to adrenal cortical hyperplasia and excess output

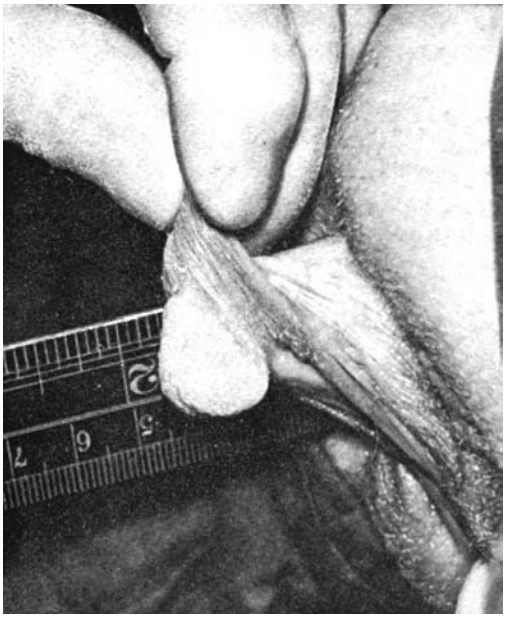


Figure 10.10 Female hermaphrodite showing hypertrophy of the phallus, masculine appearance of the glans and rudimentary scrotal sac.

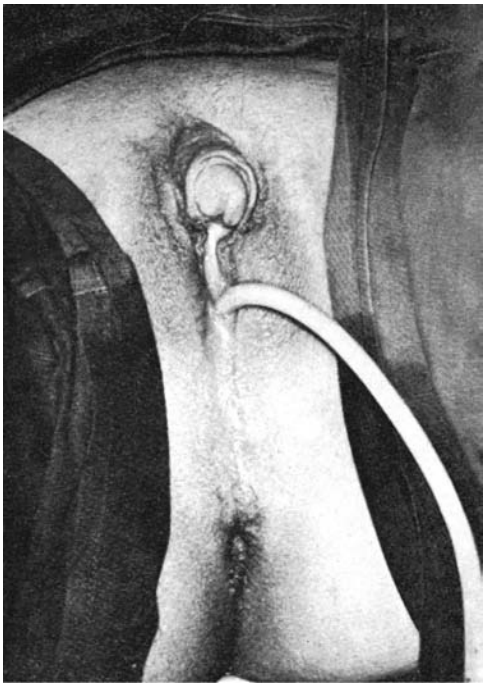


Figure 10.11 Same patient as in Figure 10.8, with a catheter in the immature vagina.

of androgens, notably 17-hydroxyprogesterone. The main androgenic activity of 17-hydroxyprogesterone is due to its conversion into D4-androstenedione and hence to other orthodox androgens. These androgens are responsible for phallus of the female pseudohermaphrodite showing hypertrophy, the masculine appearance of the glans, and the persistence of fusion of the labia majora to resemble a scrotum (Figure 10.10). The miniature vagina opens into the urogenital sinus and the external appearance is that of a

male with hypospadias (Figure 10.11). The diagnostic feature is the very high value of 17-ketosteroids and 17-hydroxyprogesterone (>8 mg/mL) excreted. As expected, the chromosomal pattern in these girls is XX. Ultrasound should look for ovarian and adrenal tumour. Electrolytes should be monitored, as there is a possibility of hyperkalaemia and hyponatraemia.

The treatment of this condition consists in the administration of cortisone or hydrocortisone or the newer synthetic corticosteroids such as prednisone or prednisolone (2.5 mg twice daily is an adequate maintenance dose in the adult and will restore the output of 17-ketosteroids to normal). The continued use of these drugs carries certain dangers of adrenal deficiency due to suppression of ACTH, and this especially operates at times of stress such as when a patient needs an anaesthetic, at which time cortisone coverage should be given during the period of stress (i.e. 1 day before, on the day of operation and for 3 days afterwards). Dose of cortisone is 0.15 mg/kg in four divided doses in a child. In a child with salt-losing condition, fludrocortisone 50–100 mcg daily with IV saline is recommended.

The vulval abnormality is corrected by a small plastic operation, and as a rule, it is wise to amputate the hypertrophied clitoris between 5 and 10 years of age. Clitoroplasty with conservation of glans is preferred to amputation. Separation of labial folds should be corrected at puberty. Menarche is often delayed and fertility is reduced in these girls.

Certain cases of virilization of the fetus in utero have been reported following the use of progesterone in the pregnant mother. The synthetic progestogens, ethisterone and norethisterone are comparatively more androgenic. In fact, all progestogens if given in sufficient dosage are suspect with the exception of 17-hydroxyprogesterone caproate so that if progestogen is to be used at all in the pregnant woman, this is the drug of choice.

The effect on the fetus depends largely on the duration of the pregnancy at the time of administration and the dosage employed. If progestogens are given before the 12th to 14th weeks of gestation, the neonatal picture may be similar to that of the intrauterine adrenogenital syndrome, i.e. enlarged phallus and imperforate perineal membrane. The virilism is, however, nonprogressive.

Postnatal Adrenogenital Syndrome. This can be due to excessive output of ACTH from a basophil adenoma of the anterior pituitary (Cushing's syndrome), which gives rise to adrenal cortical hyperplasia. An adrenal tumour that can be benign or malignant has the same effect. An adrenal tumour is not dependent on pituitary influence. In undiagnosed case, initial accelerated skeletal maturation is followed by early epiphyseal fusion and stunted height. Precocious puberty and increased libido with aggressive behaviour is reported in a few cases. Sterility is common. Cortisol therapy can avoid these undesirable effects. The male with this syndrome also presents with these features.

Virilizing Tumours and Conditions of the Ovary

The virilizing tumours and conditions of the ovary are arrhenoblastoma, hilus cell tumour, polycystic ovary and hyperthecosis. These ovarian causes of virilism produce a clinical picture somewhat similar to the postnatal adrenogenital syndrome and are due to excess of testosterone secreted by the ovary. In the postnatal variety of virilism, the genital tract is normal, but the clitoris enlarges, the uterus atrophies with resulting amenorrhoea, the voice deepens, hirsutism is marked and the breasts atrophy. 17-ketosteroids excretion is raised only if the adrenal is hyperplastic or neoplastic, whereas with a virilizing ovarian tumour, it is unaltered.

Treatment

Female Pseudohermaphroditism

- If the fault is an enzyme block at the level of 17-hydroxyprogesterone, the administration of cortisone or synthetic corticosteroids will effectively control the excess production of ACTH. The external genitalia can be restored to a feminine pattern by plastic surgery, e.g. the formation of an artificial vagina by McIndoe's operation if the patient is engaged or married. Cortisone therapy, if successful, may restore menstruation in a patient with amenorrhoea. It is important in such patients to correct any anatomical defects of the lower genital tract in order to obviate the complication of retained menstrual products such as haematocolpos or haematometra.
- If the virilism is due to a tumour, surgical removal is the method of choice. This also applies to ovarian androgenic tumours.
- A regular maintenance dose of oestrogen is usually effective in restoring some of the secondary sex characteristics, e.g. breast development. Additional intermittent progesterone therapy prevents breast and uterine malignancy.
- The most effective treatment of facial hirsutism is shaving and cosmetics.

Investigations and Management of the Intersexual Patient

In the determination of a patient's sex, the following investigations are required:

- Genetic, chromosomal or nuclear sexing is simple and reliable from a study of buccal smear, skin biopsy or neutrophil examination.
- The external genitalia should be examined, preferably under anaesthesia, when, for example, a vagina may be discovered concealed by fusion of the labia majora. Contrast radiography is sometimes helpful.
- Gonadal biopsy of the testis in an apparent male.
- Laparotomy or laparoscopic directed gonadal biopsy in the apparent female provides an opportunity for examination of the internal genitalia. The presence of

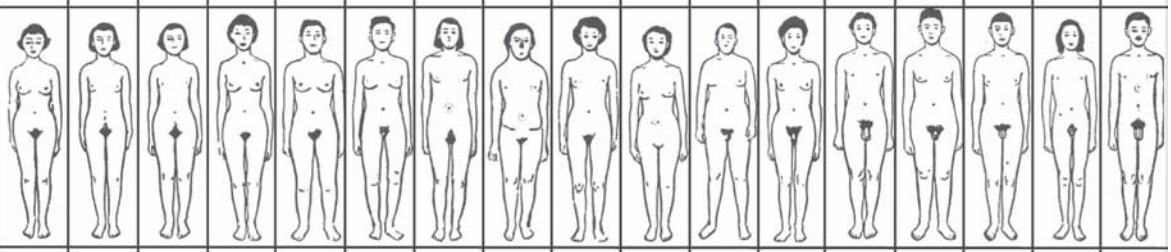
	Normal female	Simple constitutional masculinism	Adreno-genital masculinism	Female homosexual	Female transvestism	Female intersex 1 without adrenal disorder	True hermaph-roditism	Turner's syndrome	Swyer's syndrome	Male intersex II testicular feminization syndrome	Klinefelter's syndrome	Male transvestism	Male homosexual	Adreno-genital feminism	Simple constitutional feminism	Male with hypospadias	Normal male
NUCLEAR SEX CHROMATIN	+	+ but lesser% in polymorphs	+	+ occasionally – in polymorphs	+	+	+ or –	– rarely +	–	–	+ rarely –	+ rarely –	–	–	–	–	–
GONADS	○ ○	○ ○	○ ○	○ ○	○ ○	○ ○	○ ●		?	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●
OESTROGENS	normal F.			normal F.	normal F.	normal F.			high	normal M.	not increased	n. to n. for male	normal M.	probably > n. for male		normal M.	normal M.
HORMONES																	
ANDROGENS	normal F.	increased for female	increased for female ++	normal F.	normal F.	normal F.	normal or low	low	normal	normal M.	< normal	deficient for male	normal M.	increased ++	diminished for male	normal M.	normal M.
EXTERNAL ANATOMY																	
PENIS PHALLUS: CLITORIS	normal size	normal size	enlarged	normal to enlarged	normal to enlarged	enlarged ++	normal penis or enlarged clitoris	normal size	normal to enlarged	normal size	small to moderate size	small	normal size	normal size	small	small (often mistaken for enlarged clitoris)	normal size
MICTURITION	○ +	○ +	○ +	○ +	○ +	○ +	○ +	○ +	○ +	○ +	♂	♂	♂	♂	♂	○ +	♂
MENSTRUATION	normal	irregular or amenorrhoea	absent	normal or irregular	normal or irregular	normal	usually absent	absent	amenorrhoea	absent							
FERTILITY	+	+ or –	–	+	+	–	–	–	–	–	–	– or +	+	–	+	–	+
PSYCHOLOGICAL SEX	F.	F.	F.	M. or F.	Neutral or M.	F. or M.	F. or M.	F.	F.	F.	Neutral or M.	Neutral or F.	M., F. or both	M.	M. or rarely F.	M.	M.
AETIOLOGY	genetic	genetic or hormone	genetic or hormone	genetic or psychological	genetic	genetic	genetic	genetic	genetic	genetic	genetic	genetic	genetic psychological	hormone	genetic or hormone	genetic	genetic

Figure 10.12 The spectrum of sex: possible sexual aberrations in diagrammatic and tabular form.

rudimentary or underdeveloped Müllerian structures strongly suggests a female sex. It is important to note that during a laparoscopic biopsy of a streak ovary, the ureter that is in close proximity to it is vulnerable to injury.

- Ultrasound is an alternative to laparoscopy. It may also throw light on some accompanying Wolffian anomalies.
- Estimation of oestrogen, 17-ketosteroids, testosterone and 17-hydroxyprogesterone in the urine.
- Estimation of serum electrolytes.
- IV pyelogram to detect any coexisting renal anomalies, magnetic resonance imaging (MRI) for suspected adrenal neoplasm, radiography of the pituitary fossa and the skeleton.
- Psychological assessment of the patient's sexuality.

The gynaecologist will naturally consult his or her endocrinology and psychiatry colleagues before finally deciding on the diagnosis and treatment, which is usually best deferred until puberty when the pragmatic sex of the individual declares itself, i.e. the sex to which the individual shows greater inclination and attitude. At this consultation, the parents should be available as their cooperation and intelligent supervision are vital to the ultimate interest of the intersexual individual (Figure 10.12).

Hirsutism

Hirsutism is defined as distribution of coarse hair in a female normally present in a male, i.e. upper lip, chin, chest, lower abdomen and thighs. Hirsutism may or may not be associated with menstrual disturbances such as oligomenorrhoea and amenorrhoea. Virilization refers to a condition of hirsutism associated with other male characteristics such as temporal baldness, hoarse voice, clitoromegaly and muscle enlargement as well as defeminization such as amenorrhoea and breast atrophy.

Endocrinology

In a woman, androgens are secreted by the ovaries and the adrenal glands in varying proportions. To some extent, they are produced by the peripheral conversion of androstenedione in the fat. The androgens produced are as follows: 25% comes from the adrenal gland, 25% from ovaries and rest from the peripheral conversion of androstenedione.

1. *Testosterone* (T), 0.2–0.3 mg daily – constitutes 25% of the total. Fifty percent from ovaries (0.2–0.8 ng/mL blood level).

2. *Dehydroepiandrostenedione* (DHEA), 20 mg daily (serum level 130–980 ng/mL).
3. *Androstenedione* (AD), 3 mg daily (1.5 mg from ovary).
4. Dehydroepiandrosterone sulphate (DHEAS) – 0.5–2.8 mcg/mL (adrenal gland) 17-hydroxyprogesterone >800 ng/dL in congenital hyperplasia.

T is bound to serum hormone-binding globulin (SHBG). SHBG production in the liver is inhibited by androgens and is increased by oestrogen and thyroid hormone. Low oestrogen and thyroid hormone cause fall in SHBG level, and this results in some testosterone being released into the blood circulation as free T, which can cause hirsutism. Similarly, obesity causes fall in SHBG as well as more peripheral conversion of androstenedione to T.

Ferriman and Gallwey described scoring system in nine body areas on a scale of 0–4 and quantified hair growth. A score >8 is defined as hirsutism.

Causes of Hirsutism

- Genetic and ethnic.
- Excess androgen or increased sensitivity of the pilosebaceous unit to T.
- Liver disease when the level of SHBG level drops.
- **Ovarian.** Polycystic ovarian disease (PCOD), hyperthecosis, masculinizing ovarian tumours, e.g. arrhenoblastoma, hilus cell tumour.
- **Adrenal.** Congenital adrenal hyperplasia, Cushing's syndrome, adrenal tumour (1%–2% cases).
- **Drugs.** Androgens; progestogens with androgenic effect, viz. 19-norsteroids, and levonorgestrel anabolic steroids, phenytoin, danazol, minoxidil.
- **Others.** Obesity, hypothyroidism, anovulatory hypo-oestrogenism, idiopathic – 15%, hyperprolactinaemia.
- *Hirsutism occurs early in congenital adrenal hyperplasia, around puberty in PCOD and in elderly women at menopause.*

Clinical Features

- **PCOD** accounts for 80% of hirsutism and is characterized by oligomenorrhoea, obesity, hirsutism and often infertility. Both the ovaries are enlarged and covered with a thick, smooth, fibrotic, pearly white capsule. Multiple small cysts 2–8 mm in size are present at the periphery of the ovary, and the ovarian stroma is increased due to theca cell hyperplasia. Ultrasound reveals the ovarian morphology clearly, and diagnosis can be accurately established. LH level is raised even in the preovulatory phase of the menstrual cycle causing a high LH/FSH ratio (more than 1). This results in anovulation, high oestrogen level, but absence of progesterone. About 50% of women with PCOD will show raised levels of androgens (T, androgen deprivation (AD) and DHEA). T level although raised remains below 200 ng/dL, unlike that in ovarian tumour (see also Ch. 32).
- **Masculinizing ovarian tumours** cause defeminization such as breast atrophy and amenorrhoea besides hirsutism, hoarseness of voice and muscular development. Clinical examination may not always detect a small tumour. Laparoscopy, ultrasound and MRI may be required to locate the tumour. T level is raised above 200 ng/dL. Removal of the tumour restores the menstrual cycle, but hoarseness of voice and existing hirsutism may require appropriate management.
- **Congenital adrenal hyperplasia** is diagnosed and treated before puberty. It is due to deficiency of enzyme 21-hydroxylase. 17-hydroxyprogesterone plasma level is raised more than 8 ng/mL. Cortisol deficiency occurs at times of stress. Dexamethasone suppression test is done by giving 1 mg of dexamethasone at night and studying a single plasma cortisol level in the morning. The level should be less than 130 nmol/L (100 mcg) – this test has low false-positive finding. Computed tomography (CT) scan of abdomen and pituitary fossa may be required.
- **Cushing's syndrome** occurs due to pituitary overproduction of ACTH or adrenal tumour. The diagnosis is established by dexamethasone test, ACTH level estimation and CT scan of the pituitary and adrenal glands. DHEA and AD are raised in this syndrome.
- **Hyperprolactinaemia** may be due to enlargement of the pituitary gland or due to a pituitary tumour. Prolactin levels exceed 100 ng/mL. A CT scan will help in the diagnosis; mild hyperprolactinaemia occurs in PCOD.

Investigations

History

The onset and speed of progression help to determine the cause of hirsutism and virilism. The change in the voice, breast shrinkage, amenorrhoea indicate defeminization and possibility of an ovarian tumour. History of drug intake will help in the management. Infertility may indicate anovulation and possible PCOD.

Examination

Degree of hirsutism should be noted, so also any change in the voice. Breast palpation, search for any abdominal tumour, clitoral enlargement and pelvic mass by bimanual examination should be carried out.

Hormonal Study

This includes study of T, DHEA and AD levels and of thyroid hormones. Preovulatory LH and FSH levels will need to be estimated. In PCOD, LH level exceeds 10 IU/L; T >2.5 nmol/L and SHBG <30 nmol/L. T level >6 nmol/L is seen in ovarian tumour and hyperthecosis. Normal prolactin level is up to 25 ng/mL. Cortisol level should be <100 mcg/mL.

In adrenal tumour, DHEAs are raised >700–800 mcg/dL. It is a better estimate than 24-h urine estimation of 17-ketosteroid.

17-alpha hydroxyprogesterone >800 ng/dL is seen in CAS, plasma testosterone >200 ng/dL is seen in ovarian and adrenal tumours.

Ultrasound Scan

It is useful to detect an ovarian tumour, PCOD and adrenal tumour.

CT scan and MRI are needed in case pituitary or adrenal tumour is suspected.

Laparoscopic visualization of pelvic organs, dexamethasone and ACTH tests are necessary.

Management

1. **Treat the cause.** Removal of ovarian and adrenal tumour will stop further hirsutism. Existing facial hair needs treatment. Virilization will cease following removal of a masculinizing ovarian tumour, but hoarseness of voice may persist. Menstrual cycles are restored and breasts start growing. PCOD will require to be treated with ovulation induction/laparoscopic laser or cautery for puncture of cysts. This is preferably done under video pelviscopic vision. Infertility will need ovulation induction drugs, and an elderly woman should receive cyclical progestogen therapy to prevent endometrial hyperplasia and cancer developing from unopposed oestrogen stimulation. Metformin 500 mg t.i.d. for 8 weeks reduces hyperinsulinaemia seen in PCOD.
2. **Drugs.** Dexamethasone 0.25–0.5 mg daily at night will control adrenal hyperplasia if DHEA is raised. Sometimes combined oral contraceptive pills (OCPs) may be needed in addition to dexamethasone to suppress androgens. *Suppression of androgens* with combined OCPs, not containing androgenic progestogen such as norethisterone and levonorgestrel, will suppress ovarian androgens. Oestrogen is not only antiandrogenic but by stimulating production of SHBG will bind circulating testosterone to SHBG, thus suppressing its peripheral action on the hair follicles. Antiandrogens used are (1) spironolactone and (2) cyproterone acetate.
   - Spironolactone in a dose of 100–200 mg daily blocks the androgen receptors, reduces its production and increases its metabolism, and thus prevents further hirsutism in 60% cases. It is best given with combined oral pills to avoid irregular menstruation and prevent the possible feminization of the male fetus if the female conceives during this therapy. The side effects include a transient diuresis, menstrual irregularity (polymenorrhagia 10%) and breast enlargement. Occasionally hyperkalaemia and hyponatraemia may occur. Maintenance dose after 6–12 months is 50 mg spironolactone with OCPs (see also Chapter 43). Drospirenone 3 mg with 30 mcg oestradiol (Yasmin, Janya, Tarana) used cyclically for 3 weeks is found very effective in hirsutism in PCOD.
   - Cyproterone acetate is a potent progestogen, a synthetic derivative of 17 alpha-hydroxyprogesterone; it inhibits DHT binding to its receptors at the periphery and has a weak corticosteroid effect. It is given combined with oestrogen as 50–100 mg cyproterone daily for the first 10 days of the menstrual cycle with 30–50 mcg of ethinyl oestradiol (EE) for 21 days. After 6–12 months, maintenance dose of 5–10 mg cyproterone acetate with EE will be effective in preventing recurrence of hirsutism. The effect becomes apparent after 4 months of treatment. Oral contraceptives regularize the cycle and prevent pregnancy. Oestrogen present in the pills avoids menopausal symptoms and also raises the serum hormone binding capacity, which binds the androgen and reduces insulin-like growth factor. Side effects are weight gain, nausea and headache, rarely liver damage.
3. **Weight reduction** will elevate SHBG and bind free testosterone, thus reducing its peripheral action on hair follicles.
4. **Cosmetics.** Bleaching, waxing, shaving, and laser are useful in removal of facial hair. Electrolysis is highly satisfactory in treating hirsutism.
5. **New drugs** available are
   - *Flutamide* (nonsteroidal) 250 mg b.d. for 3 weeks cyclically with oral contraceptives for 6 months blocks the androgen effect at the receptor level. Side effects are dry skin, oligomenorrhoea and liver damage. It is faster acting than spironolactone.
   - *Finasteride* 5 mg daily for 6 months blocks the conversion of T to potent androgen and is safer than flutamide. It reduces conversion of T to DHT.

Polycystic ovarian disease is detailed in Chapter 32. Summary of causes and management of hirsutism is explained in Table 10.2.

Acne

Acne is a mild form of hirsutism seen in young girls. This should be treated with Dianette pill containing 35 mcg E_2, 2 mg cyproterone acetate starting on the first day of cycle for 21 days each cycle. Cimetidine 1.5 mg daily also helps, but it can cause galactorrhoea, and the drug is very expensive. Vanique (eflornithine) 11.5% cream is also effective; antibiotic creams such as clindamycin 1%, erythromycin 2% and retinoids also help. Vanique cream is applied twice daily for 24 weeks – some develop allergic dermatitis and mild burning sensation.

- Isotretinoin suppress sebaceous gland secretion
- Dutasteride (Avodart) is 5-alfa-reductase inhibitor is under trial. It inhibits DHT production in 99% cases. It is contraindicated in pregnancy.

True Hermaphrodite

True hermaphrodite is an individual with ovotestes or ovary on one side and testes on the other side. The uterus and vagina develop and the person menstruates. In addition, the external genitalia is of male phenotype. Since the individual is brought up as male until puberty, it may be prudent to retain the male gender, do mastectomy and hysterectomy.

TABLE 10.2 Summary of causes and management of hirsutism

Cause	Mechanism	Diagnostic Information	Treatment
Ovarian androgens	Androgen-producing tumours (Sertoli, Leydig cell, Hilar cell tumours)	• Rapid progress • High testosterone(T) level • Pelvic mass present • Clitoromegaly	• Surgical excision of functioning tumour
	Polycystic ovary syndrome	• Long term duration • Mild elevation of testosterone (T) • Elevated LH/FSH ratio • Anovulation • Infertility • Irregular menstruation/ amenorrhoea • Obesity	• Oral contraceptive pills, antiandrogens • Weight control • Metformin • Changes in life style • Laparoscopic ovarian drilling • ART procedures
	Luteoma of pregnancy/theca lutein cysts	• Onset during pregnancy	Conservative management
Adrenal androgens	Androgen-producing tumour	• Rapid onset • High DHEAS • Abdominal mass present • Clitoromegally	• Remove tumour
	• Congenital adrenal hyperplasia (late onset) 21-hydoxylase deficiency	• Elevated serum 17-dihydroxy progesterone	• Glucocorticoid replacement and suppression
	• Cushing syndrome	• Elevated plasma cortisol	• Varies as to cause
Exogenous androgens	• Hormonal drugs	• Methyltestosterone • Anabolic steroids • Danazol	• Withdraw offending drug
Hair follicle sensitivity	• Excessive conversion of DHT in hair follicle	• Long duration • Family history • Racial trait	• Spironolactone • Cyproterone acetate • Flutamide • Depilatories • Electrolysis • Cosmetic treatments – waxing/shaving
Exogenous causes of hypertrichosis	• Nonhormonal medications	• Phenytoin • Diazoxide • Minoxidil • Streptomycin • Penicillamine	• Withdraw offending medications
	• Pathologic states	• Hypothyroidism • Anorexia • Dermatomyositis • Porphyria	• Treat the cause
	• Normal states	• Old age • Ethnic trait • Pregnancy	• Observation • Cosmetic therapy

T helps to develop secondary sexual characters of the male phenotype. The plastic surgery on the phallus may be required, and sexual function is possible. Fertility, however, may remain low.

Psychological Sex

Homosexuality, transvestism and transsexuality are abnormal sexual behaviours. Transsexuality is defined as a disturbance of gender identity in which a person anatomically of one gender has an intense and persistent desire for medical, surgical and legal change of sex and lives as a member of the opposite gender. These are psychosexual patients and need careful handling and a lot of counselling before taking and accepting the individual's decision. Initially, hormone therapy followed by surgery will be needed to reconstruct the body phenotype of the desired gender. Oestrogen for a male and progestogen for the female will reduce the secondary sexual characters over a period of 1–2 years. This makes reconstructive surgery easier, apart from the fact that it gives the individual to assert her or his decision over the change of sex.

Key Points

- Intersexuality is a difficult gynaecological problem to tackle, because the condition is extremely rare and the experience of the gynaecologist is limited.
- Detailed knowledge on genetic sex, hormonal influences coupled with investigations are required to make the accurate diagnosis and conduct the appropriate management.
- Hirsutism is now increasingly encountered in young women as the incidence of PCOD has increased. Other causes are idiopathic, adrenal, drug administration, hypothyroidism and hyperprolactinaemia.
- Ultrasound and hormonal profile study are necessary.
- Various drugs used in hirsutism are cyproterone acetate, spironolactone, finasteride and combined hormonal pills.
- Acne is a cosmetic problem and demands treatment.
- Varieties of intersex now can be diagnosed based on chromosomal study. Surgical management allows an individual to live near-normal life as possible.
- Virilism requires immediate management, otherwise certain masculinizing features will persist despite treating the cause. These persistent features are deepening of voice and baldness.

Self-Assessment

1. Describe the phenotypic appearances of individuals with sex chromosomal abnormalities.
2. Enumerate the components contributing to determination of sex.
3. What are the common causes of hirsutism? Describe their management.
4. Describe the features of Swyer's syndrome, Turner's syndrome and Klinefelter syndrome.
5. Define Virilism. Describe its clinical features, types and management of this disorder.

Suggested Reading

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Chapter 11

Sexually Transmitted Diseases

CHAPTER OUTLINE

Symptoms caused by infections of the lower genital tract are amongst the most common complaints amongst gynaecologic patients. Often these are initiated or aggravated through sexual activity.

Sexually transmitted infections (STIs) have become a global threat to the health of the population, and its increasing incidence is due to promiscuity and frequent change of partners. Genital tract infection can lead to pelvic inflammatory disease (PID), infertility and ectopic pregnancy if the fallopian tubes are involved. Viral infections are liable to cause vulval and cervical cancers. Obstetric complications include repeated pregnancy losses, intrauterine fetal death, neonatal eye, throat infections and septicaemia. Vertical transmission to the fetus and neonate is known in women with syphilis and human immunodeficiency viral (HIV) diseases. Antenatal routine testing and treatment can avoid or reduce this transmission.

Of all the infections known, bacterial vaginosis accounts for 40–50% cases, monilial infection for 20–25% cases and trichomonad infection for 15–20% cases. The others are rare, though the incidence of chlamydial infection is increasing.

Types of infections:

- Bacterial—syphilis, gonorrhoea, Chlamydia, lymphogranuloma, *Mycoplasma genitalia,* chancroid.
- Viral—human papillomavirus (HPV), herpes simplex virus, HIV.
- Protozoa—*Trichomonas vaginalis.*
- Fungal—Candida.
- Infestations—scabies, pediculosis.

Most of the genital tract infections are sexually transmitted. However, unscreened blood transfusions can also spread syphilis, HIV and hepatitis B virus. Other rare causes are infected needles, toilets and towels.

Vulvar Infections

The normal vulva is composed of the skin consisting of stratified squamous epithelium. It contains sebaceous, sweat and apocrine glands, underlying subcutaneous tissue and the specialized Bartholin's glands. Vulvar pruritus and burning account for approximately 10–15% of presenting complaints (Ch. 11).

Parasites (Pediculosis Pubis)

Pediculosis pubis (crab louse *or Phthirus pubis*) is one of the most contagious sexually transmitted diseases (STDs). It is also transmitted through intimate contact, shared towels or sheets. These parasites deposit their eggs at the base of hair follicles. The louse feeds on human blood (Figure 11.1).

Figure 11.1 Crab louse (*Phthirus pubis*). (Source: Robert S. Dill, Associate Professor, Biological Sciences, Bergen Community College.)

Clinical Features

The patient complains of intense itching in the pubic area; there may be presence of a vulvar rash. The intense itching can cause insomnia, irritation and social embarrassment.

Diagnosis

Diagnosis is established on inspection—finding of eggs/lice in the pubic hair. The louse can be identified under the microscope.

Treatment

Local application of permethrin cream 5%—two applications 10 days apart—to kill newly hatched eggs or local application of gamma-benzene hexachloride 1% as lotion/cream or shampoo after showering so that the drug effects last for 12 h on 2 successive days. This treatment is contraindicated in pregnant and nursing mothers. All clothes should be properly laundered.

Scabies

Itch mite: It is transmitted through close contact/fomites.

Clinical Features

It generally affects the flexure aspects of the elbows and wrists, buttocks and the external genitalia. The adult female burrows beneath the skin to lay its eggs. The patients suffer from intense burning along with intermittent episodes of intense itching / burning. Itching is more severe at night. It may present as papules, vesicles or burrows.

Diagnosis

It is established on microscopic examination of skin scrapings under oil.

Treatment

It consists of local application of permethrin cream 5% bid for 2 successive days or application of 30 mL of lotion over the entire skin surface leaving it on for 12 h. Pruritus may persist for a while; this should be controlled with antihistamines. Treatment should be withheld during pregnancy and lactation. Clothes should be properly laundered.

Molluscum Contagiosum

It is a benign viral infection caused by the *poxvirus.* It is spread by close sexual or nonsexual contact and by autoinoculation. The incubation period ranges from several weeks to months.

Clinical Features

The patient presents with a crop of small domed vesicles with central umbilication measuring 1–5 mm in size. White waxy material can be expressed out of it.

Diagnosis

Giemsa staining of the discharge (white waxy material) reveals intracytoplasmic molluscum bodies confirmatory of the diagnosis.

Treatment

It consists of evacuation of the white material, excision of the nodule with a dermal curet and treatment of the base with Monsel's solution (ferric subsulphate) or 85% trichloracetic acid. Cryotherapy and electrocoagulation may be considered as an alternative therapy.

Condylomata Acuminata (Figures 11.2 and 11.3)

Also called venereal warts, these are caused by the HPV, which is a small DNA double-ended virus. These warts spread diffusely over the whole of the vulval area. The verrucous growths may appear discrete or coalesce to form large cauliflower-like growths. They affect the skin of the

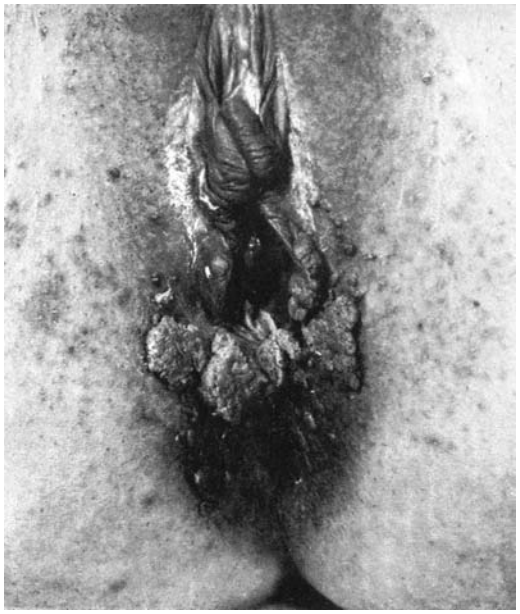

Figure 11.2 Condyloma acuminatum of the vulva.

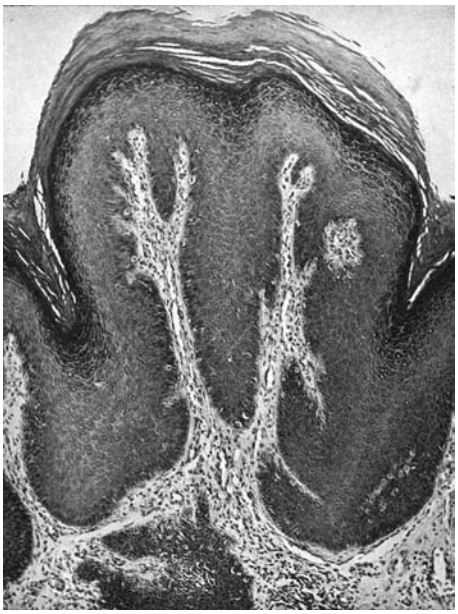

Figure 11.3 Section of condyloma acuminatum showing marked hyperkeratosis of squamous epithelium and round cell infiltration of the corium (×87).

labia majora, perineum, perianal region and vagina. The growths are seen in women of the childbearing age and are mainly sexually transmitted. Vaginal discharge, oral contraceptives and pregnancy favour their growth. There are several varieties of the HPV of which HPV 6, 11, 16 and 18 as well as 31, 32 and 33 are of significance to the gynaecologist. HPV 6, 16 and 18 are implicated in the development of condyloma acuminatum and cancers of the cervix and vulva. The presence of koilocytes constitutes the histological marker for the virus. Apart from koilocytes, other histological features are perinuclear halo, multinucleation, organophilic cytoplasm acanthosis and chronic inflammatory infiltrate. Dysplasia may be seen in warts in elderly women. The typing of virus is based on DNA, DNA hybridization and polymerase chain reaction (PCR). A small DNA virus, 55 nm in diameter, is epitheliotropic and contributes to 15% of all cancers. In young women, the infection is transient in 90% and disappears without any alteration in DNA. In older women, it often persists and progresses to carcinoma in situ in 30% cases in 1–3 years and cancer of the cervix, both adenocarcinoma and squamous cell cancer.

Condyloma is associated with vulval, vaginal and cervical cancers in 20% cases. Liver and cervical cancers account for about 80% virus-related cancers.

Diagnosis

Colposcopic study of this lesion aided by acetic acid application is important in the diagnosis of lesions on the cervix and 1% toluidine blue staining for the vulval lesions. The abnormal vulval skin with the abnormal nuclei retains the blue dye, whereas the normal skin allows the dye to be washed off. Acetic acid can cause burning in the vulva and it should be diluted to 50% before use. Vulval skin is first smeared with water-soluble K-Y jelly and treated with dilute acetic acid. The vascular pattern is studied. The abnormal areas stained with toluidine blue are biopsied.

Cytology. Koilocytes, with perinuclear halo, multinucleation and orangeophilic cytoplasm.

Histology. Acanthosis, chronic inflammatory infiltration, and sometimes dysplasia cells.

Viral tests. DNA test, hybridization, PCR staining. CD_4 count shows immune functioning.

Colposcopic Findings

Meisels described colposcopic appearance of condylomas as patches of raised projection of acetowhite epithelium with speckled appearance. Immunochemical technique can demonstrate viral antigen in the tissue sections.

Treatment

Young women with flat condyloma may be observed for 6 months, especially when it develops during pregnancy, because the lesions often disappear spontaneously. Local application of podophyllin 25% in alcohol or podophyllin 20% in tincture benzoin for 6 h daily or 25% trichloracetic acid plus 5% fluorouracil causes sloughing off of small warts in 3–4 days in 70–80% cases. The treatment may need to be repeated weekly as the warts recur at 3–6 weeks' interval. Local podophylline cream (podofilox) is also available. This treatment is, however, contraindicated in the first trimester of pregnancy because the drug is absorbed into the circulation and is cytotoxic causing abortion and peripheral neuropathy. This treatment is also contraindicated in vaginal and cervical lesions because of severe inflammatory reaction provoked at these sites. The larger lesions are best removed by diathermy loop or laser ablation. The surgical excision of a localized growth is another alternative. Associated syphilis and malignancy need to be excluded. The husband should be treated simultaneously or protected from infection by advising the use of condoms. Vulval and vaginal warts during pregnancy mandate caesarean section to avoid papilloma laryngitis in the neonate.

Lately, Ikic et al advocated interferon local ointment or cream or intralesional injection. The cream is applied four to five times daily 1 g each time (1 g contains 2×106 IU), with total daily dose of 6 g for 8 weeks. Ninety per cent lesions regress by then. Intramuscular injection of 2×106 IU of interferon daily for 10 days yields 90% success. Side effects are fever, myalgia and headache. *Cream is preferred to injection as the latter is painful. Interferon inhibits the viral and cellular growth.* Apart from surgery, the warts can be removed by cryosurgery, diathermy or laser. *Needless to say that biopsy is mandatory to rule out malignancy. Pap smear of the cervix is also required to rule out cervical malignancy.*

Other measures include the following:

- Improve body immunity with antioxidants such as vitamin C and folic acid.
- No smoking.

- Vaccines at 0, 1 and 6 months before exposure to sexual activity in adolescent girls and boys are available, though expensive. Bivalent vaccine against HPV 16 and 18 is known as Cervarix. Quadrivalent vaccine against HPV 6, 11, 16 and 18 is known as Gardasil or Silgard. The high cost of vaccine precludes the prophylactic use in general population as of today. Cervarix is given at 0, 1 and 6 months. Gardasil at 0, 2 and 6 months.
- Inosiplex is immunomodulator used as adjunct to conventional therapy. Orally, it is given 5 mg/kg daily for 12 weeks. About 20% complete response and 40% partial response is reported.
- Imiquimod cream applied three times a week for 4 months cures 75% cases, but recurrence occurs in 15% cases. Some develop local erythematous reaction to the cream.

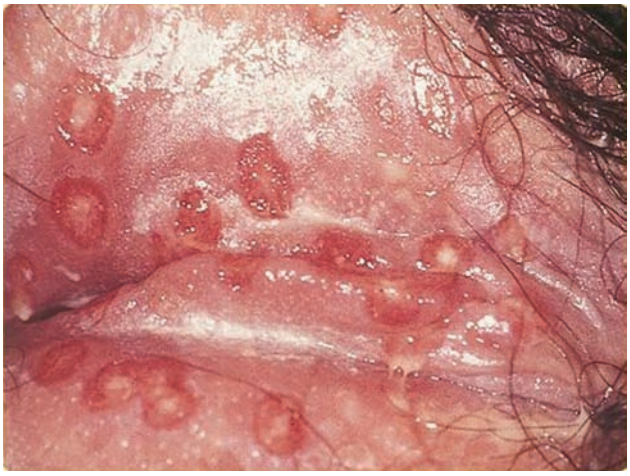

Figure 11.4 Recurrent herpes genitalis. (Source: Wikimedia commons.)

Genital Ulcers

STIs like genital herpes, granuloma inguinale (donovanosis), lymphogranuloma venereum (LGV), chancroid and syphilis often present with ulcerative lesions of the vulva.

Genital Herpes

It is a recurrent STD infection caused by the double-stranded DNA of *herpes simplex virus (almost 80% are type-II infections)*. The prevalence of the disease has reached epidemic proportions in the developed countries of the world. The *incubation period* is 3–7 days. Herpes simplex virus type I affects only 30% vulval lesions.

It mostly affects women between 20 and 30 years.

Clinical Features

Primary Infection. The patient often complains of constitutional symptoms such as malaise, fever and vulval paraesthesia followed by appearance of vesicles on the vulva resulting in ulcers, which are shallow and painful. These often coalesce. Multiple crops of vesicles and ulcers tend to occur in 2–6 weeks. The lesions peak in 7 days and last for approximately 2 weeks. The outbreak is self-limited. The lesions heal without scarring. Viral shedding, however, tends to continue for weeks after the appearance of lesions.

Recurrent Herpetic Outbreaks (Figure 11. 4)**.** These are generally of shorter duration and milder in severity of symptom. Prodromal symptoms of burning or itching in the affected area often precede the attacks. Systemic symptoms are generally absent. About 50% of the affected women experience their first recurrence within 6 months and have on an average about four recurrences within the first year; thereafter, the episodes of recurrences tend to occur at variable intervals. Latent herpes virus residing in the dorsal root ganglia of S_2, S_3 and S_4 may get reactivated whenever the immune system gets compromised as seen during pregnancy or any other immunocompromised state.

Complications

Known complications include encephalitis, urinary tract involvement causing retention of urine, severe pain or both.

Diagnosis

Diagnosis is essentially based on clinical inspection of the lesions; immunologic or cytologic tests are not very sensitive; viral cultures from swabs taken from the base of the vesicles are positive in 90% cases. In 6 weeks, NAAT offers greater sensitivity than the culture. Biopsy reveals characteristic 'ground glass appearance' of the cellular nuclei and numerous small intracellular basophilic particles and acidophilic inclusion bodies. Cytology shows multinucleated giant cells. The antibody detection in serum and PCR staining is also diagnostic. Antibodies can be detected 2 weeks after the infection.

Treatment

- **Aims of the treatment include the following:**
  - To shorten the duration of the attack.
  - Prevent complications.
  - Prevent recurrences.
  - Diminish risks of transmission.
- The virus cannot be effectively eradicated.
- In severe cases, administer acyclovir 5 mg/kg body weight intravenously every 8 h for 5 days.
- Treat primary outbreaks: Prescribe oral 200 mg acyclovir five times daily for 5 days. Local application of acyclovir cream provides relief and accelerates healing of local lesions. Thus, *treatment reduces the duration and severity of the attack but does not prevent latency of the disease or episodes of recurrence.* Valacyclovir 500 mg bd or famciclovir 125 –250 mg bd is also effective, given for 7 days.
- Valaciclovir 250 mg BD × 7 days is also effective.
- Betadine is locally effective.
- Counselling: The couple is advised to abstain from intercourse from the time of experiencing prodromal symptoms until total re-epithelialization of the lesions takes place. These patients are more susceptible to HIV infection and other STD infections.

- Caesarean section is recommended in the presence of active infection, to avoid neonatal infection.

Vaccine to genital herpes is not yet available, but immune enhancers reduce the frequency of recurrences. Imiquimod is being tried, but clinical trial is lacking.

Granuloma Inguinale (Donovanosis) (Figure 11.5)

The causative organism of granuloma inguinale is *Calymmatobacterium granulomatis*. It is a Gram-negative bacillus causing chronic ulcerative infection of the vulva. It is prevalent in the tropics. It is not only highly contagious but is transmitted through repeated sexual or nonsexual contact. The *incubation period* is 1–12 weeks.

Clinical Features

It begins as a painless nodule which later ulcerates to form multiple beefy red painless ulcers that tend to coalesce, the vulva is progressively destroyed and minimal adenopathy may occur.

Diagnosis

Microscopic examination of smears from the lesion/biopsy specimens reveals pathognomonic intracytoplasmic Donovan bodies and clusters of bacteria with a bipolar (safety-pin) appearance (Gram negative). Blue–black staining organisms are seen in the cytoplasm of mononuclear cells.

Treatment

- Tetracycline 500 mg every 6 h for 2–3 weeks or until complete cure occurs.
- Chloramphenicol 500 mg orally three times daily for 21 days is effective, but because of the possible adverse toxic effects of the drug, it is not very popular. Alternatively, gentamycin 1 mg/kg IM 8 h for 2 weeks is effective.

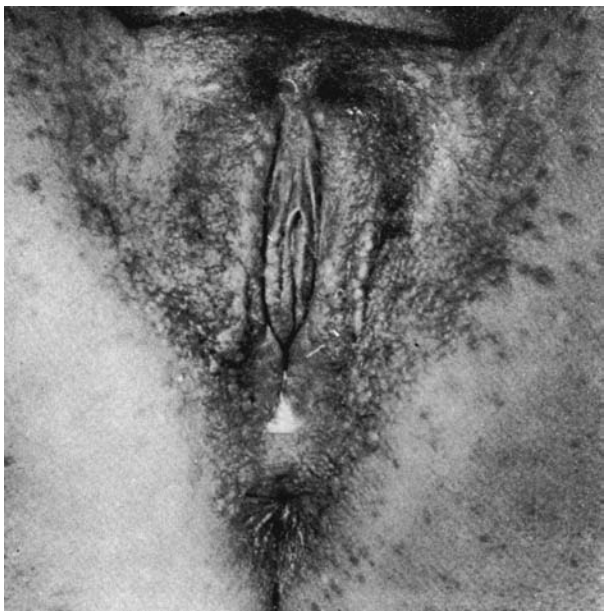

Figure 11.5 Granuloma inguinale.

- Surgical treatment of excision may be required if medical treatment fails.

Lymphogranuloma Venereum

It is an uncommon STD that affects men more commonly than women. It is generally prevalent in Africa and Asia.

Risk Factors

- Sexually active before the age of 20 years.
- Multiple sexual partners.
- Low socioeconomic status.
- History of having suffered from other STDs.

The incubation period is 7–21 days.

Pathophysiology

The causative organism is *Chlamydia trachomatis* (any one of the 'L' serotypes 1, 2 and 3), intracellular bacteria Gram negative. *Sexual transmission*: In women, the organism is carried by lymphatic drainage from the genital lesion to the perirectal, both inguinal and pelvic lymph nodes. Rectal involvement is common in females and occurs by contiguous spread from the perirectal nodes leading to proctocolitis and rectal strictures formation. The drainage is primarily to the inguinal nodes leading to bubo formation; this may burst, ulcerate or cause sinus. It can also affect the urethra, perineum and cervix.

Clinical Features

The lesion starts as painless vesicopustular eruption that heals spontaneously. After some weeks, the sequelae of lymphatic spread begin with hardly any clinical manifestations. The general features are fever, headache, malaise and arthralgia.

Diagnosis

It is essentially a clinical diagnosis. Determination of LGV is extremely difficult until late stage of the disease.

Investigations

The *Frei test* based on delayed skin hypersensitivity to the antigen becomes positive 2–8 weeks after primary infection. The *complement fixation test* is more sensitive than the Frei test. Culture can be grown. Inclusion bodies in the smear can be detected. DNA probing is specific.

Complications

Complications are the result of scar tissue formation. It includes the following: (a) proctitis, (b) severe stricture formation leading to intestinal obstruction, (c) rectovaginal fistulae following stricture formation and (d) vulvar cancer.

Treatment

Treatment with tetracyclines 500 mg 6 h, doxycycline 100 mg bid orally for 3 weeks or sulphonamides or erythromycin 500 mg orally every 6 h daily for 3–6 weeks are equally effective in eradicating the disease. However, aspiration of fluctuant bubo and palliative surgical interventions

may be required to correct complicating sequelae of the disease. Other antibiotics are amoxycillin 500 mg tid for 7 days and azithromycin 1 g single dose. The partner should be treated.

Mycoplasma Genitalium

Mycoplasma genitalium, first discovered in 1983, is an intracellular organism lacking cell wall, not stained by Gram stain. It is difficult to culture and takes weeks or months. NAAT (nucleic acid amplification test) and PCR are the detection tests. No commercial test available. The infection causes urethritis, endocervicilis and PID.

- Moxifloxacine 400 mg OD × 7 days.
- Azithromycin 500 mg stat and 250 mg 6 h × 4 days.

Chancroid (Soft Sore)

It is an acute STD caused by small Gram-negative bacilli *Haemophilus ducreyi (anaerobe)*. It is common in the underdeveloped countries of the world. It affects males five to ten times more often than females. It may facilitate the spread of HIV infections. It is highly contagious, but it requires the presence of broken/traumatized skin for entry. The *incubation period is* 3–6 days.

Clinical Features

Initially, there appears a small papule that develops into a painful pustule that ulcerates. Multiple lesions at various stages of development may be evident at one and the same time. The ulcers are shallow, ragged and painful. Often a unilateral inguinal lymphadenopathy may be evident in 50% cases. Recurrence rate at the same site has been observed in 10% cases. The ulcers are sharply demarked without induration. Distal spread is rare. In 10% soft sore is associated with syphilis or herpes.

Diagnosis

This is based on investigation of the purulent discharge from the lesion or aspirate from the lymph node showing on Gram staining the typical extracellular 'school of fish' appearance. Culture, ELISA test and PCR staining can also be used as diagnostic tests.

Treatment

Recommendations include the following options:

- Azithromycin 1.0 g orally as a single dose with 98% effectiveness.
- Erythromycin 500 mg orally every 6 h for 7 days.
- Alternatives include ceftriaxone 250 mg IM as a single dose or orally trimethoprim and sulphamethoxazole (Bactrim DS) bid for 7 days or oral ciprofloxacin 500 mg bid for 3 days.
- Spectinomycin 2 g IM as a single dose.
- The woman should be screened for other STDs.

Syphilis (Figure 11.6)

It is a sexually transmitted infection caused by the motile spirochete *Treponema pallidum*. Humans are natural hosts. It is also spread by contact with broken skin/intact mucous membrane. The most frequent entry sites in the female include vulva, vagina and cervix.

Clinical Features

When the disease goes untreated, its natural evolution is as follows.

Primary Syphilis. The classic lesion designated as the chancre appears within 9–90 days from the first exposure. The macular lesion becomes papular and then ulcerates. The ulcer(s) is painless and firm, with a punched out base and rolled edges. Left unattended, these heal within 3–9 weeks. There occurs an accompanying painless inguinal, discrete lymphadenopathy. The latent period is 8 weeks after inoculation and 3–6 weeks after chancre. The serological test becomes positive 1–4 weeks after chancre.

Secondary Syphilis. This is evidence of widespread dissemination of the spirochetes.

Onset of systemic manifestations includes symptoms such as malaise, headache, loss of appetite, sore throat and the appearance of a generalized symmetric, asymptomatic maculopapular rash on the palms and soles of the feet. It is not uncommon to find a generalized adenopathy in 50% cases. *Condylomata lata* are the classic findings; these are highly contagious exophytic broad excrescences that ulcerate. These are commonly seen on the vulva, perianal area and upper thighs. After 2–6 weeks, it passes into the phase of latent syphilis. There are no clinical manifestations present; however, the serologic test for syphilis is positive. This stage lasts for 2–10 weeks (Figure 11.7).

Tertiary Syphilis. Syphilis left untreated may develop complications in about a third of the affected patients 5–20 years

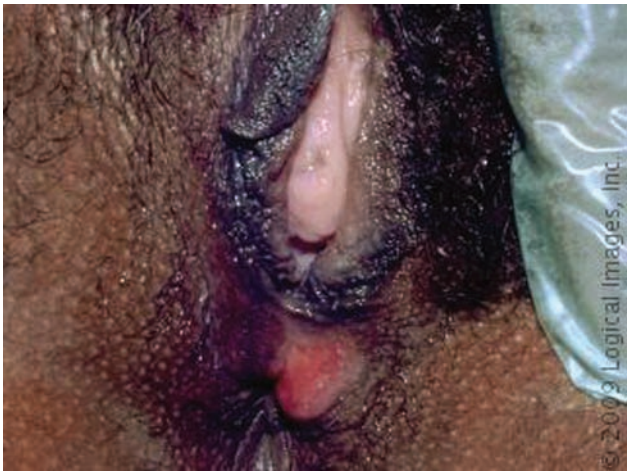

Figure 11.6 Hard chancre of syphilis. (Source: Logical images, www.logicalimages.com.)

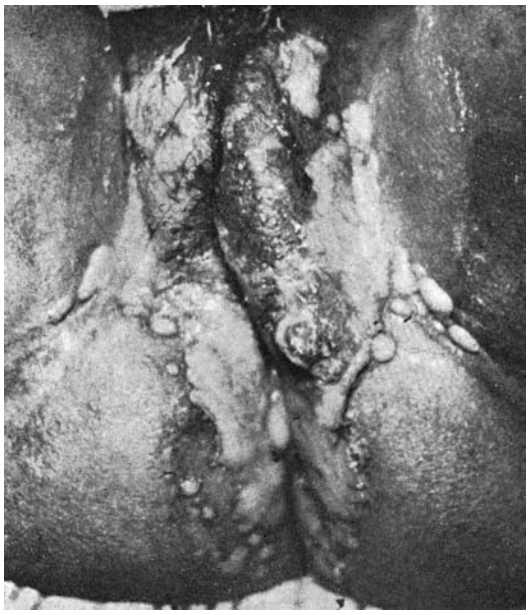

Figure 11.7 Early condylomas of secondary syphilis.

after the chancre has disappeared. The disease remains latent in the rest. Manifestations of diffuse organ system involvement include the following:

- *Neurosyphilis:* Manifested as meningitis, tabes dorsalis or paresis and mental disease.
- *Cardiosyphilis:* Manifesting as valvular disease, aortitis and aneurysm.
- *Skin manifestations* such as gummas.

During pregnancy, syphilis can cause late abortion and still birth. Congenital syphilis manifests few weeks after birth.

Laboratory Investigations

These include the following:

- Primary syphilis: Dark field microscopy of chancre scrapings reveals spirochetes. Serological test (VDRL test) at this stage is negative.
- Secondary syphilis: Dark field microscopy of scrapings from condylomata lata reveals spirochetes. Serological test (VDRL test) is positive. Immunofluorescent technique is also available.
- Tertiary syphilis: Serological test (VDRL test) is positive. Lumbar puncture and examination of cerebrospinal fluid is recommended in cases of suspected neurosyphilis.
- Confirmatory tests such as the fluorescent titre antibody (FTA) absorption test and the microhaemagglutination assay for antibodies to *Treponema pallidum* (MHA-TP) are advocated. The important point to remember is *false-positive VDRL is seen in women with lupus erythematosus*.
- Biopsy may be needed to differentiate it from tubercular and cancerous ulcer.
- PCR testing is now available.

Treatment

The following are recommended:

- Screen for other STDs and HIV.
- Counselling about treatment, expected course of the disease, risk of fetal transmission and its sequelae in case of pregnancy.
- Treating all sexual partners of infected individual.
- Specific treatment: (a) Generally, 2.4 million units of benzathine penicillin are given IM. (b) If latent disease is present for over a year, the dose of penicillin is repeated weekly for 3 weeks. Patients who are allergic to penicillin should undergo desensitization or they should be prescribed erythromycin as an alternative drug.
- Doxycycline 100 mg bd × 14 days.
- Erythromycin 500 mg qid × 14 days.
- Azithromycin 500 mg od × 10 days.
- Amoxycillin 500 mg qid × 14 days.
- Follow-up serology titres should show a decrease of fourfold in their serologic titres after 3–6 months.
- Recommend use of barrier contraceptives to prevent spread of the disease.
- Seek joint consultation with specialist in STD.

Vaginitis

Gonococcal Vulvovaginitis

This is an STD that can lead to sequelae adversely affecting reproductive functions.

Epidemiology

The causative organism is a Gram-negative intracellular diplococcus called *Neisseria gonorrhoea.* The incubation period is 2–10 days. The vaginal squamous epithelium is resistant to gonococcal infection. The gonococci attack the columnar epithelium of glands of Skene, Bartholin, urethra and its glands, cervix and fallopian tubes. It ascends in a piggy-back fashion attached to the sperms to reach the fallopian tubes. It is destroyed easily by drying, heat, sunlight and disinfectants. *Sites for bacterial recovery:* These include the urethra, cervix, anal canal and pharynx. *Principal sites of invasion:* Columnar epithelium of the genital tract, transitional epithelium of the urethra and Bartholin's gland. *Infection rates:* The likelihood of contracting infection from woman to man is 35% for men and 75% for women from male. Childhood infection occurs due to contamination of infected material.

Diagnosis

Early clinical findings: Gonorrhoea is an asymptomatic infection in the pharynx, cervix and anal canal/rectum. *Complaints*: Urinary frequency and dysuria, dyspareunia, rectal discomfort, vaginal discharge. Vulvovaginal/perineal infection often results in inflammation, discharge, irritation causing pruritus and dysuria. Examination reveals swollen, painful external genitalia, purulent vaginal discharge,

erythema surrounding external urinary meatus, opening of the Bartholin's ducts, vaginitis and endocervicitis. *Late clinical findings:* Bartholinitis, Bartholin's abscess, Bartholin's cyst, tubo-ovarian abscess, pyosalpinx, hydrosalpinx and blocked tubes. The disseminated infection may lead to polyarthralgia, tenosynovitis, dermatitis, pericarditis, endocarditis, meningitis and ophthalmologic manifestations causing conjunctivitis and uveitis. End result of chronic pelvic infection causes chronic pelvic pain, dysmenorrhoea, menorrhagia, infertility with fixed retroversion and at times dyspareunia. In the past, it was the cause of neonatal ophthalmitis occurring in newborns born to infected mothers. The routine practice of instilling in all neonates sulphacetamide/antibiotic eye drops has helped to control this problem.

As much as 50–80% women may remain asymptomatic.

Laboratory Investigations

These include Gram staining of smear prepared from any suspicious discharge. The terminal urethra and endocervix are favoured sites for obtaining the discharge. Culture from urethra and cervix on Thayer–Martin medium or blood agar, and McLeod chocolate agar in 5% CO_2 moist atmosphere.

Complement fixation tests and PCR staining are also possible.

NAAT from urine, endocervical discharge—95% sensitive is now in vogue. If NAAT is positive, there is no need of culture.

Self-collected samples yield similar results to that prepared by the physician.

Laparoscopy reveals, apart from tubal disease, a band of fibrous tissue on right side stretching from fallopian tube to the under surface of the liver (Fitz–Hugh Curtis syndrome) (Figure 11.8).

Complications

PID, pyosalpinx formation, tubo-ovarian abscess, pelvic abscess followed later on by hydrosalpinx formation, infertility, menstrual disturbances, chronic pelvic pain, dysmenorrhoea and dyspareunia.

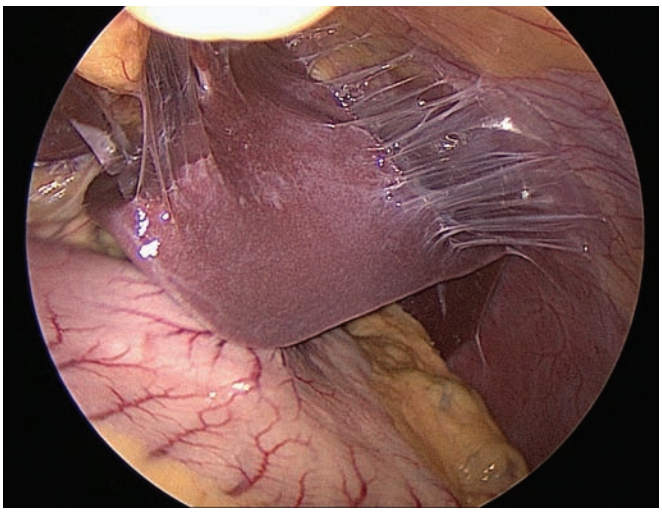

Figure 11.8 Laparoscopic view of gonococcal and chlamydial infection showing Fitz-Hugh Curtis syndrome. (Courtesy: Dr Vivek Marwah, New Delhi.)

Treatment

Treatment options include the following:

- Injecting cefoxitin 2.0 g IM plus probenecid 1.0 g orally followed by 14 days treatment with oral cap. Doxycycline 100 mg bid for 14 days or oral cap. Tetracycline 250 mg qid for 14 days.
- Ceftriaxone 250 mg IM + 1.0 g probenecid orally followed by oral cap. Doxycycline 100 mg bid for 14 days or oral tetracycline 500 mg qid for 14 days.
- Oral ciprofloxacin, levofloxacin or ofloxacin 400 mg bid followed by 14 days of clindamycin 450 mg orally qid or metronidazole 500 mg bid for 14 days.
- *Treat the male partner as well, and look for chlamydial infection and syphilis as well.*
- Injecting spectinomycin 2 g IM single dose.
- Surgery includes drainage of abscess, excision of the cyst, tuboplasty for tubal infertility.

Chlamydia

Chlamydial infection is common in young, sexually active women but rare after the age of 40 years. Two to ten per cent of pregnant women are found to have this infection during antenatal period and account for 1% of all abortions. The incubation period is 6–14 days. It is sexually transmitted by vaginal and rectal intercourse.

Chlamydia trachomatis is a small Gram-negative bacterium, an obligate intracellular parasite that appears as intracytoplasmic inclusion body, and is of two varieties, one that causes LGV and the other of nonLGV, which causes nonspecific lower genital tract infection. Often, the infection is silent and the woman is asymptomatic but may develop vaginal discharge, dysuria and frequency of micturition, and at times cervicitis. Sometimes, chlamydia may cause Reiter's syndrome with arthritis, skin lesions, conjunctivitis and genital infection. It also causes perihepatitis and Fitz-Hugh–Curtis syndrome similar to that of gonorrhoea when PID is associated with right upper abdominal pain. During pregnancy, abortion, preterm labour and intrauterine growth retardation (IUGR) may occur. Newborn suffers from conjunctivitis, nasopharyngitis, otitis media and pneumonia. Pneumonia may develop 6 weeks to 3 months after vaginal delivery. The cervix is the first site of infection but may spread upwards to develop PID and spread to the partner and neonate. It can cause chorioamnionitis and preterm labour, if infection occurs during pregnancy.

It is an STD, and by ascending upwards, it may cause salpingitis and infertility, though the symptoms of salpingitis may go unnoticed. The tubal damage is, however, more severe than that caused by the gonococcus.

In the female genital tract (cervix), sperm parameters are altered. Fragmentation of DNA causes loss of motility or dead sperms—this results in infertility.

Diagnosis

The use of fluorescein-conjugated monoclonal antibody in immunofluorescence tests on smears prepared from urethral and cervical secretion allows a direct diagnosis of the infection to be made. IgM can be detected in 30% cases of recent infection. Cervical smear shows leucocytes but no organisms. Enzyme-linked immunosorbent assay (ELISA) test can also detect the antigen. Chlamydia is cultured from the cervical tissue in 5–15% of asymptomatic women. Polymerase and ligase chain reactions are fast, highly sensitive and specific (96%), and now considered 'gold standard' in the laboratory diagnosis. Uripath-UK (clear view) is simple, rapid and near patient test.

Cervical ectopy with bleeding on touch and mucopurulent discharge is seen when the cervix is infected.

Chlamydial infection and gonococcal infection often coexist and both attack the columnar epithelium of the genital tract and urethra. Urine can be cultured in suspected chlamydial infection. Urine for PCR is simple. NAAT is also possible.

Treatment

Tetracycline 500 mg and clindamycin 500 mg 6 h for 14 days are found effective. The combination of cefoxitin and ceftriaxone with doxycycline (100 mg bid for 14 days) or tetracycline is also useful. Other drugs that are effective are amoxicillin 500 mg tid for 7 days, erythromycin 500 mg tid for 15 days and levofloxacin 300 mg tid and ofloxacin 400 mg bd for 7 days. Azithromycin 1 g orally as a single dose is found effective. During pregnancy, erythromycin or amoxicillin tid or qid is given for 7 days. Contact tracing, avoidance of sex or barrier contraceptive is necessary to avoid recurrence.

Trichomoniasis

In clinical practice, this is amongst the most common. Nearly half the patients who complain of pruritus vulvae harbour this organism. It is almost entirely a disease of the childbearing era, though young girls and postmenopausal women are not at all immune. There is no doubt that this infection is sexually transmissible but, in some instances, it can be acquired by inadequate hygiene or the use of an infected person's towels, bath or clothes. Its ingress to the vagina is favoured by a low general resistance and when the pH is raised as during a menstrual period (pH 5–6). It is not uncommon during pregnancy and is often associated with gonococcal infection.

The *Trichomonas* vaginalis is a protozoan, actively motile and slightly larger than a leucocyte and is anaerobic. Three types of trichomonas are known. Men may harbour *Trichomonas vaginalis* in the urethra and prostate. A trichomonad has four anterior flagella and one posterior flagella, and they move along the mucous membrane (Figure 11. 9A and B). The posterior flagella are responsible for motility.

Symptoms

Twenty per cent remain asymptomatic—others develop symptoms 4–28 days following sexual contact with an infected partner or contact with infected material. Seventy per cent show typical discharge, which is profuse, thin, creamy or slightly green in colour, irritating and frothy. The vaginal walls are tender, angry looking and the discharge causes pruritus and inflammation of the vulva. There are often multiple small punctate strawberry spots on the vaginal vault and portio vaginalis of the cervix (strawberry vagina). The characteristic frothy discharge is almost self-diagnostic, but the presence of secondary infection may alter and mask this initial sign. The patient may also complain of urinary symptoms, such as dysuria and frequency, and a low-grade urethritis may be discovered on examination. Abdominal pain, low backache and dyspareunia may also be complained of if pelvic infection occurs.

Diagnosis

In all suspected cases, it is necessary to examine a wet film preparation under the microscope. The preparation should be fresh, and the temperature should be at least 35°C. The *Trichomonas* is in constant motion, which distinguishes it

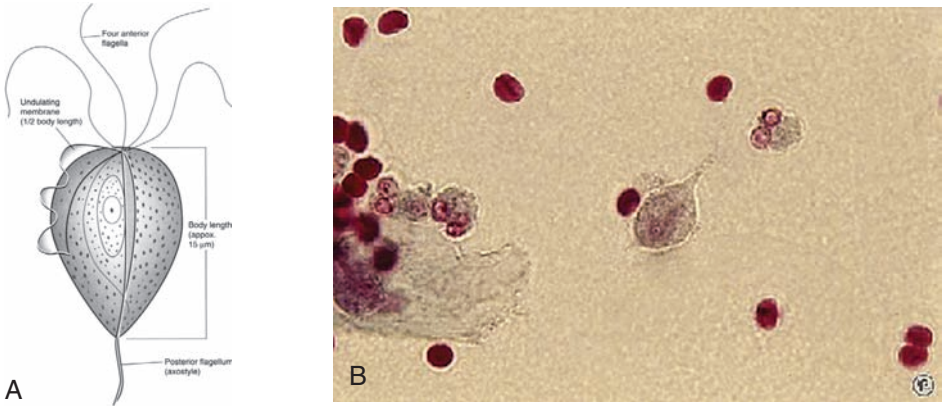

Figure 11.9 **(A)** *Trichomonas vaginalis*. The protozoa are seen only in a wet film and are of varying shapes. They may be adherent to a squamous cell, or they may be attached to pus cells (diagram after Glen Liston). **(B)** Microscopic appearance of *Trichomonas* vaginalis in a hanging drop preparation. (Source: American Society for Microbiology, http://www.asm.org/.)

from pus cells (leucocytes) (Figure 11.9). The *Trichomonas* is usually accompanied by a mixed group of secondary infecting organisms such as *Escherichia coli* and pathogenic cocci. If the wet film stained with Gram stain or Leishman stain is negative, the parasite can be cultured. The culture is 98% reliable. Trichomonas may also be diagnosed on a smear stained for cytology. The other sensitive techniques include PCR and antigen testing. Pap smear shows greyish blue pear-shaped structure without the flagella. PCR and NAAT are more sensitive tests now available.

Treatment

Metronidazole 200 mg by mouth three times a day for 7 days should be prescribed for both the partners, and they should be advised to abstain from intercourse or use a condom during therapy. It is effective in 85% of patients. It is best taken after meals, otherwise nausea and vomiting may occur.

The recent modality of treatment is to shorten the duration of therapy by giving 2 g metronidazole for 1 day only. This is convenient to take and has a better patient compliance. It should be taken at night to avoid vomiting. If this too causes vomiting, or in resistant cases consider use of alternative drugs such as tinidazole 500 mg twice daily after meals for 7 days or secnidazole in a single dose of 1000 mg daily for 2 days. Metronidazole and related drugs are best avoided in the first trimester of pregnancy. During early pregnancy, vinegar douche to lower the pH, trichofuran suppositories and Betadine gel are useful. Condoms can prevent sexual transmission of infection. The husband should be treated simultaneously, especially if the woman develops recurrent infection. Ornidazole (ORNIDA) is 5-nitroimidazole derivative. Dose is 1 g orally or 500 mg bd Ornidazole 500 mg vaginally is useful both in trichomonas infection and in bacterial vaginosis. Half-life of ornidazole given twice daily is 13 h against that of 6–8 h for metronidazole. Side effects are of gastrointestinal tract, headache, drowsiness, muscle weakness and skin reaction. For a child 25 mg bd is adequate. Recurrent infection is treated with tinidazole 500 mg qid and vaginal pessary 500 mg bd for 14 days. Prolonged use causes pancreatitis, neutropenia and neuropathy. Breast feeding is contraindicated during therapy.

Candidal (monilial) vaginitis

It is a fungal infection caused by yeast-like microorganisms called *Candida or Monilia.* The commonest species causing human disease is *Candida albicans,* which is Gram positive and grows in acid medium. It may be sexually transmitted. Almost 25% women harbour *Candida* in the vagina.

Risk Factors

These include promiscuity, immunosuppression, HIV, pregnancy, steroid therapy, following long-term broad-spectrum antibiotic therapy, oral contraception pills, diabetes mellitus, poor personal hygiene and obesity.

Clinical Features

Pruritus vulva is the cardinal symptom. It is often accompanied by vaginal irritation, dysuria, or both, and passage of thick curdy or flaky discharge. Speculum examination reveals vaginal wall congestion with curdy discharge often visible at the vulval mucocutaneous junction and in the posterior fornix.

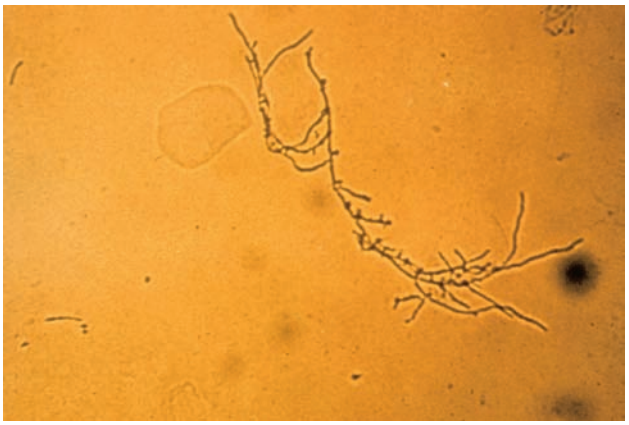

Figure 11.10 Mycelial tangles of yeast pseudohyphae in KOH wet-mount preparation. (Source: Hacker NF, Gambone JC, Hobel CJ, Hacker and Moore's Essentials of Obstetrics and Gynecology, 5th ed. Philadelphia: Elsevier, 2010.)

Diagnosis

It is essentially based on clinical findings. The diagnosis can be confirmed on microscopic examination of a smear of the vaginal discharge treated with 10% KOH solution, which dissolves all other cellular debris, leaving the mycelia and spores of the *Candida* (Figure 11.10). Gram staining of the discharge or Pap smears may also reveal presence of *Candida.* Culture on Sabouraud's agar or Nickerson's medium helps to identify *Candida*.

Pap smear shows thick red-stained hyphae and dark red spores. The colonies on culture appear as black rounded colonies 1–2 mm in diameter with yeast-like odour.

Treatment

Local intravaginal application of antifungal agents such as imidazole, miconazole, clotrimazole, butoconazole or terconazole vaginal pessaries or creams used for 3–6 days is very effective. A single dose of fluconazole 150 mg has been found to be very effective. Ideally, both partners should be treated and the underlying predisposing factor corrected to give long-term relief. Recurrent infection requires fluconazole orally 150 mg every 72 h for 3 doses and then weekly for a few weeks. Tinidazole is effective in resistant cases.

- Nystatin pessary, bd × 10 days
- Miconazole cream 2% × 7 days
- Clotrimazole 100 mg vaginal tablet × 7 days or 1% cream for 7–10 days
- Ketoconazole 400 mg daily × 5 days.

Human Immunodeficiency Virus

HIV made its first appearance in 1981, and the virus was discovered in 1983. Since then it has spread very rapidly and reached epidemic proportions (Figure 11.11).

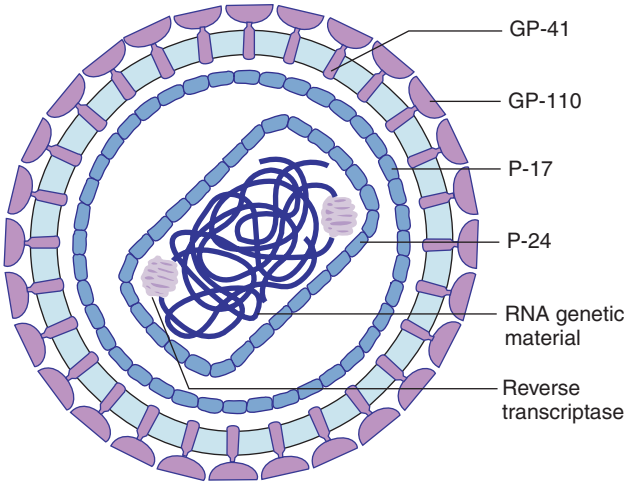

Figure 11.11 AIDS virus.

Acquired immunodeficiency syndrome (AIDS) is the clinical end stage of HIV infection resulting in severe irreversible immunosuppression and acquisition of various opportunistic infections and cancers. AIDS is the third generation of STD. Prevalence was 0.39% in 2004 and 0.3% in 2009 (from 2.6 million to 2.39 million in 2009).

Microbiology

HIV is a small RNA-retrovirus. HIV-1 and HIV-2 are members of the lentivirus subfamily. The virus gains entry into the cell through CD_4 receptor on the surface of T-cells, transcribes genomic RNA into DNA and then integrates into the DNA of the host cell. It remains as provirus until the life of the cell. It replicates within the host cells at the expense of the host cell resources. When cell death occurs, the HIV viral load is released in large numbers. HIV cells show preference for human T-cells, where it can lie dormant for many years. HIV-1 is a more severe and HIV-2 is a slowly progressive virus.

Epidemiology

High-risk group includes sex workers, associated with other STDs, smokers, cocaine users who are immunocompromised, and also those who received infected blood transfusion. Majority of HIV-infected patients belong to the childbearing age. Spread of the disease occurs through sexual contact (homosexual and heterosexual), intravenous drug users through shared use of infected needles and through contact with infected body fluids such as blood, semen, vaginal secretions, saliva, tears and breast milk. In the past, many persons got inadvertently infected through administration of HIV-contaminated blood transfusions. Health care workers handling infected subjects are vulnerable to the infection. The virus infects macrophages, white cells and T helper lymphocytes (T_4 cells).

Following initial infection, antibodies develop in 2–3 weeks' time and the person becomes seropositive. At times, it may take as much as 6 months. This period is known as 'window period'.

Natural Course of the Disease

After infection, the person may remain asymptomatic or manifest symptoms within 3–6 weeks; there are nonspecific features such as fever, headache, malaise, myalgia, arthralgia, rash and gastrointestinal upset. Thereafter, the patient enters the 'asymptomatic phase' lasting for 8–10 years. Evidences of compromised immune-like generalized enlargement of lymph nodes may become evident within 3 years, with drop in CD_4 counts. The symptoms of AIDS complex begin to manifest such as unexplained fever, rashes, thrush, weight loss, fatigue and diarrhoea. AIDS defining disease includes opportunistic infections, tuberculosis, Kaposi's sarcoma and cervical cancer.

Retrovirus has a core protein with an envelope of glycoprotein. It can be destroyed by sterilization at 56°C, for half an hour, hypochlorite, lipid solvents and glutaraldehyde.

Transverse transmission from male to female is higher than from female to male. This is because of the larger vaginal area exposed to infection and small abrasion that occur during intercourse. Male-to-female transmission per intercourse is 0.2–0.5%, but only 0.1% from female to male. In a man, this infection does not interfere with fertility in the initial stages. With advancing infection, it can cause orchitis with oligospermia and aspermia and viscous semen. In a woman, infertility is unlikely, but vertical transmission to the neonate is the big risk. Seminal wash in intrauterine insemination and IVF removes the virus and is employed if the man alone is infected.

Clinical HIV Infection

The median time from acquiring infection to full-blown AIDS is about 10 years. The clinical features of the disease include the following:

- Generalized lymphadenopathy
- Unexplained fever
- Malaise, fatigue, arthralgia, weight loss and cachexia
- Oral lesions–aphthous ulcers not responding to usual treatment, thrush and leucoplakia
- Reactivation of herpes zoster
- Recurrent oral and genital herpes, candidiasis skin infection
- Thrombocytopenia
- Molluscum contagiosum, condylomata acuminata and basal cell carcinoma
- Opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP), toxoplasmosis and cytomegalovirus infection
- Tuberculosis
- Peripheral neuropathy, encephalopathy, meningitis, myopathy, meningitis and dementia
- Kaposi's sarcoma and cancer cervix
- Perinatal transmission
- Pneumocystic carinii pneumonia

The WHO estimates that by the turn of the last century (AD 2000) about 3 million women worldwide would have died of AIDS. About 10 million children would be the victims of perinatal infection and many of these orphaned. The incidence of HIV positive in antenatal clinics has risen from 2% to almost 4–5% over the last 15 years. Many HIV-infected

women choose to become pregnant, continue their pregnancies in spite of counselling and making medical termination of pregnancy (MTP) services available to them.

Perinatal HIV Transmission

The rate of perinatal transmission without drugs is assessed at 20–30%. It may occur as transplacental transmission, intrapartum spread of disease or postpartum through lactation. The highest risk of vertical transmission of the disease is during labour. Administration of antiviral drugs to the mother during pregnancy and delivery has brought down the incidence of vertical transmission of HIV significantly to 1%. Neonatal administration of antiviral drugs and avoiding lactation has further made a downward dent into the incidence of neonatal disease.

Diagnosis

HIV infection diagnosis is based on initial screening test for specific antibodies using ELISA, usually against the core antigen or envelope antigen. All positive tests are confirmed by western blot. The median time between acquiring infection and AIDS is about 10 years. Clinical progress of the disease is monitored on the basis of CD_4 counts. It provides the basis for therapeutic intervention.

- At CD_4 counts of >500/mL, patients do not demonstrate evidence of immunosuppression.
- At CD_4 counts of 200–500/mL, patients are likely to develop symptoms and in need of intervention.
- At CD_4 counts <200/mL, patients often present with oral thrush, unexplained fever and increasing lassitude.

The 'window period' mentioned above mandates repeat test for antibodies in 6 months in a suspected case, because of false-negative repeat in the first sample. Testing for virus becomes positive earlier than testing for antibodies (window period).

Treatment

- Screening for HIV should be offered to all pregnant women, and all at risk.
- Pregnant women suffering from HIV are at increased risk of infections such as tuberculosis, bacterial pneumonitis and PCP. Prophylaxis against PCP includes aerosolized pentamidine. It appears to be safe during pregnancy. Bactrim DS (TMP/SMX-DS) is prescribed to prevent opportunistic infections Pap smear is done periodically.

NACO

With a view to control HIV infection, National AIDS control organization (NACO) in India was established.

Along with other voluntary and foreign collaboration, this organization works towards:

1. Mapping and screening high-risk cases of HIV, i.e. sex workers, single migrants, lorry drivers, homosexuals and injectable drug abusers.
2. Treating HIV cases free of cost and follow-up.
3. Avoiding spread of infection from husband to wife and vice-versa through adoption of barrier contraception and preventing spread to offsprings through adoption of proper hygienic practices.
4. Taking care of affected children and orphans.
5. Educating the public, particularly the adolescents regarding sex education and contraceptives.

Strategies to Prevent Perinatal Transmission

- Decreased fetal viral exposure by preventing chorioamnionitis and decreasing the duration of labour. Decrease the contact of the fetus from infected maternal fluids by preventing rupture of membranes and mucosal inflammation. This practice has led to increase in rates of elective caesarean section.
- Initiate zidovudine (retrovir) therapy. If the maternal CD_4 count is 500/mL, and the viral load by DNA-PCR is 10,000 copies/mL, then it is advised to initiate zidovudine at 14–16 weeks of gestation. The recommended dosage is 600 mg/day in two to three divided doses. The drug is teratogenic in the first trimester (neural tube defect) and causes maternal anaemia and neutropenia.
- *A larger viral load with a low CD_4 count mandates triple-drug therapy after proper counselling.*
- Intrapartum therapy consists of administration of zidovudine 2.0 mg/kg IV during the first hour of labour followed by 1.0 mg/kg/per hour throughout the rest of labour. Avoid amniotomy, fetal scalp electrodes and intrauterine pressure catheters. Later, advise on safe sex practices (barrier contraception) and postpartum contraception. It is preferable to avoid lactation. However, in poor countries, this advice may not be practical, in whom exclusive breast feeding (not even water) is advised.

Fetal therapy: Maternal administration of zidovudine is associated with decreased risk of vertical transmission by as much as two-thirds in mildly affected asymptomatic women. Maternal zidovudine therapy is followed by 6 weeks of neonatal zidovudine therapy in oral doses of 2.0 mg/kg IV every 6 h for 6 weeks.

Antiretroviral Therapy

Options for directly treating HIV women have greatly increased since the introduction of zidovudine, a retroviral drug that inhibits reverse transcriptase. Early trials with zidovudine monotherapy demonstrated a survival advantage and delay in the progression of AIDS defining illnesses. More recent studies have focused on combination therapies like zidovudine with didanosine or zalcitabine. Zidovudine with lamivudine may be superior. Protease inhibitors like ritonavir and indinavir appear more efficacious possibly because of better bioavailability. Data from short-term clinical trials suggest that combinations of zidovudine with ritonavir or indinavir demonstrated dramatically improved viral burdens and CD_4 counts. The combined therapy is popularly known as highly active antiretroviral therapy

(HAART). Three or more drugs in combination with different modes of action are used in HAART.

The main gynaecological problems to deal with in HIV positive women are as follows:

1. To detect other associated STD diseases and treat them.
2. Prevent further viral load (horizontal transmission) by using barrier contraceptives.
3. To avoid pregnancy and vertical transmission to the offspring by contraceptives. Since barrier methods are not effective, 'dual contraceptives' are recommended by adding hormonal contraceptives or emergency contraceptives.
4. Regular Pap smear to detect cervical intraepithelial neoplasia (CIN) disease. Excisional therapy is superior to ablation to avoid recurrence if CIN exists.
5. Vitamin A improves immunity. Avoid smoking and drug abuse.
6. Hepatitis B: Hepatitis B virus, a DNA virus, can be transmitted sexually, though the partner may remain asymptomatic carrier. The transmission is avoided by prophylactic vaccine 1 mL at zero, first and sixth month.

A single dose of Nevirapine during labour and to the newborn reduces the risk by 50%.

Prophylaxis

The medical and other personnel exposed to the viral infection should receive combined drugs within 2–4 h of exposure but definitely not more than 72 h. Needless to say, it is important to screen the women for other STDs and treat them. Nutritive support with vitamin A is needed.

Contraception

Barrier method of condom use is essential to prevent transverse transmission between the partners. Though female condom is also effective, diaphragm does not protect the woman, as considerable portion of vagina is exposed to infection. Spermicidal agents also are not effective. Circumcision is proved to reduce the transverse transmission by 70%.

If the woman is on antiviral drugs, IUCD can be inserted. If not on therapy or if she is suffering from other STDs, IUCD is not the suitable contraception, as it increases the risk of PID.

Oral combined pills are excellent contraceptives against pregnancy but do not protect against viral infection. Rather the antiviral drugs reduce the bioavailability of the contraceptive hormones, making them less effective than in HIV negative women. They, however, will improve the contraceptive effect of the condoms.

Surgical methods are not contraindicated but require the condom use also to prevent transverse transmission.

Dual contraception, one to stop transmission of infection (barrier) and one to prevent pregnancy, is strongly recommended.

Oral pills are contraindicated if the woman is on antiTB drugs. Cerazette (progestogen only pill) is permissible as contraceptive pill, or 3 monthly progestogens 9 m are effective.

Drugs

Several drugs are now available, but HAART is the best (combination of drugs).

- Zidovudine 300 mg bd
- Lamivudine 150 mg bd

One of the above drugs plus one of the following:

- Tenofovir 300 mg daily
- Nelfinavir 1250 mg bd
- Lopinavir/ritonavir three capsules bd or Indinavir 800 mg daily

Instead of zidovudine, stavudine 30–40 mg bd depending upon the body weight.

Instead of lamivudine, didanosine 400 mg daily (250 mg in a thin woman).

During therapy, haemoglobin, TLC, DLC and liver function tests should be performed periodically. These drugs cause lactic acidosis, which can cause pregnancy-induced hypertension. The drugs contraindicated during pregnancy are efavirenz, amprenavir and combination of stavudine and didanosine.

The successful treatment does not prevent transmission. It definitely reduces the viral load and reduces the risk of transmission.

If an HIV-negative woman insists on a pregnancy, intrauterine insemination with washed semen is safe. The viruses do not attach to sperms and seminal fluid rids of virus. Unprotected intercourse only around ovulation is an option, though it may expose the woman to a slight risk of infection. An HIV-positive woman should use barrier method, but may be offered intrauterine insemination at ovulation, so that the man is protected.

Breast feeding: Either exclusive breast feeding or total artificial feed is the mode of nutrition to the neonate.

The newborn can receive all immunizations except BCG vaccine if he or she proves HIV positive.

Prophylaxis

An attempt to develop vaginal microbicides has failed, but it is hoped that tenofovir may prove more specific in preventing infection in future.

i. Tenofovir vaginal gel expected to reduce transmission by 40%. No toxicity (renal) has been reported so far.

Sexually Transmitted Infections and Infertility

A link between STIs and infertility is greatly appreciated. According to the WHO report, almost 90 million with STI-related infertility are recorded annually. The highest prevalence is reported in sub-Saharan Africa. The risk factors for acquiring STI are young age indulging in sexual activity (below 30 years), multiple sex partners, no use of barrier contraceptives and sex workers.

STIs cause infertility both in a man and a woman by several mechanisms.

Gonococcal and *C. trachomatis* are mainly responsible for infertility, with other organisms playing a minor role. Recently, *M. genitalia* were discovered to cause infertility. With decreased prevalence of *N. gonorrhoea, C. trachomatis* is now the commonest organism causing infertility.

In a male, gonorrhoea causes urethritis initially, but chronic infection can ascend to cause epididymitis and orchitis and damage the upper genital tract. It is reported that unilateral epididymo-orchitis results in 25% infertility, but bilateral infection is responsible for as much as 40% cases of infertility. In a woman, it causes PID and tubal damage.

Chlamydia trachomatis is often a silent infection in both sexes (75% in female, 50% in male), but it causes extensive damage in the fallopian tube and impairs sperm morphology and sperm function by causing fragmentation of sperm nuclei, reducing motility and apoptosis (sperm death) via lipopolysaccharide component of chlamydia and intracellular changes in the tyrosine phosphorylation in the sperm. With azithromycin or doxycyline, infection can be eradicated, but recurrence is not uncommon. Therefore, it is suggested that a vaccine like that developed for HPV is the best option to prevent chlamydial infection.

M. genitalia are sexually transmitted. It colonizes in the cervix, ascends upwards and sets up PID in the female. It is difficult to culture because it takes months to cultivate, and in the meanwhile other mycoplasmas overgrow. Now with PCR, it is possible to detect this organism.

Practical Approach to Common Vaginal Infections

A woman is liable to several infections in the lower genital tract most common of which are gonorrhoea, chlamydia, trichomonad infection, monilial infection and bacterial vaginosis. The tests and cultures take time, are costly and invite more visits to the clinic.

Lately, therefore, 'syndrome management' approach is implemented. This consists of giving multiple drug therapy in one sitting and comprises 1 g azithromycin, 2 g metronidazole and 150 mg fluazide. Only those who fail to respond or those who are resistant are subjected to detailed investigations.

The following are the advantages of this approach:

1. One visit.
2. Cost-effective in most cases.
3. Quicker treatment.

Disadvantage is perhaps the woman will receive unnecessary multiple therapy if only one organism is involved.

Hepatitis B Virus

Hepatitis B virus is a DNA virus that can be transmitted sexually, though the partner may remain asymptomatic carrier. This infection can be avoided by prophylactic vaccination with 1 mL at 0, 1 and 6 months.

STDs in Adolescents

There has been an upsurge in the incidence of STDs amongst the younger generation in present times. Economic and social liberalization, widespread education, increase in social networking opportunities, migration for work, greater opportunities for interaction and intermingling between the sexes and changing moral values in society have contributed to this increase in the prevalence of STDs.

The incidence of STD is higher in homeless people, runaway adolescents, and those in detention facilities. There has been a noticeable rise in incidence of chlamydial infections and veneral warts. The practice of HBV vaccination has reduced the prevalence of hepatitis B infections. HIV infections are more common amongst drug users and alcoholics. Adolescents are often tempted to respond to their physical and emotional changes by indulging in high-risk sexual behaviour to gain peer group approval, they are often ignorant of the consequences that may follow or willfully choose to ignore them. It is not unusual to find them in relationship with multiple partners and failing to use barrier contraceptives. Clinicians treating adolescents should bear in mind to use on-site single-dose antibiotics whenever possible because of the unreliability of adolescents to return for treatment. This opportunity should be utilized to educate them about the use of condoms, and recommending immunizations whenever available. An attempt should be made to treat the partner as well.

Key Points

- STIs cause morbidities in young women in reproductive years.
- Condyloma acuminatum is caused by HPV infection (HPV 6, 11) and is a high-risk of intraepithelial neoplasia of the vulva and cervix. It requires adequate eradication and follow-up.
- Vaccines are now available, prophylactic against HPV when given before the start of sexual activity.
- Herpes virus II accounts for recurrent painful vulval ulcers. Acyclovir ointment or oral drug is the treatment of choice.
- Syphilis is more of a generalized disease, posing health problem on CVS and CNS. It can cause late abortions, stillbirth and congenital syphilis.
- Gonococcal and chlamydial infections often attack the urethra and cause vaginal infection. Ascending infection is responsible for tubal damage, PID and infertility.
- Chlamydia is a silent infection but inflicts more tubal damage than gonorrhoea.
- Trichomonal and monilial infection can be easily recognized and treated. Recurrent infection needs prolonged therapy.

- AIDS is a life-threatening health problem. HAART therapy is promising both for the woman and for the offspring, and vertical transmission is now reduced from 30 to 2%.
- HIV-positive woman needs regular follow-up with Pap smear, dual contraceptives and screening for other STD.
- Bacterial vaginosis accounts for 40–50% cases of vaginal discharge, monilia for 20–25% and trichomonad 10–15%.
- Serological tests are available for syphilis and HIV. Other infections are diagnosed by smears and cultures.

Self-Assessment

1. Enumerate the STDs encountered in clinical practice.
2. Discuss the management of chlamydial infection.
3. How would you manage a patient with gonorrhoea?
4. Discuss the management of HIV infections.
5. Discuss the problems of STDs in adolescents.

Suggested Reading

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Chapter 12

Inflammation of the Cervix and Uterus

CHAPTER OUTLINE

Acute Cervicitis

Acute cervicitis often follows sexually transmitted infections (Chlamydia trachomatis or gonorrhoea), septic abortion (criminal induced abortion) and puerperal sepsis. On inspection, the cervix appears congested, swollen with presence of mucopurulent discharge in the endocervical canal. Palpation of the cervix during clinical examination causes discomfort. These women may often complain of fullness in the lower abdomen and some backache. However, these symptoms are generally overshadowed by those caused by associated pelvic pathology.

Chronic Cervicitis

Chronic cervicitis is commonly encountered in practice. It affects almost 80% women. It commonly follows genital tract trauma sustained during childbirth, the tissue trauma may follow instrumentation (D&C), or be a sequel of a sexually transmitted disease (STD) infection.

The cervical canal is lined by columnar epithelium in which the compound racemose glands of the cervix empty their mucus secretions. Infective organisms lodged deep in these glands cannot be easily eradicated by local treatments (pessaries). Unlike the uterine endometrium, the endocervical lining is not exfoliated during menstruation, thus the infection persists as a local septic focus.

Erosion of the Cervix

Chronic cervicitis often manifests clinically as an erosion or as a Nabothian follicle. The cervical erosion results from the extension of the columnar endocervical epithelium beyond the external cervical os to replace the squamous epithelium covering the portio vaginalis of the cervix. Whenever the mouth of an endocervical gland opening gets blocked, it gets distended with inspissated secretion—resulting in a cystic bulge known as the Nabothian follicle. Erosions have been classified into three varieties: congenital erosion, erosion associated with chronic cervicitis and papillary or hormonal erosion.

Congenital erosion: The endocervical columnar epithelium grows down from the cervical canal during late intrauterine life to meet the squamous epithelium of the portio vaginalis. Whenever the histological os extends beyond the anatomical os, the cherry red endocervical epithelium appears as well-circumscribed erosion around the external cervical os. High levels of maternal oestrogen during pregnancy contribute to its occurrence. After childbirth, this entity undergoes spontaneous remission. Rarely does it persist in later life. A similar lesion may be sometimes seen in nulliparous women using oral contraceptive pills. It does not affect the woman adversely.

Erosion Associated with Chronic Cervicitis

In chronic cervicitis, pus and mucus are discharged from the cervical canal and bathe the cervix. The discharge is alkaline and tends to cause maceration of the squamous epithelium so that after a time the cells desquamate and leave a raw red area denuded of epithelium around the external os. In the process of healing, columnar epithelium from the cervical canal grows over and covers the denuded area so that macroscopically the red area is covered by smooth glistening translucent epithelium. The affected area around the external os is a simple flat erosion (Figure 12.1).

After a variable interval, the squamous epithelium of the vaginal portion of cervix replaces the columnar epithelium of the erosion, the squamous epithelium growing under the columnar epithelium and gradually pushing it away, until finally the squamous epithelium has completely grown over the eroded area. Unless chronic cervicitis has been cured in the meantime, chronic cervicitis leads to recurrent erosions

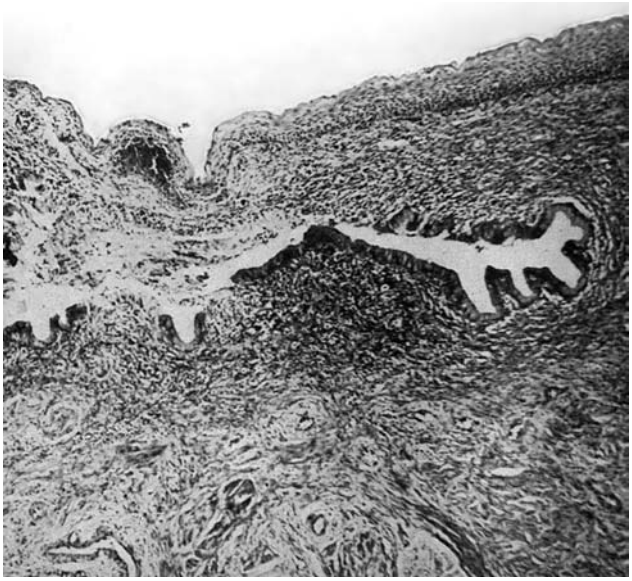

Figure 12.1 The margin of an erosion. Note the squamous epithelium on the right terminating in an area of granulation tissue with destruction of a gland (×75).

of the cervix. Sometimes, the columnar epithelial cells of endocervix undergo squamous change. This squamous downgrowth is known as epidermization. Its importance lies in the fact that, to the untutored eye, it looks like an epidermoid carcinoma which has invaded the glands. The condition is neither malignant nor premalignant (Figures 12.2 and 12.3).

Follicular cystic erosion is produced by the squamous epithelium occluding the mouths of these glands, as it replaces the columnar epithelium of the erosion during the stage of healing. The blocked glands become distended with secretion and form small cysts which can be seen with the naked eye, the so-called nabothian follicles (Figure 12.4).

Hormonal or Papillary Erosion

Hyperplasia of endocervical epithelium has been postulated to cause the papillary type of cervical erosion. One cause of this columnar epithelial hyperplasia is hormonal overactivity. These papillary erosions are therefore commonly seen in pregnancy and they tend to regress spontaneously in the puerperium. During pregnancy, oestrogen is mainly responsible for causing erosion. Women who take hormonal contraceptives also show hyperplasia of the endocervical epithelium and papillary erosion on the cervix. These regress after the drug is discontinued.

These erosions can become infected by microorganisms from the vagina, when chronic cervicitis coexists with erosion.

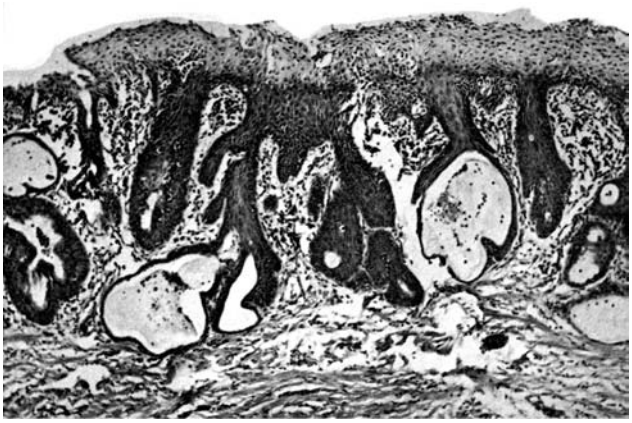

Figure 12.2 Extensive squamous metaplasia of the cervix. Note how the squamous cells apparently 'invade' the endocervical glands. This condition is not malignant.

Clinical Features

The patient may not have any symptom, but quite often presents with profuse mucoid discharge. At times, due to infection, the discharge is mucopurulent and rarely blood-stained due to congestion. Postcoital bleeding can occur. During pregnancy, erosion becomes very vascular and bleeds easily. The patient thus presents with an antepartum haemorrhage (APH). The woman may complain of low backache, abdominal pain and deep dyspareunia.

Erosion of the cervix is demonstrated by speculum examination. Erosion takes the form of a reddened area around the external os, with its inner margin continuous with the endocervical lining and with a well-defined outer margin. The reddened area of erosion may be slightly raised above the level of the squamous epithelium of the vaginal portion of the cervix and is smooth and glistening if it is covered by columnar epithelium. When associated with chronic cervicitis, the cervix feels fibrosed, bulky with nabothian follicles around the area of erosion. Mucoid discharge may be seen emanating through the os and around the erosion. The erosion is soft and bleeds easily if swabbed vigorously during examination.

Differential Diagnosis

Syphilitic ulcer, tuberculosis of the cervix, carcinoma in situ and cancer of the cervix must be ruled out and the case confirmed as erosion of the cervix. Papanicolaou smear and biopsy will therefore be required in suspected cases.

Treatment of Chronic Cervicitis and Erosion

- Asymptomatic chronic cervicitis and erosion do not require treatment.
- **Diathermy cauterization** gives satisfactory results. The tissues of the cervix are coagulated; the columnar epithelium is destroyed. The raw area on the vaginal portion of the cervix gets subsequently covered by squamous epithelium. In the cervical canal, diathermy coagulation destroys all infection lying in the depths of the racemose glands and in due course healthy epithelium grows down from the upper part of the cervical canal to cover the raw area. Endocervical cauterization requires cervical dilatation and general anaesthesia; otherwise, cervical stenosis can occur.

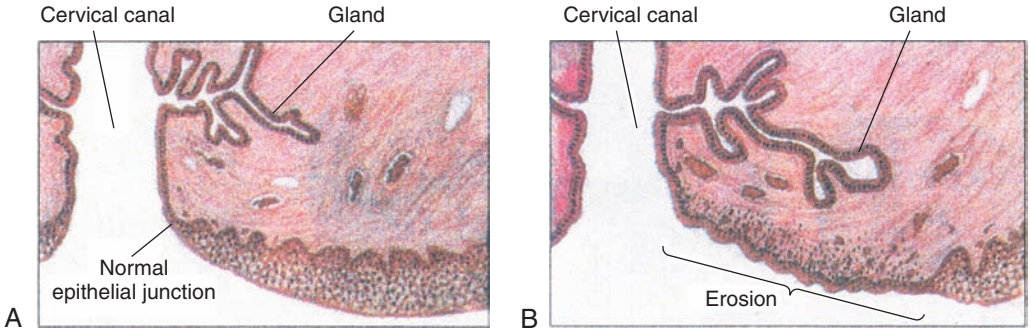

Figure 12.3 **(A)** Normal squamo-columnar junction. **(B)** Erosion.

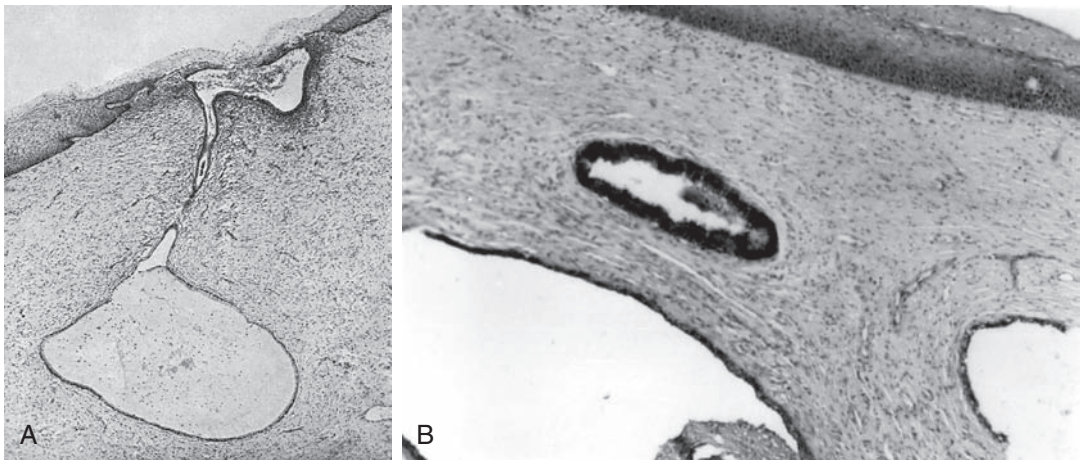

Figure 12.4 **(A)** The healing of a cervical erosion. There is early dilatation of a cervical gland due to obstruction of its duct by regenerating squamous epithelium at its mouth. Note also the flattening of the glandular epithelium by intracystic pressure. Such a dilated gland becomes a nabothian follicle (×56). **(B)** Cervix with squamous metaplasia and nabothian follicle.

- **Cryosurgery** is now being used in place of cauterization in many centres. The refrigerants used in cryosurgery are carbon dioxide (−78°C), Freon (−81°C), nitrous oxide (−88°C) and nitrogen (−186°C). All are equally effective. Cryotherapy is safer than cautery as it avoids accidental burns in the vagina and is painless. Besides, it does not require anaesthesia and is an OPD procedure. Its main disadvantage is that the patient develops copious discharge per vaginum and causes potassium loss through extensive destruction of the tissue. The patient should be advised to drink plenty of fruit juice or take potassium salt. The area epithelializes and heals in about 6 weeks. Repeat cryosurgery is required if any residual area is left untreated. Intercourse is prohibited for 6–8 weeks.
- **Laser therapy** has replaced cautery and cryosurgery in the management of chronic cervicitis and erosion in some centres. Advantages of laser are precision of excision or burning of tissue, absence of infection and haemorrhage and fast healing in 4 weeks. However, laser equipment is very expensive.
- **Conization operation**. If chronic cervicitis covers an extensive area or is not cured by any of the above methods, it may be necessary to perform conization operation, under general anaesthesia, using cold knife, diathermy or laser and a cone-shaped piece of cervical tissue removed. Prior dilatation of cervix ensures against postoperative stenosis. The cone includes the endocervical mucous membrane together with the eroded area on the vaginal portion of the cervix. There is, however, some risk of reactionary as well as secondary haemorrhage; antibiotics are therefore required after conization. Intercourse is prohibited for 6–8 weeks. In young women, deep conization of the cervix can lead to midtrimester abortion, premature labour and cervical dystocia.
- **Policresulen:** One gram of Policresulen contains 360 mg of protein. It coagulates necrotic, pathologically altered tissue without destroying the healthy tissue. Policresulen coagulates the tissue and controls bleeding by vasoconstriction. Since it can induce labour, it is contraindicated during pregnancy. Weekly application of 5 g gel for 3 min over 4 weeks is effective in 98.2%, and is useful when cryosurgery or cautery is not available. It also avoids surgery. Coitus should be avoided the day gel is applied.

Ectropion

A cervix which has been badly lacerated during childbirth shows the condition of ectropion which tends to evert the endocervical canal, the lining mucosa of which is now exposed (Figure 12.5). Ectropion can be detected by digital

Figure 12.5 Ectropion with unilateral tear of the cervix.

examination, as the external os is patulous, so that the lower part of the cervical canal can be felt with the examining finger. Chronic cervicitis usually accompanies ectropion, and the main symptom is a mucopurulent discharge. Treatment consists of excision of scar tissue and suturing the edges of the torn cervix with chromic catgut (trachelorrhaphy).

Cervical Polypi (Figure 12.6)

Mucous polypi arise from the mucous membrane of the cervical canal. They form a swelling about the size of a pea, and in rare cases may become as big as 2 cm in diameter. To the naked eye, a mucous polypus is a red vascular swelling which bleeds easily on touch and is covered by smooth glistening epithelium bathed in clear mucus. The polypus is pedunculated, the pedicle being attached to the mucous membrane of the cervical canal. The swelling is soft, smooth and slippery to touch. It is not uncommon for the polypi to be multiple so that two or three may be seen in the neighbourhood of the external os. In most cases, the polypi can be detected by palpation but small sessile polypi can be detected only by speculum examination. Histologically the polypi have a typical appearance. The surface epithelium is the high columnar type similar to that of the endocervical canal. Glands found in the stroma are racemose in type and are lined by tall columnar epithelium. The stroma is extremely vascular, containing a large number of dilated capillaries with round-celled infiltration near the lower pole of the polypus. One of the most constant features of mucous polypi of the cervix is that the surface epithelium in the region of the lower pole shows well-marked squamous metaplasia, and the squamous epithelium may penetrate into the depth of the glands (Figure 12.7).

The mucous polypi should be regarded as being produced by hyperplasia of the mucous membrane of the cervical canal which becomes thrown into folds and finally one of the folds, projecting into the cervical canal, assumes the characteristics of a polypus.

Mucous polypi usually occur in women during the childbearing period of life, but they develop also in women of menopausal age and are occasionally seen in women past the menopause. Mucous polypi cause an increased vaginal discharge, and as they bleed easily the patient may complain of irregular and postcoital bleed.

Treatment

A polypus is treated by avulsion or by torsion and no anaesthetic is needed for this. The polypus should always be sent

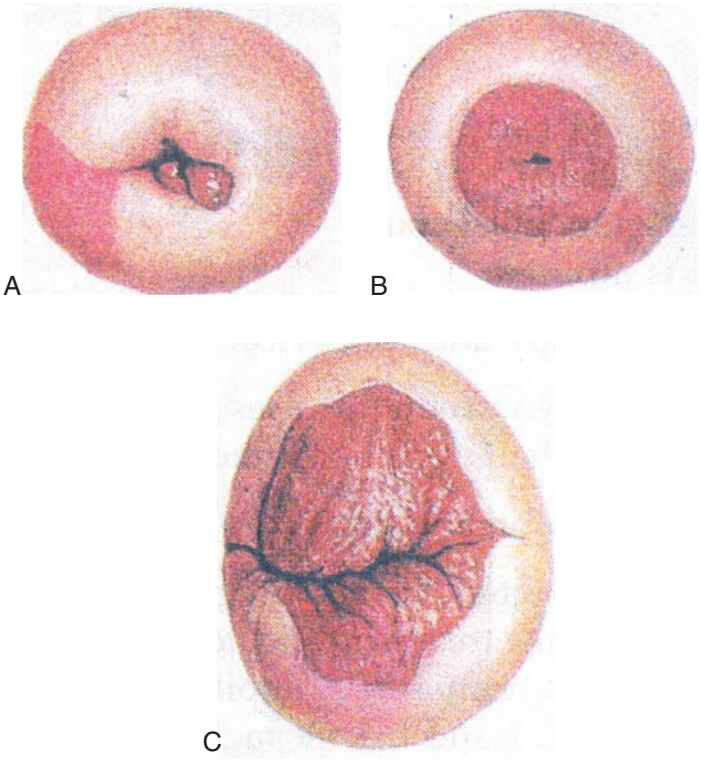

Figure 12.6 Common benign lesions in the cervix. **(A)** Polyp. **(B)** Erosion. **(C)** Eversion.

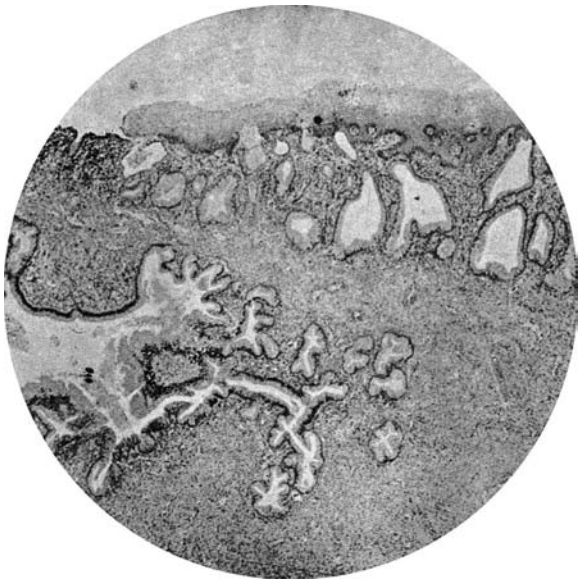

Figure 12.7 A mucous polypus of the cervix. The glands are racemose in type and the stroma is infiltrated with round cells. Above and to the right there is squamous metaplasia of the surface epithelium. The appearances are not unlike those of cervical mucous membrane.

for microscopic examination as in a very small proportion, malignant changes may be seen. It should be remembered that fresh mucous polypi may develop at a later date. Myomatous polypi may be mistaken for mucous polypi but are firm and spherical, paler in colour than mucous polypi and of a larger diameter.

If a mucous polypus persists for any length of time it is covered completely with squamous epithelium from metaplasia of its surface columnar epithelium. This form of polypus is sometimes referred to as a fibroadenomatous polypus of the cervix. The mouths of the glands may be occluded as a result of squamous epithelium growing over them so that the glands become distension cysts containing pent-up secretion. A polypus of this kind may develop a long pedicle and may actually appear at the vulva. The treatment of such a polypus is removal by torsion of the pedicle. Recurrent polypi should be removed under a general anaesthetic so that the uterine cavity can be explored and curetted. In this way an unsuspected endocervical polypus not visible to the examiner is identified and effectively dealt with as is also any endometrial polypus which may rarely be coincident. Haemorrhage can be controlled by diathermy coagulation of the base of the polypus.

Hysteroscopic avulsion of mucus polypi is recommended if the polypi are multiple.

Adenomyomatous polypus is described in Chapter 22.

Cervical Stenosis

Cervical stenosis is not uncommon. Although mostly caused by infection, other conditions can also lead to cervical stenosis.

Aetiology

- Congenital
- Traumatic—cauterization and conization
- Infection—chronic cervicitis
- Cervical cancer
- Menopausal atrophy

Clinical Features

- Congenital stenosis is rare, and causes primary amenorrhoea and haematometra. It requires plastic surgery to drain haematometra, establish menstruation and restore reproductive function. Unfortunately, restenosis is very common and may require hysterectomy in a young woman.
- Traumatic. Dilatation of cervix prior to cauterization and conization avoids stenosis. If it does follow this surgery, cervical dilatation should be performed. This type of cervical stenosis causes secondary amenorrhoea or dysmenorrhoea, infertility and sometimes haematometra.
- Infection and chronic cervicitis require cervical dilatation under anaesthesia.
- Cervical stenosis due to cancer cervix will need treatment of cancer.
- Menopausal cervical stenosis: Atrophy causes cervical stenosis. It causes pyometra. Cervical trauma may follow cervical dilatation prior to curettage or suction evacuation of uterus (MTP). This especially can occur in a nulliparous woman, and can be avoided by inserting misoprostol vaginal tablet 100 mcg 3 h prior to surgery. This softens and slightly dilates the cervix, making further instrumental dilatation easy and safe.

Acute Endometritis

Acute endometritis is caused by septic abortion, puerperal sepsis and acute gonorrhoea. In all three conditions, the other clinical features tend to overshadow the inflammation of the endometrium of the uterus.

The clinical features of septic abortion and puerperal fever, viz. high fever and purulent vaginal discharge, are well known. The uterus is tender and, because of the recent pregnancy, is larger than normal. The histological appearances of the endometrium are those to be expected in acute inflammation. The severe form of acute endometritis spreads rapidly to the neighbouring organs and leads to peritonitis, septic thrombophlebitis and septicaemia. About 20–25% of maternal mortality in India today is attributed to septic abortion and puerperal sepsis.

In acute gonorrhoea, infection of the endometrium is probably common, but causes relatively few symptoms and is overshadowed by the more acute cervicitis, urethritis and salpingitis. Menstruation that occurs during or after acute endometritis is usually excessive. The appropriate treatment is the administration of antibiotics. The patient however should be watched carefully, as salpingitis may develop from the upwards spread of the infection to the fallopian tubes. Unless it is secondarily infected by virulent organisms, the endometrium seems capable of overcoming infection partly because the infection can drain away from the uterus through the cervical canal but mainly because the superficial layers of the endometrium are shed during menstruation.

Acute endometritis can also follow the introduction of laminaria tents, dilators and particularly radium containers into the cavity of the uterus, when it gives rise to uterine bleeding and discharge. The intrauterine contraceptive devices (IUCDs) are another source of acute endometritis in 1–3% of women. The administration of antibiotics usually clears up the infection, but in the case of an IUCD, the device needs to be removed as there is a danger of infection spreading upwards to the fallopian tubes.

Chronic Endometritis

Chronic endometritis, apart from tuberculosis, is relatively uncommon in the reproductive period. The exfoliation of the endometrium provides a natural scavenging effect which prevents endometrial infection from becoming established. Senile endometritis is seen in postmenopausal women, when it causes postmenopausal bleeding. Some degree of chronic infection of the endometrium accompanies any persistent source of infection in the uterus such as infected myomatous polypi, carcinoma of the cervix and carcinoma of the body of the uterus. A foreign body such as the IUCD is liable to cause a low-grade chronic

endometritis. Tuberculous endometritis has already been described in a separate chapter.

Pyometra

Pyometra is usually seen in elderly women and is one of the best recognized forms of chronic endometritis. The clinical term 'senile endometritis' suggests a chronic infection of the endometrium, usually low-grade and demonstrable histologically. Pyometra is caused by stenosis of the cervical canal resulting from carcinoma of the cervix, as a sequela of the amputation of the cervix, as the result of radiation, and postmenopausal involution of the uterus leading to cervical stenosis. Apart from these obstructive lesions, it is a very common associate of carcinoma of the endometrium and tubercular endometritis. The pent-up discharges from glands of the endometrium collect in the uterine cavity and become infected, the infection probably reaching the body of the uterus from the vagina. In fact, senile vaginitis and senile endometritis often coexist. Later, the endometrium gets converted into granulation tissue which discharges pus into the uterus. Because the menopausal endometrium is not shed as in the reproductive years and atrophied myometrium is incapable of contracting and expelling the pus, the pus accumulates inside the uterine cavity which gets distended to produce a pyometra.

The essential symptom of chronic endometritis is blood-stained purulent discharge. The diagnosis is sometimes missed and only made when the cervix is dilated as a preliminary to a diagnostic curettage performed to exclude uterine cancer. The passage of a sound or a dilator releases a flow of pus which is often bloodstained. Sometimes the uterus is enlarged, tense and tender on bimanual examination, and these signs may be associated with fever, leucocytosis and some lower abdominal pain. When a known cancer of the cervix is accompanied by a slightly enlarged and locally tender uterus with fever, the most likely diagnosis is an associated pyometra. This can be confirmed by ultrasound. *Drainage under ultrasonic guidance in stenosed cervix will avoid perforation of the uterus.*

Treatment

The treatment of pyometra consists in dilating the cervix, draining the pus carefully under anaesthesia (general or paracervical), and taking a swab for culture and sensitivity test. If there is any suspicion of carcinoma either of the body of the uterus or cervical canal, gentle curettage must be performed a week or two after the draining of pyometra. D&C should always be done with gentleness and care, because of the risk of perforating the uterus and spreading the infection to the peritoneal cavity. If malignancy is discovered, appropriate treatment should be carried out after the pyometra has been completely drained and the infection controlled by antibiotics. Persistent pyometra definitely indicates the need for a hysterectomy and bilateral salpingo-oophorectomy in postmenopausal women. In India, another important cause of pyometra in postmenopausal women is endometrial tuberculosis, and this pathology should be looked for in the endometrial tissue if malignancy is not detected. If the uterus gets perforated, immediate hysterectomy is indicated. Vaginal misoprostol pessary (200 mcg) prior to cervical dilatation avoids cervical tear and uterine perforation.

Key Points

- The clinical features of acute cervicitis and endometritis are overshadowed by the conditions that cause them.
- Chronic cervicitis and erosion are encountered in 80% women and are the most common lesions of the cervix.
- Sometimes, cytology and biopsy are required to rule out tubercular and malignant lesion.
- Asymptomatic erosion and those seen during pregnancy do not require treatment.
- Symptomatic erosion requires diathermy, cryosurgery, laser or excisional surgery.
- Mucous polyp is removed by avulsion/torsion. Recurrent polypi should be managed by dilatation of the cervix, endometrial and endocervical curettage in addition to polypectomy.
- Cervical stenosis causes amenorrhoea, haematometra, pyometra, dysmenorrhoea, infertility.
- Pyometra requires cervical dilatation and drainage. Later, curettage and histological examination of endometrium may be required to rule out tuberculosis and carcinoma in a menopausal woman.

Self-Assessment

1. What is the aetiology of acute endometritis? How would you manage such a case?
2. Describe the inflammatory lesions affecting the cervix and their management.
3. Describe the treatment of cervical erosion.
4. What are the causes of cervical stenosis, what are its sequelae?
5. What is the differential diagnosis of suspected erosion of the cervix? How would you confirm the diagnosis?

Suggested Reading

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Chapter 13

Pelvic Inflammatory Disease

CHAPTER OUTLINE

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) implies inflammation of the upper genital tract involving the fallopian tubes as well as the ovaries. Because most of the PIDs are due to ascending or blood-borne infection, the lesion is often bilateral, though one tube may be more affected than the other. The ovaries are so closely linked to the fallopian tubes anatomically that they are coincidentally involved in infection, and it is therefore customary to consider inflammations of the two organs together. The only exception to this involvement of both tubes and ovary is seen in mumps where the ovary is selectively attacked.

Aetiology

Normally several natural barriers to the ascent of pathogenic organisms from the vagina to the fallopian tubes exist. Intact hymen prevents ascending infection. When a virgin girl presents with PID, it is usually tubercular in nature.

The acidity of the vaginal secretion inhibits the growth of bacteria; the cervical canal has a relatively small lumen and is normally filled with a plug of alkaline mucus. The ciliary movement of endometrial lining in the uterus and the cervical canal is directed downwards and discourages the upward spread of nonmotile organisms to the cavity of the uterus. This natural protective mechanism is impaired during menstruation, after abortion and delivery, because the cervical canal becomes dilated, the protecting epithelium of the endometrium is shed, and raw surfaces are present in the cavity of the uterus. The vaginal pH is increased, rendering the genital tract more vulnerable to infection. In addition to these factors, intrauterine manipulations such as curettage for evacuation in abortion and manual removal of placenta favour entry and spread of pathogenic organisms. Intrauterine contraceptive device (IUCD) is also a source of infection, particularly when it is not introduced under aseptic conditions, or introduced in the presence of vaginal infection.

The most common cause of PID is *sexually transmitted diseases* (STD), the incidence of which has risen in the past 20 years. Gonococcal and chlamydial infections are most common, the incidence of the two varying in different communities. Sixty to seventy-five per cent of PIDs are caused by STD, of which gonorrhoea accounts for about 30% in the developed countries. The importance and high incidence of chlamydial infection has been recognized with availability of culture facilities and enzyme-linked immunosorbent assay (ELISA) kits. Penicillinase-producing gonococci resistant to penicillin have also been identified in cultures in 2–10% of the cases.

Gonococci and chlamydia travel up the genital tract along the mucous membrane to reach the fallopian tubes and cause salpingo-oophoritis. The organisms probably ride up the tract along with the motile sperms in a piggy-back fashion. Sperms also help in transportation of trichomonas similarly. Other organisms directly ascend along the lining of the genital tract. This partly explains the absence of gonococcal inflammatory disease in a woman whose husband is azoospermic. Chlamydia infection (obligate Gram-negative intracellular organisms) remains asymptomatic in the endocervix or produces minimum symptoms, and therefore the infection goes unnoticed and untreated, but the damage it causes to the tube is more devastating than with gonorrhoea (fivefold). The cervix and the urethra are the common sites where chlamydia lodge and ascend upwards. The incidence of this infection is not easy to obtain in many countries because of the lack of culture facilities. The development of immunological tests has now made it possible to detect the antibodies in the sera of infected patients. Gonococci and chlamydia create an environment for secondary invasion by other organisms normally residing in the lower genital tract. Other organisms which cause PID include: (i) mycoplasma (*M. hominis* and *M. ureolyticus*), (ii) tubercle bacillus, (iii) viruses, and (iv) *E. coli* (30%) (Table 13.1).

Mycoplasma hominis is isolated in 50% sexually active women, but detected in only 7% in PID. *Mycoplasma*

TABLE 13.1 Organisms responsible for pelvic inflammatory disease

- Sexually transmitted
  - Gonococcus
  - Chlamydia
  - Mycoplasma
  - Trichomonas
- Pyogenic
  - Aerobes
    - Staphylococci
    - Streptococci
    - *E. coli*
- Anaerobes
  - *Bacteroides fragilis, Peptococcus, Clostrididium*
  - Actinomyces (IUD)
- Tubercular salpingitis

genitalium is now the new organism that is seen to cause PID. Bacterial vaginosis can also cause upper genital tract infection. These organisms reach the tube via the lymphatics bypassing the endometrium.

The polymicrobial nature of this infection has been observed and some 40 organisms, both aerobes and anaerobes, have been implicated in PID:

Aerobes. Both Gram-positive and Gram-negative.

Anaerobes. Bacteroides fragilis (20%), fusobacteria, *Bacteroides melaninogenicus*, anaerobic cocci such as peptococci and peptostreptococci, clostridia, facultative anaerobes, *Actinomyces* (Gram-positive) and *E. coli* (30–40%).

The infection by anaerobic organisms is greatly favoured by blood loss, anaemia and tissue damage such as which occurs in septic haemorrhage. A polymicrobial infection in PID mandates the administration of more than one antibiotic.

- In India, as in other developing countries, many deliveries are conducted at home by *dais* (untrained midwives). Criminal abortions continue to take place despite Government of India's liberal policy on induced abortions. *Postabortal and puerperal sepsis* are therefore common occurrences. It is estimated that about 40–50% of all PID cases in developing countries are caused in this manner and the rest by STDs.
- Minor *operative procedures* such as D&C and hysterosalpingogram can cause ascending infection. Manual removal of placenta and evacuation of products of conception are other important sources of infection in the upper genital tract.
- The introduction of IUCDs has increased the incidence of PID threefold. This is not to condemn this method of family planning, but to emphasize the need for strict asepsis during insertion of the device and careful follow-up of the women wearing these devices. Actinomyces Gram-positive anaerobes is reported in 7% of IUCD users if the device is worn for more than 2 years as against 1% in nonusers. *It is important to note that barrier contraceptives prevent STD and pelvic infection.*
- *Tuberculosis* is blood borne in most cases and rarely ascending in nature.
- *Pelvic peritonitis* due to appendicitis, and diverticulitis may spread to involve the fallopian tube of that side.

The PID is a disease of young women, who are sexually and reproductively active. The increased promiscuity and frequent change of sex partners are mainly responsible for PID in developed countries, and amongst sex workers. Septic abortions and puerperal sepsis are the important aetiological factors in developing countries (Figure 13.1). Seventy-five per cent PID are STDs in developed countries.

Sterilization operation prevents PID by blockage of the tubes. Apart from barrier contraceptives, progestogen-containing pills produce a thick plug of mucus in the cervical canal and prevent ascent of organisms.

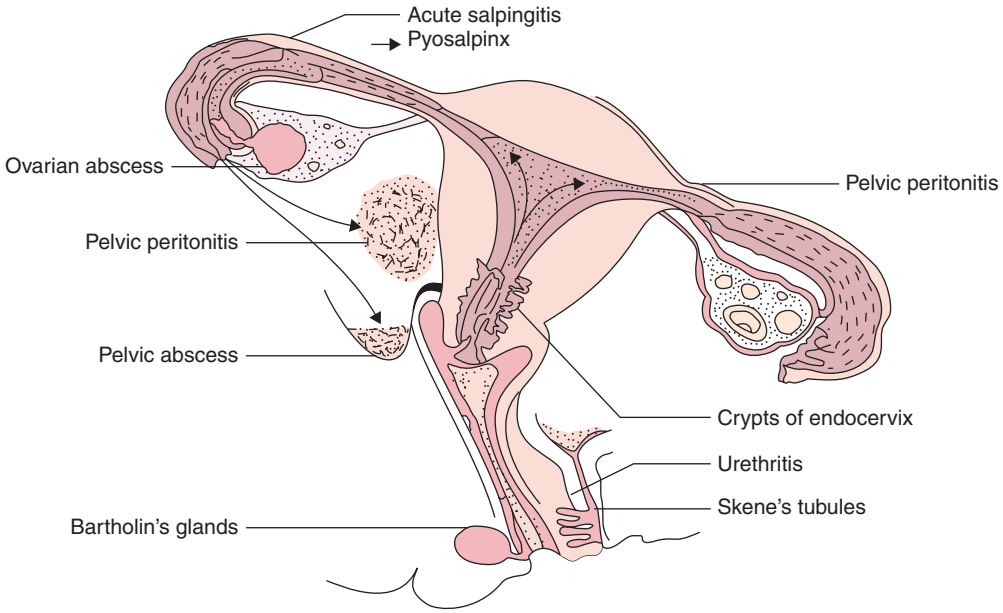

Figure 13.1 Sites of pelvic infections.

Westrom (1975) reported that women with one previous attack of PID are predisposed to another attack in 12% of the cases two attacks of PID increase the risk to 35% and three attacks to as much as 75%. Golden (2003) reported 8% recurrence in a woman with previous PID versus 1% occurrence with no PID previously.

Pathological Anatomy

Acute Salpingitis

In acute salpingitis, the fallopian tube is swollen, oedematous and hyperaemic with visible dilated vessels on the peritoneal surface. Some degree of serous exudation is seen around the fallopian tube. The sure sign of salpingitis is the discharge of seropurulent fluid from the fimbrial end of the tube, without which the diagnosis cannot be justified at laparotomy, as the peritoneal surface may be inflamed in pelvic peritonitis due to any other cause.

The mucous membrane is oedematous, infiltrated with leucocytes and plasma cells. In ascending infection, as seen in gonorrhoea, the mucous membrane is first affected. The inflammatory exudate is discharged into the lumen of the tube which now distends, mainly at the ampullary end. The ulceration of the mucous membrane that follows leads to adhesions and tubal blockage or narrowing of the lumen which may subsequently be the cause of infertility or ectopic pregnancy (Figure 13.2), as compared with the normal pregnancy (Figure 13.3).

In earlier stages, when the fimbrial end is not closed by adhesions, pus pours out into the pelvic cavity causing pelvic abscess. Eventually, with the sealing of the fimbrial end by fibrinous adhesion, pus accumulates in the tubal lumen. The ovaries are involved and a tubo-ovarian abscess (TOA) or tubo-ovarian mass results, both getting entangled in adhesions. The ampullary portion of the tube distends more than the isthmic portion, resulting in a retort-shaped pyosalpinx. An acute pyosalpinx is surrounded by adhesions which fix it to the back of the broad ligament, the ovary, the sigmoid colon, adjacent coils of intestine and posterior surface of the uterus. The wall of the tube is thickened and the tube is tense with pent-up fluid (Figures 13.4 and 13.5). On a rare occasion, the infection may spread upwards to cause generalized peritonitis, paralytic ileus and pelvic or even subdiaphragmatic and perinephric abscess. Septic thrombophlebitis, bacteraemia and metastatic abscess are rare today, because of prompt and effective antibiotic therapy.

In PID following postabortal and puerperal infection, the pathogenesis is different. The infection spreads through the

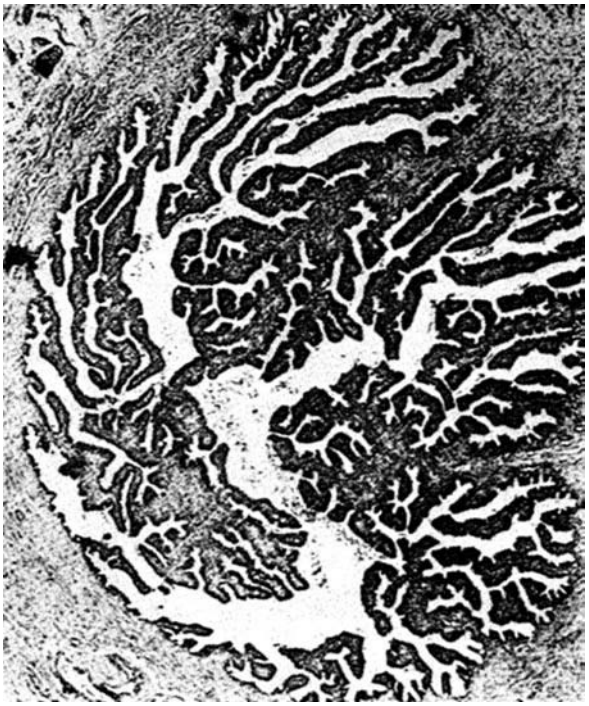

Figure 13.3 Normal fallopian tube between isthmus and ampulla. Note the convolutions of the plicae (×36).

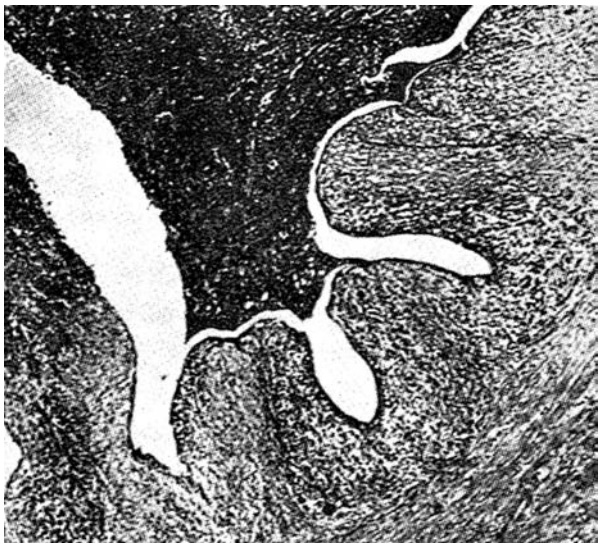

Figure 13.2 Acute suppurative salpingitis showing the tubal plicae infiltrated with inflammatory cells, with desquamation of the surface epithelium and a transudation of inflammatory cells into the lumen of the tube (×48).

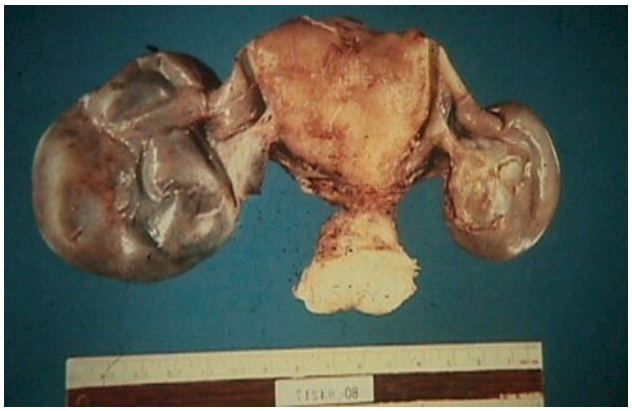

Figure 13.4 Bilateral tubo-ovarian abscess. It was impossible at operation to define or separate the ovaries from the tubes. (Source: Public domain-Brookside Press, http://www.brooksidepress.org/Products/Military_OBGYN/Textbook/Problems/Hydrosalpinx640.jpg.)

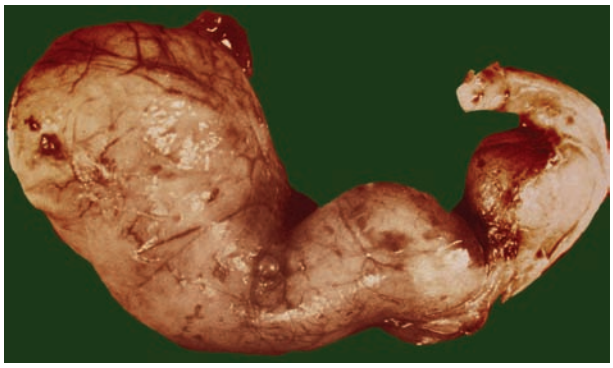

Figure 13.5 A retort-shaped pyosalpinx. (Source: H. Fox (editor), Haines and Taylor Obstetrical and Gynaecological Pathology, 3rd ed., London: Churchill Livingstone, 1987, pp. 411–456.)

cervix via lymphatics to the cellular tissue in the broad ligament, causing cellulitis. The fallopian tube is affected from the outside and the mucosa last of all. The wall of the tube is thickened considerably with hardly any distension of the lumen. Eventual involvement of mucosa ends up in blockage of the fallopian tube by multiple adhesions.

Subacute PID results from inadequate treatment or from reinfection by the infected partner, if it has been sexually transmitted. Tuberculosis also manifests in the form of recurrent pelvic infection due to secondary infection.

Chronic PID

Failure of acute pelvic infection to resolve or end result of acute infection results in chronic tubo-ovarian masses. These masses manifest in the form of:

- Hydrosalpinx
- Chronic pyosalpinx
- Chronic interstitial salpingitis
- Tubo-ovarian cyst
- Tuberculous form

Hydrosalpinx (Figures 13.6 and 13.7) If a pyosalpinx or TOA responds to antibiotics, the pus contained therein becomes sterile within 6 weeks of the initial attack, but the damage to the tube remains as chronic pyosalpinx or hydrosalpinx.

A hydrosalpinx represents the end result of a previous acute salpingitis, and is often bilateral. It is retort shaped due to enormous dilatation of the ampullary region filled with clear fluid and may be as large as 15 cm. The fimbrial end of the fallopian tube is closed; fimbriae are indrawn so that the outer surface of the hydrosalpinx is smooth and rounded. The interstitial end of the tube is curiously patent, as the dye can be visualized in the lumen during hysterosalpingogram (Figure 13.7). The wall of the hydrosalpinx is thin and translucent. At times, the hydrosalpinx is mobile and can undergo torsion. Quite often, however, the outer surface is covered with adhesions which fix the hydrosalpinx to the back of the broad ligament and the pouch of Douglas. Histology reveals flattening of the tubal plicae and exfoliation of the lining epithelium (Figure 13.8).

Figure 13.6 Right-sided hydrosalpinx. The left appendage shows less obvious but well-marked chronic salpingitis.

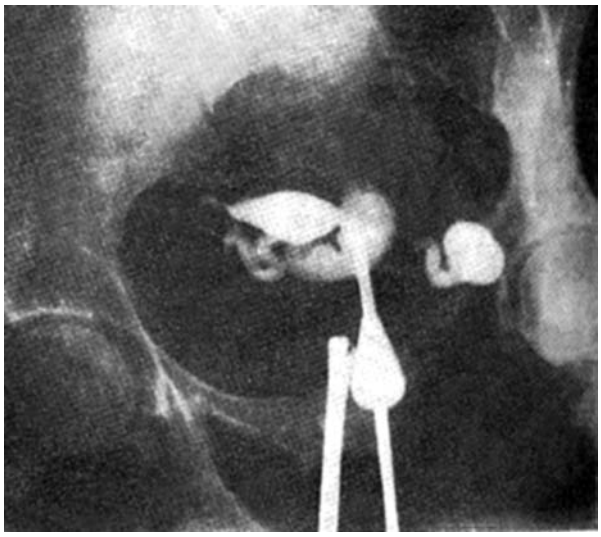

Figure 13.7 Hysterosalpingography showing bilateral hydrosalpinx.

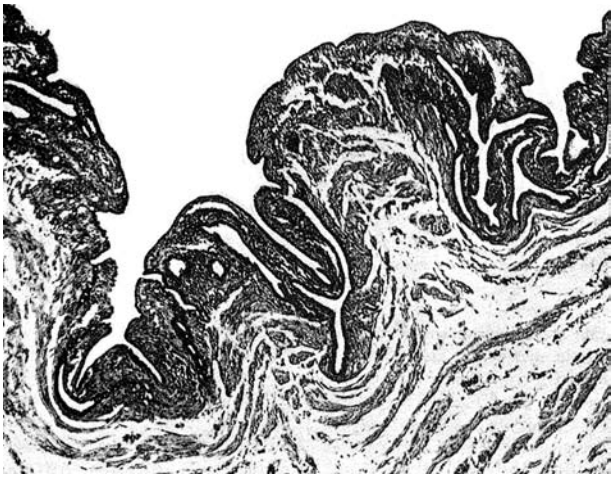

Figure 13.8 The wall of a hydrosalpinx. Note the flattening of the plicae (×60).

Chronic Pyosalpinx (Figures 13.4 and 13.5). A chronic pyosalpinx is thick walled, surrounded by dense adhesions and filled with pus. The inner wall is replaced by granulation tissue. A pyosalpinx is often fixed to the pouch of Douglas, posterior surface of the broad ligament and the uterus by dense adhesions.

Chronic Interstitial Salpingitis. In chronic interstitial salpingitis, the wall of the fallopian tube is thickened and fibrotic, but there is no accumulation of pus in the lumen. Involvement of the ovary in adhesions results in chronic salpingo-oophoritis.

Tubo-Ovarian Cyst. In tubo-ovarian cyst, a hydrosalpinx communicates with a follicular cyst of the ovary, while TOA and pyosalpinx communicate with an ovarian abscess. It is difficult to identify normal ovarian tissue in these pathological conditions.

Tuberculous Form. *Pelvic tuberculosis* is described in Chapter 14.

Chlamydial infection causes more damage to the mucosa and the wall of the tube than gonorrhoea, leading to fibrosis and tubal blockage.

Staging

The spectrum ranges from mild to moderate and severe PID. Depending upon the severity of tubal damage, Gainesville has described five stages of PID (Table 13.2).

Symptoms and Signs

Acute Pelvic Infection

A young sexually active woman is prone to PID. The most common symptom of acute PID is abdominal pain. It is bilateral and restricted to the lower abdomen. Pain spreads upwards if general peritonitis ensues. It is severe in the acute stages and is accompanied with high temperature. Vomiting may also follow. The sexually transmitted organisms may cause dysuria and vaginal discharge. Menstrual irregularity, if any, is due to preceding endometritis in case of ascending infection or to the antecedent abortion or delivery. The patient may develop uterine bleeding at a time when menstruation is not expected and the bleeding is often profuse and prolonged. In criminal abortion, the patient may deliberately conceal the history of amenorrhoea, making the diagnosis more complicated. In case of a pelvic abscess (Figure 13.9), in addition to the above symptoms, the patient develops severe diarrhoea and passes small quantity of loose motions due to rectal irritation. *Chlamydial infection pursues benign and often an asymptomatic course.*

The patient looks ill with high temperature (103–104°F). Tachycardia is present, and the tongue shows dehydration and is coated. Abdominal examination shows distension combined with tenderness and rigidity in the lower abdomen. It is rare for an abdominal swelling to be palpated in acute salpingo-oophoritis. Later, as the tenderness lessens with treatment, a tender fixed mass arising from the pelvis may be palpable. Speculum examination shows purulent discharge from the cervical canal. A torn cervix or damaged tissue is evident in postabortal sepsis and criminal abortion. Swabs should be taken from the cervix and high vagina for culture. In an acute stage, cervical movement tenderness and tenderness in the fornices are the only evidence of pelvic infection. Later on (Figure 13.10), tender

TABLE 13.2 Stages of PID

Stage I—Acute salpingitis without peritonitis—no adhesions
Stage II—Acute salpingitis with peritonitis—purulent discharge
Stage III—Acute salpingitis with superimposed tubal occlusion or tubo-ovarian complex
Stage IV—Ruptured tubo-ovarian abscess
Stage V—Tubercular salpingitis

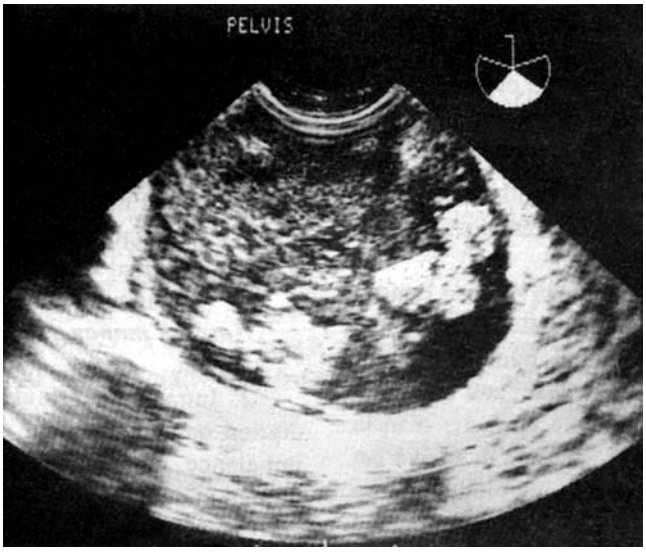

Figure 13.9 Ultrasound showing pelvic abscess.

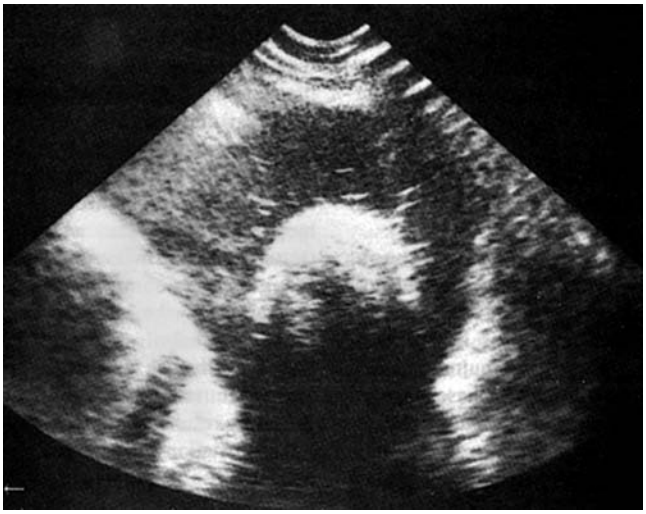

Figure 13.10 Ultrasound showing a pelvic mass.

pelvic masses are felt in the lateral fornices. These masses are fixed and at times prolapsed behind the uterus. A pelvic abscess produces a fluctuating tender swelling in the pouch of Douglas, bulging into the posterior fornix. TOA complicates PID in 30% of the cases and is the reason for hospitalization.

Differential Diagnosis

Acute Appendicitis

The pain is initially central around the umbilicus and then radiates to the right iliac fossa. Vomiting is severe, but temperature is not as high as in PID. The lower margin of the appendicular mass can be reached, but this is not so in case of PID. Vaginal discharge and menstrual irregularities are noted in PID.

Ectopic Gestation

Irregular uterine bleeding and pain are the characteristic features seen in an ectopic pregnancy too. Cervical movement pain and a tender mass are also the features demonstrable in an ectopic pregnancy. Criminal abortion with history of amenorrhoea may mimic ectopic pregnancy. Temperature however is normal or only slightly raised in ectopic pregnancy. The signs of internal haemorrhage are absent in PID. Vaginal discharge, leucocytosis and raised erythrocyte sedimentation rate (ESR) indicate the correct diagnosis of PID. Ultrasound may reveal bilateral tuboovarian mass.

Diverticulitis

Diverticulitis may simulate the clinical picture of PID, but it usually occurs after the age of 50, whereas PID is a disease of the young, sexually active females. The signs of infection are confined to the left iliac fossa in diverticulitis.

A Twisted Ovarian Cyst

A twisted ovarian or paraovarian cyst (fimbrial cyst) causes sudden pain in the abdomen with occasional vomiting, but pyrexia is usually absent or very low (Figure 13.11).

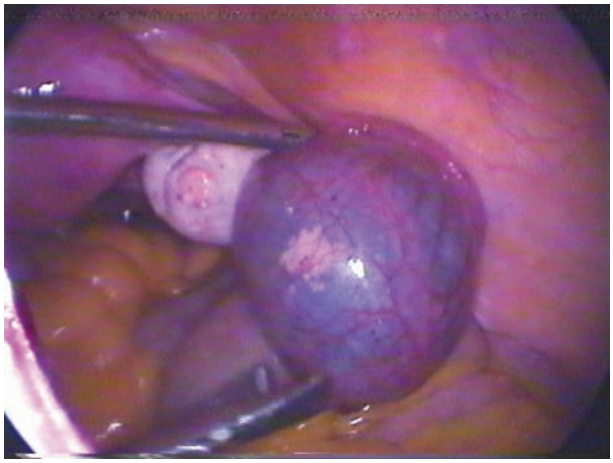

Figure 13.11 Laparoscopy revealed torsion of fimbrial cyst (Paraovarian cyst) to be the cause of acute abdominal pain.

Menstrual irregularity and vaginal discharge are absent, and an abdominal lump is felt distinctly, which will be tender. The normal-sized uterus is felt separate from the lump. Ultrasound is useful.

Inflammatory bowel disease and urinary tract infection are associated with bowel and urinary symptoms, and do not have high fever or vaginal discharge.

Ruptured Endometriotic Cyst

Ruptured endometriotic cyst can be mistaken for PID. The patient with endometriosis will have suffered dysmenorrhoea, menorrhagia and pelvic pain before this acute episode. Besides, the patient is afebrile and has no vaginal discharge.

Septic Abortion

Septic abortion may mimic the clinical features of PID; amenorrhoea preceding the abdominal pain is present in septic abortion. The treatment with antibiotics is similar in both these conditions.

Cholecystitis

Occasionally, a woman with PID complains of acute right-sided upper abdominal pain simulating cholecystitis. This is due to a fibrous band extending from the right adnexa to the under surface of the liver in PID caused by gonococcal and chlamydial infection. This goes by the name of Fitz-Hugh–Curtis syndrome.

Investigations

Clinical diagnosis is accurate in only 65–70% cases, and specific investigations are required to confirm the diagnosis as well as to identify the offending organisms. Anaemia needs correction in the presence of infection.

- Blood haemoglobin.
- Blood count reveals rise in total leucocyte count.
- ESR is also raised.
- *Cervical and high vaginal swab culture* for both aerobic and anaerobic organisms. Urethral swab culture should be done if gonorrhoea is suspected. For chlamydial infection, a long-wire swab tipped with calcium alginate is used to collect the specimen from the tube, urethra and endocervix, and this is inoculated on cycloheximide-treated McCoy cells for culture. Serological microfluorescence test for detection of IgM and IgG antibodies is useful. Polymerase chain reaction (PCR) staining is now available for chlamydia. Actinomycosis is difficult to culture and diagnosed histologically.
- Endocervix contains chlamydia and culture from the endocervix is necessary. Direct chlamydial enzyme immunoassay and direct immunofluorescence examination of the smear is also useful. In case of IUCD, vaginal smear should be studied for *Actinomyces.*
- *Blood culture* if bacteraemia sets in.
- *Blood urea and serum electrolytes.*
- *Urine* can be tested with PCR for chlamydial infection.

One must be aware, however, that a high vaginal swab culture does not always indicate or represent the bacterial flora present in the upper genital tract infection. Attempts to culture laparoscopically aspirated material or culdocentesis aspirate have been unsatisfactory. More important, gonococci and chlamydia, which are the primary organisms involved, are difficult to culture once invasion by other pathogens occurs. The antibiotic treatment based on culture report would therefore not cure all PID cases.

- *Culdocentesis* may be required to rule out an ectopic pregnancy and to establish the diagnosis of a pelvic abscess.
- *Laparoscopic examination* though recommended and practised by some should not be used in routine practice. This investigation is limited to cases in which diagnosis is uncertain and it is not easy to aspirate pus for culture. The pus extruding from the fimbrial end and adhesions are sure signs of PID. Other signs of pelvic infection besides exudates are hyperaemia of fallopian tubes, oedema and fibrinous band of Fitz-Hugh–Curtis syndrome mentioned above, seen in 15% cases.
- *C-reactive protein,* an acute-phase reactant protein generated in response to inflammation, is increased to 20–30 mg/dl or more, and distinguishes between infective and noninfective mass.
- *Ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI).* TOA appears on ultrasound as a complex cystic adnexal or cul-de-sac mass with thick irregular walls and septations. It often contains internal debris and echoes (Figures 13.9 and 13.10). This is safer and noninvasive compared to laparoscopy. 3D and 4D ultrasonography are used nowadays to define tubo-ovarian masses.

CT shows a spherical or tubular structure, with a low attenuation centre, in addition to thick walls and septations, but it is difficult to differentiate it from endometriosis. Internal gas bubbles, if seen, are pathognomonic of inflammatory mass.

MRI does not give more specific information than ultrasound, and is much more expensive.

It is important to test the woman with PID for HIV and other sexually transmitted infections. The partner should also undergo investigations for sexually transmitted infections. In a menopausal woman, tubo-ovarian mass indicates probable malignancy and should be investigated accordingly.

Chronic PID

The history of previous pelvic infection clinches the diagnosis, but often this history is not forthcoming and not recalled by the patient. The patient complains of constant low abdominal pain which gets worse before menstruation. Low backache and deep dyspareunia caused by pelvic masses prolapsed in the pouch of Douglas are common complaints. Vaginal discharge may be absent and if present, may be due to chronic cervicitis. Menorrhagia, polymenorrhagia, and congestive dysmenorrhoea are attributed to chronic pelvic congestion. Infertility results from blockage of fallopian tubes. Rectal irritation may be complained of by a few patients. The debilitating symptoms act upon the general health of these patients. Abdominal pain is due to pelvic adhesions.

Pelvic examination in chronic PID is easier than in the acute stage of the disease. The appendages are found to be tender, thickened and fixed, and an associated fixed retroversion is a very common finding. At times the uterus and appendages are densely adherent to each other, so the uterus cannot be defined separately from the pelvic masses, and along with pelvic cellulitis they form a fixed hard mass. A 'frozen pelvis' is the descriptive term used in these cases.

Differential Diagnosis

Ectopic Gestation. Ectopic gestation may be easily mistaken for PID. Pregnancy test, ultrasound and laparoscopic examination will confirm the diagnosis of ectopic pregnancy.

Uterine Fibroids. The symptoms are very similar, so also the pelvic findings if appendages are adherent to the uterus, giving the impression of an irregular enlarged uterus. Fixity and tenderness however go more in favour of chronic PID.

Pelvic Endometriosis. Pelvic endometriosis produces similar clinical features. Laparoscopic examination will confirm the diagnosis.

Ovarian Tumour. A benign ovarian tumour is unilateral and causes neither menstrual problem nor dyspareunia. A malignant ovarian tumour usually occurs in an elderly woman and is rapidly growing; hence, symptoms come up faster than in chronic PID. The tenderness is absent in an ovarian tumour. Fine-needle aspiration cytology (FNAC) can be useful. Ultrasound also identifies the ovarian tumour.

Tubercular Tubo-Ovarian Mass. Tubercular tubo-ovarian mass presents as recurrent or chronic PID. It is sometimes unilateral. Laparoscopic examination, endometrial histology and culture help in establishing the diagnosis. PCR testing of endometrial tissue can also be done.

Treatment

Aim is to treat infection, minimize tubal damage and prevent adhesions, thus avoid sequel of tubal damage.

Acute PID

The mild cases of acute PID are treated at home with antibiotics. Moderate and severe cases of PID need hospitalization. Those who need the diagnosis to be confirmed also require to be admitted for investigations, so also those who need intravenous therapy.

Treatment modalities comprise:

- Medical treatment, antimicrobial
- Minimal invasive surgery
- Major surgery

Syndromic management—laboratory tests take time and delay treatment. To avoid sequelae such as blocked tubes, chronic pelvic pain and infertility, ectopic pregnancy, the modern management is to initiate antibiotics while waiting for the final reports. This has a small risk of unnecessary treatment or overtreatment, but it is worth its while or overtreatment, but is worth it.

Hospital management consists of:

- Rest.
- Intravenous fluids in presence of dehydration or vomiting and correction of electrolyte imbalance. Ryle's tube aspiration may be needed in peritonitis with distension, in which case correct intake–output chart should be maintained.
- Analgesics, once the diagnosis is confirmed.
- *Antibiotics*. Because of the damaging effect of gonococci and chlamydia on the fallopian tubes and polymicrobial nature of the infection, it is mandatory to institute antibiotic therapy at the earliest and not wait for the culture results.

In most cases of PID, both aerobes and anaerobes form the bacterial flora, and it is essential to administer more than one antibiotic to cure the disease and prevent permanent damage to the fallopian tubes. Initially, intravenous route is resorted to, but as the infection settles down, oral therapy may be started. When the culture report is available or if the patient fails to respond to the antibiotics, appropriate change in the antibiotic therapy will be needed.

Antibiotics effective are:

- Tetracycline 500 mg qid × 10 days.
- Erythromycin 500 mg × 7 days.
- Doxycycline 100 mg bd × 10 days.
- Clindamycin 450 mg qid × 10 days.
- Gentamycin 80 mg 8 hourly × 5 days.

The *side effects* of clindamycin are skin reaction, nausea and vomiting. Other antibiotics useful are cephalosporins, and penicillin with beta-lactamase inhibitors.

The following are the newer antibiotic regimens:

1. Cefoxitin 2 g intravenously 6-hourly + Doxycycline, 100 mg IV followed by oral route.
2. Azithromycin 500 mg IV 6-hourly for 2 days, then orally for chlamydia.
3. Ofloxacin 400 mg orally bd × 14 days. Cefotetan 2 g intravenously 12-hourly plus doxycycline 100 mg bd orally/IV. Drugs are continued for at least 48 h after the clinical improvement. After the discharge from the hospital, doxycycline is continued 100 mg for 10–14 days.
4. Levofloxacin 500 mg bd for 14 days with or without metronidazole.
5. Clindamycin 900 mg intravenously every 8-hourly plus gentamicin loading dose IV or IM (2 mg/kg) followed by maintenance dose (1.5 mg/kg) 8-hourly (regimen continued for at least 48 h after the clinical improvement); after discharge, doxycycline is given 100 mg bd orally for 10–14 days or clindamycin 450 mg orally 5 times a day for 10–14 days.

Newer cephalosporins, i.e. ceftizoxime, cephalotaxine and ceftriaxone, may be given. In penicillin-resistant gonococci, amoxicillin 3 g orally, metronidazole 500 mg intravenously 8-hourly, and azithromycin 1 g single dose for gonorrhoea and chlamydia are the alternatives.

RCOG green top guideline now recommends a single dose of IM Ceftriaxone 250 mg followed by oral doxycycline 100 mg twice daily with metronidazole 400 mg twice daily × 14 days as outpatient treatment or ceftriaxone IM followed by Azithromycin 1 g per week × 2 weeks.

Placentrex (aqueous extract of fresh placenta) 2 mL intramuscularly daily or alternate days (total of 10 injections) has multipronged anti-inflammatory action. It also causes tissue regeneration, wound healing, and has significant immunotropic action involving both humoral and cellular immunity.

Partner should be investigated and treated. There is no need to remove IUCD if the woman responds to antibiotics. Failed response calls for its removal. Barrier contraceptives should be recommended thereafter.

Surgical Treatment. Surgery may be needed in the following conditions:

- Drainage of a pelvic abscess by colpotomy (Figure 13.12).
- Dilatation and evacuation of septic products of conception or for haemorrhage in postabortal sepsis.
- Acute spreading peritonitis resistant to full course of chemotherapy. The presence of pyoperitoneum mandates laparotomy. Laparotomy, drainage of pus and insertion of corrugated drainage have saved many a life.
- Intestinal obstruction.
- Suspected intestinal injury as diagnosed in a criminal abortion.
- Ruptured TOA.

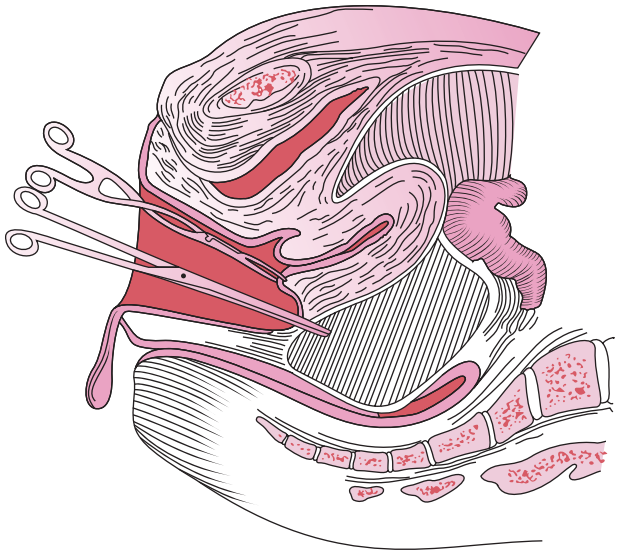

Figure 13.12 Posterior colpotomy for pelvic abscess.

Minimal Invasive Surgery. Minimal invasive surgery is required in TOA if:

- The size of the abscess is more than 10 cm.
- The abscess fails to respond to antibiotics in 48–72 h.
- Abscess ruptures.
- Pyoperitoneum.

Minimal invasive surgery is done by *laparoscopic* drainage of the TOA or posterior colpotomy (Figure 13.12).

Ultrasound-guided vaginal aspiration of pelvic abscess with or without drainage yields 70% success. Sequelae include rupture of abscess during aspiration, pelvic vein thrombosis and chronic infection.

Percutaneous abscess drainage (PAD) under CT/ultrasound guidance of abdominal mass and pyoperitoneum yields 50% success and reduces the need for major surgery, with its associated mortality and morbidity. It also preserves the ovarian function and shortens the hospital stay. However, bowel injury is a risk in abdominal drainage.

Disadvantages of PAD are septicaemia, bladder and bowel injury, haemorrhage and recurrence.

Minimal invasive surgery has late *complications* of recurrence, chronic PID, tubal blockage and chronic pelvic pain. The minimal surgery has the advantage of minimal ovarian tissue damage in young women.

Follow-up is important.

Chronic PID

Chronic PID needs surgical treatment as the condition indicates the end result of acute infection and that some form of pelvic pathology has ensued. Surgery depends upon the age and parity of the patient, the symptoms and pelvic pathology.

In a young woman, conservative surgery in the form of salpingectomy and salpingo-oophorectomy is performed. When extensive damage precludes conservative management or when the patient is multiparous and of an older age group, abdominal hysterectomy with bilateral salpingo-oophorectomy is needed.

In a mild case of PID adequately treated, the tubal damage may be minimal but the infection may lead to infertility. Such a patient will need some form of tuboplasty depending upon the site of tubal blockage, or in vitro fertilization.

Tuboplasty is required if the tubal lumen is blocked. Hysteroscopic falloposcopy or laparoscopic salpingoscopy should assess the extent of damage and decide the success rate of tuboplasty.

Laparoscopic breaking of external adhesions either by laser or by electrocautery is indicated if the tubal blockage is due to external adhesions.

If IVF is considered necessary, removal of hydrosalpinx or bilateral tubal ligation should be undertaken prior to IVF. This will improve the success rate and prevent ectopic pregnancy.

Hysteroscopic balloon plasty or cannulation is successful if the block is due to luminal debris or mild stricture. Tuberculosis is described in Chapter 14.

Prognosis

Boer–Meisel system of prognostic evaluation has been described and depends upon:

- Extent of adhesions.
- Nature of adhesions, such as flimsy or dense adhesions.
- Size of hydrosalpinx.
- Macroscopic condition of hydrosalpinx.
- Thickness of the tubal wall.

End Results

Although mortality has come down considerably in recent years with effective antibiotics, PID remains the source of considerable morbidity in the form of chronic pelvic pain, menorrhagia, ectopic pregnancy (tenfold) and infertility which would in turn require further surgical procedures, both investigatory and therapeutic. Other symptoms are backache, dyspareunia and vaginal discharge, recurrent PID.

It has been stated that despite adequate treatment, 15% of patients fail to respond to chemotherapy, 20–25% have at least one recurrence and 20% develop chronic pelvic pain (Te Linde). About 15% suffer from infertility and 8% of those who conceive will have an ectopic pregnancy.

Prophylaxis (Table 13.3)

- Hospital delivery is ideal. Realizing that the country cannot provide enough beds and that it is not easy for the rural women to come to the urban centres for delivery, the Government of India has started training programme for *dais* in aseptic techniques. This should reduce the incidence of puerperal infection.

TABLE 13.3 Antimicrobial prophylaxis for gynaecological procedures

Procedure	Antibiotics	Dose
Hysterectomy	Cefazolin Cefoxitin Cefotetan	1–2 g single dose IV
	Metronidazole	500 mg IV 8 hourly × 24 h
Hysterosalpingogram	Doxycycline	100 mg bd × 5 days
MTP D&C	Doxycycline	100 mg orally 1 h before and 200 mg after the procedure

- Induced abortions are carried out free of cost in government institutions to avoid criminal abortions in India. Though one continues to see such postabortal septic cases admitted to the hospitals, the number has definitely come down during the last two decades or so.
- Contraception. Barrier methods prevent STD. Oral contraceptives, especially minipills, are also effective. IUCD causes PID in 5%, but is popular in India and any reduction in its use would severely compromise the national family planning programme. To avoid PID, it is necessary to see that only trained personnel introduce the device under aseptic conditions. Vaginal infection should be treated prior to insertion of the device.
- Sex education. Young women should be educated regarding the risk of STD. The awareness of AIDS and its fatal outcome would perhaps motivate women against frequent change of sexual partners, or at least use barrier method of contraception.
- Female condom known as Femshield has been recently devised, which covers the cervix, entire vagina and the external genitalia, and is highly effective not only as a barrier method, but is also protective against AIDS and STD. Femshield may have a better compliance than the male condom.
- Contact tracing and treatment of partner is also necessary.

Rare Variety of PID: Actinomyces

Actinomyces is an anaerobic Gram-positive filamentous, nonsporing bacterial infection often associated with IUCD. The incidence is 7% with IUCD worn for more than 2 years against 1% in nonusers. The woman develops fever, abdominal pain, abnormal bleeding and discharge. Sulphur granules can be recognized. The infection is treated with 250,000 units/kg daily of penicillin IV in four doses for 2–6 weeks. Thereafter, oral 100 mg/kg daily in divided doses is administered for 3–12 months. Other antibiotics are tetracycline, erythromycin, clindamycin and chloramphenicol.

Key Points

- PID implies inflammation of the upper genital tract involving the uterus and the adnexa.
- Natural barriers exist to protect the ascent of organisms from the vagina to the upper genital tract; these include the ciliary movement of the endosalpinx downwards, the periodic shedding of the endometrium, the thick cervical mucus plug in the endocervical canal and the acidic pH of the vagina.
- The natural protective barrier may get breached during menstruation, abortion and the puerperium; intrauterine instrumentation or the insertion of an IUCD may initiate infection.
- Both aerobes and anaerobes may be implicated; however, amongst the common causes of infection are STDs caused by chlamydia and gonococci. Septic abortions are often the result of pregnancy termination carried out under unhygienic conditions, often by quacks. Bleeding, anaemia, tissue damage and lack of proper asepsis predispose to this life-threatening eventuality.
- Tuberculous infection is usually blood borne. It affects both the adnexae.
- Clinically the patient suffers from manifestations such as abdominal pain, leucorrhoea, menorrhagia, congestive dysmenorrhoea, dyspareunia, backache and infertility. The uterus is often retroverted with restricted mobility and there may be thickening of the appendages which are painful on palpation.
- Use of barrier contraceptives, observance of proper asepsis during instrumental manipulations and prompt treatment of suspected infection are the best approaches to safeguard the patient from infections.
- IUCD should not be inserted in a nullipara because it may lead to pelvic infection and infertility.
- Prophylactic antibiotics during surgery can mitigate PID.
- Sex education, using barrier contraceptives, can reduce sexually transmitted infections and thereby avoid PID.

Self-Assessment

1. What are the causes of PIDs?
2. Discuss the clinical features and management of chronic PID.
3. What are the complications and sequelae of PIDs?

Suggested Reading

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Chapter

14

Tuberculosis of the Genital Tract

CHAPTER OUTLINE

Introduction

Tuberculosis has been recognized as a disease entity since ancient times. But the credit for the first authentic description of genital tuberculosis is attributed to Morgagni (1744) who first described the autopsy findings of genital tuberculosis in a young woman aged 20 years who had died of tuberculosis. In his report, he clearly mentioned that the uterus and tubes were filled with caseous material. Robert Koch discovered the organism *Mycobacterium tuberculosis* in 1882. Since the early part of the twentieth century, the incidence of general tuberculosis and as its consequence, pelvic tuberculosis have progressively declined in the developed countries of the world, so that the disease has become rare in many industrialized countries of Europe and America. However, it still continues to be seen amongst the destitute, immigrants of Asian and African descent in UK and in the inner city communities of USA. The disease continues to be rampant in developing countries of Latin America and Asia. It is endemic in India. The actual incidence of pelvic tuberculosis is difficult to assess as many patients are asymptomatic, therefore the disease often comes to light only incidentally during the course of investigation for a gynaecological complaint. Schaefer (1970) reported that 4–12% of women dying from pulmonary tuberculosis manifest evidence of genital involvement. He further mentioned that 5–10% of infertile women suffer from tuberculosis. In India, Malkani (1975) reported an incidence of 9.3% in infertility patients in New Delhi. Padubidri V. from New Delhi reported tuberculosis in 4% of all endometrial aspirations examined. Usha Krishna et al. (1979) from Mumbai reported an incidence of genital tuberculosis in 13% infertile women. Chitra Kumar et al. (2000) from Darbhanga (Bihar) reported an incidence of genital tuberculosis in 18.6% infertile women. Surveys from Mumbai about the prevalence of tuberculosis amongst infertile women reported by several authors have been mentioned here—Merchant (1989) reported an incidence of 14.7%, Parikh et al. (1995) reported genital TB as the cause of infertility in 15.3% and Desai et al. (1995) reported a high incidence of 39% in patients referred for assisted reproduction procedures. Classically, female genital tuberculosis has been described as a disease of young women with 80% of these diagnosed between the ages of 20–40 years, although the disease has also been reported in older women around menopause and occasionally even thereafter. Falks (1980) reported that 46% of his patients of genital tuberculosis from Sweden were aged over 50 years.

Pathogenesis

The causative agent is commonly *M. tuberculosis* (95%), but in a few cases it is caused by the *Mycobacterium bovis* (5%), particularly in underdeveloped countries where effective tuberculosis control programmes for cattle are not in place and pasteurization of milk not routinely practiced. These organisms are identified on routine staining of infected material with Ziehl–Neelsen's acid-fast stain. Genital tuberculosis occurs almost always secondary to a primary focus elsewhere, the commonest site being the lungs (50%), but rarely from other sites such as lymph nodes (40%), the kidneys, joints, gastrointestinal tract or as part of a generalized miliary infection. The mode of spread is generally haematogenous or via lymphatics, and rarely from direct contiguity with an intra-abdominal organ or affected peritoneum (Schaefer, 1976; Siegler, 1979). Once the genital tract has been colonized, the granulomata containing viable tubercle bacilli form within the various pelvic organs. Following the development of tubercular hypersensitivity, these foci become generally silent and long intervals of many years, often extending sometimes to over a decade, may pass before reactivation of the focus takes place. The active growth and increase in blood supply to the genital organs around menarche constitutes the event leading to its reactivation and establishment of the disease process. The genital infection

thus acquired in childhood may remain dormant until puberty. As a rule, *the fallopian tubes are the first to be involved*; hence the disease is commonly bilateral in distribution, with subsequent dissemination to other genital organs and the peritoneum. Bilateral pelvic lymph nodes involvement often follows. Vulvo-vaginal involvement is usually secondary to uterine involvement.

Primary genital tuberculosis is rare; there are reports in literature of cases of primary genital tuberculosis affecting the vulva and cervix, in which the sexual partner has been suspected to be the source of the disease (1%). The presence of *M. tuberculosis* organisms in the semen of men suffering from urogenital tuberculosis has been well documented. Apart from semen being a source of infection, the practice of using saliva for lubrication prior to intercourse by some men may also be a source of infection in cases of open pulmonary tuberculosis. Pathology of genital tuberculosis:

The general distribution of involvement of reproductive organs in cases of genital tuberculosis has been assessed as by Schaefer as follows:

1. Fallopian tubes 90–100%
2. Endometrium 50–60%
3. Ovaries 20–30%
4. Cervix 5–15%
5. Vulva and vagina .....<1%

In a more recent survey of over 1400 cases of genital tuberculosis by Nogales-Ortiz et al., they found involvement of the fallopian tubes in 100% of their cases, endometrium in 79%, myometrium in 20%, cervix in approximately 25% and the ovaries in only 11% of cases.

When the tubercle bacilli infect a susceptible host, the initial reaction is a polymorphonuclear inflammatory exudate. Within 48 h this is replaced by mononuclear cells, which become the primary sites for intracellular tubercle replication. As cellular immunity develops, destruction of the tubercle bacilli begins, leading to caseation necrosis. Later, reactivation of the lesion leads to the classical granulomatous lesion characterized by central caseation and necrosis surrounded by concentric layers of epithelioid cells and giant cells with peripheral distribution of lymphocytes, monocytes and fibroblasts.

Genital Tract Lesions

Detailed description of lesions follows:

Fallopian tubes: Involvement of the tubes is close to 100%, and is bilateral. It is secondary to haematogenous spread from a primary focus usually in the lungs, and less commonly to lymphatic spread from the bowel or direct transperitoneal extension from a nearby focus such as the appendix or the large bowel. The tubal mucosa is the most favourable nidus for bloodborne spread of the disease resulting in endosalpingitis—usually bilateral. It is the earliest lesion with a propensity for transluminal spread to the ovary and endometrium. Thus, the fallopian tubes play the central role in the initiation and dissemination of pelvic tuberculosis, although occasionally the cervix and endometrium can be infected primarily from the bloodstream. The fallopian tubes may appear normal at first appearance, but in minimal disease, they may appear thickened with the feel of a whip-like consistency. There may be evidence of tubercles on the surface (tuberculous exosalpingitis). At times, following direct extension of tuberculosis from adjacent organs, the exosalpingitis manifests in the form of diffusely spread miliary tubercles on the serosal surface of the fallopian tube, the ampullary part of the tube appears dilated with the fimbriae end open and pouting. This lesion has been described as the *tobacco-pouch appearance (*Figure 14.1*)*.

In over 50% cases, the tubes are enlarged in diameter, with their external surfaces appearing roughened due to adhesions or may show presence of greyish tubercles, these may be discrete or confluent. On cut section, the lumen reveals presence of yellowish grey caseous matter or serosanguinous fluid (tuberculous haematosalpinx) and pyosalphinx. At times, violin string adhesions are noted between the right fallopian tube and the undersurface of the liver, known as Fitz-Hugh-Curtis syndrome. Leakage of infected material into the peritoneal cavity causes peritubal abscess, tuberculosis peritonitis and ascites.

In 20%, the tubes assume an elongated retort-shaped structure. The tubes remain patent in almost 25–50% cases of genital tuberculosis with minimal disease, but as the disease advances, reactive fibrosis sets in and the tubes get occluded. However, even in the advanced form of the disease presenting with bilateral tubal masses the fimbriae are often spared, giving the tubes the typical tobacco-pouch appearance (Figures 14.2 and 14.3).

Microscopically, granulomas and chronic inflammatory infiltrate may involve the full thickness of the tubal wall; on occasions these tell-tale granulomas are difficult to find. The ampullary part is the most common to be affected, the fimbriae and interstitial parts of the tubes are often spared. The brunt of the attack is borne by the endosalpinx, it often exhibits focal or widespread reactive adenomatous hyperplasia which may be severe enough to be mistaken for carcinoma. The diagnosis of tubal tuberculosis is based on the demonstration of acid-fast bacilli in the tissues, or by positive cultures or guinea pig inoculation. It is a well-known fact that the tubercle bacilli are difficult to

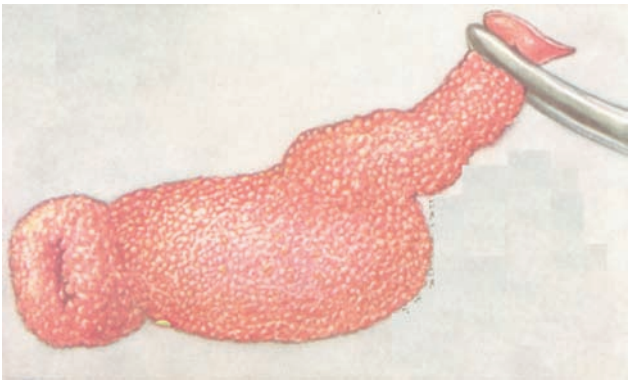

Figure 14.1 Tuberculous salpingitis.

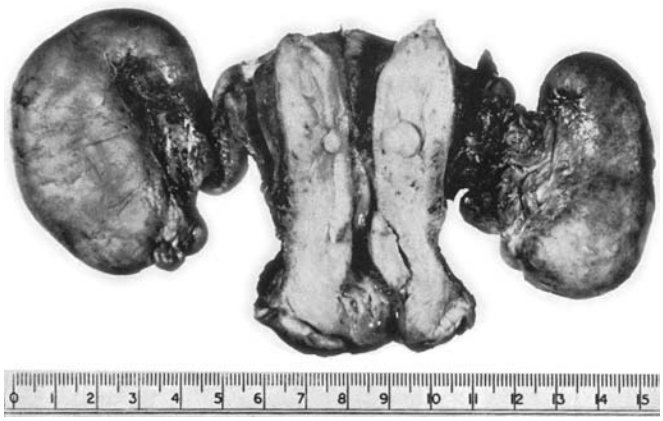

Figure 14.2 Bilateral tuberculous pyosalpinx. Note the retort-shaped tubes, absence of surface tubercles and adhesions.

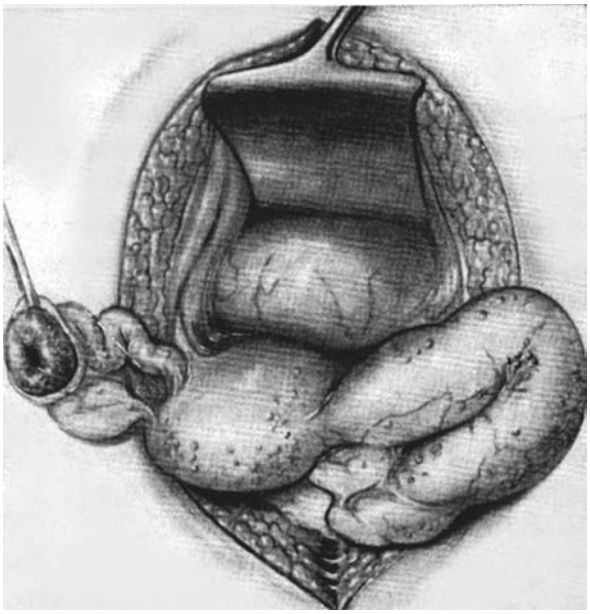

Figure 14.3 Parikh FR, Nadkarni SG, Kamat SA, et al. Genital tuberculosis in infertility. Fertil Steril 1995; 67: 497. Tuberculous uterus and adnexa. (From: Stallworthy, 1952. J Obstet Gynaecol Br Emp.)

demonstrate even with fluorescent techniques. Hence, the onus of initial suspicion lies squarely on the pathologist reporting the slide. Presently, with availability of the polymerase chain reaction technique, samples of suspicious tissue submitted for PCR testing, the diagnosis of tuberculosis can be established with certainty. The granulomas may be single or confluent with a variable tendency to frank caseation, the surrounding muscular layers show dense lymphocytic infiltration and patchy areas of fibrosis. Caseation necrosis is not uncommon in advanced cases. The mucosa often exhibits a hyperplastic adenomatous pattern with a complex network of fused papillae, and has been associated with a higher incidence of *ectopic pregnancy* (Novak and Woodruff 1979). Whether this predisposes to the occurrence of future adenocarcinoma is debatable (Novak and Woodruff 1979). The differential diagnosis includes foreign body granulomas usually related to previous hysterosalpingography or surgery, sarcoidosis, Crohn's disease or associated with *Enterobius vermicularis*.

Uterus—tuberculosis of the endometrium: The endometrium is involved in about 50–60% of all cases of genital tuberculosis. Grossly the endometrium appears unremarkable in the majority of cases because of cyclic menstrual shedding. Endometrial histology reveals the characteristic lesion showing central caseation, surrounded by epithelioid cells and stroma infiltrated with giant cells (Figure 14.4A and B). Tuberculosis is a descending infection from the fallopian tube, and the cornual ends are the first to be involved.

Occasionally there may be ulcerative, granular or fungating lesions. Other times, the uterine cavity may appear smooth and devoid of endometrium, attempts at curettage yielding scanty or no material. The cavity may appear shrunken due to underlying fibrosis. The tubal ostia may appear recessed and narrowed, like golf holes. In 2–5% of cases, total destruction of the endometrium with resulting amenorrhoea secondary to end organ failure may lead to pyometra formation in case the internal os gets occluded. At times the cavity may be partially

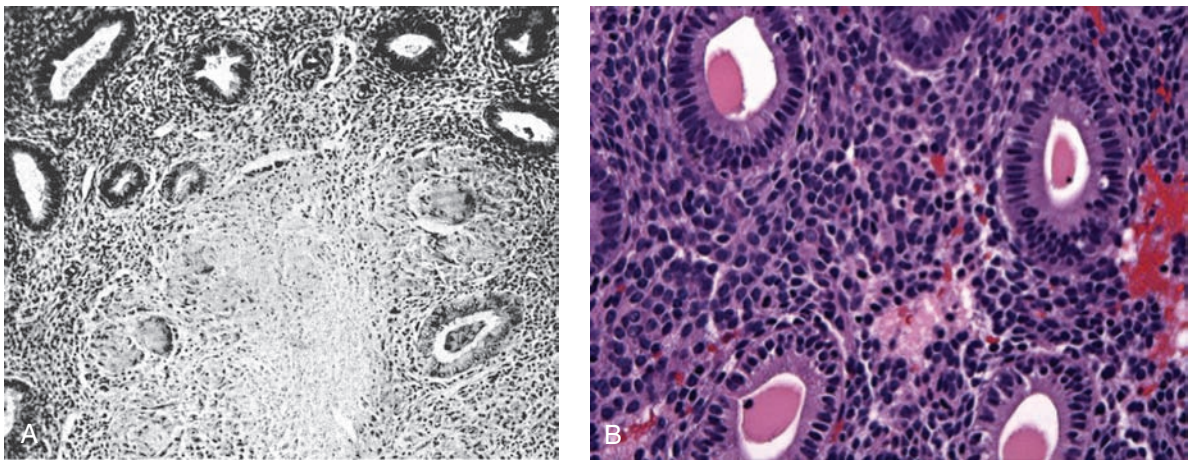

Figure 14.4 **(A), (B)** Tuberculous endometritis depicting typical giant cells in the stroma (×115). (Source: Textbook of Gynaecology, India: Elsevier, 2008.)

or extensively obliterated with intrauterine adhesions appearing as strands, ridges or thick bands (Asherman syndrome).

Endometrial lesions are frequently focal and typically immature since they tend to be shed monthly except in cases of amenorrhoea or pyometra. It is believed that the endometrium is regularly reinfected from the tubes or from the basal layer of the endometrium which is not shed monthly. Granulomas are best identified on endometrial sampling on day 24–26 of the cycle or within a few hours of the onset of menses (Figure 14.4).

Ovaries: These are involved in 20–30% of cases of genital tuberculosis. Most frequently this is a perioophoritis resulting from a spread from the adjacent fallopian tubes, when the ovary seems to be encased amongst adhesions. However, it may sometimes follow a haematogenous spread and cause caseating granulomas within the parenchyma of the ovary.

Cervix: There are no gross changes in the cervix. Ulcerative lesions are uncommon. Occasionally a polypoidal hypertrophic lesion mimicking cancer of the cervix may be seen. Microscopy may reveal scarce granulomatous lesions surrounded by large numbers of lymphocytes. Reactive hyperplasia of the glandular epithelium may lead to papilla formation, sometimes there may be evidence of epithelial atypia. On examination, the patient reveals presence of an ulcer on the cervix covered with yellowish-brown offensive discharge, it may bleed on touch. Cervical biopsy reveals the diagnosis of tuberculosis. The effect of involvement of the endocervical mucosa is associated with increase in secretion of mucin. The cervical involvement is mostly due to descending spread from the infected uterine cavity, or on occasions primarily from the husband suffering from genital tuberculosis through sexual intercourse.

Vulva and vagina: Tuberculosis of the vulva is rare compared to the incidence in the rest of the female genital tract (1%). Vulval lesions arise by direct extension from lesions in the genital tract, or as an exogenous infection. Children as well as adults may be affected. Exogenous infection may arise from sputum or through sexual intercourse with a partner suffering from either tubercular epididymitis or renal tuberculosis. Bartholin's gland may be affected alone, often unilaterally with a focus of tuberculosis elsewhere. In all cases, lymph nodes would be involved. Bartholin's gland may reveal induration or abscess formation. With the recent epidemic of HIV sweeping through many countries globally, the reduced body resistance has favoured an upsurge in tuberculosis. Clinically a vulval lesion may appear as a discharging ulcer, sinus or a nodular hypertrophic lesion (Figure 14.5). A vaginal nodule may ulcerate and cause a discharging sinus. Microscopy reveals the typical tubercular granuloma.

Ulcerative vaginal lesions whenever present are always found to be coexistent with cervical disease. Tuberculous vaginitis has also been reported. The diagnosis has been made on cervico-vaginal smears. Ulcerative lesions often heal by fibrosis causing vaginal stenosis. *Recto-vaginal fistula* is a rare complication of genital tuberculosis.

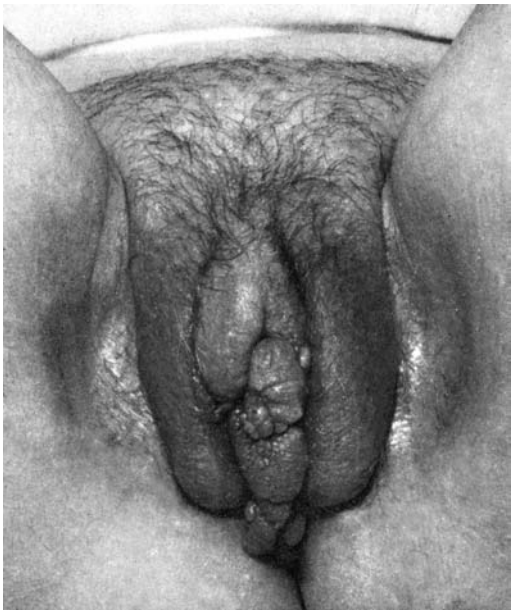

Figure 14.5 Hypertrophic tuberculosis of vulva. Note considerable oedema of labia majora and elephantiasis-like appearance of labia minora. (From: Macleod and Read, Gynaecology, 5th ed. Churchill, 1955.)

Clinical Features of Genital Tuberculosis

It is an important observation that about 10–15% of women suffering from genital tuberculosis are asymptomatic and 15% of them have successfully conceived earlier. However, the leading presenting complaints in women suffering from genital tuberculosis include infertility, menstrual irregularities, abdominal pain, vaginal discharge and suspicion of neoplasm. Fistula formation is a rare occurrence. Sometimes general symptoms of low-grade temperature, weight loss, fatigue and a feeling of listlessness may raise the suspicion of hitherto unsuspected diagnosis of genital tuberculosis. Pelvic examination often reveals nothing significant; in 20% cases the adnexae may feel thickened or cord like, tubo-ovarian masses may be palpable. These may be tender if secondarily infected. In cases of non-healing scars following surgery, suspect the possibility of tuberculosis, biopsy from the scar tissue will reveal the diagnosis. Clinical features of genital tuberculosis are as follows:

- Asymptomatic—10%
- General condition—fever, malaise
- Abdominal pain–lump, chronic pelvic pain
- Menstrual—puberty, menorrhagia, oligo-amenorrhoea followed by menorrhagia, postmenopausal bleeding
- Infertility

Infertility: This is an important presenting symptom. In fact, in 35–60% cases it may be the only complaint for which the patient seeks medical attention. Of these women, about 75% present with primary infertility and 25% give history of previous conceptions. In almost half of these

cases there may be a history forthcoming about a past infection or contact with a person suffering from tuberculosis. In any suspicious case, it may be wise to obtain histological report on the endometrium early in the course of the work-up for infertility. Infertility is attributed to tubal damage and endometrial adhesions (Asherman syndrome), and at times ovarian damage.

Menstrual irregularity: This has been observed in 10–40% of cases. The menstrual disturbances reported include menorrhagia, menometrorrhagia, intermenstrual bleeding, oligomenorrhoea, hypomenorrhoea, amenorrhoea and even postmenopausal bleeding. In the West, dysfunctional bleeding is more frequently encountered, whereas in India oligomenorrhoea and hypomenorrhoea are seen more frequently, this has been attributed to the higher association with pulmonary disease in our country. Tuberculosis should be suspected if puberty menorrhagia does not respond to medical therapy.

Chronic pelvic pain: This pain may be dull aching in type, sometimes aggravated premenstrually, or it might be intermittent in nature.

Vaginal discharge: Bloodstained vaginal discharge, postcoital bleeding, leucorrhoea and serosanguinous/seropurulent discharge from ulcers are occasionally encountered from lower genital tract tubercular lesions.

Abdominal mass: There are case reports of women presenting with a mass in the abdomen, genital tuberculosis may present as a mass consisting of rolled-up omentum, with dense adhesions to the uterus and adnexae. The history of associated menstrual disturbances accompanying the presence of fixed abdomino-pelvic mass should raise the suspicion of genital tuberculosis. Encysted ascites, matted intestinal loops, uterine pyometra and adnexal masses masquerade as lumps. A doughy feel on palpation of the abdomen is suggestive of tuberculous peritonitis. Other symptoms include dysmenorrhoea, dyspareunia and repeated episodes of pelvic inflammatory disease (PID). A virginal girl presenting with a pelvic inflammatory mass is almost always of tubercular origin. PID which fails to respond to the standard treatment, and recurrent PID is often due to tuberculosis.

Fistula formation: This complication generally follows surgical interventions such as draining of an abscess, or abdominal panhysterectomy.

Ectopic pregnancy: Women with genital tuberculosis rarely conceive. However, patients successfully treated for the disease have a high risk of ectopic pregnancy. The high risk is attributed to residual tubal scarring causing narrowing and distortion of the tube.

Pregnancy prospects: Treatment of patients with genital tuberculosis for infertility has generally yielded poor results. In case pregnancy occurs, the risk of ectopic pregnancy and abortions is substantially high. However, live pregnancies have been reported. In women with tubal disease but having receptive endometrium and a normal uterus, cases of successful pregnancy outcomes have been reported with assisted reproductive techniques. However, in case of the endometrium being unfavourable and nonreceptive, surrogate pregnancy may need to be considered.

Investigations

General: Routine investigations may reveal nothing significant.

1. **Complete blood count:** A differential WBC count often shows presence of *lymphocytosis.*
2. **Erythrocyte sedimentation rate (ESR):** This is frequently raised. However, ESR is a nonspecific investigation.
3. **Mantoux test:** A positive test is indicative of exposure to tubercle bacilli in the past. It has been reported to be positive in more than 90% of cases. A negative test goes against tuberculosis. QuantiFERON test is superior to Mantoux test.
4. **Hysterosalpingography** reveals features suggestive of genital tuberculosis in many patients, where endometrial biopsy has failed to reveal the diagnosis. Hysterosalpingography should not be performed if genital tuberculosis is suspected because of spread of infection. If performed in an asymptomatic woman, it shows the following (Figures 14.6–14.8):
   - A rigid nonperistaltic pipe-like tube (lead pipe appearance)
   - Beading and variation in the filling defect
   - Calcification of the tube
   - Cornual block
   - A jagged fluffiness of the tubal outline
   - Tobacco-pouch appearance of hydrosalpinx and pyosalpinx
5. **The ELISA tests—IgG and IgM:** In recent times, mycobacterial purified protein antigens used in enzyme-linked immunoabsorbent assay (ELISA) have been favourably evaluated.
6. **Ultrasound examination:** It can reveal an abdominal mass, but cannot identify its nature. However, ultrasonic guided fine-needle aspiration cytology (FNAC) from the adnexal mass is feasible, so also USG-guided transvaginal tri-cut biopsy of the peritoneum is an alternative to laparoscopic biopsy of the peritoneal tissue.

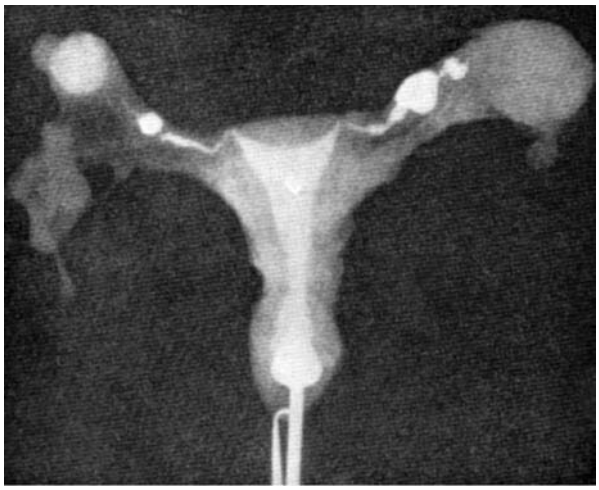

Figure 14.6 Tuberculous tubes and uterus injected after removal. (From: Stallworthy, 1952, J Obst Gynaecol Br Emp.)

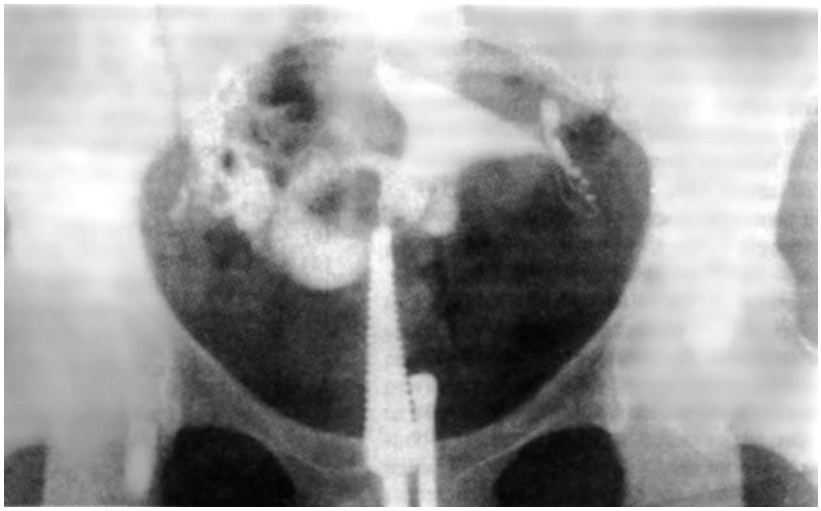

Figure 14.7 Beaded appearance of the fallopian tube and extravasation of the dye in pelvic tuberculosis.

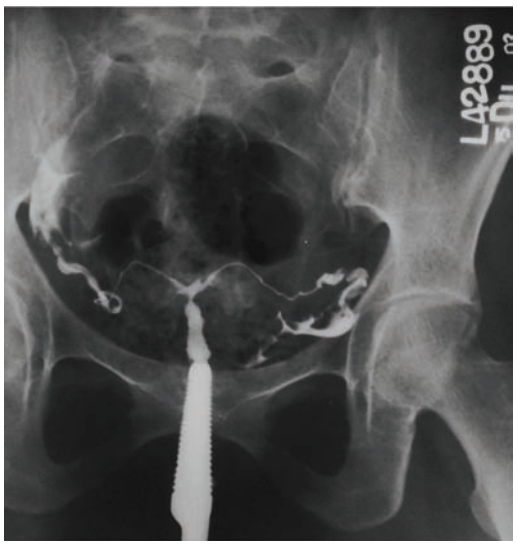

Figure 14.8 HSG showing reduced size of the uterine cavity with irregularity of lumen outline and adhesions suggestive of Asherman syndrome (Courtesy: Dr K K Saxena, New Delhi.)

7. **Endometrial Histology and PCR testing:** Endometrium tissue is obtained at D&C/hysteroscopy directed biopsy. The ideal time for planning this procedure is the late premenstrual phase. The reason being that the tubercles are present in the superficial layers of the endometrium and are shed during menstruation. The endometrial scrapings are divided into three portions: (i) for histopathology and (ii) for *polymerase chain reaction (PCR) testing.* This test has been used successfully for detecting tuberculosis in endometrial biopsy taken from affected tissues. PCR is a rapid, sensitive and specific method of detecting mycobacterial DNA, and report is available in 24 h. False negative in 8% and false positive in 2–3% cases is reported. (iii) Guinea pig inoculation and tissue culture. In case of positive culture, the bacteriologist should further attempt to type the bacillus and test its sensitivity. Acid-fast staining of endometrial tissues to detect *M. tuberculosis* is not accurate.
8. **Hysteroscopy:** This often reveals the presence of synechiae, partial obliteration of the cavity, recessed golf-hole appearance of tubal ostia, or rarely presence of ulcers.
9. **Laparoscopy:** Diagnostic laparoscopy is extensively employed to establish the diagnosis of genital tuberculosis/abdomino-pelvic tuberculosis. Tuberculous lesions can be seen on the parietal peritoneum, intestinal serosa, omentum, surface of the uterus and fallopian tubes (thickened rigid tubes/hydrosalpinx, pyosalpinx, tubo-ovarian adnexal masses.) Histology and PCR testing from selected tissue biopsies often help to settle the diagnosis.
10. **Tissue biopsy:** Local excision tissue biopsies from suspected lesions from the lower genital tract (vulva and vagina) submitted for histology help to establish the diagnosis.
11. **Chest X-ray (CXR):** To detect site of primary lesion
12. **Radiography of bones:** In case of suspected tuberculous pathology.
13. **Nucleic acid amplification technique detects tuberculosis within a few hours compared to culture (NAAT).**
    - CA 125 is at times raised, but is nonspecific.

    Other tests to be considered in selective situations include:
14. **Gas chromatography:** Direct demonstration of compounds characteristic of mycobacteria shows great promise (90% sensitive) to provide rapid diagnosis.
15. **SAFA** (soluble antigen fluorescence antibody) test has been evaluated, the drawback has been a false positive reporting of 11%.
16. **BACTEC:** This is a rapid culture method where radioactive carbon-labelled substrate such as palmitic acid or formic acid is used as marker for bacterial growth. It takes 5–7 days to culture.
17. **Semen culture:** Advised in patients with vulvovaginal tuberculous lesions.
18. **Biochemical markers:** Ascitic fluid is tested for presence of markers such as adenosine and deaminase activity. The test is highly specific and sensitive.

Differential Diagnosis

The clinician has to consider several other possibilities before settling on the diagnosis of female genital tuberculosis (FGT):

1. ***Ovarian cyst, broad ligament cyst, encysted fluid:*** These cysts are fixed and immobile. However, the menstrual history is usually normal unlike in women with tubercular encysted lesion. Any history of previous extragenital tuberculosis goes in favour of genital tuberculosis.
2. ***PID:*** Infertility and menstrual disturbances are common to both PID and FGT. However, history of frequent recurrences of failure of response to treatment should raise the suspicion of genital tuberculosis.
3. ***Ectopic pregnancy:*** History of delayed menses, abdominal pain and presence of a unilateral adnexal mass should raise the suspicion of ectopic pregnancy. Urine pregnancy test, Transvaginal sonography with colour Doppler blood flow studies and diagnostic laparoscopy should help in the management of the case.
4. ***Carcinoma cervix:*** In women presenting with local cervical lesions (ulcer, polypoidal growth) clinical findings such as lack of induration, lack of friability should raise suspicion of alternative pathology. Tissue biopsy and histological examination should help to settle the issue.
5. ***Elephantiasis of the vulva:*** Filariasis of the vulva can mimic hypertrophic tuberculosis of the vulva. Biopsy helps to establish the diagnosis.
6. ***Pregnancy:*** Amenorrhoea and abdominal mass may raise the suspicion of pregnancy.
7. ***Puberty menorrhagia and postmenopausal bleeding*** due to other causes need to be excluded.
8. ***Fungal infections and sarcoidosis*** cause granulomatous lesions—histologically resembling tubercular granulomas.

Treatment

Most patients enjoy good health and there is no need for hospitalization. Only those who have fever and abdominal pain are admitted to the hospital in the initial stages of the treatment.

Chemotherapy

The first line of treatment is with antitubercular drugs (Table 14.1). WHO recommends rifampicin (450–600 mg daily depending upon the body weight) combined with 300 mg of isoniazid daily in a single oral dose before breakfast. Rifampicin is hepatotoxic and liver function tests (LFTs) should be undertaken before instituting this drug. Pyrazinamide is a new oral drug (1.5–2.0 g daily in three divided doses) which is very effective against slow multiplying organisms and enhances the effect of rifampicin but it causes hyperuricaemia. The modern therapy consists of rifampicin, isoniazid and pyrazinamide for 2 months, followed by rifampicin and isoniazid biweekly for another 5–6 months. This short course gives quick and successful results, prevents emergence of drug-resistant bacilli. Corticosteroids 4 mg daily may be needed in an ill patient. Some prefer to add ethambutol, 15 mg per kg body weight in a single dose after breakfast or 50 mg per kg/body weight twice weekly during the first 2–3 months. Ethambutol should not be administered for a longer period as it may affect the vision (optic neuritis) and cause skin rash. Ophthalmic examination is mandatory before starting the drug. Oral contraceptives should not be combined with rifampicin. Pyridoxine (B_6) 10 mg daily prevents peripheral neuritis. The oral contraceptives are not effective in the presence of rifampicin, as the latter interferes with their absorption.

Resistant cases associated with HIV need extended treatment for a year.

The new drugs introduced in resistant cases are (Table 14.2):

- Capreomycin
- Kanamycin
- Ethionamide
- *para*-Aminosalicylic acid
- Cycloserine

The main failure of treatment is due to noncompliance and incomplete treatment.

For good compliance, Revised National TB control programme (RNTCP) of India in 2004 incorporated DOT strategy (Direct Observed Treatment). It covered 87% population with 72% detection rate and 86% treatment success, with a sevenfold decline death rate from 29% to 4%.

DOTs—short course therapy of 6 months.

First 2 months

- Isoniazid—15 mg/kg body weight
- Rifampicin—450–600 mg
- Pyrazinamide—30 mg/body weight
- Ethambutol—30 mg/kg body weight

Three times a week.

TABLE 14.1 Chemotherapeutic drugs for tuberculosis

Drug	Action	Side Effects
Rifampicin 10 mg/kg od daily	Bactericidal	Hepatotoxic, fever, purpuric rash, orange urine
Isoniazid 5–10 mg/kg od daily	Bactericidal	Hepatotoxic, peripheral neuritis, hypersensitivity
Pyrazinamide 25–30 mg/kg od	Bactericidal	Hepatitis, hyperuricaemia
Ethambutol 15 mg/kg od	Bacteriostatic	Optic neuritis, skin rash

TABLE 14.2 Drugs used in resistant cases

Drug	Dose	Side Effects
1. Capreomycin	15–30 mg/kg IM	Auditory, vestibular and renal toxicity
2. Kanamycin	15–30 mg/kg IM	Auditory, vestibular and renal toxicity
3. Ethionamide	15–30 mg/kg IM	Hepatitis hypersensitivity
4. *para*-Aminosalicylic acid	150 mg/kg	Hepatitis, GI tract
5. Cycloserine	15–20 mg (1 g maximum)	Psychosis, convulsions, skin rash

Next 4 months—continue with Rifampicin and Isoniazid (same dose) three times a week.

Resistant Cases (8 months course)
First 2 months—streptomycin three times a week + 4 doses as above
Third month—4 drugs as above
Next 3 months—Isoniazid, rifampicin, ethambutol (same dose) three times a week.

HIV TB patients should also receive HAART therapy.

Surgery

Indications of surgery are progression of the disease, persistent active lesion, persistence of large inflammatory masses, i.e. pyosalpinx and pyometra; persistence of symptoms, i.e. pain, menorrhagia, and persistence of fistula, despite the chemotherapy.

Contraindications to surgery are active lesions elsewhere in the body and plastic adhesions of bowels. Any attempt to separate the adhesions would result in trauma and bowel fistula. *Surgery should be preceded by several weeks of chemotherapy, followed by a full course of chemotherapy.*

Types of surgery

- Total hysterectomy with removal of ovaries and the fallopian tubes. It is very rarely required today.
- Vulvectomy in cases of hypertrophied vulva.
- Tuboplasty is contraindicated. Any surgery on the tube to improve fertility would cause reactivation of the disease. Moreover, fertility cannot be restored when the tubal walls are damaged.
- Removal of adnexal mass in a young woman.
- Drainage of pyometra.
- Fistula repair.

Follow-Up

The patient needs to be followed up for at least 5 years, as reactivation of the lesion during this period has been reported. A yearly or when indicated earlier curettage should be carried out to check for any reactivation. Hysterosalpingogram is however not advisable, as it may reactivate the dormant infection.

Prognosis

Nearly 90% of the cases get cured with chemotherapy. Fertility, however, is restored in only 10% cases. Of those who conceive, 50% have a tubal pregnancy, 20–30% abort. Only 2% of women with genital tuberculosis will have live births.

In Vitro Fertilization

Women successfully treated for genital tuberculosis are now offered assisted reproduction by in vitro fertilization. Marcus et al. have reported 40% success, provided the endometrium is normal.

Key Points

- Tuberculosis of the genital tract is common in India, and is secondary to primary focus in the lungs (50%), lymph nodes (40%), urinary tract (5%) and bones and joints (5%).
- The infection primarily attacks the fallopian tubes causing PID. Later it spreads downwards, causing uterine synechiae and Asherman syndrome. Cervical and vulval lesions are very rare.
- Very often, genital tuberculosis remains silent and goes unnoticed. Infertility, amenorrhoea, abdominal mass and pain develop in an advanced stage.
- D&C, laparoscopy and blood tests discover its existence.
- Newer techniques such as PCR NAAT and Bactec rapid culture methods which offer results in 24 h and 5–7 days, respectively, are now being employed. NAAT detects tuberculosis in a few hours.
- Treatment is essentially medical. Surgery may be required if the disease persists and does not respond to drugs, and the treatment is hysterectomy and bilateral salpingo-oophorectomy, and removal of tubo-ovarian mass in a young woman.
- Reactivation may occur within 5 years; therefore, follow-up becomes necessary.
- Pregnancy rate following treatment is only 10%, of which one-third abort and another 50% develop ectopic pregnancy.
- High degree of suspicion is required in an asymptomatic woman, especially in an infertile woman.

Self-Assessment

1. Describe the pathogenesis of female genital tuberculosis.
2. Describe the lesions of the female genital tract caused by tubercular infection.

3. How would you investigate a case of suspected genital tuberculosis?
4. Describe the common clinical manifestations of genital tuberculosis.
5. How would you treat a patient of genital tuberculosis?

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Chapter 15

Injuries of the Female Genital Tract

CHAPTER OUTLINE

The female genital tract injuries are mostly obstetrical. Gynaecological and traumatic injuries are rare. They need to be recognized and repaired immediately to avoid bleeding, infection, painful scar and symptoms related to the associated injury to the neighbouring structure.

Obstetric Injuries

Most injuries of the female genital tract occur during childbirth. In a normal delivery, the circular fibres which surround the external cervical os are torn laterally on each side so that an anterior and a posterior lip of the cervix become differentiated. As a result of stretching, the vagina becomes more patulous, and through laceration the hymen is subsequently represented by irregular tags of skin termed the carunculae myrtiformes. A superficial laceration of the perineal skin of the first degree is common even in uncomplicated deliveries.

In abnormal labour and when obstetrical manipulations have been carried out, or as a result of inexpert technique, injuries of the birth canal are frequent. Severe lacerations of the perineum are perhaps the most common form of birth injury. Tears of the vagina may be caused by rotation of the head with forceps or may take the form of extension of tears either of the perineum or the cervix. Severe lacerations of the cervix are usually caused by violent uterine contractions at the end of the first stage of labour; others result from the delivery of a posterior position of the occiput and some from cervical dystocia. A vesicovaginal fistula may result from ischaemic necrosis or a difficult forceps delivery in cases of disproportion, while a rectovaginal fistula is the result of a complete tear of the perineum or a suture which perforates the rectal wall. Extensive vaginal laceration causes fibrosis and atresia, which may lead to dyspareunia and even apareunia.

The majority of obstetric injuries are theoretically preventable. A case of disproportion should be recognized antenatally and be treated in time by caesarean section. Lacerations of the cervix and extensive tears of the perineum, although avoidable, should be treated by immediate suturing. One of the worst injuries in obstetric practice in India is rupture of the uterus. It occurs mostly in delivery cases conducted at home when obstructed labour is not diagnosed by the midwife. Uterine rupture carries a very high maternal mortality and morbidity.

Obstetric trauma during childbirth can involve more than one organ. The perineum and the vaginal walls are most vulnerable; however, on occasions, childbirth trauma is known to badly injure the cervix, vaginal vault, cause colporrhexis and even extend into the uterus resulting in uterine rupture.

Perineal Tears

These are not uncommon, and thorough inspection of the perineum and lower genital tract under a good light is mandatory after any instrumental or assisted vaginal delivery and after spontaneous labour whenever traumatic postpartum haemorrhage is diagnosed. Small lacerations that are not bleeding may be left alone. All other injuries must be surgically repaired, preferably in an operation theatre. Presence of a competent assistant and availability of an anaesthesiologist during the procedure are of immense help. All bleeders should be meticulously attended to. The tear should be repaired in layers. Sometimes, a small bleeder

may be overlooked, this may lead to a perineal haematoma. In such an event, it is important to evacuate the haematoma at the earliest, ensure haemostasis and repair the wound promptly. At times blood transfusion may be indicated to correct shock.

The common risk factors predisposing to perineal floor injuries are listed below:

1. Overstretching of the perineum:
   - Big-sized baby
   - Prolonged labour (dystocia)
   - Occipitoposterior presentations
   - Vaginal instrumental-assisted delivery
   - After-coming head in breech presentations
   - Midline episiotomy
2. Rapid stretching of the perineum:
   - Breech presentation
   - Precipitate labour
3. Rigid perineum:
   - Elderly gravida
   - Vulval oedema
   - Scarred perineum following previous surgery
   - Repair of previous complete perineal tear

Prevention of Perineal Tears

This rests on the timely adoption of the following measures:

1. Supporting the perineum and permitting gradual egress of the presenting part during delivery
2. Timely episiotomy if the stretched perineum seems likely to tear
3. It is advisable to perform an episiotomy while undertaking any instrumental-assisted vaginal delivery
4. It is advisable to perform an episiotomy while conducting assisted vaginal breech delivery
5. In patients having history of successful repair of complete perineal tear, repair of genital tract fistula or difficult genital tract prolapse, it would be advisable to opt out for a caesarean section as the optimum route for delivery.

Vaginal Tears

Isolated vaginal tears or lacerations without involvement of the perineum are usually found following instrumental or manipulative vaginal deliveries. These should be promptly repaired after delivery to prevent undue blood loss. Sometimes, it is advisable to pack the vagina with sterile roller gauze soaked in glycerine acriflavine to provide local compression; the pack should be removed in 24 h.

Cervical Tears

These may follow instrumental vaginal delivery, in shoulder dystocia, or manipulations during vaginal breech delivery. The fact that there is vaginal bleeding in excess of expectation in the presence of a well-contracted uterus, should raise suspicion of genital tract trauma. Speculum examination and packing of the cervix against the vaginal vault permits satisfactory visualization of the vaginal walls. Thereafter, the entire rim of the cervix should be inspected between ring forceps to identify any cervical tear and repair the same.

Colporrhexis

Rupture of the vaginal vault is called colporrhexis. There may be concomitant tear of the cervix. If this injury is extensive, it may lead to formation of broad ligament haematoma requiring laparotomy. Suturing of the rent should suffice. There is danger to the uterine vessels and ureter during repair. Great care should be exercised to avoid complications.

Injuries Due to Coitus

A slight amount of haemorrhage from the torn edges of the ruptured hymen is normal after defloration, but the haemorrhage is sometimes very severe, particularly when the tear has spread forward to the region of the vestibule. The haemorrhage can usually be controlled by the application of gauze pressure, but suturing under anaesthesia is often required and blood transfusion may be necessary.

Bruising of the vaginal wall is not uncommon in the early days of married life, and a urethritis may result from bruising of the urethra. Such cases (honeymoon pyelitis) are seen frequently and it is not uncommon for ascending pyelonephritis to result.

Lacerations of the vagina caused by coitus are occasionally seen. Violent coitus or rape in young girls, forceful penetration in postmenopausal women having atrophy of the vagina, or in the presence of such malformations as an imperforate vaginal septum, extensive and serious injuries are known to occur. These lacerations may be of variable types. It often takes the form of a longitudinal tear of the anterior vaginal wall. Cases have been recorded where the posterior vaginal wall has been torn through and the peritoneal cavity opened up and both bladder and rectum may be involved in serious coital injuries. Similar injuries may occur in patients upon whom vaginal operations have been previously performed, especially if coitus takes place soon after the operation. All patients who have had a vaginal operation should be warned to avoid coitus for 2 months. A similar injury can occur after the operation of total hysterectomy when the recently sewn vaginal vault may be disrupted by coitus. Large or small bowel and omentum can prolapse into the vagina with resulting shock and peritonitis. Severe haemorrhage follows injuries of this kind. When the injuries are small, treatment consists in plugging the vagina, provided thorough inspection has excluded the possibility of extensive or internal injury. In more severe cases, it is necessary to suture the laceration under anaesthesia. If the bowel has prolapsed, it is imperative to open the abdomen so that a complete inspection of the gastrointestinal tract (GIT) from the jejunum to the rectum can be made. Damage to bowel or mesentery can then be assessed and the correct treatment performed under direct vision. It is interesting to note that quite apart from the coitus or direct injury, a spontaneous rupture of the vagina can occur in the upper posterior one-third. The patients are usually

elderly and the vagina is atrophic. The cause is usually a violent bout of coughing or some severe strain associated with a sudden rise in intra-abdominal pressure. The treatment is the same as for coital injuries.

Direct Trauma and Vulval Haematoma

Injuries to the vulva as the result of direct trauma are not uncommon. Such accidents as falling astride gates and chairs are frequent and usually produce bruising of the labia majora. In more severe cases, large haematoma develops in the labia majora and the effused blood spreads widely in the lax connective tissues. This is specially seen when the laceration involves the region of the clitoris and the erectile tissue around the vaginal orifice. Comparable haematomas of the vulva are sometimes caused by the rupture of varicose veins of the labia majora during pregnancy, and the large swelling may obstruct the delivery (Figure 15.1).

One of the most common causes of the vulvovaginal haematoma is the inadequate haemostasis during suturing of an episiotomy or a perineal tear. The important complications of haematoma of the vulva are haemorrhage with subsequent anaemia and local infection. A vulval haematoma presents a painful tender swelling, bluish black in appearance. The patient may look pale and she may be in a condition of shock which is out of proportion to the clinical blood loss. A small haematoma responds well to bed rest, sitz bath and magnesium sulphate fomentation. Antibiotic is given to prevent infection. With large haematoma, it is sometimes necessary to incise the swelling under anaesthesia and to turn out the clot. If the haemostasis is difficult to secure, packing with drainage is employed, but this leads to prolonged convalescence. The deep penetrating injuries require immediate operation, suture and repair of the injured structure. If there is least suspicion of visceral injury or if the pouch of Douglas has been opened, laparotomy must be performed and perforation of the bowel or bladder sutured. A temporary colostomy may be necessary if the rectum has been injured.

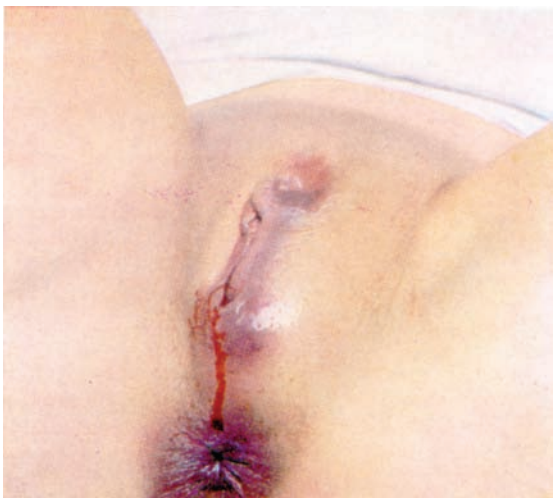

Figure 15.1 Vulval haematoma.

Pelvic Haematoma

Pelvic haematomas are of two types. Infralevator haematoma following perineal tear or episiotomy has been described above.

Supralevator haematoma results in broad ligament haematoma. It follows cervical tear involving the uterine vessels, uterine rupture (spontaneous or caesarean scar rupture) and uterine tear during uterine surgery. The diagnosis may be delayed if it is small. A large haematoma causes hypotension, tachycardia and pallor. A tender swelling is felt on one side of the uterus in the broad ligament.

Management depends upon the size of the haematoma.

- Conservative with observation: A small haematoma gets gradually absorbed. Antibiotics should be given.
- Laparotomy: If the bleeder cannot be identified as is the usual case, the broad ligament should be packed for 24 h and one end of the pack brought out of the abdominal wound to be removed later. Blood transfusion may be required.
- Hysterectomy for uterine rupture.
- Internal iliac ligation to control bleeding.
- Embolization of internal iliac artery.

It is important to identify the ureter and avoid trauma during hysterectomy.

Mutilation

This practice of genital mutilation is even now prevalent in African countries, parts of Asia and amongst Arabs. It involves partial or total removal of external genital organs, for nonmedical reasons. It involves partial or total removal of the clitoris and prepuce (type I), clitoris with labia minora (type II), cutting and apposing labia minora (type III) or pricking, piercing, incision and cauterization (type IV).

Immediate complications are:

- Bleeding—haematoma
- Pain
- Infection

Long-term adverse effects are:

- Severe persistent pain due to unprotected nerve endings.
- Dyspareunia, apareunia.
- Haematoma with forceful intercourse.
- Infection with scar.
- Transmission of HIV, tetanus.
- Retention of urine, haematocolpos.
- Difficult childbirth and need for caesarean delivery.
- Psychological trauma of mutilation and distorted anatomy of the external genitalia.

Injuries Due to Foreign Bodies and Instruments

Vagina

An extraordinary variety of bizarre foreign bodies have been recovered from the vagina including safety-pins, hair grips,

pencils and small jam jars. The patient is often mentally retarded or a young child, and in both these a persistent and a malodorous discharge should always suggest the presence of a foreign body.

Neglected or forgotten objects employed therapeutically. The most frequently found is the ring pessary used in prolapse. Some of these have remained in the vagina for many years and have become encrusted with phosphatic deposits. These neglected pessaries can cause severe ulceration of the posterior fornix and later vaginal carcinoma. Less traumatic are forgotten swabs and tampons which cause a foul purulent discharge.

Contraceptive devices such as cervical caps and diaphragms, even a mislaid condom when retained, can cause discharge and ulceration.

Instrumental damage is caused during attempted criminal abortion. Sound, gums, elastic bougies, knitting needles and the like have caused perforation of the vagina into the bladder, rectum, pouch of Douglas and the parametrium.

Very rarely, a needle can break during suturing of an episiotomy and a piece may remain there without causing symptoms. This is accidentally discovered during a subsequent confinement.

Obstetric cervical tear occurs during precipitate labour or instrumental delivery.

The commonest cervical tear occurs during cervical dilatation with the metal dilator and this causes bleeding and later an incompetent os. Cervical stenosis follows conization and amputation as in Fothergill operation for prolapse and cauterization of cervix for cervical erosion. This can lead to haematometra and infertility.

Uterus

Foreign bodies in the uterus are almost always intrauterine contraceptive appliances such as copper T. These are inserted in the first place by a qualified practitioner but may be neglected or forgotten by the patient. They cause ulceration of the endometrium and can give rise to a serious ascending infection with inflammatory tubo-ovarian masses. The foreign body may also be a cause of menorrhagia.

The other foreign body met within the uterus has usually been introduced in order to procure abortion. Serious intrauterine infections often result in pelvic abscess from acute salpingo-oophoritis.

Perforation of the uterus may occur during dilatation and curettage (D&C) and medical termination of pregnancy (MTP).

Perforative injuries during hysteroscopic operative procedures such as transcervical resection of endometrium or division of the uterine septum have been known. These should not be treated lightly; the possibility of injury to hollow viscera, or vessels, must always be borne in mind and necessary surgical measures implemented to ensure patient safety.

Asherman syndrome with uterine synechiae follows vigorous curettage or uterine packing to control haemorrhage, manual removal of the placenta and uterine infection.

Treatment

Treatment of vaginal foreign bodies is to remove them, if necessary, under anaesthesia. Simple local antiseptic douches are sufficient for after treatment. If, however, the vagina has been perforated, chemotherapy is indicated, and if there are signs of peritoneal infection or bowel damage, as with criminal abortion, laparotomy is needed.

Uterine foreign bodies should be removed under anaesthesia and, if infection is present, a swab taken and the correct chemotherapy given. Adnexal involvement if resistant to chemotherapy, e.g. large persistent masses with recurrent fever and constitutional upset, call for laparotomy and their surgical removal. In young women, it is sometimes possible to conserve the uterus and part of one ovary. When the pelvic organs are grossly disorganized by the pelvic inflammatory disease (PID), total hysterectomy and bilateral salpingo-oophorectomy is the only logical answer. Fortunately, these severe infections from uterine foreign bodies are rare.

Chemical and Other Burns of the Vagina

The most common cause of these is the use of strong chemicals such as Lysol, permanganate or corrosive sublimate. The dangerous complication of this type of burn is that during healing extensive vaginal adhesions and fibrosis will obliterate the canal and prevent coitus, and even cause retention of menstrual discharge with haematometra and pyometra. Plastic reconstruction is the only answer to this problem.

Douches administered at too high a temperature are another cause of burn. This is a culpable error on part of the operator.

During the operation of cauterization of the cervix by cautery or diathermy, it is quite easy to burn the vagina directly or by conduction. Fortunately, cryosurgery has today replaced cauterization of the cervix and burn injuries of this nature are rare. Laser therapy for cervical lesions and vaginal cancer in situ can also cause burns.

It must be remembered that the radium inserted into the vagina for carcinoma of the cervix always causes radiation burn. During the process of healing, the vaginal vault frequently becomes obliterated by adhesive vaginitis and fibrosis.

Treatment

Most vaginal burns, unless severe, heal with expectant treatment. Those resulting in extensive scarring and atresia will require plastic surgery.

Injuries of the Perineum

A minor degree of laceration of the perineal body often occurs during childbirth irrespective of the skill with which

the delivery is performed. Some degree of perineal laceration occurs in nearly all normal deliveries while the incidence is greater if obstetric operations have been performed. Lacerations are five to six times more frequent with primiparae than with multiparae.

It is customary to grade lacerations of the perineum into four degrees. In the first degree, the laceration is restricted to the skin of the fourchette. In the second degree, the muscles of the perineal body are torn through, while in the third degree the tear extends partially backwards through the external sphincter of the anus. In the fourth degree, the sphincter is torn and anal mucosa is also involved. A rare type of tear is the central tear of the perineum when the head penetrates first through the posterior vaginal wall, then through the perineal body and appears through the skin of the perineum. It usually occurs in patients with a contracted outlet.

Perineal Lacerations

An occult injury to the perineum without noticeable injury occurs in 0.5–2% women following vaginal delivery.

As much as 35% primipara women have shown to have sustained occult sphincter injury as seen on ano-endosonogram.

First-degree lacerations, restricted to the skin of the fourchette, have no influence upon the integrity of the pelvic floor, but if the lacerations are not sutured after delivery, the vaginal orifice becomes more patulous. In practice, small lacerations of the fourchette are not sutured unless they extend to the skin of the perineum, where they are more likely to become infected and to cause pain.

Second-degree lacerations should always be sutured carefully immediately after delivery. The pelvic floor is weakened unless the injury to the muscles of the perineal body is efficiently repaired. If the decussating fibres of the levator ani muscles are torn through, the hiatus urogenitalis becomes patulous and prolapse of the vagina and the uterus is likely to develop, unless these lacerations are sutured immediately after delivery.

With extensive second-degree tears, the patient should be given a local, regional pudendal block or general anaesthetic, placed in the lithotomy position, and the torn muscles of the perineum identified and sutured together with catgut. The torn edges of the vagina and the skin of the perineum should then be sutured together with catgut. The essential part of the after treatment of perineal lacerations consists in keeping the perineum clean. Frequent swabbing is therefore imperative during the puerperium. The wound should be cleaned with an antiseptic solution such as Betadine after micturition and defaecation. Antibiotics are required.

Third- and fourth-degree tears are much more important, because unless they are efficiently repaired immediately after delivery, the patient becomes incontinent of faeces and flatus. Amongst the predisposing causes of complete tear of the perineum are forceps delivery in the persistent occipitoposterior positions, and extraction of the after coming head in breech presentation. Large heads and precipitate labours are also contributory factors, but the most common cause is vigorous pulling in the wrong direction during forceps delivery, especially with Kielland's forceps, so that no opportunity is given for the head to be delivered by the natural mechanism of extension. A properly performed episiotomy will very largely eliminate the risk of a third- and fourth-degree tear. This type of tear is more common with median episiotomy than mediolateral episiotomy.

Complete tear of the perineum should be repaired as soon as possible after the delivery. A practitioner should not undertake the repair of a complete tear of the perineum single-handedly. The operation should be undertaken under anaesthesia with the patient lying in the lithotomy position in good light and with good assistance. The operation should be regarded as a surgical emergency and there is no excuse for delay. As facilities may not be available in the patient's home, she should be transferred to a hospital.

The immediate repair of a complete tear of the perineum is a relatively simple procedure, since the muscles of the perineal body, though torn, can be distinguished without much difficulty. The surrounding skin is first cleaned and the operation area isolated with sterile towels. A sterile pack is placed in the vagina and the limits of the laceration defined with tissue forceps. The rectum and the anal canal are first repaired with Vicryl '0' sutures inserted with an atraumatic needle. A few Lembert sutures are then introduced to invaginate the torn edges of the bowel wall. The muscles of the perineal body are now sutured together, and every effort should be made to obtain exact anatomical reposition. Particular attention must be paid to the sphincter ani muscle, and at least two Vicryl sutures should be used to draw the cut edges together. The tears in the vaginal wall and in the skin of the perineum are now repaired with interrupted catgut sutures. Care should be taken to avoid tying the sutures too tightly; otherwise, oedema of the perineum will lead to severe pain and cause the stitches to cut through. If a complete tear of the perineum is treated by immediate suture, the end result is satisfactory if correct anatomical reposition has been attained. If primary union of the vagina and the perineal skin is not obtained the wound should be kept clean and encouraged to granulate by frequent sitz baths. The end results are often functionally good in spite of the initial breakdown of the suture line. The bowels should be confined for at least 5 days, solid foods withheld and intestinal antiseptics given, along with stool softeners. Systemic antibiotics are necessary.

Lately, instead of end-to-end suturing of the torn sphincter muscles, overlap technique is recommended to yield a stronger sphincteric control.

Old-Standing Complete Tears

Various degrees of complete perineal tears, usually resulting from careless attempts at immediate suturing, are not unusual. The rectal wall may be torn through as high as 5 cm or more along the posterior vaginal wall, but in most

cases only the anal canal is involved. The appearance of the perineum in cases of old complete tear is characteristic. The red glistening mucous membrane of the anal canal and rectum protrudes and fuse directly with the vaginal wall without any of the perineal tissues intervening. Laterally, on each side, on a level with the anus, is the depression in the skin which corresponds to the position of the severed edge of the torn external sphincter (Figure 15.2). Behind the anus are the radial folds in the skin which are corrugated by the underlying contracted subcutaneous sphincter. The external sphincter is only present posteriorly and the absence of the sphincteric grip is appreciated by inserting a finger into the anus.

One of the most interesting features of the complete tear of the perineum is that it is very rarely if ever associated with prolapse, although the decussating fibres of the levator ani muscles have been torn through. The reason is that the patient continuously draws together the two levator ani muscles in an effort to close the bowel so that by constant use the tone of the muscles becomes exceptionally good. This firmness and good development of the levator muscles is found on clinical examination when the levator muscles are palpated.

Symptoms

The patient complains of incontinence of faeces and flatus. A few patients develop the tone of the levator muscles so well that they only suffer incontinence of flatus. These women will complain of incontinence of faeces only if they develop diarrhoea.

Apart from clinical examination, a gap in the sphincter can be identified by perineal ultrasound or magnetic resonance imaging (MRI).

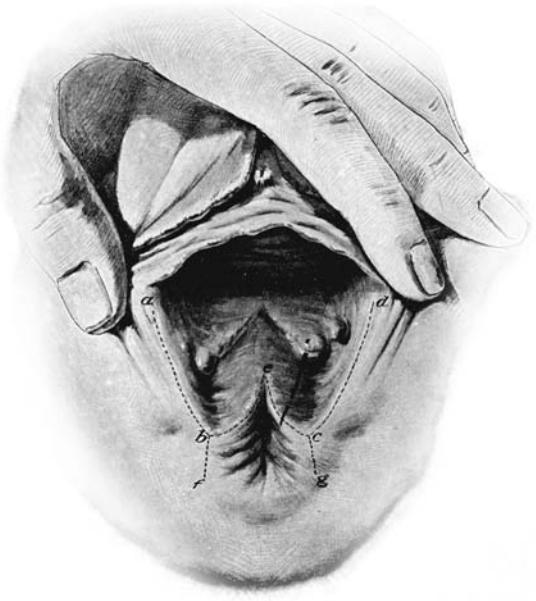

Figure 15.2 Complete tear of the perineum. The dotted line illustrates the position of the incision made in the operation of repair (a) and (d) represent the two ends of the torn fourchette, the dimples adjacent to (b) and (c) mark the situation of the cut edges of the external sphincter.

Treatment

The treatment of complete tear of the perineum is operative. The technical difficulties are much greater in old cases than in those operated upon immediately after delivery. The optimum time for operation in the case of old tears is 3–6 months after delivery. If the operation is attempted earlier than this, healing by first intention is exceptional while if the operation is further delayed, dense scar tissue may be deposited which adds to the operative difficulties. Preoperative preparation is of importance, and the patient should be kept in the hospital for a couple of days before the operation during which time the bowels should be emptied by aperients and enemas, and the vagina disinfected by douching and by insertion of gauze packs soaked in flavine 1 in 1000 or Betadine lotion. The bacterial flora of the bowel should be controlled by phthalylsulphathiazole or neomycin, given in large doses for 3 days before the operation. The patient should be put on a nonresidual diet such as milk and fluid for 2 days prior to surgery. Various techniques have been described in the operative treatment of complete tears of the perineum, but the underlying principles are the same in all. The rectum must be dissected from the vagina by incising the intervening scar tissue and by dissecting upwards in the rectovaginal septum.

Perhaps the most important step in the operation is to dissect the rectum clear of scar tissue and to mobilize it so that it can be brought down, without tension to the anal region. The tear in the rectum and anal canal is now repaired by excising scar tissue, freshening the cut edges and suturing them together with fine Vicryl sutures mounted on an atraumatic needle and tied within the bowel. The needles, forceps and scissors used during this step are discarded. The wound in the bowel is now invaginated with a layer of interrupted Lembert sutures. Next, the deep muscles of the perineal body and the levator ani are identified and sutured together with no. 0 or 1 catgut. It is important to ensure that the muscles are dissected clear of scar tissue and are mobilized. The next important step in the operation is to suture together the torn edges of the external sphincter. These must be carefully defined, dissected clear of scar tissue and sutured together with three or four separate Vicryl sutures. The remains of the superficial muscles of the perineum are now sutured together with catgut and then the cut edges of the vagina and the perineum are repaired, interrupted catgut sutures being used. These principles are uniformly followed in the various methods described for the treatment of a complete tear of the perineum. The modifications depend solely upon the position of the incisions made in the vaginal walls and in the skin of the perineum, and these, in their turn, depend not upon any particular technique, but upon the type of complete tear which is to be repaired (Figure 15.3).

Lately, many gynaecologists believe in overlap of sphincteric sutures to strengthen the tone and function of the sphincter, though others feel this overlap technique has no bearing on the surgical outcome. This remains a controversial point as of today.

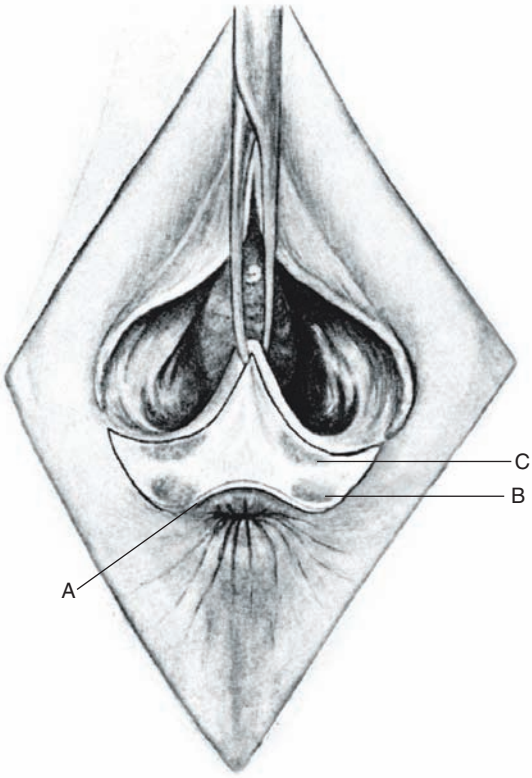

Figure 15.3 Operation for repair of a complete perineal tear. An area of scarred skin is excised and the mucous membrane of the anal canal freshened at the edge. The rectum is then mobilied and pulled down. Three structures must be defined, freed of scar tissue and mobilized, namely (A) the mucous membrane of the anal canal, (B) the external sphincter and (C) the levator ani muscles. First the edges of the anal canal mucosa must be sutured together, then the cut edge of the sphincter and lastly the levator muscles. Afterwards the cut edges of the posterior vaginal wall and the skin of the perineum are sutured.

After Treatment

The most important part of the after treatment is to keep the wound dry. The perineum should be swabbed after micturition and defaecation with antiseptic solution and subsequently powdered. Betadine is the antiseptic solution of choice these days, and it is effective. The bowels should be confined until at least the fifth day of the operation. To achieve this, the patient is given only intravenous fluids for the first 2 days and oral fluids the next 2 days. On the fifth day, she receives olive oil enema. As in all operations on the perineum, retention of urine is a common complication, it may be advisable to leave a Foley's catheter for a few days in the immediate postoperative period. Sulphathiazole or neomycin administered preoperatively should be continued for at least a week postoperatively. Systemic chemotherapy is necessary to prevent infection and it should be given for a week. The end result is usually good. Another complication that may develop is a rectovaginal fistula which is usually the result of faulty technique but also may be due to infection and breakdown of sutures.

Vaginal Lacerations

Vaginal lacerations commonly occur following assisted instrumental vaginal deliveries (forceps or vacuum extraction), difficult breech extractions, or following shoulder dystocia. It is a good practice to inspect the lower genital tract under a good light after expulsion of the placenta, identify all tears and suture them meticulously. Sometimes a cervical tear may extend to the vault of the vagina and cause profuse bleeding. Suturing must be done with great care to avoid injury to the ureter. Tears extending to the base of the broad ligament may lead to a broad ligament haematoma which may require recourse to a laparotomy for its evacuation.

Cervical Lacerations

Minor injuries are common and need no treatment. Bilateral transverse tears of the cervix end up as ectropions. Extensive tears involving the sphincter of the cervix may lead to preterm deliveries or habitual painless mid-trimester abortions due to incompetent cervix, necessitating surgical cerclage in future pregnancies. In women with a flat pelvis, the anterior lip of the cervix may get caught between the fetal head and the pubic symphysis resulting in an anterior bucket handle tear. Rarely in women with a small gynaecoid pelvis, a trial of labour may result in circumferential ischaemic necrosis of the lower part of the cervix and end up with an annular detachment of the cervix. The cervical suturing should be undertaken under general anaesthesia. Care should be taken to avoid bladder injury anteriorly and ureter laterally.

Rupture of the Uterus

Rupture of the uterus is almost entirely a complication of pregnancy and labour. It is common in multiparae, usually following a neglected, obstructed delivery. Misuse of oxytocics, or dehiscence of a previous uterine scar (caesarean section), rarely a haematometra or pyometra, may rupture spontaneously as a result of distension and thinning of the atrophic myometrium. Depending upon the cause and extension of tear, suturing or hysterectomy is performed.

Perforation of the Uterus

In the nonpregnant state, perforation of the uterus occurs mainly during the operation of dilatation and curettage. The perforation is more common if the uterus is soft as in pregnancy and in malignancy. The atrophic uterus of a menopausal woman can easily be perforated during curettage for postmenopausal bleeding. Spontaneous perforation may also occur with intrauterine contraceptive devices. The intrauterine device may perforate the wall of the uterus, but remains within the myometrium. At times it

perforates through the entire thickness of the myometrium and either lies freely in the peritoneal cavity or more often gets embedded in the abdominal viscera.

If the uterus is empty and not malignant, laparotomy may not be necessary. Simple observation is all that is required. In the presence of pyometra and malignancy, immediate hysterectomy is strongly advised. If the abdominal viscera, i.e. the intestine, prolapses through the perforation and is seen protruding in the vagina, immediate laparotomy becomes mandatory. The repair of the intestinal injury or resection and end-to-end anastomosis will be required depending upon the extent of the damage to the intestine. If the uterus contains products of conception, repair of the rent will suffice. If the perforation is a large one or if the patient has completed her family, hysterectomy is the operation of choice. Uterine injury has been recently reported during hysteroscopic excision of the uterine septum. Excision under laparoscopic supervision can avoid this injury. The uterine perforation can also occur during ablation of endometrium through a hysteroscope in cases of dysfunctional uterine bleeding (DUB).

Key Points

- Many genital tract injuries originate from an obstetric cause. Difficult vaginal instrumental-assisted childbirth can cause traumatic injuries.
- Coital injuries may cause alarming haemorrhage. Severe lacerations and penetrating injury entering the pouch of Douglas require emergency surgical attention.
- Vulval haematomas: Small haematomas may be observed. Large haematomas need surgical evacuation.
- Foreign bodies in the vagina cause inflammation and ulceration and rarely lead to fistula formation.
- Chemical burns generally occur due to use of corrosive substances. Strictures may follow as a sequela. Laser burn is now the common cause of vaginal burn.
- Old healed perineal tears cause faecal incontinence. Timely detection and surgical correction prevents morbidity.
- Cervical tear causes incompetent os and repeated pregnancy losses. Cervical stenosis can cause haematometra or infertility.
- Uterine rupture occurs during labour and carries a high morbidity.

Self-Assessment

1. Describe the common types of pelvic floor injuries encountered in practice.
2. How would you manage a case of vulval haematoma?
3. How would you manage a case of complete perineal tear?
4. Describe the causes and management of chemical burns of the vagina.
5. Describe the practice of genital mutilation. What complications may follow this procedure?
6. Describe the outcome of long retained foreign bodies in the vagina of children.
7. Describe the genital injuries following coitus.

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Chapter 16

Injuries to the Intestinal Tract

CHAPTER OUTLINE

The close anatomical relation of the lower female genital tract is apt to cause injury to the rectum and anal canal sometime or the other. This is reported during vaginal delivery and vaginal surgery. Similarly, abdominal gynaecological surgery may inadvertently injure the bowel. The use of cautery and laser therapy in gynaecology may inflict burn injury to the gastrointestinal tract (GIT), and this becomes noticeable a few days after the therapy.

It is important therefore to realize the risk of varieties of injuries to the small and large bowels in obstetrics and gynaecology.

This chapter deals with the types of injuries, causes and preventive and therapeutic measures to deal with them. Although the general surgeon may be called to tackle the problem, the gynaecologist should be able, at least, to diagnose and manage a few of them.

Injuries to the bowel in obstetrics are as follows:

1. Vaginal delivery
   - Third- and fourth-degree perineal tear
   - Rectovaginal fistula
   - Faecal incontinence
   - Stricture of the anal canal and rectum
2. Caesarean delivery
   - Intestinal injury
3. During medical termination of pregnancy (MTP)

The bowel problems seen in gynaecology are as follows:

1. Congenital rectovaginal fistula
2. Penetrating injury—accidents
3. Infective—sexually transmitted infections
   - Rectal abscess
4. During surgery
   - Abdominal
   - Vaginal surgery—postvaginal repair and vaginoplasty
   - Endoscopic—laparoscopy and hysteroscopy
5. Genital cancer
6. Radiotherapy for cancer of the female genital organs

Vaginal Delivery

The injury to the anal sphincter, anal canal and sometimes the rectum during vaginal delivery is more common in a primipara. A big baby, prolonged labour, occipitoposterior presentation, breech and forceps delivery are factors leading to higher incidence of bowel injury.

The injury may be a direct muscle trauma, injury to the pelvic floor muscles or to the nerve supply of the anal canal (pudendal nerve).

The symptoms appear soon after the delivery if a tear occurs, or may appear years later due to stretching when a woman develops anal wall prolapse or faecal incontinence.

The injury to the pelvic floor muscles will cause both stress incontinence of urine and faecal incontinence besides genital prolapse.

Faecal Incontinence

Normal anatomy of the anal canal and maintenance of continence of faeces:

The anal canal is 3–4 cm in length and is surrounded by the internal sphincter above and external sphincter below. The internal sphincter represents the expanded distal portion of the circular smooth muscle of the rectum and is innervated by autonomic nerves. The external sphincter is a striated muscle and is innervated by the pudendal nerve (sacral 2–4). The anal pressure remains above the rectal pressure and internal sphincter remains contracted in a continent woman, and opens only when the rectum distends aided by intraabdominal pressure. The external sphincter muscle is supplemented by the puborectalis muscle of the levator ani and this prevents or defers defaecation when the suitable situation does not prevail. In addition, the rectum forms an angle of 60–130° with the

anal canal, and this also helps to keep the internal sphincter closed, and prevents stool from entering the anal canal. During defaecation, the angle straightens out and allows the faecal matter to enter the anal canal. The levator ani muscles relax, so also the external sphincter. The pelvic floor descends by 2 cm. The anal canal widens and shortens during defecation.

Faecal incontinence is defined as loss of normal control leading to involuntary leakage of faecal contents. Depending upon the degree of incontinence, flatus, loose motion (diarrhoea) or solid stool leaks out.

Faecal incontinence is reported in 0.5–2% women following vaginal delivery. Women are more prone to faecal incontinence than men, and elderly women suffer more than younger women. Faecal incontinence may follow some years after the delivery, but many develop it within 6 months of delivery. Primiparas are more inclined than the multiparas. The occult damage to the internal sphincter occurs in 35% women following first vaginal delivery, though the perineum appears intact. This is revealed by anal endosonography.

Aetiology

Several causes are known to cause faecal incontinence, but the most important factor in women is obstetric trauma during vaginal delivery. These causes are as follows:

- Prolonged labour which can stretch the levator ani muscle or damage the pudendal nerve.
- Difficult forceps delivery.
- Occipitoposterior presentation of the fetus, big baby.
- Rigid perineum.
- Episiotomy does not always safeguard against sphincter damage. Midline episiotomy increases risk of injury to the sphincter, compared to mediolateral episiotomy.
- Third- and fourth-degree perineal tears, by tearing the external sphincter, lead to faecal incontinence.

Nonobstetric causes are as follows:

- Neurogenic, dementia, cerebrovascular accident, spinal cord lesion.
- Bowel diseases such as inflammatory disease, cancer and rectal prolapse.
- Radiotherapy for cancer of the genital tract.

Urge incontinence results from injury to the external sphincter when the woman is unable to hold on until she can reach the toilet.

History

The woman may develop faecal incontinence soon after the delivery (usually first vaginal delivery) or some years later if the damage is mild. Further weakening of the pelvic floor muscle support and sphincteric control with advancing age is the cause of delay for the onset of symptoms. Many a times, the woman is reluctant to reveal this history due to shyness, unless directly questioned.

On examination, perineal tear may be obvious, but damage to the internal sphincter shows no external injury and certain investigations are required.

Occasionally, faecal incontinence may follow pelvic surgery.

Investigations

- Proctoscopy and sigmoidoscopy for rectal disease.
- Manometry to measure the anal canal pressure. Normal pressure is 45–100 mm H_2O.
- Electromyelography to detect nerve injury to the muscle (pudendal neuropathy).
- Ten hertz (10 Hz) ultrasound scanning of the anal canal has now replaced electromyelography. Ultrasound scanning detects a defect in the sphincter (Figure 16.1).
- MRI.

Treatment

Management of faecal incontinence comprises the following:

- *Medical*—loperamide and codeine phosphate increase the resting tone of the anal sphincters and also cure urge incontinence.
- Fibre diet makes the stool firm.
- Antidiarrhoeal treatment in inflammatory diseases of the bowel.
- Physiotherapy and biofeedback training are time consuming, but nerve injury recovers in 2 weeks in 60% of early cases.
- Sacral nerve stimulation with a probe improves pudendal nerve stimulation and tones up the levator ani muscles.
- Surgery—surgery is required for extensive perineal tear, fistula and anal prolapse. Rectopexy for rectal prolapse cures incontinence. The woman should be delivered by caesarean section followed by successive repair.

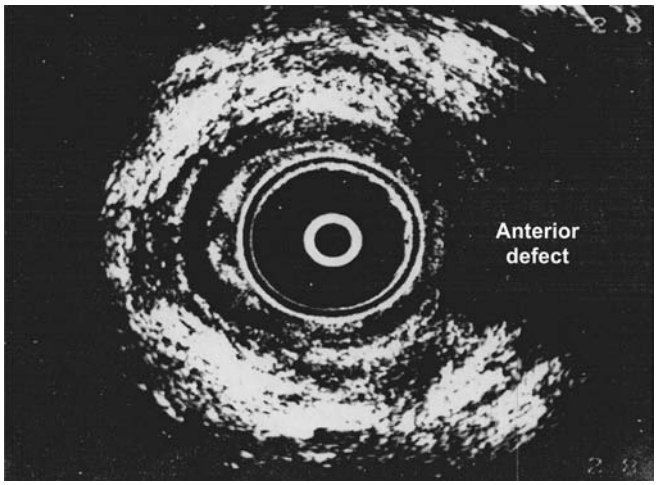

Figure 16.1 Defect in external anal sphincter.

Rectovaginal Fistula

The majority of rectovaginal fistulae result from obstetric injuries, usually a complete tear of the perineum which has been imperfectly sutured immediately after delivery (Figure 16.2). It has already been pointed out that the repair of a complete tear of the perineum should be undertaken carefully, with the patient in the lithotomy position and under anaesthesia. If, for instance, a few sutures are placed through the lower part of the anal canal and the upper part of the tear in the rectum is not accurately sutured, a fistulous opening may form between the rectum and vagina. Rectovaginal fistulae may occur after operation for old complete tears of the perineum if the wound breaks down, or if the rectum is not properly mobilized before the repair of the wound in the rectal wall. These fistulae occur also after the operation of perineorrhaphy in thin, elderly patients when the anterior wall of the rectum is accidentally opened.

Other causes are tuberculosis, which is not uncommon in India, and lymphogranuloma inguinale. In advanced carcinoma of the cervix, when the growth has spread down the posterior vaginal wall, a rectovaginal fistula eventually results. Such fistulae also occur following radiation treatment of carcinoma of the cervix or the vagina, or following Wertheim's operation for the same condition. A fistula following radiotherapy may occur 3 months to several years after radiotherapy and such a fistula is surrounded by extensive stricture. It is difficult to cure a malignant fistula and it can only be treated by some form of posterior pelvic exenteration or a palliative colostomy. Primary carcinoma of the bowel can also extend forward and involve the vagina to cause rectovaginal fistula. Congenital rectovaginal fistula is rarely seen and is the result of maldevelopment of the lower part of the rectum and anal canal. In such cases, it is customary to perform preliminary colostomy before plastic operation. Diverticulitis, rectal abscess and direct trauma are the rare causes of fistula.

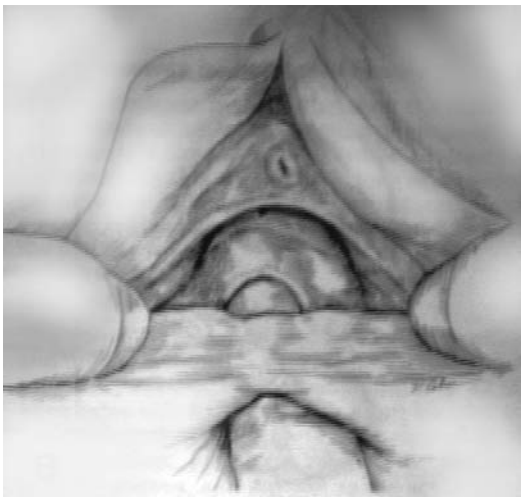

Figure 16.2 Examining finger passed through rectum seen to emerge into the vagina through rectovaginal fistula.

In case of a pelvic abscess when there is collection of pus in the pouch of Douglas, the abscess sometimes bursts into the rectum and a rectovaginal fistula develops, particularly if the abscess is surgically opened up through the posterior fornix. There is a form of rectovaginal fistula which follows infection in an anal crypt with resultant abscess formation, which bursts into the vagina. These cases are difficult to treat surgically, and good results cannot be expected until the entire fistulous tract into the anal canal has been excised. This necessitates division of the external sphincter and follows the principles laid down in the treatment of fistula-in-ano. The patient complains of incontinence of faeces and flatus. A large fistula can easily be identified, but a small one is very difficult to detect, especially if it is surrounded by dense fibrosis. Proctoscopy, sigmoidoscopy and injection of radiopaque dye will be needed to trace the fistulous tract.

Treatment

The traumatic form of rectovaginal fistula is treated by operation. Preoperative treatment is important and the bowel should be emptied with enema, and the vagina disinfected by douches and gauze packs soaked in antiseptic solutions such as flavine or Betadine. Phthalylsulphathiazole or neomycin should be given for a few days before operation to sterilize the bowel contents.

With a small rectovaginal fistula above an intact perineal body, an unusual event, it is sometimes feasible to excise the fistulous track and close the defect successfully by a local operation. It will, however, be more commonly found that the perineal body below the fistula is inadequate and that the levators are not approximated. In fact, in many rectovaginal fistulae, there is merely a thin skin bridge below the fistula and often the anal sphincter itself is incompetent. When, in addition to these perineal defects, the fistula is very large, the best treatment is to cut the skin bridge in the midline and convert the fistula into a complete perineal tear. This is then repaired exactly as described for perineal repair (Ch. 15) and the results are usually satisfactory. A high rectovaginal fistula may require a preliminary colostomy. The fistula due to cancer of the cervix or rectum requires an exenteration operation. A fistula following radiotherapy for cancer may be successfully closed by colpocleisis. This operation consists of obliteration of the vaginal cavity after denuding the entire vaginal mucosa.

The surgeon may be involved in complicated rectal surgery.

Optimal mode of future delivery is not defined; and the decision is individualized. However, most gynaecologists believe in performing elective caesarean section to avoid further damage to the sphincter.

Bowel Injury

Aetiology

- *While entering the peritoneal cavity*, the risk factors are obesity, previous surgery, gynaecological pathology such

as pelvic endometriosis, pelvic inflammatory disease (PID), cancer surgery and previous irradiation.

- *Laparoscopy*. It is not uncommon to perforate the bowel with the Veress needle or the trocar. The use of cautery or laser during laparoscopic surgery can cause burns to the intestine. This will be detected about 5–7 days later, when the woman returns with peritonitis and ileus.
- *Hysteroscopic resection of a uterine septum,* or transcervical resection of endometrium (TCRE) in dysfunctional uterine bleeding (DUB), can cause uterine perforation and thermal heat can cause intestinal burn.
- *Dilation and curettage (D&C).* It is rare to damage the intestine during gynaecological D&C, though some cases have been reported.

Types of injury—perforation, laceration and crush injuries are likely to occur in gynaecological surgery.

Diagnosis

Most of the above injuries can be recognized at surgery. Burn injuries, however, take about a week to present as peritonitis and fistula.

Surgical Treatment

Caesarean section performed following prolonged second stage can also cause injury to the anal sphincter and anal wall. More commonly, however, it is the small bowel that gets injured during caesarean section, more so if the intestine is adherent to the parietal peritoneum through previous surgery.

MTP

Apart from criminal abortion, the bowel can be injured during MTP if the uterine perforation goes unnoticed and a loop of intestine is pulled through the perforation. Immediate laparotomy is required and bowel injury dealt with. Criminal abortion causes maximum injury.

Sexually transmitted infections can cause extensive stricture around the anus (i.e. condyloma venereum).

Surgery

It is rare to injure the bowel during gynaecological surgery and the incidence quoted varies between 0.3 and 0.8%.

1. A small injury less than 5 mm in the small bowel can be effectively closed by a purse-string or transverse sutures in two layers.
2. A larger laceration may need resection and end-to-end anastomosis.
3. Colonic injury needs preliminary colostomy.

Rectal injury occurs mainly during vaginal surgery such as posterior vaginal repair for prolapse, repair of perineal tear, exenteration operation and vaginoplasty.

A small tear can be sutured immediately, but a large hole needs preliminary colostomy.

Radiation causes fistula or stricture. Colpocleisis can cure the fistula.

The gynaecologist should not hesitate to ask for a general surgeon's assistance. In case of doubt or a major injury, surgical assistance is necessary.

Prevention

Obstetric injuries can be avoided by proper obstetric management.

During gynaecological surgery, the high-risk factors should be remembered. A sharp dissection in endometriosis and PID can avoid laceration. The surgeon should be careful while using cautery or laser during laparoscopic surgery.

Key Points

- Bowel injury is observed in 0.3–0.8% of gynaecological cases.
- Anal canal and rectal injuries are mostly obstetrical, inflicted during a difficult or operative vaginal delivery. It is rarely encountered during an operation on the posterior vaginal wall.
- Intestinal and rectal injuries can occur during gynaecological operations on PID and endometriosis, when extensive pelvic adhesions have to be dissected.
- Intestinal injuries are increasingly reported following laparoscopic surgery when cautery and laser are used.
- Hysteroscopic uterine perforation leading to intestinal burn and peritonitis are reported with transcervical endometrial resection and excision of the uterine septum.
- The endoscopic burn injuries are, however, not immediately recognized and symptoms develop 5–7 days later.
- Treatment of intestinal injury is surgical suturing or resection and end-to-end anastomosis. Bowel injury may require preliminary colostomy.
- The help of the general or gastrointestinal surgeon should be sought in major bowel injury.
- Obstetric trauma during vaginal delivery cannot always be avoided. Immediate diagnosis and surgical repair can prevent or minimize the distressful symptom of faecal incontinence.

Self-Assessment

1. How would you manage a patient of faecal incontinence?
2. How would you manage a patient with rectovaginal fistula?
3. What are the common causes of bowel injury during obstetric/gynaecologic surgery? How would you recognize the same? What precautions help to avoid intestinal injuries?
4. What are the causes of intestinal injury during laparoscopy? How would you safeguard against the same?
5. Enumerate the situations leading to bowel injury in obstetric practice.

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Chapter 17

Diseases of the Urinary System

CHAPTER OUTLINE

Urinary symptoms are frequently complained of by the gynaecological patients. Gynaecological disorders and pelvic operations often contribute towards their occurrence or aggravation. On occasions, the underlying disease may be neurological and have no gynaecological bearing. Hence, it is important for the gynaecologist to identify urinary problems attributable to gynaecological causes in order to institute rational therapy. The establishment of a proper diagnosis will call for a detailed history, meticulous examination and often a full urological investigation including laboratory tests, cystoscopy, radiological evaluation, cystometry and ultrasound scanning.

A sole kidney may be located in the pelvis and mistaken for a tumour. The dire consequence of its removal in a mistaken identity is very obvious.

Because of the close association between the urinary and genital organs embryologically, malformation of one organ may also reveal malformation of the other and it should be searched for.

Common Urinary Malfunctions

Common urinary malfunctions include difficulty in micturition, retention and incontinence (Fig. 17.3).

Acute urinary retention follows sudden inability to void urine. The condition causes discomfort and pain. Catheterization yields a large volume of urine. Detailed interrogation often reveals the cause. An attempt must be made to exclude the neurological causes (especially in patients who experience inability to void urine, but experience no painful sensation). Most patients with disorders of bladder sensation experience pain rather than lack of bladder sensation. Elderly women, smokers and those exposed to chemicals are vulnerable to bladder cancer; accompanying haematuria must raise the suspicion of cancer.

Acute Retention of Urine

Causes

Several causes may contribute to the occurrence of retention of urine.

Postoperative Retention

Urinary retention is common after surgical operations on the vagina and perineum. Postoperative oedema may cause obstruction to the flow of urine, and pain from the pelvic region may lead to a reflex spasm of the bladder sphincter. Radical operations such as Wertheim's hysterectomy involve extensive dissection causing denervation of the bladder, leaving the patient with an insensitive bladder comparable to a neurological bladder. The treatment of postoperative retention consists in timely, continuous catheterization until the residual urine comes down to less than 100 mL. Urinary antiseptics and analgesics should be concomitantly administered. Spinal and epidural anaesthesia accounts for retention of urine in the first 12–24 h of postoperative period. Surgery for stress incontinence and the vagina also causes retention of urine.

Puerperal Retention

After delivery, the patient is often unable to appreciate the filling of the bladder as a result of bruising of the vagina and painful perineal wound.

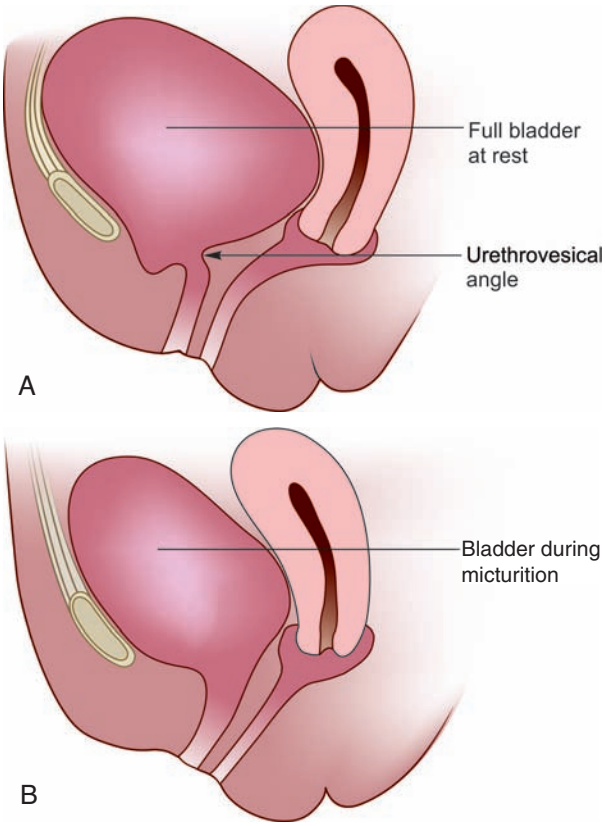

Figure 17.1 Radiographic tracing of urethra and bladder: **(A)** At rest and **(B)** during micturition.

Obstructive Conditions

Obstructive conditions intrinsic to the urethra are rare causes. Cicatricial stenosis may follow surgery on the bladder neck for a fistula or lower down in the urethra for a caruncle. Inflammatory stenosis following gonorrhoea is rare in women. Sling operations for stress incontinence performed with undue enthusiasm may occlude the bladder neck and cause retention which can only be relieved by cutting the sling. Cancer of the cervix, vagina, bladder or urethra may lead to extensive tissue infiltration and obstruction to the flow of urine.

Space-Occupying Lesions in the Pelvis

Space-occupying lesions in the pelvis may obstruct the urethra or bladder neck region. Some of the lesions encountered are as follows:

- Haematocolpos in adolescent girls
- Retroverted gravid uterus at about 14 weeks of gestation
- Haematocele complicating an ectopic gestation
- Cervical myomas or a posterior uterine wall myoma impacted in the pouch of Douglas
- Ovarian neoplasm impacted in the pelvis
- Deeply engaged presenting part during labour may cause pressure on the vesicourethral junction

Neurological Causes

Spinal cord lesions, disseminated sclerosis, tabes dorsalis and denervation of the bladder during extensive surgery for malignant disease in the pelvis are recognized causes.

Anticholinergic and antidepressant drugs may also cause retention.

Chronic Retention

Chronic retention of urine in old women is due to bladder neck obstruction.

Treatment of urinary retention: In the presence of an organic lesion, attend to the removal of the primary cause.

Retention of urine due to a retroverted gravid uterus is encountered relatively frequently. This occurs between the 12th and 14th week of pregnancy, when the retroverted gravid uterus fails to grow out of the pelvis into the abdominal cavity. The anterior vaginal wall and the attached urethra get unduly stretched as the retroverted gravid uterus sinks low into the pelvic cavity. Sometimes, the urethral meatus may be drawn upwards into the vagina. A soft rubber catheter can be usually passed into the bladder without difficulty suggesting that rather than occlusion of the urethra, it is the disturbance of the reflex mechanism of voiding which causes the retention.

On examination, the full bladder is palpable as an abdominal mass. On pelvic examination, the cervix is lifted up high under the symphysis pubis and the gravid uterus is palpable as a large mass filling up the pouch of Douglas.

The treatment consists of a slow, deliberate emptying of the bladder by an indwelling catheter draining into a sterile drainage bag over 12–14 h. The patient is encouraged to lie on her face so that posture and gravity assist the gravid uterus to assume the anteverted position. Digital reposition of the gravid uterus is neither safe nor successful, hence not recommended.

Urethral Syndrome

A patient with urethral syndrome is usually a postmenopausal woman complaining of dysuria, frequency of micturition and occasional stress incontinence. Urine is sterile. The cause of urethral syndrome is oestrogen deficiency at menopause causing weakening of the internal urethral sphincter and urethral mucosal changes. Oestrogen cream applied vaginally improves the blood supply to the urethral sphincter and urethral mucosa, and cures the symptoms in about 3 months.

In a young woman, urethral syndrome is associated with sterile urine, but the presence of pus cells indicates probable infection with tubercle bacilli or chlamydia.

Difficult Micturition

Difficulty in emptying the bladder is a symptom present in those conditions which eventually produce retention of urine. It also occurs in growths of the bladder and urinary calculi. One of the most common gynaecological causes of difficulty of micturition is a severe degree of prolapse of the anterior vaginal wall and procidentia. When such patients strain to micturate, the anterior vaginal wall prolapses and the bladder descends so that a large sacculation of the bladder comes to lie below the level of the internal urinary meatus. The more the patient strains, the less likely is she to

empty her bladder, as the urine is forced down into the cystocele instead of into the urethra. The only way the act of micturition can be started by the patient is by her own digital manipulation by pushing back the prolapsed anterior vaginal wall and the uterus. Treatment consists of anterior colporrhaphy combined with a pelvic floor repair, and vaginal hysterectomy if indicated.

Painful Micturition

Pain may be present either during or immediately following the act of micturition. Pain during micturition is usually of vesical origin due to infection but may be of urethral origin and referred to the urethra itself, whereas an intrinsic lesion of the bladder gives rise to bladder spasm felt in the mid-hypogastrium so that, as soon as the patient has voided urine, she has an urge to pass urine again though the bladder is empty. Gonococcal urethritis causes scalding pain as urine passes over the inflamed mucous membrane. Other causes of painful micturition are tender caruncles at the meatus, prolapse of the urethral mucous membrane and disease of the vulva such as kraurosis and carcinoma of the urethral meatus. The recently consummated marriage somewhat traumatizes the urethra and leads to pain and frequency of micturition. This has been called honeymoon cystitis. All operations performed upon or near the urethra and instrumentation of the canal, even with a soft catheter, cause some degree of dysuria. Painful micturition is a prominent symptom in cystitis; the pain is experienced at the end of micturition when the inflamed surfaces of the bladder come into apposition. Other conditions which cause painful micturition are papilloma, carcinoma, tuberculosis and stone. One important cause of dysuria and pain is radiation cystitis, which in severe degrees can cause a small-capacity irritable bladder. This is seen after a radium treatment for carcinoma of the cervix and can be very distressing. The urine should be examined in all cases where the symptom is present, and the presence of infection excluded or confirmed by culture. Cystourethroscopy must be performed to exclude the presence of the more serious causes of dysuria. The postradiation bladder often shows telangiectasia of the vessels in the region of the trigone.

Increased Frequency of Micturition

Voiding urine at least seven times during day and at least once during night is considered frequency of micturition. Frequency of micturition is one of the most common symptoms complained of by gynaecological patients, and although many causes of frequency lie in the urinary tract, a large number are gynaecological. The nongynaecological causes are diabetes mellitus, diabetes insipidus or one phase of incipient renal failure, when urinary output increases. Frequency of micturition is present when the patient passes small amount of urine at short intervals and it is often associated with other symptoms of bladder irritability such as urgency of micturition and incontinence. The symptoms always develop with cystitis, whatever the cause of the cystitis may be, whether *Escherichia coli* infection, tuberculous infection, stone or growth. Frequency of micturition is a normal symptom of early pregnancy and develops again during the last few weeks when the presenting part enters the pelvis. Pressure upon the bladder by pelvic tumours such as myomas of the uterus and ovarian cysts also cause frequency. The symptom is often complained of by patients with cystocele, mainly because a chronic cystitis is usually coincident and also because of incomplete emptying of the bladder. Inflammatory swellings around the bladder such as parametritis and inflamed appendages also lead to frequency. Infiltration of the bladder by carcinoma of the cervix or of the vagina will cause frequency of micturition. Apart from the urological causes, the symptom also develops in retention overflow when the bladder is overdistended. One very important cause of frequency is bladder neurosis. In the fully established bladder neurosis, the patient's life is ultimately dominated by her bladder—though this at first only happens in the day time. The condition is readily misdiagnosed as stress incontinence. The urine is sterile, with normal cystoscopy and no local cause discoverable.

The investigation of frequency of micturition requires, in addition to the usual gynaecological examination, a complete examination of the urine, urine culture test, cystoscopy and intravenous pyelography and ultrasound scanning.

Treatment is by simple applied psychotherapy, bladder discipline and sedatives. Increased frequency due to an organic lesion, usually cystitis, occurs equally at night as during the day, and the nocturia score gives a rough indication of the severity of the condition.

Other causes of frequency need prompt treatment.

Incontinence of Urine

In true incontinence of urine, due to a vesicovaginal or ureterovaginal fistula, the urine is discharged involuntarily and continuously so that the patient is constantly wet, and the bladder is always empty without residual urine in case of a vesicovaginal fistula and only contains half the expected normal in case of a ureterovaginal fistula. True or complete incontinence of urine is present besides urinary fistulae, in malformations such as ectopia vesicae, ectopic ureter opening into the vagina and in some diseases of the spinal cord.

False or partial incontinence is much more common. It is exemplified by the nocturnal enuresis in young girls when the urine is voided during sleep and when local reflex caused by threadworms may be found. One of the most common types of partial incontinence is the stress incontinence with prolapse of the anterior vaginal wall, when the patient voids very small quantities of urine involuntarily while sneezing, coughing or laughing. The condition also develops during pregnancy and immediately after delivery during the early weeks of the puerperium although majority of cases are seen at a later date.

An important condition that is readily confused with stress incontinence is urge incontinence. In this condition, the patient must pass urine at a moment's notice and,

unless she is quick about it, she is unable to control her bladder which empties some of its contents before she can reach the lavatory. As a point of differential diagnosis from stress incontinence, the amount of urine lost in urge incontinence is always considerable and sometimes the bladder is completely emptied involuntarily. This catastrophe is preceded by an extreme desire to pass urine. In stress incontinence, the amount of urine lost is minimal and measurable in a few millilitres, and there is no previous desire to pass urine. Urge incontinence is more common than true stress incontinence. The condition is essentially due to detrusor instability, which overcomes the sphincter which is normal. Cystoscopy is normal apart from a decreased bladder capacity. The condition is largely functional, but there may be an organic base. For example, urge incontinence is often associated with true cystitis or urinary infection.

Cystitis

The female urethra always contains microorganisms such as coliform bacilli, streptococci, staphylococci and Döderlein's bacilli, which should be regarded its normal inhabitants. These microorganisms neither cause urethritis unless the urethral tissues are damaged nor spread upwards to the bladder unless they are transported by catheterization. The catheter is undoubtedly the most common cause of lower urinary tract infection (UTI). However gentle and meticulously aseptic the technique, no matter of what material the catheter is constructed, once it has been passed there is a danger of infection.

As the catheter is almost an integral part of all deliveries and of all gynaecological operations, the incidence of cystitis must be accepted at a figure in the region of 80%, understandably highest in those patients requiring frequent catheterization or an indwelling catheter. The logical answer is to abolish the use of catheters as a routine preoperative measure in minor pelvic surgery and only to use them when strictly indicated, in which case a urinary antiseptic is a prudent prophylactic precaution.

Another method of infection of the bladder is by a descending infection from the kidney, such as may occur with renal tuberculosis and chronic pyelonephritis. Organisms may also reach the bladder from adjacent structures such as an inflamed cervix and parametritic infections. The bladder may perhaps be infected by way of the bloodstream, and in other cases by lymphatic spread from the genitalia or the bowel. The organisms found in urine in cystitis are *E. coli,* streptococci, staphylococci, *Bacillus proteus,* the tubercle bacilli and occasionally other organisms, such as *Pseudomonas pyocyanea*. Gonococcal cystitis is relatively rare and almost invariably follows instrumentation. The organism which is found most frequently is *E. coli*. This organism is now supposed to attack the bladder secondarily to an original infection by other organisms and subsequently to overgrow and replace the primary infection. On the other hand, it is well established that cystitis due to a primary *E. coli* infection is occasionally encountered. As the result of antibiotic treatment, *P. pyocyanea* sometimes becomes the dominant infecting organism because of its resistance to antibiotics relative to the other infecting organisms.

Symptoms

The symptoms and signs of cystitis are painful and frequent micturition, pain over the bladder, strangury and passage of pus in the urine. As the bladder fills up with urine, its sensitive inflamed mucous membrane causes pain and a desire to micturate. Pain is also experienced at the end of the act of micturition when the adjacent inflamed surfaces of the bladder come into contact. In urethritis, pain is felt after the urine has been voided. Frequency of micturition may be extreme, the patient having to pass urine every 15 min. The symptoms of acute cystitis are severe, and patients are deprived of sleep and soon become exhausted. The temperature is raised, but it soon falls if proper treatment is employed. A persistent high temperature is usually due to infection ascending to the kidney, causing pyelonephritis when constitutional symptoms are more marked and rigours may occur. With pyelonephritis, the kidney is always tender to palpation in the costovertebral angle, and the patient will complain of pain localized to the loin which radiates down the ureter into the lower quadrant of the abdomen. In chronic cystitis, pain and strangury are less prominent symptoms, but frequency of micturition and pyuria are always present. Chronic cystitis may persist for months or even years without causing symptoms and signs other than frequency of micturition and pyuria.

Diagnosis

The diagnosis of acute cystitis is made from the characteristic symptoms and by an examination of the urine. Difficulty may be experienced in distinguishing between acute urethritis and acute cystitis. In acute urethritis, pain is experienced during the act of micturition. There is no abdominal pain or tenderness, and frequency is not extreme. In both conditions, the urine contains pus and organisms. In acute urethritis, harm may be done by catheterization or cystoscopy, since the instrumentation may carry infection to the bladder. Similarly, the inflamed mucous membrane is readily damaged and bleeds easily. Urethritis can be diagnosed by massaging the urethra against the back of the symphysis pubis, when pus will be expressed from the external meatus. Another simple method of distinguishing between acute urethritis and cystitis is the three-glass test, when in urethritis the third specimen will be clear of pus, but more contaminated with pus in cystitis.

Treatment

Cystitis must be treated by the administration of large quantities of fluids by mouth, at least 2.5 L every 24 h. Plain water, alkaline drinks, milk and weak tea should be given. Alcohol in any form is contraindicated, as it aggravates the symptoms. In the acute phase, the patient must stay in bed and some relief may be obtained by the application of a hot water bottle over the bladder region. The pain is best treated with spasmolytics such as codeine and belladonna. Large quantities of citrates should be given by

mouth, as much as 3 g of potassium citrate being given three to four times a day.

The organisms which have been cultured are as a routine tested for sensitivity against the various antibiotics, and the bacteriological report will indicate which drug should be used for a given patient. Since most lower UTIs are due to *E. coli,* which is nearly always sensitive to nitrofurantoin, this drug is particularly useful as a prophylactic and as specific therapy for the established infection. Drugs such as norfloxacin/ciprofloxacin/pefloxacin/and sparfloxacin in appropriate doses have been found to be very effective, and are amongst the first-line drugs selected by clinicians in present-day practice.

Chronic Cystitis

Chronic cystitis caused by descending infection from the kidney is a urological problem and such patients should be handed over to the urologist.

Pyelonephritis (Pyelitis)

Pyelonephritis is a complication of the urinary infections. The urinary infections of postoperative and of puerperal cystitis often spread to the kidneys to cause pyelonephritis. Pyelonephritis of pregnancy is not uncommon and the infective organism is usually *E. coli*. Ascending pyelonephritis is a common complication of late carcinoma of the cervix and vagina, either as a result of the growth ulcerating into the bladder or through involvement of the ureter in the growth, and a large number of patients, at least 60%, with carcinoma of the cervix die from uraemia induced by pyelonephritis. Recurrent attacks of pyelonephritis also occur in patients who have had ureterocolic transplantation, either for the relief of incurable fistula or because the bladder has been removed in exenteration operation for advanced pelvic cancer. The signs and symptoms of pyelonephritis are pain and tenderness in the loins, with high temperature and frequent rigours, headache, vomiting and furring of the tongue. Frequency of micturition is present due to the associated cystitis. In acute pyelonephritis, the affected kidney region is exquisitely tender, while in chronic pyelonephritis, tenderness and rigidity along the course of the ureter can often be detected on abdominal examination. The urine is turbid and contains pus cells and organisms. In pyelonephritis, toxaemia is well marked, the blood urea is raised and casts are found in the urine.

Treatment

Treatment consists in keeping the patient in bed lying on the unaffected side to prevent pressure upon the tender renal angle. Copious fluids must be administered. The same drugs are given as in cystitis.

Pyelonephritis which does not respond to the usual methods of treatment or which recurs after initial successful treatment becomes a urological problem and the patient should be transferred to the care of an urologist.

Diseases of the Female Urethra

Urethritis

Aetiology

Inflammatory disorders of the urethra are fairly common. Sexually transmitted diseases caused by the gonococcus, *Chlamydia trachomatis, Trichomonas, Candida* and certain viruses may lead to this disorder.

The lower urethra is usually affected, as vulvovaginitis is a common accompaniment. Vigorous and frequent sexual intercourse often aggravates the problem. Honeymoon cystitis is a distinct clinical entity following coital injury to the urethra and the bladder base.

Menopausal women suffer from thinning of the vaginal epithelium and urethral lining due to oestrogen deficiency; these women are susceptible to trauma and infection which may lead to urethritis.

Use of chemicals, deodorants, douches, vaginal contraceptives and tampons may lead to allergic or chemical reactions causing vulvovaginitis and urethritis.

Symptoms

The common symptoms of urethritis are frequency of micturition and dysuria. The patient complains of pain during micturition and not at the end of micturition as seen in cystitis. Examination may reveal a red urethral orifice, and milking of the urethra may yield a purulent discharge. Culture and microscopy of the urethral discharge help to establish the diagnosis.

Treatment

Treatment consists of administration of appropriate antimicrobials. Antibiotics such as ampicillin, tetracycline or cephalosporins may be used as indicated by culture. The patient should be encouraged to maintain an adequate fluid intake, and menopausal women should be given supplementary vaginal oestrogen cream to improve the atrophic state of the vagina and the urethra. The patient should be advised to avoid all irritants such as deodorants, vaginal contraceptives and douches.

Urethral Caruncle

Urethral caruncle is not an uncommon condition. It is frequently encountered in postmenopausal women. The atrophic vulva and vagina and introitus leave the urethral meatus exposed to infection. The posterior urethral mucosa becomes swollen, congested and pouts out like a cherry from the posterior wall of the external meatus (Figures 17.2 and 17.3).

The patient may present with postcoital bleeding, dyspareunia, pain and dysuria. In all women complaining of postmenopausal bleeding, it is important to exclude genital tract malignancy by cytology, endometrial histology and sonographic evaluation of the pelvis.

The caruncle is treated by diathermy excision. Simultaneous administration of oestrogen helps in recovery, and

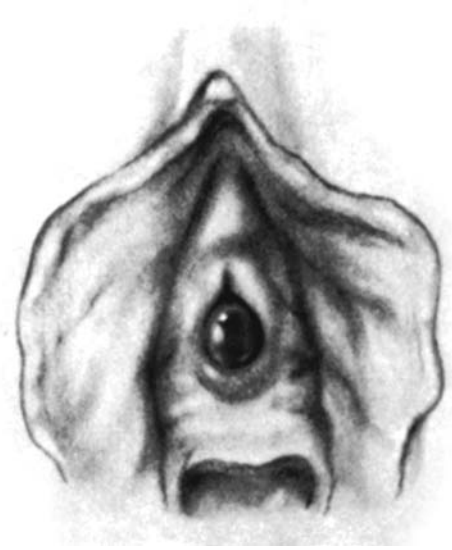

Figure 17.2 A urethral caruncle.

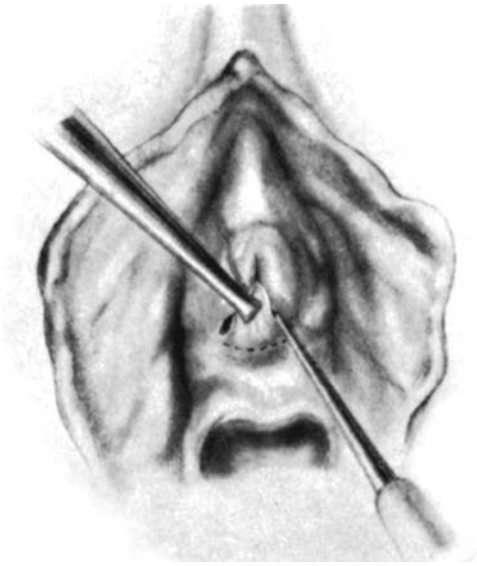

Figure 17.3 Operation for removal of urethral caruncle by diathermy excision.

this is prescribed on a long-term basis; intermittent progestogens must be also used, to avoid uterine and breast cancer developing as a result of long-term use of unopposed oestrogen. Local oestrogen cream may be preferred to oral hormone.

Urethral Prolapse

This uncommon condition is seen in the very young and the old. Chronic straining and oestrogen deficiency contribute to its occurrence. Surgical excision of the excess of mucosa, followed by suturing of the urethral mucosa to the circumference of the urethral meatus by interrupted sutures corrects the condition. Spontaneous prolapse of urethral mucosa is rarely reported in children.

Urethral Diverticulum

The woman complains of nonspecific symptoms such as urinary frequency, dysuria, dyspareunia and dribbling, urgency or incontinence of urine. A swelling may be noted in the urethral region. The differential diagnosis includes urethrocele, Gartner's duct cyst or a Skene's gland abscess. Treatment comprises antibiotic therapy followed by surgical excision or marsupialization. Urethral stricture and fistula are the likely postoperative complications.

Urethral Stenosis

The common sites of narrowing are the region of the bladder neck and the meatus. It may be congenital in origin or the result of infection, injury, neoplasm or a diverticulum. The patient complains of a poor stream, straining at micturition and repeated UTI. Urethroscopy may reveal a narrowing of the passage and trabeculation of the walls of the bladder. Treatment consists of control of infection and surgical removal of any existing cyst or tumour. Intermittent urethral dilatation, urethrotomy and reconstructive urethroplasty may be needed in select cases.

Urinary Fistulae

In women, most urinary fistulae result either from injury to the urinary tract during gynaecologic operations or from obstetric damage. In India, obstetric fistulae are more common than the gynaecological or radiological fistulae, because of difficult home deliveries conducted by dais when obstructed labour is not recognized. The most common form of fistula is vesicovaginal, in which there is a communication between the bladder and the upper third of the anterior vaginal wall. Next in order of frequency is ureterovaginal fistula, which is usually caused by injury to the ureter during gynaecological operations. Urinary fistulae can be classified as follows:

Vesical fistulae: Vesicovaginal, vesicocervical, vesicouterine, vesicoabdominal and vesicointestinal
Ureteric fistulae: Ureterovaginal and ureteroabdominal

For further details, refer to Chapter 18.

Ureteric Obstruction

Ureteric compression and obstruction occur from extraneous sources. Many conditions in the female pelvis are associated with the threat of ureteric obstruction. These are discussed below.

Uterine Prolapse

In complete procidentia of the uterus, the main supporting structures, namely the Mackenrodt's ligaments, are greatly

elongated, and in their descent with the uterus, a loop of the ureter is drawn down on either side to lie outside the vaginal orifice. This process causes an acute angulation of the ureters. Hence, it is not surprising that it gives rise to hydroureter and hydronephrosis. The uterine arteries may also compress the ureter as they become elongated by the descent of the uterus. Many of these patients have a chronic urinary infection and this, associated with ureteric obstruction, may seriously impair the renal functions and render them poor surgical risks for any repair operation.

Pelvic Tumours

Pelvic tumours may cause compression and obstruction to the ureter, and this is especially true of the myoma which lies firmly embedded in the pelvis. Ovarian cysts, benign and malignant, pelvic endometriosis and inflammatory disease and broad ligament tumours produce the same picture. Such patients should have thorough urological investigations before operation since roughly half of them would show some ureteric obstruction, and this may well account for postoperative urinary infection. Removal of these tumours will restore the urinary tract to normal in 70% of cases. The worst offenders are those in whom the obstruction is due to pelvic inflammatory disease, and advanced cancer of the cervix in which permanent stricture formation may have occurred in a segment of the ureter.

Carcinoma of the Cervix

Although the ureter is guarded by a tough sheath in the ureteric canal against actual malignant infiltration, its situation in this tunnel is a grave danger since it is particularly subject to compression. It is an absolute dictum that no case of cancer of the cervix should ever be treated by surgery or radiation until a preliminary urographic study has been made. Those patients who show ureteric obstruction have a definitely poorer prognosis and it must be remembered that in 70% cases, patients of the carcinoma of the cervix die not of their primary disease but of bilateral renal obstruction. In these patients, the surgeon's knife has been regarded in the past as a great menace to the ureter, but effective radiation of an infiltrated parametrium is an equal if not greater menace, since the resulting fibrosis eventually strangles the ureter. This postradiation process is not immediate or spectacular but may develop over months or even years, and the patient may well be cured of the local disease to succumb at a later date to the urinary obstruction (Chapter 38, Cervical Intraepithelial Neoplasia, Carcinoma of Cervix).

Obstruction at the Site of Fistula

Many ureteric fistulae heal spontaneously and, while this is a gratifying process to the surgeon and the patient, the net result of such a cicatrix may be disastrous to the affected kidney. By the same token, ureteroureteric anastomosis of a ureter sectioned too high to be implanted into the bladder is unfortunately too often followed by stricture formation at the site of the junction. Such a patient should be carefully followed up by a competent urologist, and frequent pyelograms should control the conduct of the case. A periodic dilatation may well save the kidney, but many of these patients end up with a nephrectomy.

Pregnancy and Urinary Problems

All gynaecologists are conversant with the fact that pregnancy has a profound effect on the ureter and kidney. This is due to the specific action of progesterone on all smooth muscles throughout the body. The gastrointestinal tract and gall bladder, the musculature of the veins and the ligaments of the spine and the pelvis are all affected. The changes are most remarkable, however, in the urinary tract and appear by the fourth month to reach a maximum at term. After pregnancy, this process of hydroureter slowly involutes and should return to normal by the end of the puerperium, certainly by the third month. If, however, a severe infection results in pyelonephritis of pregnancy, the process of involution may never be completed and permanent damage may result in chronic pyelonephritis. The cause of this ureteric dilatation is not the compression from the growing uterus since it occurs before such obstruction can operate. It is more frequently noticed on the right than the left and is probably due to some distortion of the ureteric canal by dextrorotation and dextroposition of the pregnant uterus, which is so frequent a finding at caesarean section.

Key Points

- Urinary symptoms are commonly encountered in gynaecological practice. The gynaecological diseases, pelvic operations and difficult vaginal deliveries contribute towards most of the urinary complaints.
- Since neurological disorder may also be the underlying cause, the gynaecologist must elicit a gynaecological cause before undertaking surgery.
- Apart from postoperative and puerperal retention, obstructive conditions are haematocolpos, haematocele, retroverted gravid uterus, fibroids, and an ovarian tumour and bladder neck obstruction in old women.
- Urethral syndrome is noticed in postmenopausal women with oestrogen deficiency and is effectively treated with short-term oestrogen vaginal cream.
- Urinary fistula in developing countries is mostly obstetric in origin. In developed countries, urinary fistula follows trauma to the bladder during difficult surgery.

Self-Assessment

1. How would you investigate and treat acute urinary retention in a woman?

2. Describe the urethral syndrome. How would you treat it?
3. Describe the management of dysuria.
4. Discuss the management of urinary incontinence in middle-aged women.
5. What are the clinical manifestations of infection of the female urinary system. Discuss its management.

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Chapter

18

Genital Fistulae and Urinary Incontinence

CHAPTER OUTLINE

The urinary system and the female genital systems are closely related embryologically, anatomically and functionally.

It is therefore not surprising that urinary fistulae result from obstetric and gynaecological operations and gynaecological diseases.

Genital Fistulae

Genital fistulae are abnormal epithelialized communication tracts between the genital tract and the urinary or alimentary tract or both.

Injuries to the urethra, bladder, ureter or the rectum and anal canal can occur during childbirth or during pelvic surgery. Genital tract malignancy in its advanced form is known to involve these pelvic organs and cause fistulae. Lastly, radiation therapy can cause tissue necrosis and fistula formation.

In developing countries, the vast majority of genital fistulae continue to be obstetric in origin. Even in the present times in rural India, it is not uncommon to encounter obstetric emergency cases of prolonged, neglected and obstructed labour. These potentially infected and dehydrated patients may often narrate the history of attempted manipulation or vaginal instrumentation which has failed to accomplish childbirth or resulted in a difficult traumatic delivery with poor perinatal outcome. In such women, the bladder and vaginal walls which have undergone prolonged ischaemic changes, ultimately end up with tissue necrosis and fistula formation.

In the developed countries of the world, operative trauma during pelvic surgery constitutes the most common cause of genital fistulae.

Aetiology

The common causes of genital fistulae have been detailed below.

Obstetric Injury

Prolonged obstructed labour, difficult instrumental or manipulative deliveries such as forceps delivery or forceps rotation may cause injury to the bladder neck and urethra. The surgeon must take care to avoid injury to the urinary bladder during caesarean section. The bladder is most vulnerable (particularly if it is not empty) during its mobilization from the front of the lower segment prior to placing the transverse incision on the stretched lower segment to deliver the fetal head. Bladder injury may follow extension of the lower segment incision anteriorly to the bladder during delivery of a deeply impacted fetal head in the pelvis. The bladder or ureter may be inadvertently included in the suture line while suturing the lower uterine segment. Repeat caesarean section is at a higher risk for bladder injury. The perforators and spicules of bone during craniotomy operation and symphysiotomy operation also cause injury. Rupture of uterus is another cause of urinary fistula, if the bladder is also torn.

Operation Injury

The bladder and the pelvic ureter are vulnerable to injury during gynaecological surgery. These may result from poor exposure of the organs, faulty technique or due to distorted anatomy caused by tumour or fibrosis, or previous surgery.

Bladder injury may ensue during its dissection from the cervix in abdominal or vaginal hysterectomy and during caesarean section when the bladder needs to be dissected from the lower uterine segment. The injury is most likely to occur in a woman with previous caesarean section. Other causes are pelvic adhesions, cervical fibroid and sling operations for stress incontinence.

Fifty per cent ureteric injuries occur during gynaecological surgery. Ureteric injuries can be serious and not recognized at operation. Only one-third are detected immediately and repaired. Others are discovered only in the postoperative period.

The causes of uterine fistula are:

- Congenital fistula—rare—occurs in double ureters.
- Direct injury such as cutting (partial or complete), clamping, ligaturing or including it in a suture to obtain haemostasis.
- The ureter receives rich vascular supply on the lateral aspect of the ureter below the pelvic brim and the dissection on the lateral aspect can cause avascularity. Devascularization follows denuding of the ureter and stripping it off its blood supply during cancer surgery.
- Thermal injury (cautery or laser during laparoscopic surgery).

Sites of injury:

- At the infundibulopelvic ligament.
- Wertheim hysterectomy while dissecting the ureter in the parametrial tissue.
- Near the cervix and vaginal vault as the ureter is close to it and the uterine vessel also is proximal to it during hysterectomy. Clamping the uterine vessel may include the ureter anteriorly.
- Near the bladder during bladder dissection.
- Near the brim, during ligation of the internal iliac artery.
- Near the uterosacral ligament. During laparoscopic uterosacral nerve ablation, and vault closure during hysterectomy and in endometriosis.
- Vaginal hysterectomy in procidentia.

The risk of injury is high when the surgery is undertaken for pelvic endometriosis, pelvic inflammatory disease, cervical and broad ligament, Wertheim hysterectomy when the ureter anatomy is distorted. The left ureter is more close to the cervix and is liable to injury, but overall it depends upon the position of the ureter.

Other nonsurgical injuries to the bladder occur due to impalement injuries, criminal abortion, bladder stone, tuberculosis of the bladder, cancer of the bladder and cervix, and radiotherapy for cancer. Rare infections are tuberculosis lymphogranuloma venereum, schistosomiasis and actinomycosis.

Radiotherapy

The bladder cannot tolerate the same dose of irradiation as the cervix. Hence, following irradiation therapy, genital fistulae may follow in course of time if the bladder is not protected against high dose.

Laparoscopic Injuries

Direct trocar injuries to the urinary bladder have been reported, so also injury to the ureter, bowel, sigmoid colon and rectum. Their identification in time and prompt repair prevent long-term sequelae.

Anatomic Classification of Urinary Fistulae

It is important to group bladder fistulae according to their anatomic location. This has an important bearing on the selection of approach for surgical repair, the technique of repair, complications to be anticipated and prognosis.

Urinary fistulae are classified (Figure 18.1) as:

- Urethrovaginal fistula.
- Vesical fistula at various levels [vesicovaginal fistula (VVF)].
- Ureterovaginal and ureteroabdominal fistula.
- Vesicouterine fistula.

Clinical Features (Table 18.1)

The fistulous tract is lined by epithelium, fibrous and granulation tissue, or malignant tissue depending upon the cause.

Vesicovaginal Fistula (VVF)

In India, 80–90% of the bladder fistulae are a result of the obstetrical causes. The patient presents with the complaint

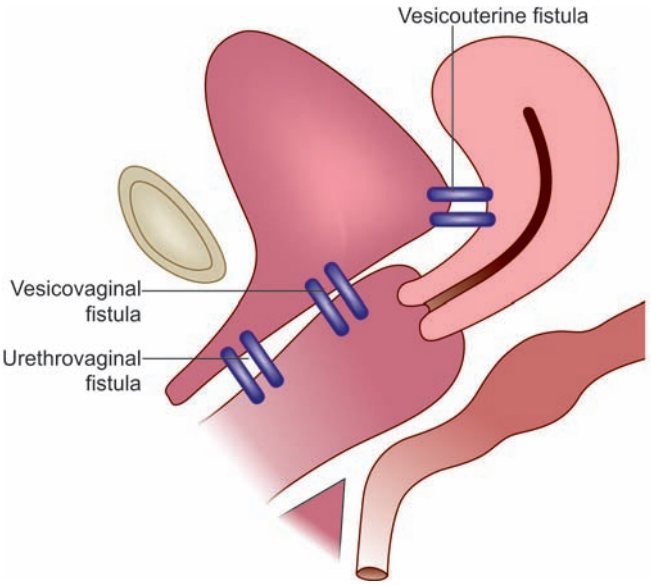

Figure 18.1 Diagrammatic representations of urethrovaginal, vesicovaginal and vesicouterine fistulae.

TABLE 18.1 Clinical features of fistulas

	Bladder Fistula	Ureteric Fistula
Aetiology	Mostly obstetric causes Prolonged labour—operative—vaginal caesarean section. Sometimes gynaecological causes such as sling operations for stress incontinence, hysterectomy	During caesarean section—mostly gynaecological surgeries
Clinical	Continuous dribbling of urine—no micturition	Continuous dribbling of urine but can also micturate
Methylene swab test	Swab stains with methylene blue	Swab stains with urine—but not with methylene blue
IVP	Normal	Hydronephrosis on the affected side

of constant dribbling of urine (true incontinence). The constant wetness in the genital areas leads to excoriation of the vagina, vulva, perineum and thigh. These women are depressed and often treated as social outcasts. Some develop amenorrhoea and bladder stones. The most common type in our country is VVF (Figures 18.2 and 18.3) at the bladder neck region following difficult childbirth. The woman with an obstetric fistula is invariably short statured with a contracted pelvis and suffers secondary amenorrhoea. Whenever a fistula is suspected, it is a good practice to examine the patient in the knee–chest position under a good light. A speculum introduced to retract the posterior vaginal wall exposes the fistula and urine collection in the vagina, and enables clinical assessment of its size, location and number; a bimanual examination provides information about its fixity and extent of scarring of the surrounding tissue. A positive methylene blue test confirms the diagnosis and helps the surgeon to plan a repair operation (Figure 18.4).

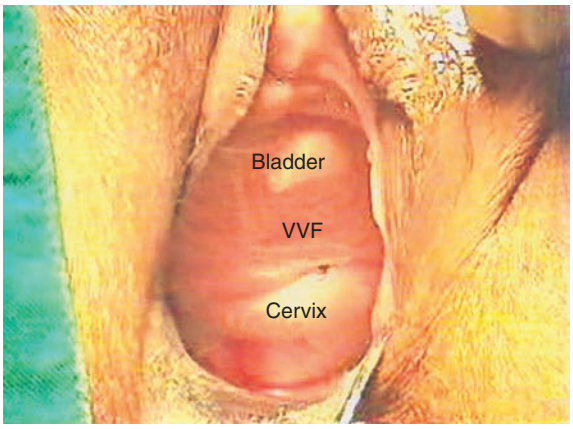

Figure 18.2 Vesicovaginal fistula.

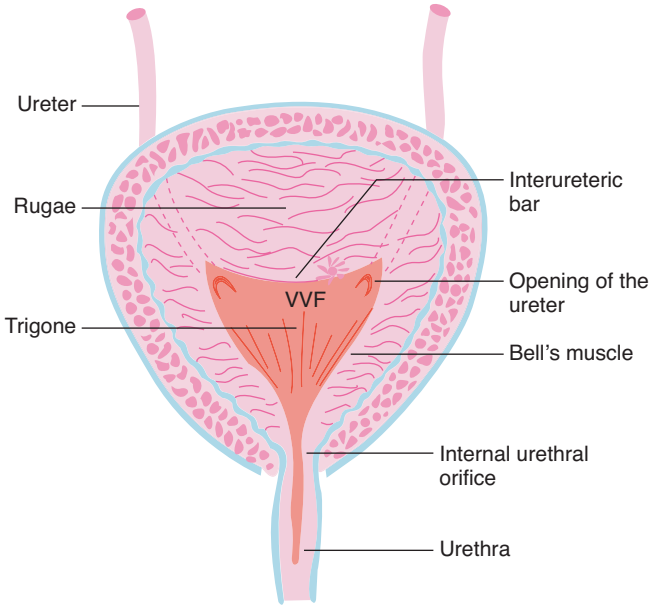

Figure 18.3 Transvesical view of vesicovaginal fistula.

Ureteric Fistulae (Figures 18.5–18.8)

Ureteric fistulae result from direct injury or devascularization of the pelvic ureter during gynaecological surgery, during Wertheim's operation for carcinoma of the cervix.

In case of transection of the ureter, the woman develops urinary leak into the peritoneal cavity immediately. Because of failure to recognize and repair the trauma forthwith, these women have a stormy postoperative course and present with nausea and vomiting, abdominal distension and ileus, associated with rise of temperature and leucocytosis, and loin pain.

In case of obstruction as a result of ligating one or both ureters, the clinical features differ. If both ureters have been tied (5–10%), there is no passage of urine, the patient complains of pain in the flanks, and palpation in the renal angles reveals tender enlarged kidneys.

The woman develops fever, haematuria, loin tenderness and oliguria.

In case of necrosis of the ureter following denudation, the urinary leak is delayed. It generally starts 2 weeks or later after surgery, when the woman starts dribbling from the vagina apart from passing urine from the urethra. Unilateral injury causes oliguria, fever and pain in the renal angle on that side, apart from dribbling.

Late complications—stricture with hydronephrosis, infection.

Investigations

Urinary Fistulae

Investigations for urinary fistulae include the following:

Besides the usual tests of urine examination, complete blood count, renal function tests and serum electrolytes, the following special tests are useful in planning corrective procedures:

- Urine culture is mandatory before surgery, and infection should be treated. The urine is collected by catheterization in case of VVF.
- Sonography of the kidney, ureter and bladder. A cystic mass (urinoma) due to collection of urine can also be identified.
- Descending intravenous pyelography (IVP). IVP reveals hydronephrosis, hydro-ureter and the site of ureteric obstruction.
- Cystoscopy with indigo carmine excretion test (5 mL intravenously) enables the visualization of the dye from each ureteric orifice individually (Figure 18.7A and B) and identifies which ureter is damaged.
- Ureteric catheterization will detect the side and site of ureter damage.
- In case the fistula is small and not clearly visible, methylene blue test is applied.
- *Methylene blue—2-swab test.* A catheter is introduced into the bladder through the urethra. The vaginal cavity is packed with three sterile swabs; 50–100 mL of dilute methylene blue dye is injected into the bladder through the catheter. If there is a VVF present, the methylene blue dye stains the uppermost swab. If the lowermost

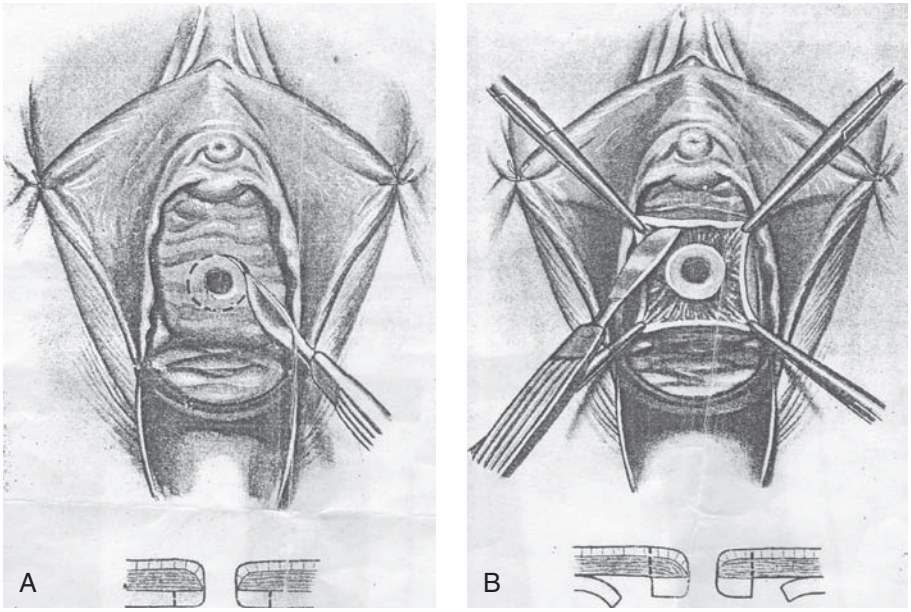

Figure 18.4 **(A)** Repair of a fistula. A circular incision is made through the vagina around the fistula. **(B)** Repair of a vesicovaginal fistula. The vaginal wall is now dissected away from the bladder with utmost care to obtain a maximum degree of mobilization of the bladder.

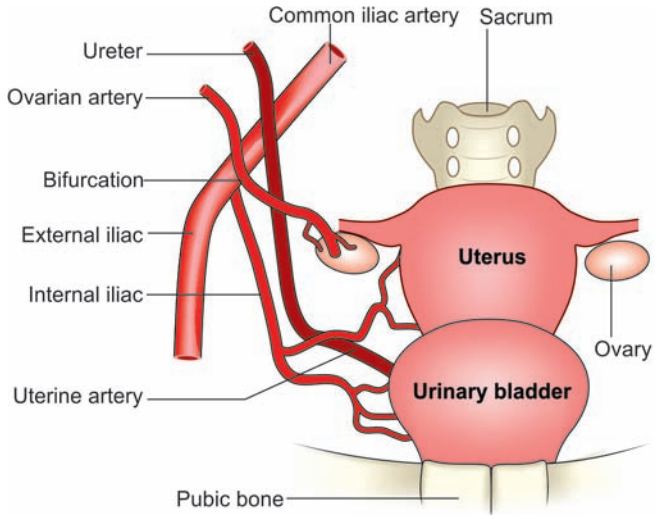

Figure 18.5 Relations of the pelvic ureter. It crosses the bifurcation of common iliac vessels, lies close to ovarian vessels and then crosses the uterine artery to enter the ureteric tunnel.

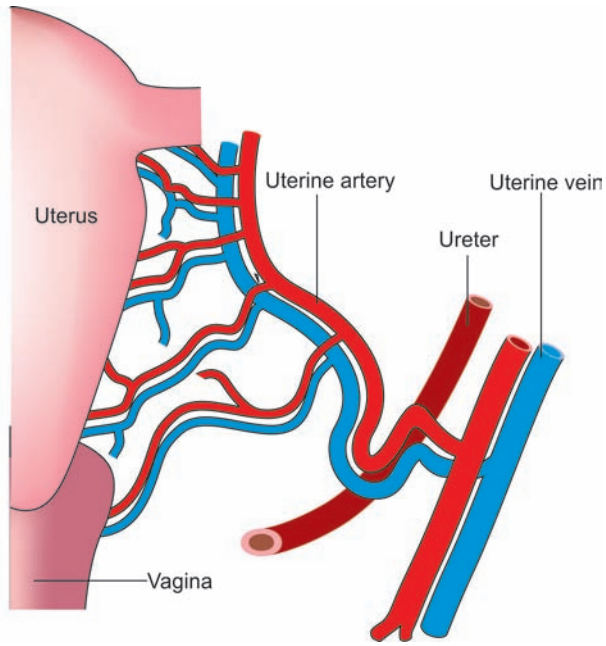

Figure 18.6 Uterine artery and ureter. The ureter crosses under the uterine artery.

swab gets stained, the leak is from the urethra. If the swabs do not take up the stain, but get wet with urine, the leak is from the ureter. Oral pyridium (100 mg) stains urine orange and is easily recognized in the vagina; it does not however identify the site of fistula.

- Metal catheter not only identifies a fistula, but confirms the patency of the urethra. Magnetic resonance imaging (MRI) ultrasound may be rarely needed.
- Ultrasound-hydronephrosis.

Management

Vesicovaginal Fistula

In case bladder damage is suspected in a difficult childbirth, an indwelling catheter and prolonged draining of the bladder, antibiotics and supportive therapy is recommended. Spontaneous healing of small fistulae is known to occur. However, in case of established fistula, it is better to wait for about 3 months for all tissue inflammation to subside, tissue vascularization to improve and local infection to be cleared before surgery is undertaken.

In case of a fistula following cancer, a biopsy should be taken from the edge of the fistula and presence of cancer ruled out prior to surgery.

- Most vesicovaginal fistulae should be repaired vaginally. The Latzko procedure of denuding the vaginal epithelium all around the fistulous edge, freshening the edge

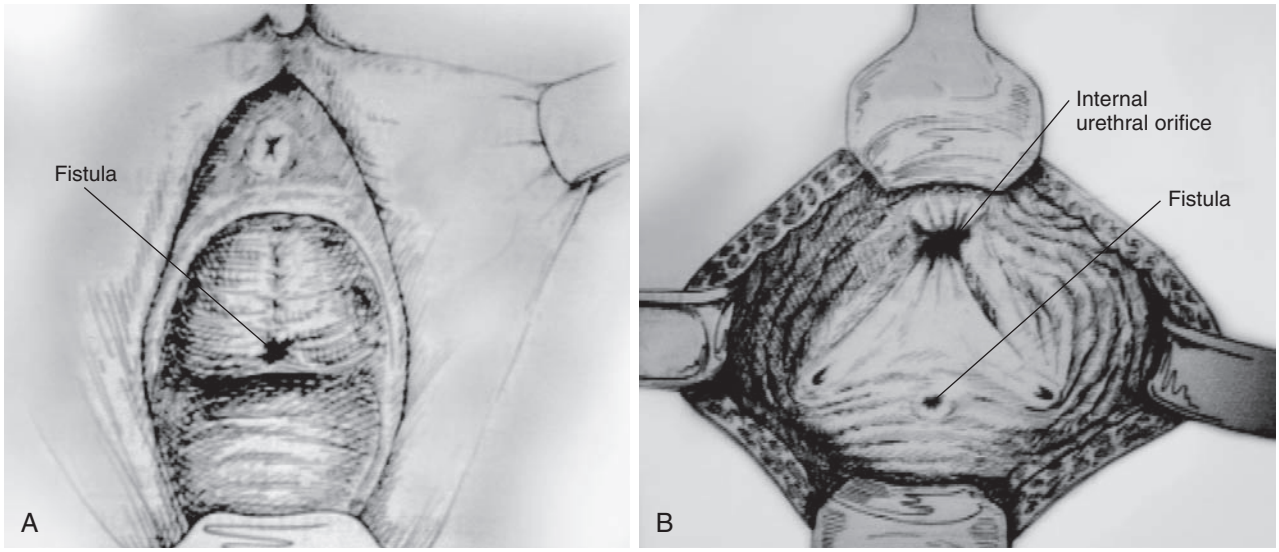

Figure 18.7 **(A)** Small midline vesicovaginal fistula. **(B)** Cystoscopic view showing relation of vesicovaginal fistula to the trigone.

and approximating the wide raw surfaces with rows of absorbable sutures is often successful. This technique is suited to posthysterectomy fistula that is caused by cancer cervix. It however leads to narrowing of the vagina or atresia.

- The Chassar Moir technique of widely separating the vagina and bladder all around by the flap-splitting method and suturing the bladder and vagina separately in two layers is the most practised. Absence of tension on the suture line promotes healing. It is preferable to see that the suture lines on the bladder and vagina do not overlap. Haemostasis should be meticulous to ensure success. In cases of extensive fibrosis, omental grafts, interpositioning of Martius' graft or gracilis muscle graft between the bladder and vaginal walls improves the blood supply at the site of repair and promotes healing. Flap-splitting surgery has the advantage of tension-free sutures and avoidance of superior position of bladder over the vaginal suture.
- If one attempt fails to heal the fistula, a second vaginal repair can be undertaken after a period of 3 months. In case of a large fistula close to or involving the ureteric orifice, vaginal repair may be difficult, and also in cases of failure of previous surgical attempts to repair the fistula by the vaginal route, a transvesical or transabdominal approach is recommended to achieve successful closure.
- In case of extensive loss of bladder tissue, previous repetitive failures to close the fistula or radiation fistula which fails to heal, the surgeon must consider procedures for urinary diversion like implantation of the ureters into the sigmoid colon, creating an ileal loop bladder into which the ureters are implanted, or a rectal bladder—an operation in which the terminal sigmoid colon is brought out as a colostomy. The distal end of the rectosigmoid is sutured and closed and the ureters implanted into the terminal rectal pouch, which acts as a urinary receptacle. The dangers of ureteric implantation into the large bowel include a higher incidence of ascending infection to the kidneys and the risk of electrolyte imbalance leading to hyperchloraemic acidosis as well as stricture at the site of implantation.
- If the fistula repair fails, one should wait for at least 3 months before attempting a second repair. The fistula located at the vaginal vault following hysterectomy is the most difficult to repair.
- Fistula caused by cancer cervix may require anterior exenteration operation.

Postoperative management includes:

- Continuous bladder drainage for 14 days. Some prefer suprapubic drainage.
- Antibiotics—urine infection should be treated adequately. After removal of catheter, the woman is advised to pass urine frequently as the bladder capacity may have been reduced.

No vaginal or speculum examination or intercourse is allowed for 3 months after the surgery. Caesarean section is indicated following successful fistula repair. Stress incontinence following VVF repair is due to rigid urethra, loss of vesicourethral angle, small bladder and short urethra.

Ureteric Fistulae (Figure 18.3)

Most ureteric fistulas are traumatic, rarely ectopic ureter causes dribbling of urine apart from passing urine from other kidney.

Only one-third cases of ureteric trauma are recognized intraoperatively. In case of total obstruction following bilateral ureteric ligation anuria will ensue, sonography will reveal bilateral hydronephrosis and dilated ureters up to the site of the block. The renal function tests reveal rise in creatinine level. If the obstruction is detected early and the offending ligatures removed and the ureters stented, recovery is possible. However, if the ureters are damaged, these

should be implanted into the bladder. In case the diagnosis is delayed, as happens in cases of unilateral ureteric block, the symptoms of loin pain and fever gradually subside and the kidney on the affected site undergoes atrophy.

In case of ureteric transection, partial or complete, a pyelography fails to show part or whole of the ureter on the transected site and there may be pooling of the urine in the peritoneal cavity. The immediate treatment is percutaneous nephrostomy and retrograde dye injection under fluoroscopy to help identify the site of transection. If the injury is partial transection, a cystoscopic catheterization and stenting of the ureter at the site of injury may be attempted. In case of complete transection, urinary diversion by nephrostomy is advisable to tide over the crisis, followed later with repair surgery. In case the transection is recognized during surgery itself, the surgeon must either undertake anastomosis at the site of injury or implant the cut end of the ureter into the bladder or perform a Boari-flap operation of ureteroneocystostomy. Ureteroureteric anastomosis is also sometimes possible, but the risk of stricture should be remembered. Fixing the dome of the bladder to the psoas muscle relieves tension on the implanted ureter. Ureteric stricture and infection are the sequels of ureteric implantation and need to be observed.

When ureteric damage goes unnoticed, following hectic postoperative period, fever settles down, but patient starts dribbling urine from the vagina around the 10th–12th day. Urine collects in the vagina, but the woman also micturates, and oliguria is noticed. It is difficult to visualize the fistulous opening. Methylene blue test recognizes the ureteric fistula. Cystoscopy, retrograde catheterization show absence of urine coming from the affected side and site of blockage, respectively. IVP will be required to detect hydroureter/hydronephrosis. Urine culture and kidney function tests are also required.

One should not wait for the kidney damage to occur and perform laparotomy; it should be performed at the earliest, once the inflammation and infection subside.

The surgery comprises:

- Uretero-ureteral anastomosis with the stent inserted.
- Implantation of the ureter into the bladder.
- Psoas muscle stitch to the dome of the bladder to avoid stretching and tension on the ureter.
- Boari's operation.
- Ileal bladder.

Prophylaxis. In a difficult surgery, it is prudent to trace the ureter from the pelvic brim downwards before clamping any vessel or cutting the tissues. The ureter is identified by its position (may be distorted or abnormally placed in pelvic diseases), pale glistening appearance and peristaltic movement when stroked.

In a difficult case, some gynaecologists prefer to insert the ureteric stent before starting the surgery, but this does not always prevent ureteric damage if devascularization occurs during its dissection.

Since the blood supply to the pelvic ureter comes from lateral side, the dissection of the ureter should be done on its medial side, and devascularization and ischaemia should be avoided.

Vesicouterine Fistula

Vesicouterine fistula is a rare variety of fistula, usually caused during caesarean section or uterine rupture or placenta accreta. The patient's symptoms are unlike those of lower urinary tract fistula. The patient remains continent, as urine does not dribble into the uterine cavity. The patient however complains of cyclical haematuria, menstrual blood trickling through the fistula into the bladder. The other cause of cyclical haematuria is bladder endometriosis and intrauterine contraceptive device (IUCD) perforation into the bladder. Cystoscopy will reveal the true pathology. Methylene blue injected into the uterine cavity will show a leak into the bladder. Occasional prolonged bladder catheterization may close the fistula. Otherwise the treatment is by abdominal repair. This is known by Youssef's syndrome. Omental or gracilis graft is sometimes required.

Urethrovaginal Fistula

The patient is continent and dry, but dribbles urine only during the act of micturition. A speculum examination will show the fistulous opening clearly. Vaginal repair is often successful, but urethral stricture may follow. A big fistula may need a graft technique. The urethral fistula is encountered following surgery for paravaginal cyst and urethral diverticulum. Penetrating injury following a fall or during criminal abortion can cause urethral fistula. Urethral reconstructive surgery is required.

Stress Urinary Incontinence (Figure 18.6A)

Incontinence of Urine

Incontinence may be stress incontinence, urge incontinence or true incontinence. The common type of stress incontinence is associated with cystocele and genital prolapse when the woman voids a small quantity of urine involuntarily while sneezing, coughing or laughing. The condition also develops during pregnancy and soon after delivery.

Stress incontinence is confused with urge incontinence. In urge incontinence, the woman wants to pass urine at a moment's notice, and unless she is quick about it, she passes urine in large quantity before reaching the lavatory. The amount of urine passed is considerable. In stress incontinence, there is no desire to pass urine, but dribbles a small quantity on stress. Both are bothersome symptoms and affect the quality of life.

Urinary incontinence may indicate a symptom, a sign or a condition. The patient complains of involuntary leakage of urine which she finds socially and hygienically unacceptable. The sign is the objective demonstration of urine loss, and the condition is the underlying pathophysiologic mechanism responsible for the urine leak.

The symptom of involuntary urine loss may be associated with stressful activity like coughing, sneezing, straining or other physical activity (stress incontinence). The

involuntary urine loss may follow a strong desire and need to void (urge incontinence) or there may be continuous urinary leak (true incontinence), as in a fistula.

Mechanism of Female Urinary Incontinence

Ultrasound and MRI have recently improved our knowledge on the anatomy of the lower urinary tract and validated some of the urodynamic investigations of stress incontinence.

Several factors contribute to stress incontinence. In normal conditions, internal urinary sphincter lies above the levator ani muscles. Upper half of the urethra lies above and the lower half below the levator ani muscles (Figure 18.8).

The continence mainly relies on the internal sphincter at the neck of the bladder and is maintained by the urethral closure pressure. The urethral closure pressure is the intraurethral pressure minus the intravesical pressure (closure pressure is the difference between the vesical and urethral pressure). Normal urethral closure pressure is more than 20 cm of water when the upper urethra and bladder neck remain above the levator muscles and the urethrovesical angle is more than 100°. Under this condition, the abdominal pressure is transmitted equally to the bladder and the urethra, maintaining the closure pressure. When due to atony of pelvic floor muscles or damage to the pudendal nerve during vaginal delivery the bladder neck descends below the levator ani muscles and the urethrovesical angle is lost, the abdominal pressure is transmitted only to the bladder, reducing the urethral closure pressure when incontinence occurs. The vascular plexus as well as the longitudinal fibres of the urethra maintain the tone during the filling phase (Figures 18.9–18.11). Extrinsic control of the bladder neck is provided by striated smooth muscles. Internal sphincter consists of two loops of smooth muscle fibres: one loop pulls the sphincter anteriorly and the other loop posteriorly and maintains the urethrovesical angle. The tone of the levator ani muscles, pudendal nerve and pubovesical fascia also contribute to urinary continence. Lateral attachment of the urethra to arcus tendineus and pubococcygeus muscle limits urethral mobility and maintains continence.

Genuine Stress Incontinence

Genuine stress incontinence (GSI) occurs when the bladder pressure exceeds urethral pressure during physical stress in the absence of detrusor contraction. It is defined as a small involuntary leakage of urine with increased abdominal pressure in the absence of detrusor contraction.

Aetiology. It is generally due to anatomical changes in the urinary tract such as hypermobility of urethra (80%), loss of posterior angle or sphincteric dysfunction.

- Age: Older menopausal women with loss of pelvic muscle tone are liable to develop GSI (oestrogen deficiency).
- Multiparous women after repeated childbirth are prone to loss of tone of the pelvic floor muscles.
- Obesity, smoking, prolapse and constipation.
- Pregnancy and puerperium—during pregnancy, stress incontinence is due to the progesterone hormonal effect and the pressure of the gravid uterus on the bladder neck. During puerperium, the stress incontinence is caused by the descent of the bladder neck, the loss of urethrovesical angle due to pudendal nerve denervation, and diminished tone and stretching of levator ani muscles during vaginal delivery.
- Hereditary—loss of collagen tissue.
- Repair of VVF and urethral fibrosis may also cause GSI.

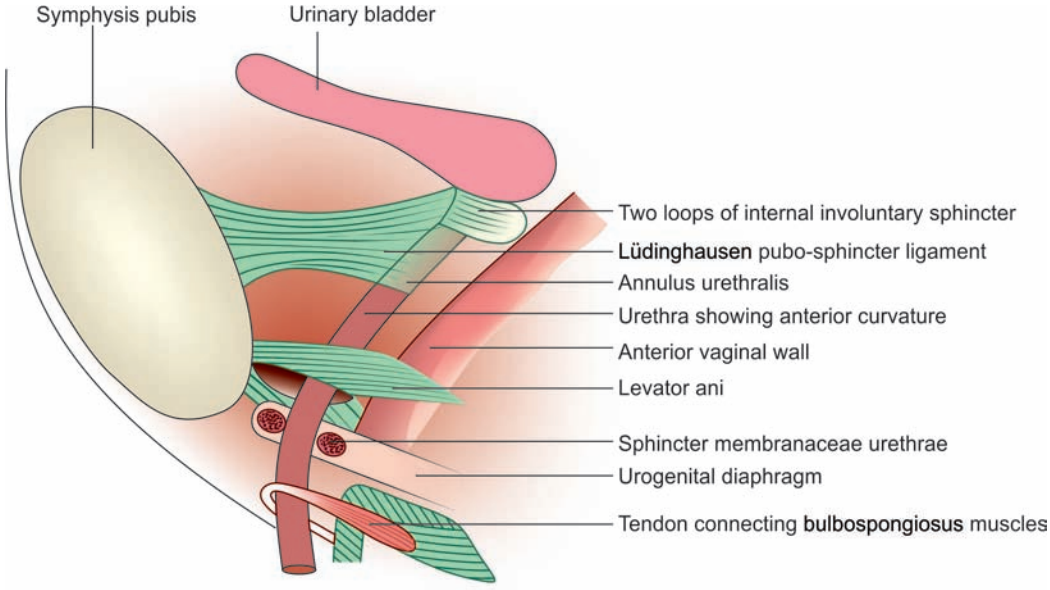

Figure 18.8 Normal support of internal sphincter.

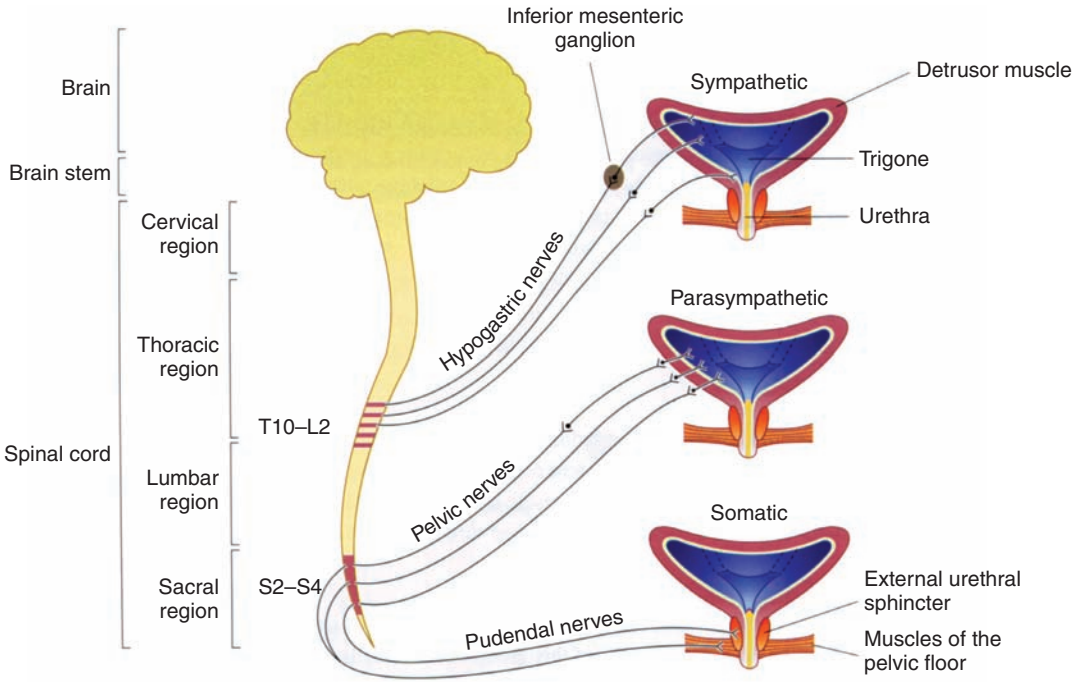

Figure 18.9 Normal control of micturition.

GSI is the only kind which can be cured by surgical procedures, hence the importance of making a correct diagnosis prior to planning any surgical repair.

Urge Incontinence

Urge incontinence (motor) is commonly the result of detrusor muscle overactivity (detrusor instability, DI). Sensory urgency is an intense desire to void that is not associated with detrusor pressure. Unconscious incontinence is often the result of a neuropathic bladder; the underlying cause of the involuntary urine loss may be retention of urine with overflow.

Primary Clinical Evaluation

History

A menopausal obese woman with previous vaginal deliveries is at a risk of urinary stress incontinence. Patients with GSI usually complain of the passage of a single spurt of urine at the height of physical exertion like sneezing or coughing without the urge to urinate. Patients with motor urge incontinence admit to a strong desire to void, which if not complied with immediately, leads to a considerable involuntary passage of urine. History of diabetes, pulmonary disease is relevant.

Local pathology in the bladder and urethra may lead to frequency of micturition, i.e. infection, lowered capacity of the bladder, lowered compliance of the bladder because of chronic fibrosis of the bladder interfering with its contraction pattern following radiotherapy, tuberculosis or diabetes. Organic neurological diseases may adversely affect bladder function. These include multiple sclerosis, tabes dorsalis and subacute combined degeneration of the cord. Major pelvic dissection during radical operations on the uterus and rectum cause widespread damage to the splanchnic nerves in the deeper parts of the cardinal ligaments. The nervi erigentes carry the parasympathetic motor supply to the detrusor muscle of the bladder and interference with this pathway can cause distressing disturbances of bladder function. Extraurethral causes of urinary incontinence include true continence of genitourinary fistulae discussed earlier and rare conditions like an ectopic ureter.

Physical Examination

A clinical examination, including pelvic and speculum examination, and a thorough neurological assessment should be undertaken. An attempt should be made to assess the anatomic defects of pelvic supports and the tone of the levator muscles. Note the increase in urethral and urethrovesical junction mobility. Assess vaginal wall prolapse and senile vaginal changes. Elderly postmenopausal women benefit from oestrogen therapy, when follow-up examination reveals a healthy pliable vaginal wall.

GSI is graded as follows:

- Grade I. Incontinence with only severe stress, such as coughing, sneezing and jogging.
- Grade II. Incontinence with moderate stress, such as fast walk, going up and down the stairs.
- Grade III. Incontinence with mild stress such as standing.

From the surgical procedure point of view, three types of GSI have been described:

- Type I. GSI occurs due to loss of posterior urethrovesical angle alone.

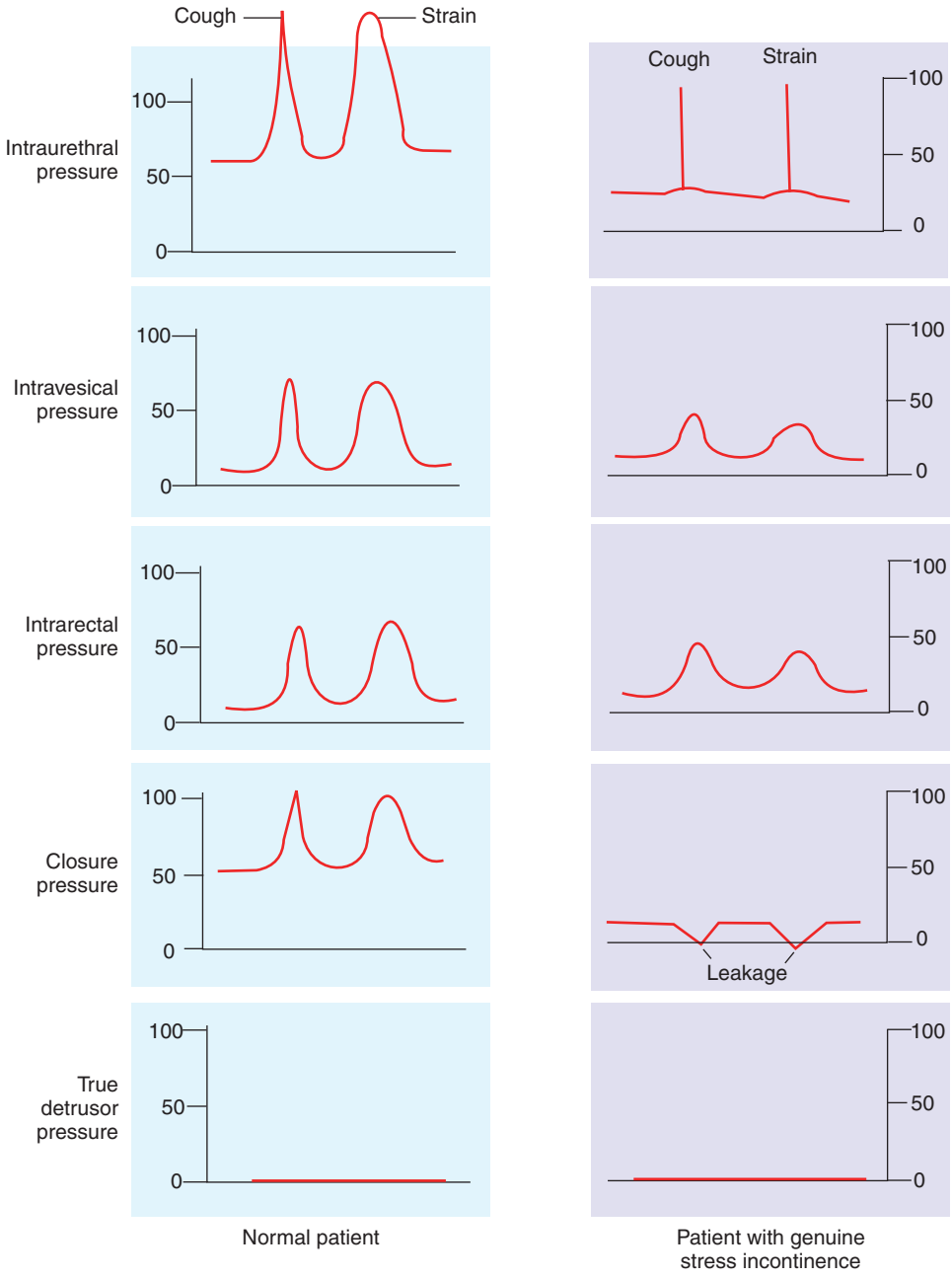

Figure 18.10 Comparison of urethral and vesical pressure in normal subject and one suffering from genuine stress urinary incontinence.

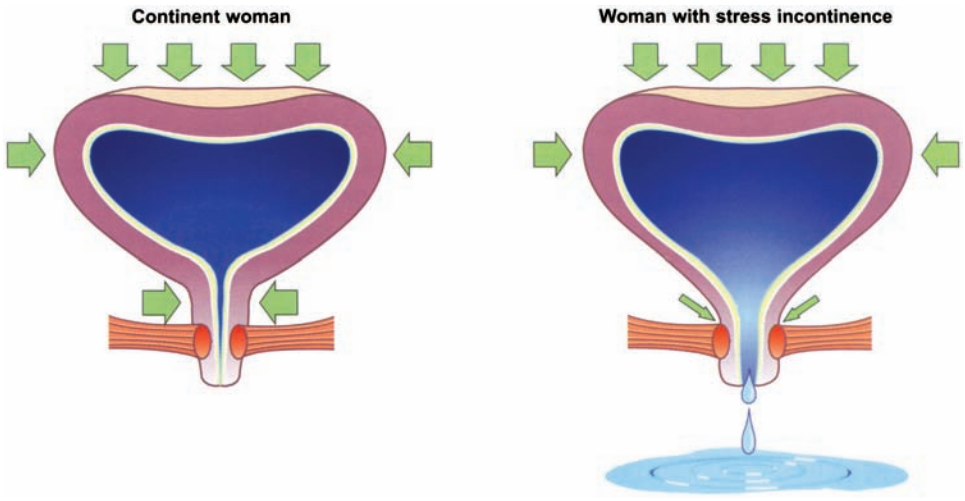

Figure 18.11 SUI mechanism.

- Type II. Loss of posterior urethrovesical angle as well as urethral hypermobility.
- Type III. It is due to intrinsic sphincter deficiency.

Investigations

Special investigations are not routinely required for GSI if medical therapy is applied. However, prior to surgical management of GSI and in urge incontinence, investigations should confirm the presence or absence of GSI.

Urine culture. Blood sugar in residual urine.

Investigations include: (i) stress test, (ii) cotton swab test, (iii) Marshall and Bonney's test, (iv) urethroscopy and (v) urodynamic studies.

Stress Test

Stress test is an excellent method of demonstrating objectively the presence of GSI. The patient is asked to void urine. She is then catheterized with full aseptic precautions to determine the volume of residual urine present. Ultrasound is done and residual urine measured. The urine sample is sent for culture. Thereafter 250 mL of warm saline is instilled into the bladder. The patient is then made to squat on a preweighed absorbent pad placed on the floor. She is asked to cough and strain. Objective evidence of urine leak is noted. The leak can be grossly quantitated as mild, moderate or severe. The patient is then placed supine in the lithotomy position and asked to strain or cough for further evidence of stress incontinence. The absorbent pad is weighed at the end of the test. A net weight gain of 2 g or more is indicative of GSI.

Urine culture before invasive investigations is mandatory. It is necessary to rule out urinary infection by culture before undertaking invasive investigations because of the following reasons:

- The symptoms may be due to urinary infection.
- Invasive procedures should not be undertaken in the presence of infection.
- Urinary infection may interfere with interpretations of invasive procedures.

These tests are also required if the GSI recurs following surgery:

- Blood sugar for diabetes.
- Residual urine (ultrasound).

Normal Cystometric Findings

Parameter	Normal Findings
Residual urine	<50 mL
First desire to void urine	150–250 mL
Bladder capacity	500–600 mL
Detrusor pressure	
During filling	<15 cm H_2O
During voiding	<70 cm H_2O
Urine flow	>15 m/s

Cotton Swab Stick Test

A Q-tip cotton swab stick dipped in Xylocaine Jelly is placed in the urethra. The patient is asked to strain and cough. Initially the cotton swab stick will be parallel to the floor. In patients with no GSI the cotton swab stick will normally reach an angle not exceeding 10–15° above the horizontal. This angle increases by 20° or more, commonly 50–70° in most positive cases. A positive test indicates sufficient degree of bladder neck descent. Unfortunately, all patients with GSI may not have a positive test. This test if positive obviates the need for a head chain cystourethrogram. However, this test is not very specific and does not indicate the severity and type of surgery the woman requires (Figure 18.12).

Marshall and Bonney's Test

In patients with a positive stress test, absence of leakage of urine following bladder neck elevation is indicative of beneficial outcome following surgical repair. In the Bonney's test, two fingers are placed in the vagina at the urethrovesical junction, on either side of the urethra and the bladder neck region elevated. On straining or coughing absence of leakage of urine indicates a positive test. In the Marshall test, the vagina in the region of the bladder neck is infiltrated with local anaesthetic, and the area elevated with an open Allis clamp. Failure to demonstrate leakage of urine on coughing is indicative of a positive test. Instead of fingers, Hodge pessary may be used to elevate the bladder neck.

Urethroscopy

The Robertson urethroscope using a gas medium permits satisfactory visual evaluation of the urethra, trigone and the bladder neck regions. Urethroscopy provides information about the opening pressure, presence or absence of urethritis, presence of diverticula or a rigid urethra. The urethrovesical junction can be observed during bladder filling with a hold command, during coughing or during Valsalva manoeuvre.

Urodynamic Evaluation

These are a group of tests to study the pattern of storage and evacuation of urine. *These tests are required when clinical diagnosis is not clear prior to surgery*.

Cystometry. Measurement of pressures within the bladder and the urethra during artificial filling of the bladder with CO_2 or fluid helps to differentiate true stress incontinence, detrusor, urgency instability and other types of incontinence. The relationship between the bladder and urethral pressures can be most helpful in planning the correct treatment.

Urethrocystometry. Normal findings are: At rest 150 mL urine causes 2–8 cm water pressure which rises to 15 cm water at filling. Urethral pressure average 40 cm water, and less than 20 cm water pressure leads to incontinence.

Uroflowmetry. Measurement of urine flow rate and volume provides an objective, noninvasive measure of voiding function.

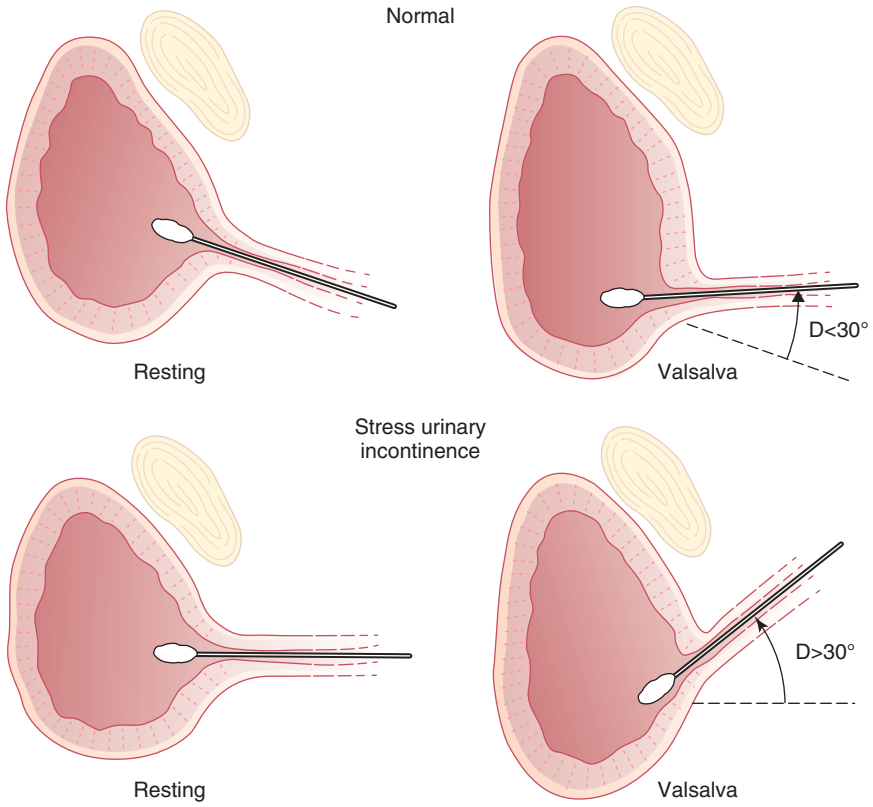

Figure 18.12 Diagrammatic representation of Q-tip cotton swab test. (Source: Hacker NF, Gambone JC, Hobel CJ, Hacker and Moore's Essentials of Obstetrics and Gynecology, 5th ed. Philadelphia: Elsevier, 2010.)

Micturition Cystourethrography. Normally, a continent woman demonstrates a well-marked posterior urethrovesical angle of about 100°. Loss of posterior urethrovesical angle causes stress incontinence in many women. Colposuspension and sling operations are based on restoring this angle surgically.

Uroprofilometry. Uroprofilometry measures the dynamic urethral pressures and diagnoses urethral instability and urethral diverticulum. It is a gold standard in the diagnosis of GSI.

The normal flow is 15–25 mL/s. Flow below 10 mL/s occurs in atonic bladder and in obstruction, which is confirmed by cystometry. Increased bladder pressure >50 cm water and low flow suggests obstruction.

Ultrasound. Ultrasound is useful in measuring the bladder volume and residual urine. A bladder wall thickness of more than 6 mm suggests DI. Bladder stone can be seen.

Videocystourethrography. Videocystourethrography is the new gold standard urodynamic investigation to study the lower urinary tract dysfunction. It combines the pressure studies with the video position of the bladder neck and urethrovesical angle.

MRI Studies. MRI studies the defects in the pelvic floor muscles and the supporting fasciae. Appropriate surgery to buttress the bladder neck will cure incontinence.

Sophisticated *neurophysiological testing* is required when the neurological component for stress incontinence is suspected.

Residual urine by ultrasound shows incomplete voiding.

Treatment

It is important to rule out DI before any surgery; otherwise, the symptoms will worsen.

Treatment comprises (Table 18.2):

- Conservative therapy
- Surgical repair

Main aim is to improve the quality of life.

Conservative Treatment

Conservative treatment should be the first line of treatment, especially in younger women. It is cheap, has fewer complications and does not compromise future surgery if so required.

Conservative therapy is also applied to the elderly and frail women unfit for surgery, and during the 6 months after the delivery. It is also applicable in previous failed surgery, DI and women desirous of childbearing.

The treatment comprises:

- Physiotherapy
- Drugs
- Intraurethral and vaginal devices
- Electric stimulation

TABLE 18.2 Management of stress incontinence

Conservative	Drugs	Surgery
1st line of treatment • Young woman • Frail, old woman • Postpartum, previous failed surgery 1. Kegel pelvic floor exercises × 4–6 months 2. Electric/magnetic stimulation for nerve damage, magnetic stimulation 3. Artificial urinary sphincter in neurological condition 4. Vaginal cones	• Oestrogen cream in menopausal woman • Venlafaxine 75 mg daily • Imipramine 10–20 mg BD	If others fail • Vaginal (Kelly) • Abdominal Marshall–Marchetti–Krantz and Pereyra Burch • Combined vaginal and abdominal suspension • Slings • Tension-free sling • Transobturator type Laparoscopic suspension of bladder neck

- Artificial urinary sphincter
- Weight loss
- Reduce caffeine intake and stop smoking
- Bladder training and timed voiding

Physiotherapy. Suited for Grade I GSI. Pelvic floor exercises for 4–6 months with or without electrical stimulation make patient's life tolerable in 60% cases. Weight loss and exercise are all beneficial. It takes 8–12 weeks before any improvement is seen.

Kegel pelvic floor exercises work best in younger women, mild stress incontinence associated with urethral hypermobility with no damage to internal sphincter. It is also effective in urge incontinence, as these exercises tone up the levator ani muscles and internal sphincter.

Drugs. Alpha-adrenergic drugs may help to constrict the bladder neck and reduce the frequency of stress incontinence. Oestrogen cream is useful in menopausal women. Phenylpropanolamine enhances urethral pressure. Venlafaxine 75 mg daily is a serotonin (5-Ht) and noradrenaline reuptake inhibitor and is the latest drug. It causes mild transient nausea and mild cardiac effect. Imipramine 10–20 mg BD.

Intraurethral and Vaginal Devices. These have been tried with some success. A ring pessary in genital prolapse may reduce stress incontinence in some women. Contiform is a silastic vaginal cone available in India. It is placed during the day and removed and cleaned at night. The cone needs changing every 6 weeks. It is successful in 85% of the cases. Vaginal cones weighing 20–100 g are available. A small cone is used initially, larger ones later. The cone is inserted in the vagina and held in by contraction of the levator ani muscles as long as possible, thereby toning up these muscles. They are not useful in menopausal women with weak levator ani muscles or in the presence of vaginal scar. Toxic shock syndrome can occur if retained for a long period.

Electric Stimulation. Electric stimulation to the pelvic floor muscles has also been tried during physiotherapy if the stress incontinence is caused by denervation of the pudendal nerve during delivery. Magnetic stimulation is lately employed. It is especially useful in a old woman with weak pelvic floor muscles.

Artificial Urinary Sphincter. Artificial urinary sphincter (AUS) (Figure 18.13) 800 model is used in neurological conditions, and those with previous surgical failure and sphincteric dysfunction. Though 80% success is reported, equipment is expensive, can cause infection and mechanical failure.

Genuine Stress Incontinence. A postmenopausal woman with senile changes in the vagina, hypotonic urethra and mild stress incontinence may benefit immensely with oestrogen replacement therapy, preferably cream applied locally. A woman with chronic cough, constipation and allergic rhinitis or excessive physical activity may improve with medical measures. Avoiding aggravating factors like smoking, straining or undue physical exertion also play a complementary role. Successful surgery for GSI restores the relationship between the bladder, urethra and the urogenital diaphragm.

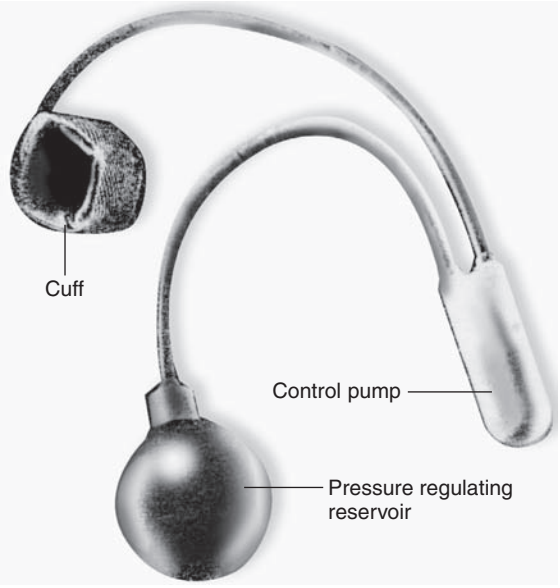

Figure 18.13 Artificial urinary sphincter.

The *goals* of surgical repair of GSI include:

- Repositioning the proximal urethra to a high retropubic position to maximize proper urethral compression.
- Preserving vesicourethral angle to facilitate urethral compression.
- Preserving the compressibility and pliability of the urethra.
- Preserving the integrity of the sphincteric mechanism.

Surgical Repair of Stress Urinary Incontinence

Various surgical procedures (over 100) have been designed over the years: some of these existing procedures will be discussed in broad terms below. It is however recommended that *any surgery should be deferred in a young woman and conservative method employed initially*. Future pregnancy may mar the good result of surgery or caesarean delivery may be required.

Primary surgery offers the best results, therefore selection should be most appropriate.

Vaginal Operations. These include anterior colporrhaphy, with plication of the bladder neck (Kelly's repair), or apposing the medial fibres of the puborectalis muscles in the midline under the bladder neck region to elevate the same (Pacey's repair).

Abdominal Operations. These operations are of retropubic colposuspension like the Marshall–Marchetti–Krantz operation which sutures the bladder neck and vaginal vault to the periosteum of the back of the pubic symphysis, or the Burch colposuspension which aims at vaginal suspension using the iliopectineal ligaments rather than the periosteum of the back of the symphysis pubis. Osteitis may follow Marshall–Marchetti–Krantz operation. Because of this and a low cure rate, this operation has been more or less replaced by the sling operation.

Combined Abdominal and Vaginal Operations. The Pereyra operation is performed by the vaginal route. A Foley's catheter is inserted and its bulb distended with 5 ml of saline. Traction on the bulb helps to identify the bladder neck and urethra. Two parallel incisions are made on either side of the urethra in the region of the bladder neck. Paraurethral spaces are created by blunt dissection. A helical suture is passed through the paraurethral tissues and its ends threaded into a needle, which is advanced through the endopelvic fascia into the retropubic space. The needle is now advanced close to the back of the pubic bones to penetrate the rectus abdominis muscle where it can be palpated and guided into a small midline transverse suprapubic incision in the abdominal wall. A similar paraurethral tissue sling can be pulled up on the other side with a helical suture. After appropriate traction which elevates the bladder neck adequately, the helical sutures are fixed to the aponeurosis of the anterior abdominal wall. As an extension of this principle, fascial slings or nylon mesh slings placed under the bladder neck region vaginally can be made to sling up the bladder neck like a 'hammock' (The Razz and Stamey modifications are becoming increasingly more popular) with 50% success rate.

Immediate complications of sling operations are:

- Bleeding.
- Trauma.
- Urinary infection.

Late complications are:

- Bladder dysfunction.
- Erosion of the sling.
- Prolapse of posterior vaginal wall and enterocele as the intra-abdominal pressure is exerted on the posterior vaginal wall.

Burch Colposuspension (Figures 18.14 and 18.16). After the retropubic space is reached, nonabsorbable sutures of (3–4) polyglycolic acid are placed on the lateral fornices (paravaginal tissue) lateral to the bladder base and the bladder neck fixed to the ipsilateral iliopectineal ligament on either side. Eighty-five per cent success is balanced against the development of enterocele and rectocele postoperatively due to transmission of intra-abdominal pressure. Burch operation, though popular until recently,

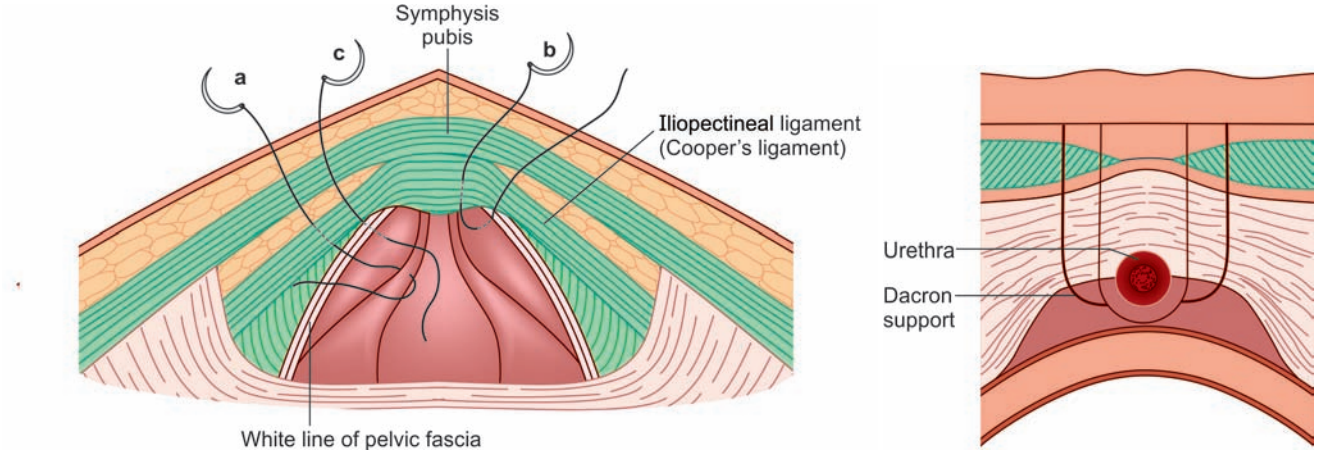

Figure 18.14 **(A)** Colposuspension (Burch operation). (a) Burch colposuspension (b) colposuspension using the white line of pelvic fascia (c) MMK procedure. **(B)** Modified Stamey method of endoscopic colposuspension.

has now been superseded by tension-free vaginal T-tape. Burch operation causes bleeding in 3%, bladder trauma in 6%, venous thrombosis in 1% and voiding difficulties in as much as 25% cases.

Laparoscopic Colposuspension. This operation has been successfully accomplished laparoscopically using the extraperitoneal route or the transperitoneal route. Lately, however, 40% failure rate is reported.

Intravesical Bladder Neck Plication. This operation is resorted to only exceptionally.

Tension-Free Vaginal Tape. The tape does not elevate the urethra, but provides a resistant platform in the mid-urethra that maintains continence against intra-abdominal pressure. It was designed by Petros (1993) and Ulmstem (1996). This technique is good for obese women, as it does not causes detrusor dysfunction.

Tension-free vaginal tape (TVT; Figures 18.15 and 18.16) has been designed from nontissue reactive synthetic material (prolene). After exposing the region of the bladder neck on vaginal dissection, the hammock of the tape is placed underneath it to provide support at the mid-urethral level, the lateral extensions are brought out paraurethrally onto the skin at the level of the pubic symphysis and the vaginal incision is closed. After adjusting the proper elevation of the bladder neck region, the extra length of the lateral arms of the tape is cut. The operation can be performed under local anaesthesia. Under local anaesthesia, tension can be checked by asking the woman to cough. Cystoscopy avoids inadvertent bladder entry. Success rate of 88–90% is claimed at the end of 3 years. This procedure also does not require catheterization postoperatively. Two per cent require removal, 5% have voiding problem. This surgery is employed in:

- Previously failed surgery
- Internal sphincter dysfunction
- Mobile urethra

Figure 18.15 Transobturator tape.

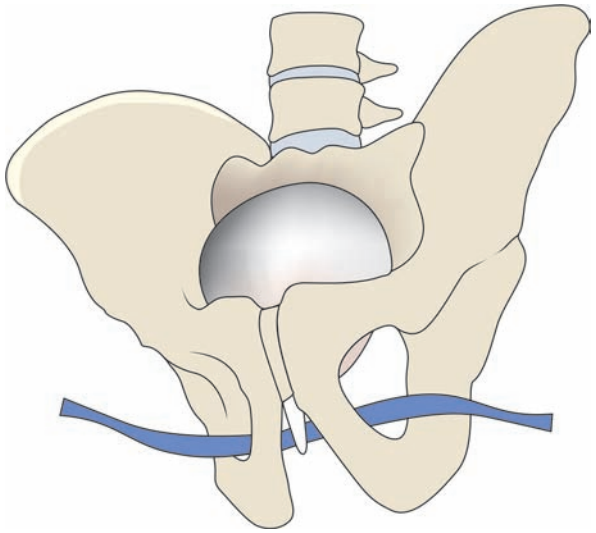

Figure 18.16 Tension-free vaginal tape device.

Transobturator tape (TOT) (Figure 18.17)

Designed by Delorme (2001), this mid-urethral tape avoids passing through retropubic space. Instead, a hammock is inserted mid-urethra by passing the trocar from the thigh through obturator canal. This reduces the risk of bladder perforation and cystoscopy is not required. It is good for obese women.

Mid-urethral sling is good for urethral hypermobility, whereas other slings are for internal sphincter dysfunction.

Periurethral collagen injection. Glutaraldehyde cross-linked bovine collagen (Contigen, Bard) is commercially available for periurethral injection. A dose of 2.5 mL is injected at 3 and 9 o'clock positions into the submucosa of the proximal urethra near the bladder base under cystoscopic vision. It can be undertaken as an office procedure for mild cases, but is often reserved for cases of surgical failures. Objective relief is obtained in about 50% of cases. However, allergic reactions to the collagen injection have been reported. The procedure raises the urethral pressure by external compression and is useful in sphincteric dysfunction. It is used in internal sphincter dysfunction. It can cause retention of urine and may require reinjection.

Recently, micronized silicon rubber particles suspended in nonsilicon gel known as uroplasty has been used with success. Local reaction with fibrosis is less seen with uroplasty than with collagen. Durasphere is nondegradable and nonallergic and longer acting. Bulkamid is a type of hydrogel.

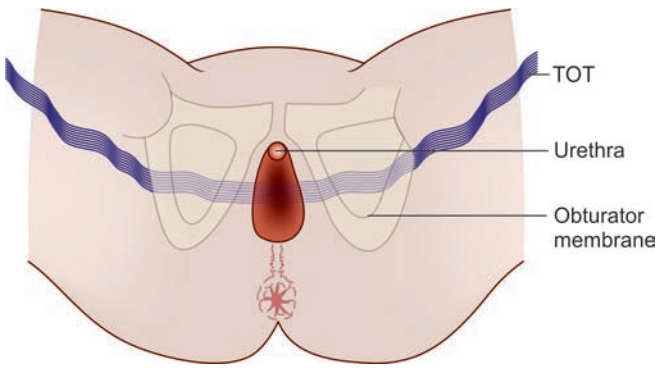

Figure 18.17 Transobturator tape (TOT) procedure. The tape is placed under the mid-urethra, taken through the obturator membrane to be fixed to the thigh.

Complications. The following complications can occur with these operations:

- Injury to the bladder, urethra
- Haematoma in the retropubic space
- Infection
- Breakdown of sutures
- Voiding difficulties, retention of urine
- Incomplete bladder emptying and repeated urinary infections
- Late problems include erosion of nonabsorbable sutures into the bladder, urethra or vagina resulting in infection, fistula or stone formation
- DI follows surgery for GSI in 1–10% cases
- Failure

Outcome following surgical repair of GSI. Potential reasons for failure include:

- Surgical failure—sutures cut out because of poor placement of sutures, inadequate mobilization of the bladder neck and proximal urethra, postoperative haematoma formation/infection.
- Incorrect choice of operation—mainly the result of incomplete or incorrect preoperative assessment of the cause of urinary incontinence.
- Development of incontinence due to other causes like fistula formation, DI or pipe-stem urethra previously not present.

With the passage of time, the results of all kinds of incontinence surgery tend to deteriorate. Long-term follow-up data suggest (Table 18.3) cure rates of different surgical procedures.

Detrusor Instability

Incontinence occurs when the detrusor muscle contracts spontaneously or on provocation during the filling phase while attempting inhibition of micturition. It is more common in old women with decreased bladder capacity, decreased sensation and central nervous system (CNS) inhibition. It is often caused by overactivity of parasympathetic nerves.

Aetiology

DI may be:

- Functional and psychosomatic.
- Detrusor hyperreflexia (neuropathy) in certain medical conditions such as diabetic neuropathy, a cerebrovascular accident, multiple sclerosis, spinal injury and parkinsonism.
- It occurs following surgery for GSI if the bladder neck is placed too high and tightly sutured. It is seen in 1% of the cases following anterior repair, 5.8% after endoscopic bladder neck suspension, and 10% following colposuspension and sling operation.
- Idiopathic. Ten per cent men and 30% women over 40 have DI.
- Urinary infection.

TABLE 18.3 Cure rate of different surgical procedures

Operation for Repair of GSI	Long-Term Cure (%)
1. Bladder buttress operation	67.8
2. Marshall–Marchetti–Krantz operation	89.5
3. Colposuspension	89.8
4. Endoscopic suspension	86.7
5. Vaginal sling operations	93.9

Modified from Jarvis 1994 and Leach 1997.

Pathophysiology

Increased alpha-adrenergic and cholinergic activity is responsible for this condition.

Symptoms

A woman develops involuntary escape of urine with urge to urinate. This urge is accompanied by frequency more than seven times during the day and at least once during the night. There could also be bedwetting during sleep. DI also occurs during sexual intercourse and with the sound of water, hand-washing.

Investigations

- Neurological examination especially in an old woman.
- Blood sugar.
- Urine culture will indicate if the urinary infection is the cause of frequency and urge.
- Cystometry. The normal pressure of 15 cm water at 200 mL exceeds in DI. Cystoscopy is normal. Bladder capacity may be reduced.
- Other investigations may be required to rule out other causes of associated bladder neck instability.
- Ultrasound shows a thick bladder wall more than 6 mm in DI and residual urine, apart from urethrovesical angle posteriorly.

Differential Diagnosis—interstitial cystitis has urge, but no dribbling.

Treatment

- Low caffeine and nonsmoking.
- Bladder training.
- Restricted fluid intake and weight reduction.

Treatment is medical. Anticholinergic drugs are useful. Some of them are (Table 18.4):

- Urispas (flavoxate) is a musculotropic and has a direct action on the smooth muscle, 200 mg t.i.d., antispasmodic and analgesic.

Side effects include headache, nausea, constipation, dry mouth and blurred vision. It is contraindicated in glaucoma and cognitive impairment.

- Dicyclomine HCl 10 mg four times daily.
- Pro-Banthine 15–90 mg four times daily.
- Oxybutynin HCl: 5–10 mg t.i.d. Extended release OD better.

TABLE 18.4 Dosage and side effects of anticholinergic drugs

Drugs	Dosage	Side Effects
• Urispas (flavoxate)	200 mg t.i.d. Antispasmodic action On detrusor muscle, an analgesic	Headache, nausea, dry mouth, blurred vision
• Dicyclomine HCL	100 mg q.i.d.	Headache, nausea, dry mouth, blurred vision
• Pro-Banthine	15–90 mg q.i.d.	Headache, nausea, dry mouth, blurred vision
• Oxybutynin HCL	5–10 mg t.i.d.	Cognitive impairment, not to be given to elderly women. Outflow obstruction, glaucoma, myasthenia gravis
• Imipramine	50–100 mg at night × 3 months	Sedation, constipation, blurred vision
• Tolterodine (Roliten, Terol)	2 mg b.d.	Less side effects
• Duloxetine	40–80 mg b.d. × 3 months	Headache, nausea, dry mouth, blurred vision
• Solifenacin (soliten)	5 mg daily × 12 months	Decreased libido
• Darifenacin [antidepressant (Depsol)]	7.5–15 mg daily	Under trial

- Imipramine (tricyclic antidepressant) 50 to 100 mg at night for 3 months is 70% successful. It causes sedation, constipation and blurred vision in 10%. Not for elderly women.

The drugs cure incontinence in 60% cases. New drugs are tolterodine tartrate 2 mg b.i.d. (extend release OD 4 mg) and propiverine. These drugs cause less of dry mouth compared to Urispas. Darifenacin and trospium chloride are under trial.

Duloxetine is a serotonin norepinephrine reuptake inhibitor. Dose of 40–80 mg b.d. orally for 3 months improves the bladder capacity. Nausea and dry mouth are its side effects. It increases the bladder capacity, but decreases libido.

Japan has added a new B_2-adrenergic receptor agonist 'Mirabegron'—results are awaited.

If the drugs fail, posterior tibial nerve stimulation (PTNS) should be tried. PTNS—neuromodulation is indirectly applied on the 3rd sacral nerve via a needle electrode and connected to a stimulator. 30 min stimulation 3 monthly is practised.

If the drugs fail, transvesical injection of phenol is tried. A volume of 10 mL of 6% phenol injected into the trigone; 60% benefit for a short period but at the end of 1 year only 2% are relieved. Sloughing and fistula can occur. Acupuncture may be useful in some cases, urethral dilatation is successful in a few cases when the drugs fail. Augmentation 'Clam' cystoplasty involving augmentation of bladder capacity with a (25 cm length) segment of ileum gives 95% cure. It is a major surgery that requires self-catheterization and mucous secretion by ileal mucosa can be troublesome. Twenty-five per cent complain of other urinary problems and 5% develop adenocarcinoma of the ileal segment. Augmental cystoplasty requires self-catheterization, causes stone formation, urinary infection as well as electrolyte imbalance and malignancy.

Botox (a Botulinum toxin A).

Injection of Botulinum toxin A (neurotoxin) produced by anaerobia bacteria *Clostridium botulinum* into the detrusor muscle inhibits acetylcholine release at the neuromuscular junction, increases bladder compliance and its capacity, the effect lasts 9–12 months (introduced in 2011).

Side effects: Retention of urine and requires self-catheterization, normally in the first 6 weeks. It is recommended in resistant DI and may supersede surgery in future, but more trial is required. Done via cystoscopy, 15–30 different detrusor muscle sites are injected under direct vision. Though side effects of anticholinergic therapy are avoided, this technique has a higher rate of urinary retention and urinary infection. Detrusor myectomy creates a diverticulum and improves bladder capacity.

Oestrogen cream improves incontinence in postmenopausal women.

Restricting fluid intake, psychotherapy and treating the cause are also of importance.

Bladder drilling or training disciplines the bladder to hold the urine for a longer period.

1-Deamino-8-D-arginine vasopressin (DDAVP) is a synthetic antidiuretic hormone (ADH) analogue. Peptide or intranasal 20–40 mcg at night cures nocturnal enuresis. Nausea, hyponatraemia and fluid retention may occur with this drug. It is contraindicated in coronary heart disease, hypertension and epilepsy in elderly women. Oral tablets are now available.

Medical therapy should be applied for 5–12 failures; the nerve stimulation and surgery should be employed only if medical therapy fails.

Biofeedback uses visual and auditory signals to demonstrate the strength of detrusor activity. Hypnotherapy helps in psychological women.

Neuromodulatory—sacral nerve stimulation for refractory urge incontinence. It comprises surgical implantation of a generator to provide stimulation to the sacral nerve. It is very expensive, 60% subjective relief is reported. Pain at the insertion is complained by 40% women.

PTNS is also attempted.

Key Points

- Genital fistulae of obstetric origin are decreasing in number as a result of improved obstetric care. However, they still contribute a major share of all genital fistulae seen in clinical practice in India.
- Genital fistulae occur following prolonged unsupervised obstructed labour, following difficult vaginal instrumental deliveries, and occasionally as a complication of caesarean section.
- Genital tract fistulae have been reported following gynaecological operations. The bladder or ureter may get involved. Investigations including methylene blue dye test, descending pyelography, cystoscopy and ureteric catheterization may be required to settle the diagnosis. Surgical correction is possible in most cases.
- Besides obstetric and surgical trauma, advanced genital cancers and radiation injuries can cause fistulae. To alleviate symptoms, the surgeon may have to resort to palliative procedures such as surgical diversion of the urinary tract.
- GSI requires to be differentiated from urge incontinence, DI and a neurological bladder. Surgical repair in selected cases gives gratifying results, but the long-term results are not satisfactory. Primary treatment should be conservative.
- DI caused by an overactive bladder muscle is dealt with by various drugs. Surgery is rarely resorted, but surgical complications are also major problems.
- Burch operation is recommended for hypermobility of the urethra, but is now superseded by tension-free vaginal tape.
- TOT is considered superior to TVT, as it avoids retropubic space, osteitis, and bladder injury.
- Botox injection may replace surgery but requires a longer trial in DI.
- Various drugs available (extended release) should be tried first, along with physiotherapy, before surgery is undertaken, for DI.

Self-Assessment

1. Discuss the causes of vesicovaginal fistula.
2. How will you investigate, diagnose and manage the vesicovaginal fistula?
3. What are the causes of ureteric fistula?
4. Discuss the management of ureteric fistula.
5. What are the causes of genuine stress incontinence?
6. How will you manage a case of genuine stress incontinence in a woman of 40 years?
7. Discuss the causes and management of detrusor instability.

Suggested Reading

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Chapter 19 Infertility and Sterility

CHAPTER OUTLINE

Conception results from the fertilization of the ovum by a spermatozoon. Much information is now available on the biological process whereby the spermatozoon enters the ovum as fertilization can be studied in vitro, in IVF programme.

The mechanism whereby spermatozoa pass along the uterus is not properly explained. As ciliary movement of the cervical and endometrial epithelia is downwards, the spermatozoa must migrate against the ciliary current. It can only be assumed that spermatozoa, which live in an attractive alkaline medium of the seminal fluid (pH 8), find the acid environment of the vaginal secretion (pH 4.5) lethal in a matter of 2–4 h. The cervix has the same pH as the seminal fluid and is undoubtedly and demonstrably attractive to the spermatozoa. Spermatozoa are powerful, fast swimmers, and from the time of ejaculation to the time of arrival in the ampulla of the tube, it takes about 60 min for the spermatozoa to cover the intervening 20 cm. This distance when compared to the size of a spermatozoon represents a rapid and purposeful travel. The subendothelial layer of the endometrium exhibits increased upward peristalsis during the follicular phase near ovulation time, and this may hasten the migration of sperms into the fallopian tube.

It is now generally accepted that though a spermatozoon after ejaculation may remain motile for a long period, its useful life span is limited to 24 h, and after this short interval, it is less capable of performing its biological duty. The period of survival of a mature ovum is probably even shorter than that of a spermatozoon, and the time which elapses after its escape from a ripe Graafian follicle and its entry into the fallopian tube during which it is potentially fertilizable is estimated at 12 h and rarely up to 24 h. The significance of this statement is that coitus, to be capable of fertilization, must take place in the 24-h period around ovulation. Ovulation most commonly occurs 14 days before the onset of the next period, though variations are known.

The fimbriae of the fallopian tube by muscular contraction spread out over the ovary at the time of ovulation, a movement which simplifies the transport of the discharged ovum into the lumen of the fallopian tube. Furthermore, the musculature of the fallopian tube undergoes rhythmical contractions, especially at the time of ovulation. It is most likely the peristaltic contraction of the fallopian tube that determines the transport of the ovum towards the cavity of the uterus. The sperm that reaches the ovum first penetrates the zona pellucida and normally inhibits entry by other sperms. By the time the fertilized egg enters the uterine cavity, the endometrium has grown under the effect of progesterone into secretory endometrium and is ready to receive the egg for implantation and provide its nutrition.

On general biological principles, the blame of infertility should be shared between the two partners. It is not uncommon for patients to complain of difficulty during coitus when they have little knowledge of the correct method to be employed. During sexual intercourse, the erectile tissues around the vaginal orifice become engorged and the vaginal orifice becomes more patulous. There is a discharge of mucus from the ducts of Bartholin's glands which acts as a lubricant. The female orgasm is induced by stimulation of the clitoris partly during the penetration of the penis and partly as the result of the clitoris being rhythmically pressed against the male after penetration. The importance of the extragenital areas of sexual stimulation must not be forgotten. These erogenic areas vary with the individual and their susceptibility to stimulation is equally variable, but their

aggregate response is cumulative and plays a vital part in the ultimate achievement of an orgasm. There is some evidence that the mucous secretion contained in the cervical canal is extruded into the vagina during the orgasm. The seminal fluid is mainly deposited in the posterior fornix of the vagina, but it is possible that some of it is ejaculated directly into the cervical canal. It is also believed that the contractions of the uterus and the fallopian tubes during the female orgasm cause seminal fluid to be aspirated into the cavity of the uterus, and it is possible that this aspiration effect is responsible, in part at least, for the migration of spermatozoa upwards into the fallopian tubes. A more likely suggestion is that rhythmic contractions of the pelvic muscles direct the seminal ejaculate towards the cervix, where the propulsive power of the spermatozoa provides the forward momentum. The female orgasm is not essential for conception, and it is not uncommon to see women who have conceived without full consummation of the marriage and in whom the hymen is intact. In such cases the spermatozoa, having been deposited around the hymen, migrate through their own motility along the whole length of the vagina and uterus.

Vaginismus

Vaginismus is regarded as hyperaesthesia which leads to spasm of the sphincter vagina and the levator ani muscles during attempted coitus or when an attempt is made to examine the patient vaginally. In primary vaginismus there is no organic lesion present, whereas in secondary vaginismus some obvious painful lesion in the region of the genital tract can be found on examination. In primary vaginismus, when the patient is being examined and an attempt is made to inspect the vulva by separating the labia, a muscle spasm is induced whereby the thighs are drawn together, the levator muscles become tonically contracted and the patient cries out and endeavours to push the medical attendant away from her. In secondary vaginismus, a minor degree of spasm is induced by painful local lesions such as small infected lacerations of the hymen, urethral caruncle, vulvitis, or a sequela of vaginal operations for the repair of prolapse when, as a result of the operation, the calibre of the introitus and the vagina is narrowed. The operation scar is naturally sensitive for some weeks after the repair, and premature attempts at coitus are painful. It is thus easy for organic dyspareunia to lead to a protective spasm in order to avoid the pain of coitus. The spasm is not unlike that seen in primary vaginismus, although it is never of the same degree. Removal of the cause will cure this condition, whereas true vaginismus requires prolonged therapy and the results are not always satisfactory.

Typical primary vaginismus always has a psychoneurotic basis. Frequently, a history of mental trauma during adolescence can be traced, and in most women with vaginismus, there is a subconscious dread of sexual intercourse. This anxiety neurosis is all too often the result of enthusiastic but clumsy technique on the part of her husband, dating from the time of the first consummation of her marriage. Sometimes, it dates from a guilt complex engendered by an early, clandestine and extramarital association.

If the patient suffering from vaginismus is examined under an anaesthetic, bimanual pelvic examination will most likely reveal no organic abnormality whatsoever. The capacity and calibre of the vagina is normal and it easily admits two fingers. Occasionally, the hymen is incompletely ruptured and the introitus inadequately dilated, but these findings are rare and their correction by plastic enlargement, though logical, does little to relieve the subsequent spasm since it is psychogenic rather than organic. Fortunately, vaginismus is rarely encountered in recent times.

Treatment

The first essential of treatment is to win the confidence and cooperation of both husband and wife, interviewed separately. The interview demands great tact and experience, and is time-consuming, but if conducted correctly is most rewarding. Once the confidence of the couple is won over, the true cause of the trouble will usually be disclosed, and simple instruction in its rectification may often suffice.

If the patient is obsessed with the idea that her genital tract is maldeveloped, she should be examined under an anaesthetic. At this examination, the normality of her lower genital tract is confirmed. The vagina is stretched to three fingers after which a large plastic dilator is inserted.

When the patient recovers from the anaesthetic, this large dilator is removed and its visual presence demonstrates to her beyond argument that her vagina is of normal capacity. She is then instructed by demonstration to pass a slightly smaller dilator and is supplied with one to be introduced at will every day at home to gain enough confidence and overcome any unfounded fears. The regular passage of the dilator should convince her that there is no obstruction to coitus.

If a rigid hymen appreciated as a sickle-like band resistant to stretching is encountered under anaesthesia, the operation of perineotomy (or Fenton's operation) should be performed. A longitudinal incision is made in the midline through the lower third of the posterior vaginal wall and skin of the perineum. After undercutting the tissues on each side and dividing the superficial muscles of the perineum, the wound is closed by interrupted sutures so that the scar lies transversely. The incision should be made of a length such that the vaginal orifice subsequently admits three fingers. After this operation of plastic enlargement of the introitus, it is useful to pass a medium-sized plastic dilator daily, and the patient is supplied with one for use. Coitus should not be attempted until the perineotomy wound has healed soundly, usually in 3 or 4 weeks.

Botulinum neurotoxin type A injection into levator ani muscle 4 weekly improves vaginismus.

Dyspareunia

The term *dyspareunia* is loosely used for difficult as well as painful coitus. The following classification of the causes of dyspareunia is suggested.

Due to the Male Partner

- Gross congenital abnormality of the penis.
- Impotence, usually partial, e.g. failure to maintain an erection long enough for penetration.
- Premature ejaculation.
- Complete and surprising ignorance in the technique of coitus.

Due to the Female Partner

1. Painful lesions in the region of the introitus, such as vulvitis (acute and chronic), urethral caruncle, Bartholin's cyst or abscess, tender scar from obstetric trauma or operation and painful lesions of the anal canal, notably fissures.
2. Obstructive conditions at the vaginal introitus:
   - Rigid or imperforate hymen and painful carunculae myrtiformes giving rise to spasm.
   - Narrow introitus due to congenital hypoplasia, kraurosis or lichen sclerosus—poor lubrication in a menopausal woman.
   - Traumatic stenosis due to obstetric injury followed by scarring, such as painful episiotomy scar, tightly sewn perineal tear or perineorrhaphy operation, mutilation, vulvodynia and vulvar vestibulitis.
   - Cicatrization due to chemical burns.
   - The functional spasm of vaginismus.
   - A large tender Bartholin's cyst is occasionally obstructive to entry.
3. Obstructive conditions above the vaginal introitus:
   - Congenital stenosis and the various maldevelopments—i.e. partial noncanalization of the vagina.
   - Acquired stenosis—chemical burns are rare but the important causes here are the result of surgical operation. Vaginal hysterectomy and prolapse repairs, Wertheim's operation, radium insertion and radiation therapy result in narrowing and shortening of the vagina. Sometimes, the anterior and posterior suture lines of a colporrhaphy become densely adherent and fuse to form a stout septum which allows only partial penetration.
   - Benign and malignant tumours of the vagina are rare causes of obstruction. *Dry vagina in a menopausal woman.*
4. Uterine conditions which are not obstructive but because they are painful give rise to collision dyspareunia:
   - Cervicitis. Chronic inflammatory lesions of the cervix associated with parametritis can cause pain. Deep dyspareunia is due to:
   - Chronic parametritis and parametrial scars.
   - Adenomyosis uterus.
   - A fixed retroversion associated with chronic pelvic inflammatory disease (PID).
5. Lesions of the uterine appendages:
   - Prolapsed ovaries associated with retroversion cause deep dyspareunia.
   - Acute and chronic salpingo-oophoritis. Ovarian residual syndrome.
   - Endometriosis of the pouch of Douglas, rectovaginal septum and uterosacral ligaments.
6. Extragenital lesions in the bowel, such as diverticulitis of the sigmoid colon usually adherent to the left appendages and uterus, and cystitis.

Difficult coitus. Difficult coitus may be caused by many of the same factors that are responsible for painful coitus. If the cause is insuperable, such as bony ankylosis of the hip in extreme adduction, consummation may be impossible and the correct term is not dyspareunia but apareunia. The latter naturally occurs with severe developmental defects of the vagina such as failure of canalization (vaginal aplasia).

Investigations

Investigations should be conducted along similar lines to that of vaginismus. Clinically, dyspareunia is divided into the following:

1. Superficial: The pain occurs when penetration is attempted and the causative lesion is therefore to be expected at or near the introitus.
2. Deep seated, when the pain is not associated with penetration but is felt only after this has occurred and is usually localized in the depth of the vagina.
3. Postcoital dyspareunia, a less well-known entity, sometimes associated with the deep-seated variety. Here the patient complains of an aching soreness which lasts for several hours after the completion of the act.

Deep-seated dyspareunia is usually organic and is associated with ovarian pathology such as prolapsed and tender ovaries in association with retroversion, endometriosis or chronic PID.

Treatment

The treatment consists in dealing with the cause. Local abnormalities at the vulva can usually be cured by appropriate treatment, but when dyspareunia is caused by abnormalities in the pouch of Douglas, an abdominal operation is necessary. The ovaries may be freed from adhesions, endometriosis and chocolate cysts can be excised and the uterus can be fixed in a position of anteversion by an operation of ventrosuspension. Oestrogen cream is effective in a menopausal woman.

- K-Y Jelly (lubricant) and Rejois vaginal moisturizer two to three times a week relieves dyspareunia due to lower genital tract. Postural change may help.
- Lignocaine ointment is an anaesthetic drug that relieves pain.

When all possible organic causes of the dyspareunia have been eliminated, psychogenic possibilities must be considered; patient enquiry may then elicit the true cause, such as fear of pregnancy, frigidity, marital disharmony or some unhappy sexual experience in the past.

Infertility and Sterility

According to WHO, positive reproductive health of a woman is a state of complete physical, mental and social

well-being and not merely absence of disease related to reproductive system and functions.

Infertility implies apparent failure of a couple to conceive, while sterility indicates absolute inability to conceive, for one or more reasons. If a couple fails to achieve pregnancy after 1 year of 'unprotected' and regular intercourse, it is an indication to investigate the couple. This is based on the observation that 80% of normal couples achieve conception within a year. It is observed that 50% conceive within 3 months of regular, unprotected intercourse, 75% in 6 months and 80–85% conceive within a year. Infertility is termed primary if conception has never occurred, and secondary if the patient fails to conceive after having achieved a previous conception. The incidence of infertility in any community varies between 5 and 15%.

Physiological sterility is present before puberty and after menopause. It must be remembered, however, that a girl may conceive before menstruation if the first ovum to be shed is fertilized, but this is rare because the initial cycles are usually anovulatory. After menopause, pregnancy is very rare and nearly impossible for the same reason that the menopausal ovaries contain no Graafian follicles. A physiological sterility during pregnancy is due to inhibition of ovulation once conception occurs. The infertility of the lactation period is regarded as relative. The time of return of ovulation and menstruation during lactation is variable and unpredictable. Two per cent of nonlactating women show evidence of ovulation in the first month following delivery and 33% ovulate before the first menstruation. The duration of amenorrhoea after the childbirth is on an average 2 months, but may be longer in nursing mothers. Regularly lactating women experience a longer duration of amenorrhoea and ovulation is delayed for at least 3 months, or even longer at times (6 months). Optimal age for conception is 20–35 years in a woman. Over the age of 40 years the fertility rate is reduced, and there is an increased risk of chromosomal abnormalities and other malformations in the fetus. For a man age is less important, but after 50 years, decreased libido and sexual dysfunction reduce fertility and predispose to malformed fetus Therefore, it may be prudent to proceed with investigations of apparent infertility in a woman near or over the age of 35 years, instead of waiting for a year, if she seeks gynaecological help.

Conception is the result of successful fertilization of the female egg by the sperm. Hence, the couple should be counselled individually and then together because both partners contribute varyingly to the occurrence of the infertile state. It is mandatory to investigate both the partners simultaneously, carry out the necessary tests and adopt appropriate measures to enhance the fertility potential of each individual partner.

Issues Involved

The major goals involved in the comprehensive investigations of the infertile couple are as follows:

- Identification and correction of causes contributing to the infertile state over a short span of time.
- Providing accurate information, education and counselling to both the partners, and explaining the nature of therapy and the cost.
- Providing counselling about alternative management of infertility if pregnancy fails or is not possible (sterility) should be provided. This may include discussions on the roles of assisted reproductive techniques, artificial insemination and the option of adoption. Prognosis and success rate of each should be discussed. It is also important to realize the futility of repeating the same investigations by different doctors which may be frustrating to the couple apart from the expense incurred. It may be prudent on the part of the doctor to study the previous records before asking for a repeat test.

Prognosis

The increased age of the woman, duration of infertility, and primary infertility carry a poor prognosis, and are the risk factors in infertility management.

Theoretical Considerations

During the initial counselling, it is important to explain to both the partners, in a simple language, the process of reproduction with the help of charts and models. Explain that it is possible to find faulty function in both partners, and often overlapping causes exist, hence the need to evaluate and treat both the partners concurrently.

Male Infertility

Spermatogenesis. The sperms are formed in the lining of the seminiferous tubules from the germinal cells—spermatogonia (Figure 19.1).

Spermatogonia are diploid germinal cells which divide by mitosis into spermatocysts. These undergo reduction division (meiosis I) into haploid secondary spermatocysts, which by meiosis II develop into spermatids. These spermatids develop into compact, virtually cytoplasm-free sperms with condensed DNA in the head, capped by apical acrosome and a tail (Figure 19.2). These sperms are incapable of fertilization until they undergo capacitation in the female cervical canal. The entire process of spermatogenesis takes 74 days, and inclusive of transport in the ductal system occupies 3 months. They are present in the testes in different stages of development at any one time. The testes produce 200–300 million sperms daily. Capacitation can also be induced following incubation in a culture media in in vitro fertilization (IVF). Cervix provides the following:

1. Nutrition to the sperms.
2. Alkaline medium to survive.
3. Sieves out abnormal sperms.
4. Causes capacitation of sperms, which take about 1 h.
5. Storage until upward propulsion occurs.

Acrosome reaction is an important component of capacitation for zonal penetration into the oocyte. Acrosome is a modified lysosome over the sperm head. The overlying

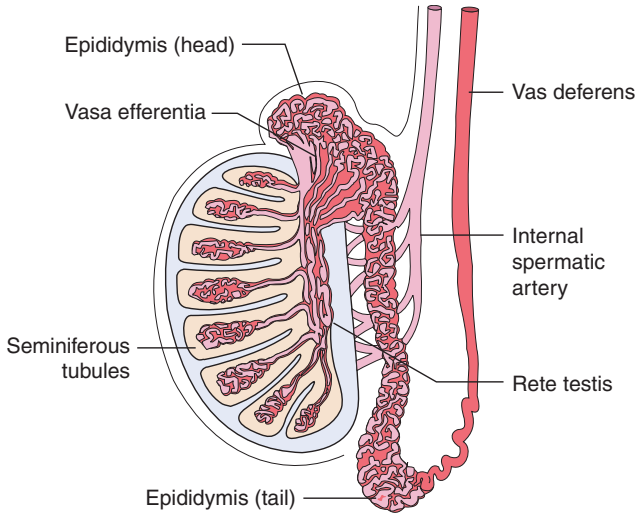

Figure 19.1 Normal anatomy of the testes.

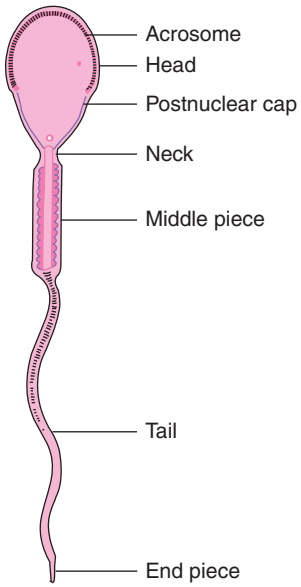

Figure 19.2 Normal sperm.

membrane becomes unstable, breaks down and releases hyaluronidase enzyme, which allows corona radiata and zonal penetration.

The Sertoli cells line the seminiferous tubules and extend from the base of the membrane to the lumen. They support the spermatids and possess receptors for follicle-stimulating hormone (FSH) and testosterone. The tropic effect of FSH and testosterone on spermatogenesis is mediated via the Sertoli cells. There are four sperms per Sertoli cell. The Sertoli cells produce Müllerian inhibitory factor which prevents the development of Müllerian system. The Sertoli cells also produce testosterone-binding protein which maintains high level of testosterone within the testis. This is necessary for continuous spermatogenesis.

Endocrine Control

The spermatogenesis depends on the hypothalamic–anterior pituitary–testicular functions. Gonadotropin-releasing hormone (GnRH) stimulates the anterior pituitary gland to secrete FSH and luteinizing hormone (LH). FSH acts on Sertoli cells and LH triggers testosterone secretion by the Leydig cells (interstitial cells). The concentration of testosterone is higher in the testes than in the plasma. The testosterone in turn exerts a negative feedback to the pituitary gland, as well as the hypothalamus (Figure 19.3).

A total of 60% of serum testosterone is bound to sex hormones binding globulin (SHBG) and 20% to albumin. A small portion is converted to oestrogen. Two per cent free testosterone is converted to dihydrotestosterone by 5 alpha reductase which acts on hair follicles and is responsible for male phenotype.

Sertoli cells also secrete inhibin B which in turn inhibits FSH but stimulates LH secretion.

Fertilization. Following capacitation, a mature sperm meets the ovum in the ampullary portion of the fallopian tube. By acrosomal reaction and hyaluronidase release, it penetrates the zona pellucida, which in turn prevents entry of other sperms (polyspermia). It is possible to aspirate the polar body or a blastocyst cell for genetic study of the embryo, without disturbing further development of the embryo.

Pathology of Infertility

In one-third of all cases, the male is directly responsible, in one-third both partners are at fault and in the remaining third the cause of failure is attributed entirely to the female. These figures are perhaps extremes and it might be more appropriate to distribute the fault evenly between the two partners.

Faults in the Male. The factors involved include:

- Disorders of spermatogenesis—50%
- Obstruction of the efferent ducts—30%
- Disorders of sperm motility—15%
- Sexual dysfunction
- Unexplained—15%

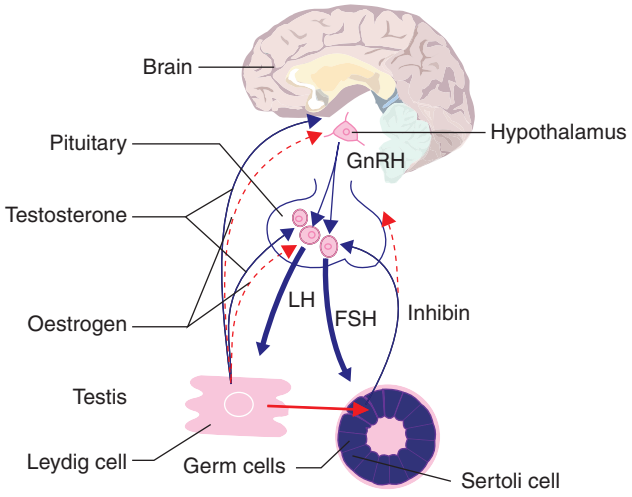

Figure 19.3 Endocrine control of spermatogenesis.

For adequate spermatogenesis, the testicle must lie in its correct position in the scrotum, where the temperature is slightly cooler than elsewhere in the body. The factors which raise the scrotal temperature can adversely influence spermatogenesis, e.g. the occupation of men who work as stokers or in blast furnaces and are subjected to excessive heat, the wearing of a tight scrotal support and the presence of a varicocele. The ectopic or undescended testicle provides the best example of the adverse effect of temperature on spermatogenesis. The collecting apparatus of the epididymis may be damaged by trauma or inflammatory disease, notably gonorrhoea or tuberculosis. The vas deferens itself may be occluded, and this is specially to be suspected if there is a herniorrhaphy scar and doubly so if the scar is bilateral. Chronic inflammatory disease of the prostate and seminal vesicle may be associated with male infertility. Congenital lesions of the penile urethra such as hypospadias provide an obvious mechanical explanation for imperfect insemination. A history of mumps, venereal disease, diabetes, thyroid or tuberculosis may suggest testicular atrophy or obstruction. The occupation of the male, history of excessive smoking, indulging in excessive alcohol consumption and chewing tobacco and *gutka* may also suggest poor spermatogenesis. Accidental or operative trauma, e.g. blow on the testicle with haematoma formation and subsequent atrophy, or operation for hernia, varicocele or hydrocele may suggest a degenerative lesion of the testes or obstruction to the vas. About 1–2% males suffer from genetic defects such as Klinefelter's syndrome with 47 XXY chromosomes.

5% men are azoospermic.

Aetiological Classification

1. Genetic—abnormal Y chromosome and XXY in Klinefelter's syndrome. Mutation of short or long arm Y chromosome.
2. Disorders of spermatogenesis.
   A. Hormonal (pretesticular):
      - Hypothalamic disorder, Kallman's syndrome.
      - Pituitary secretion of FSH, LH.
      - Hyperprolactinaemia causing impotence or diminished libido.
      - Hypothyroidism, adrenal gland disorder and diabetes.

   B. Primary testicular disorders (testicular):
      - Idiopathic, varicocele, absent germ cells.
      - Chromosomal defect, i.e. Klinefelter's syndrome.
      - Cryptorchidism.
      - Drugs, radiation, calcium channel blocker, anticonvulsants, antihypertensives, spironolactone and cimetidine.
      - Orchitis (traumatic, mumps, TB, gonorrhoea).
      - Chronic illness.
      - Immunological disorders (5%).
      - Immotility due to absence of dynein arms. Absent cilia in Kartagener's syndrome (15%).
3. Duct obstruction (posttesticular). Congenital absence, inflammatory block (gonococcal, tubercular), surgical trauma, Young's syndrome (inspissated mucus) associated with sinusitis and bronchiectasis. *E. coli*, staphylococci, chlamydial infection, mycoplasma genitalis cause DNA fragmentation of sperm, decreased motility and apoptosis. Antibodies to genital infection cause (1) chronic pain, (2) infertility and (3) adverse pregnancy outcome.
4. Accessory gland disorders: Prostatitis, vesiculitis and congenital absence of vas in cystic fibrosis.
5. Disorders of sperms and vesicular fluid:
   - Sperm antibodies and low fructose in seminal plasma. Immotile cilia syndrome (Kartagener's syndrome).
   - Sperm acrosome defect.
   - Zona pellucida binding defect.
   - Zona pellucida penetration defect.
   - Oocyte fusion defect.
6. Sexual dysfunctions:
   - Low-frequency coitus—wrong time, low libido.
   - Impotence, hypospadias.
   - Premature ejaculation.
   - Retrograde ejaculation.
7. Psychological and environmental factors such as smoking, alcohol consumption, tobacco chewing, diabetes and drugs—antihypertensive, antipsychotics, cimetidine, sex steroids (excess testosterone and anabolic used by athletes) chemotherapy, nitrofurantoin, beta-blockers, spironolactone, oestrogen.
8. Obesity increases peripheral conversion of androgen to oestrogen and affects fertility.
9. Chronic illness.

Investigations

1. **History.** History includes age of the man, previous children, duration of infertility, and any contraception practiced and for how long. This gives a true picture of the duration of infertility.
   - The coital frequency and timing related to ovulation.
   - The occupation—a frequent traveller or working in a hot place.
   - Habit of smoking, alcohol, tobacco and drugs.
   - History of tuberculosis, sexually transmitted infection, diabetes and chronic illness. Diabetic neuropathy can cause impotence and retrograde ejaculation. Fever of any cause can suppress spermatogenesis for as long as 6 months. Chronic respiratory disease.
   - Operation on the hernia or scrotum, undescended testis.
   - Any coital problem such as premature and retrograde ejaculation, failure to ejaculate.
2. **General examination** can be postponed in a male until after the semen analysis. A normal report rules out any general and local cause for male infertility and male examination is not mandatory. One can move on to further investigations. Abnormal semen analysis calls for general and local examination.
   - General height—increased height in Kallman and Klinefelters syndrome is due to late closure of epiphyses of the bones.
   - Weight and obesity may be hormonal defects.

- The secondary sex characters are abnormal in Klinefelter's syndrome, i.e. gynaecomastia associated with Turner-like stigmata.
- Thyroid enlargement, enlarged breasts and hirsutism are noted. Blood pressure should be checked.

3. **Local examination** includes examination of penis and scrotum, and surgical scar. The normal scrotal volume is 15–35 mL (average 18 mL). Testicular volume of less than 6 mL is seen in atropic testes and in Klinefelter's syndrome. The testes should be well placed in the scrotum. The epididymis should be palpated for enlargement and thickness. The vas feels thickened in inflamed conditions. Rectal examination concludes the prostate examination. The presence of varicocele (mainly left side) can be demonstrated when man is standing, and on Doppler ultrasound.

Special investigations comprise the following:

- Semen analysis.
- Hormonal assays.
- Testicular biopsy—for histology, genetic study and cryopreservation in assisted reproduction (intracytoplasmic sperm insemination).
- Immunological tests.
- Patency of vas.
- Chromosomal study.

Not all of the above investigations are required in a male. Stepwise investigations will not only save time but avoid unnecessary and elaborate tests which not only prove useless and expensive, but stressful and frustrating to the man.

Semen analysis. The most important part of the male investigation is the semen analysis, and certain points regarding the method and timing of collection of the specimen are noteworthy. The best specimen is one obtained by masturbation in the vicinity of the laboratory, since this guarantees its freshness. If this is objectionable to the man, coitus interruptus into a wide necked bottle may be employed. Another method is the postcoital test described later. The production of a condom specimen is to be discouraged as the condom contains spermicidal chemicals and a false low reading may thereby be obtained. The best specimen will be produced if a short period of abstinence of 3–5 days is observed. A more prolonged period of abstinence does not yield better results. A typical normal specimen should show the following features when examined within 2 h of production (earlier the better). The semen should coagulate soon after ejaculation due to enzyme in the seminal vesicle, but liquefy in 30 min because of prostatic enzyme. The semen is greyish white in colour.

- Total volume, 3–5 mL (average 3.5 mL), viscous.
- Sperm count, 60–120 million/mL (average 100 million). Ten motile sperms per high field are considered normal.
- Motility 80–90% (average 80% forward motility).
- Morphology, 80% or more normal (average 80%).
- Sperm agglutination <2.

In 2010, WHO laid down the latest criteria for normal semen quality and minimal reference.

WHO 2010 semen analysis:

- Volume—2 mL (1.5 mL)
- PH—7.2–7.8
- Viscosity <3 (scale 0–4)
- Sperm concentration 20 million/mL or more (15 million/mL)
- Total sperm count >40 million/per ejaculate or more
- Motility >50% or more with progressive motility
- Morphology >14% strict criteria (4%)
- Viability >75% or more (50%)
- White blood cells <1 million/mL
- Round cells <5 million/mL
- Sperm agglutination <2

Low volume due to:

- Incomplete abstinence, collection
- Abnormalities in the seminal vesicles
- Partial vas obstruction
- Retrograde ejaculation
- Hypogonadism

Pus cells should be absent. The seminal fluid is normally viscous with a pH of 7.2–7.8, and contains fructose.

Aspermia—means no semen.
Azoospermia—implies no sperm in semen.
Oligospermia—low sperm count.
Asthenospermia—no motile sperm or diminished motility.
Necrospermia—dead sperms.
Teratospermia—abnormal morphology of sperms.

A normal sperm is motile, 50 μ in length, half the size of ovum and consists of a head covered by an acrosomal cap, neck, body and tail.

Hypospermia means low volume, less than 1.5 mL. This may be due to improper collection or retrograde ejaculation.

Hyperspermia with more than 5.5 mL means prolonged abstinence or inflammation of seminal vesicle.

The most important factor is the density of the sperm population, and counts below 20 million/mL are usually associated with infertility. Oligospermia is mild when the count is 10–20 million, moderate when 5–10 million, and severe when less than 5 million/mL sperms are seen.

If one report shows abnormal findings, the patient should be instructed to produce another specimen after a month or so. During this time, the patient should be advised to take a good nutritional diet and restrict smoking and consumption of alcohol. He should take cold or tepid bath and discard tight underwear. Only after three negative or below average counts, he should be proclaimed azoospermic or oligospermic. If so, chromosomal study should be done (Table 19.1).

A few normal sperms and normal testosterone suggest retrograde ejaculation. Do urine test (centrifuge) and see if sperm are seen—use it for IUI, IVF.

Postcoital test (*Sims' or Huhner's test, PCT*). The couple is advised intercourse close to ovulation time preferably in the early hours of the morning. The woman presents herself at the clinic within 2 h after the intercourse. The

TABLE 19.1 Latest WHO recommendations for normal semen analysis reference values

- Volume: 1.5–5.0 mL
- pH: >7.2
- Viscosity: <3 (scale 0–4)
- Sperm concentration: >20 million/mL
- Total sperm number: >40 million/ejaculate
- Percent motility: >50%
- Forward progression: >2 (scale 0–4)
- Normal morphology: >50% normal
- Round cells: <5 million/mL
- Sperm agglutination: <2 (scale 0–3)

Source: WHO guidelines.

mucus is aspirated from the cervical canal and spread over a glass slide. Another smear made from the posterior fornix serves as a control. Normally 10–50 motile sperms are seen per high-power field in cervical mucus. If there are less than 10 sperms, proper semen analysis should be undertaken. The sperms should show progressive, but not rotatory movements. The presence of antispermal antibodies in the cervical mucus imparts shaky or rotatory movements to the sperms or may totally immobilize them. The cervical mucus is simultaneously examined for its quantity, viscosity and fern test. The advantage of this test is that the cervical mucus can be simultaneously studied for oestrogenic effect and ovulation, its capability to allow sperm penetration and the presence of any antisperm antibodies. The test is useless in the presence of cervical infection, which should be treated before performing the postcoital test. Immunological factor is encountered in 5% cases. This test is less employed lately, and many gynaecologists consider this obsolete. This is because they resort to IUI if semen analysis is abnormal.

A test called the *Miller–Kurzrok* test consists of placing ovulation mucus on a glass slide alongside the specimen of the husband's semen and studying the penetration of sperms under the microscope. Normal cervical mucus permits invasion by motile sperms. Penetration less than 3 cm at 30 min is abnormal.

Sperm penetration test. The physiological profile of the sperms can be studied in vitro by using the zona-free hamster egg, which resembles the human ovum. A normal sperm is capable of penetrating the zona-free hamster egg, showing its fertilizing capacity. The test is expensive and not reliable.

Sperm agglutination tests, immobilization tests and immunoglobulin specific assays are available to detect immunological defects in the semen.

Semen–cervical mucus contact test. Equal quantity of semen and mucus is mixed, so that there is no interface. In the presence of antibodies more than 25% sperms show jerky or shaky movements by 30 min. The cross-check with the donor semen will indicate the source of antibodies, whether it is cervical or seminal antibodies.

Testicular biopsy. Testicular biopsy is indicated in azoospermia to distinguish between testicular failure and obstruction in the vas deferens. It also reveals whether the seminiferous tubules are normal but unstimulated by the anterior pituitary gland, or whether they are incapable of function due to primary gonadal failure. Testicular biopsy will establish which of the factor is at fault (Figures 19.4 and 19.5). The biopsy can also diagnose genital tuberculosis. The tri-cut biopsy under local anaesthesia is simple to perform. One to three per cent males have endocrine dysfunction. *In recent times, the testicular biopsy has a very big role to play. Apart from chromosomal and histological study, the testicular tissue provides cryopreservation in assisted reproduction.* The spermatozoa as well as spermatids extracted from the testicular tissue can be used in intracytoplasmic semen insemination (ICSI) in assisted reproduction. Sperm morphology is studied by preparing a slide, air-drying, fixing it with 70% alcohol and staining with Pap stain.

FSH level. A high FSH level denotes primary gonadal failure. A normal level in azoospermia suggests obstructive lesion in the vas or epididymis. A low FSH level indicates pituitary or hypothalamic failure and a need for FSH/LH/GnRH

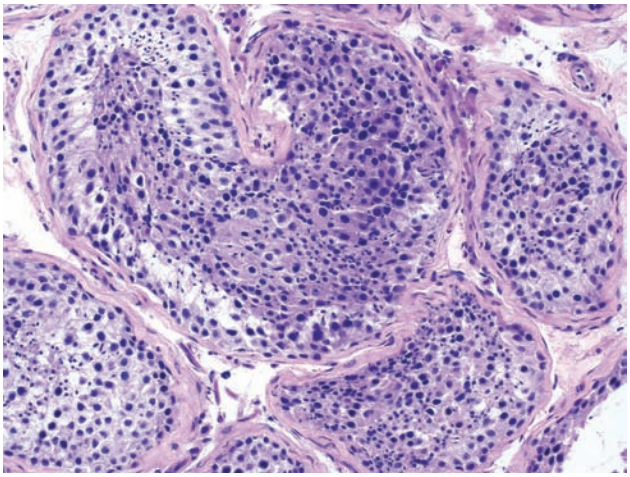

Figure 19.4 Testicular biopsy. Normal seminiferous tubules. Note spermatozoa in lumen (×250). (Source: Dharam Ramnani, MD, Richmond, VA, http://www.webpathology.com/image.asp?case=27&n=1.)

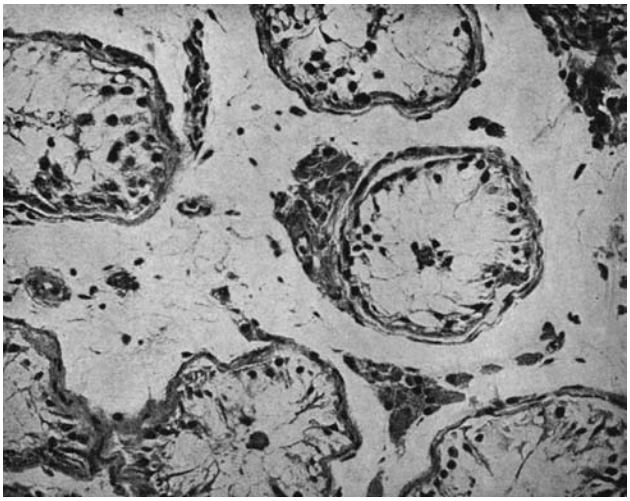

Figure 19.5 Testicular biopsy. Tubular atrophy showing Sertoli cells only (×250). (From: Macleod and Read, Gynaecology, 5th ed. Churchill, 1955.)

treatment. Prolactin level more than 30 ng/mL indicates hyperprolactinaemia requiring treatment. Low testosterone level indicates low LH or Leydig cell dysfunction. No response to GnRH suggests pituitary failure.

Chromosomal study. Karyotyping should be undertaken in azoospermic men, as 15–20% of them have chromosomal disorders. The most common disorder is Klinefelter's syndrome with 47 XXY karyotype.

Immunological disorders. A recent interest in immunological aspects of infertility has led to the detection of various sperm antibodies, both in the seminal plasma and in the cervical mucus. Immunological factors may be important aetiologically in up to 5% of patients with male infertility. Immunological test is required in abnormal postcoital test, abnormal semen profile and unexplained infertility. ELISA and RIA tests determine antibodies to sperm, seminal plasma and cervical secretion.

Ultrasound scanning. The ultrasound scanning of the scrotum detects scrotal volume and hydrocele and is useful in ultrasound-guided biopsy. Colour flow Doppler and scrotal thermography detect varicocele.

- Vasogram. It is required when normal FSH level is associated with azoospermia.
- Urine examination. In suspected retrograde ejaculation, postejaculatory urine is made alkaline and centrifuged. The presence of sperms in the urine proves retrograde ejaculation.
- Fragmentation of sperms suggests infection. Chlamydial and other infections should be investigated.
- Sperm fertilization potential.

In IVF, this test is useful in selecting the best sperm for fertilization. This is called hypo-osmotic swelling test (HOS). The sperms are treated with hypo osmotic saline. If the sperm membrane is intact, the sperms swell up and coiling occurs. These are the best sperms.

Management of Male Infertility

Management is based on the assessment of coital function, semen examination report and the result of the postcoital and immunological tests, as well as hormonal reports (Figure 19.6).

1. Education. This involves: (i) sexual counselling—coital frequency and timing, (ii) coital position and (iii) masturbation leading to sperm dilution.
2. Substance abuse. Advice on avoidance of tobacco (smoking, chewing), moderation in consumption of alcohol and avoidance of drug abuse. Antioxidants, vitamin E improve semen parameters. Pentoxifylline 400 mg t.i.d improves sperm motility.
3. Reduce heat around the scrotum. Avoid hot baths, wear loose cotton underwear (cotton clothing to encourage ventilation), avoid strenuous activities and occupation in hot environment and control obesity.

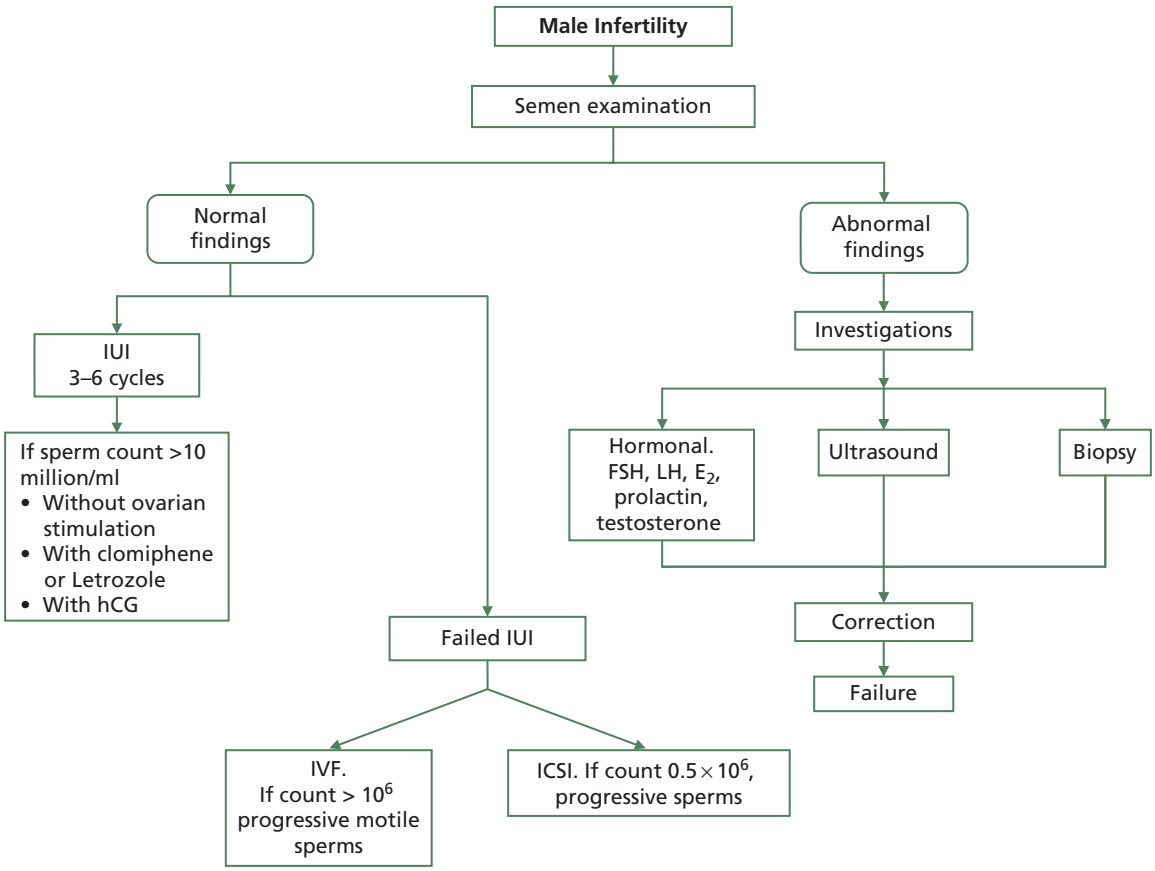

Figure 19.6 Management of male infertility.

4. Correct endocrinopathies. Prompt attention to diabetes and thyroid disorders.
5. Surgical. Surgical correction of varicocele after the diagnosis has been confirmed on ultrasound scanning helps to improve sperm motility. Though recently percutaneous embolization of varicocele is attempted, damage to the testicular artery and recurrence of varicocele make microsurgery the gold standard and the best option for varicocele. Lately, the beneficial effect of varicocele surgery is questioned by many who feel that the surgery for correction of varicocele has no role in improving male infertility. Surgical correction of the undescended testes in childhood improves the semen quality in 60–70% cases. The obstruction in the vas by vaso-vasal or vaso-epididymal anastomosis will restore patency. Ephedrine 60 mg orally four times a day for 2 weeks or α-adrenergic drug such as phenylephrine (2.5 mg) is tried in retrograde ejaculation. If this fails reconstruction of the bladder neck is recommended. Vasovasotomy in the reversal of vasectomy operation yields a poor result if an interval of more than 5 years has elapsed since vasectomy, because of the formation of sperm antibodies.
6. Antibiotics. Infection indicates the need for appropriate antibiotics to treat epididymo-orchitis, prostatitis and sexually transmitted diseases. Doxycycline 100 mg bid for 6 weeks is beneficial for chlamydial infection.
7. Role of oxidating stress on sperm function through prooxidants liberated by leucocytes, and abnormal sperms is now realized. Some have observed improved sperm count by prescribing lycopene 2 mg daily and vitamin E.

   Antioxidants contain vitamin E 100 mg, vitamin C 500–1000 mg, N-acetylcysteine 200–500 mg t.i.d., carnitine 3 g daily, selenium 225 mg, pentoxyfilline 400 mg t.i.d. Lycopene 2 mg daily for 6 months is reported to improve quality of the sperms and prevent sperm DNA damage, but data-based evidence is lacking at present.
8. Premature ejaculation. Selective serotonin reuptake inhibitors take 2 weeks to reach the therapeutic level, but dapoxetine works within 1 h; 30–60 mg is taken 1 h before intercourse.
9. Hormones. Testosterone, pituitary hormones and GnRH have all been tried to improve spermatogenesis with variable results. Bromocriptine is useful in hyperprolactinaemia.

Hormonal therapy

1. HCG 3000 IU IM thrice weekly for 12 weeks. Alternatively, 5000 IU twice weekly may be given. Lately 2500 IU dose has been recommended. Thereafter, 37.5–75 mg FSH subcutaneously is added thrice a week. Follow-up with testosterone level and semen analysis. It takes 6–9 months to produce normal semen counts. Stop FSH, but continue with HCG. 40% pregnancy rate is reported.
2. Testosterone—25–50 mg daily orally improves testicular function. A larger dose of 100–150 mg daily suppresses spermatogenesis. After a 3 month course of treatment, rebound phenomena occur with improved spermatogenesis.
3. Clomiphene—25 mg daily for 25 days followed by rest for 5 days is given cyclically for 3–6 cycles. It is recommended in hypogonadal infertility, but is not effective in hypogonadal hypopituitarism. Instead of clomiphene, letrozole 2.5 mg may be employed.
4. Human menopausal gonadotropin (hMG) 150 IU thrice a week for 6 months is recommended in pituitary inadequacy, but it may take as long as 1 year to induce spermatogenesis.
5. GnRH—is indicated in hypothalamic failure.

   GnRH 5–20 mcg subcutaneously 2 hourly for 1–2 years, preferably with add back therapy with oestrogens or progesterones. Nasal spray is also available.
6. Tamoxifen—10 mg daily for 6 months has been found effective in some cases.
7. Dexamethasone 0.5 mg daily or 50 mg prednisone daily for 10 days in each cycle for 3–6 months is recommended in the presence of spermal antibodies. About 25–40% pregnancy rate is observed, though avascular necrosis (AVN) of the head of the femur and osteopenia as side effects have to be borne in mind in prolonged therapy. Cyclosporin A 5–10 mg/kg daily for 6 months is better than corticosteroids in T-cell suppression. If corticosteroids are contraindicated, an anti-inflammatory agent such as naproxen 50 mg twice daily may lower the antibody levels.
8. Sildenafil (Viagra)—25–100 mg 1 h before intercourse improves erectile function but recent reports on cardiac ischaemic heart disease is alarming, and should be prescribed with care. Colour visual disturbances, headache, rhinitis and dyspepsia have also been reported. It is contraindicated in men on hypotensive drugs. Sildenafil is used only in erectile function, and does not improve libido. With 25–100 mg orally 1 h before intercourse, the effect lasts for 1–2 h. The drug is effective in 50–80% cases. It is contraindicated in the following:
   - Retinitis pigmentosa.
   - Diabetic retinopathy.
   - Patient on antihypertensive drugs, nitrates.
   - Cardiac disease, previous myocardial infarct, stroke.

   Self-injection of vasoactive drugs for erection is taken 5–10 min before intercourse and is 50–70% effective. Side effects are penile fibrosis, infection and prolonged erection. Prostaglandin E_1 causes penile vasodilatation. Urethral pellets are also available. Penile vascular surgery and penile prosthesis implantation rods are also available for erectile dysfunction.

   Penile implant AMS 700 is 3-piece inflatable penile prosthesis which is now available.
9. Artificial insemination. An artificial insemination with husband's semen for 4 cycles has yielded 30% overall success with 10% success per cycle. The results are better if combined with ovulation induction for multiple ovulation, and this is the practice recommended today. It is indicated in the following:
   - Chronic medical disorder.
   - Oligospermia after sperm washout.
   - Impotency—ejaculatory failure.

- Premature ejaculation, retrograde ejaculation.
- Hypospadias.
- Antispermal antibodies in the cervical mucus.
- Unexplained infertility.
- It is also possible to freeze the semen if the husband is a frequent traveller and not available at the time of ovulation for IUI. The semen can be frozen and used later in case the husband needs to undergo radiotherapy or chemotherapy.
- X–Y fractionation of sperms for sex selection, in genetic and chromosomal abnormalities.
- HIV-positive male or female.

Techniques used for artificial insemination include (i) intrauterine (IUI) and intrafallopian done via hysteroscope or by blind procedure, (ii) intracervical, (iii) pericervical and vaginal and (iv) direct intraperitoneal insemination (DIPI). The last named is used in unexplained infertility but has the risk of peritonitis. The semen is washed, concentrated and its quality improved by the 'swim-up' technique or by use of Percoll gradient. The semen with normal sperms with good motility thus obtained is then inseminated into the female genital tract. Obviously, artificial insemination is done around ovulation. About 1/2 mL of concentrated semen is injected 36 h after hCG injection when the ovarian follicle reaches 20 mm. Semen washing removes the abnormal sperms, seminal plasma containing antibodies and other debris, as well as prostaglandins.

Intrauterine insemination is normally done once around ovulation, some prefer to do twice in each cycle. IUI is repeated up to 3–6 cycles. One moves to IVF or intracytoplasmic insemination if conception fails. The IUI should be done within 90 min of collection of semen, for optimal results. Prophylactic progesterone is recommended to the woman in the luteal phase.

The artificial insemination with donor's semen has not been legalized in India and should only be undertaken in infertility centres after appropriate counselling and explanation of its implications to both the partners.

Indications are as follows:

- Azoospermia.
- Immunological factors not correctable.
- Genetic disease in the husband. Homozygous Rh positive husband with previous pregnancy losses.
- Chronic ill health and disease.

The donor for insemination is screened for HIV, sexually transmitted infection and hepatitis B, and good quality of semen confirmed. The frozen semen is stored for 6 months to minimize HIV transmission. If the donor remains HIV negative by the end of this period, the insemination is thawed and used.

Management of Azoospermia. Obstructive azoospermia requires vasogram to study the site and nature of blockage. Vaso-vasal anastomosis has been successful in a few cases. The advantage of surgery over ICSI is that it is a one time treatment and cost effective, if successful with permanent effect. Subsequent spontaneous pregnancies are possible.

Five per cent males suffer from azoospermia. Depending upon its cause, especially in hormonal deficiencies, GnRH and pituitary hormones have been used to induce spermatogenesis.

Other methods in male infertility are:

- IVF.
- Gamete intrafallopian transfer (GIFT) technique.
- Microassisted fertilization (MAF) technique.
- Microsurgical epididymal sperm aspiration (MESA) or percutaneous epididymal sperm aspiration (PESA).
- Testicular biopsy, sperm retrieval and MESA supersede other methods in modern treatment of male infertility and with improved success. Even spermatids have been utilized in assisted reproduction.

IVF. In this, induction of ovulation is done with clomiphene, FSH/LH or GnRH depending upon the woman's response to the drug. The aspiration of mature oocytes is done under ultrasonic guidance. The oocytes are kept in the specific culture for a few hours, to complete oocyte maturation. About 50,000 selected sperms are used for insemination.

Eighteen hours after insemination, oocytes are observed for the presence of pronuclei (sign of fertilization) and cultured for a further 24 h. At 2- to 4-cell stage, two-embryo transfer (ET) into the uterine cavity 1 cm below the fundus is performed. The woman is allowed to go home 2–3 h following ET. The indications for IVF are as follows: The genetic study of polar cell or embryonic cell prior to ET is possible and safe with normal growth of the embryo.

- Idiopathic or unexplained male and female infertility.
- Immunological factor in male and female.
- Blocked fallopian tubes or failed tubal surgery.
- Failed intrauterine or fallopian insemination.
- Mild endometriosis.
- Abnormal semen findings.
- Donor semen or sperm.

The indications for IVF are expected to expand with rapid improvement in its success and improved technology.

Complications. apart from hyperstimulation syndrome, multiple pregnancy and its complications, IVF can cause ectopic pregnancy in 5% and heterotropic pregnancy (ectopic + uterine) in 0.4% cases.

Three to four cycles of IVF yield 15–30% pregnancy rate. The best results are seen in women with blocked tubes, whereas poor results are seen in oligospermia, teratospermia and asthenospermia. Some clinics claim 40% and above success.

Whereas IVF avoids laparoscopic surgical procedure and general anaesthesia, and gives considerable information on fertilization process, it requires an expensive and an elaborate laboratory establishment. IVF is a costly therapy not affordable to many couples. Because of multiple pregnancy ensuing from two-ET with associated increased fetal loss through abortion, ectopic pregnancy and preterm delivery, many European centres believe in only one ET at a time,

though it takes longer for the woman to conceive. The cost of IVF therapy and the older age of women seeking assisted reproductive therapy in India have compelled the IVF specialists to continue to use two-ET method as of today.

GIFT was first described by Asch et al. in 1984. It involves aspiration of oocytes following ovulation induction either laparoscopically or under ultrasound guidance transvaginally. Laparoscopic route is preferred as it is anyway required for sperm and oocyte transfer into the fallopian tube. Two hours before aspiration, the semen is prepared, washed from the seminal plasma and left in culture medium at 37°C. The oocytes (2 per tube) are mixed with 50,000 sperms and transferred to each ampullary portion of the fallopian tube 4 cm from the fimbrial end. The volume transferred is 10–20 μ (micron).

GIFT technique allows in vivo fertilization in the natural site (fallopian tube) unlike IVF, but needs laparoscopy technique (invasive).

Lately, transfer of oocytes and sperms is attempted by transuterine catheterization of the tube (falloscopically) and laparoscopy is avoided.

The *indications* for GIFT are:

- Unexplained infertility.
- Failed intrauterine insemination (IUI).
- Male infertility.
- Immunological factor in male.
- Immunological factors in the cervix.
- Donor semen required (rare).

Both the fallopian tubes must be patent. The results are better with GIFT than IVF, i.e. 45% success versus 15–20%, but success rate with IVF is improving; besides laparoscopy is not required. Abortion rate of 10–15%, ectopic pregnancy (7%) and multiple pregnancy (20–50%) have been reported with GIFT.

Disadvantage—fertilization cannot be confirmed.

MAF *process in vitro*. These sophisticated expensive techniques are needed for the following reasons:

- IVF or GIFT fails due to fertilization failure.
- Immunologically derived infertility.
- Sperm binds to zona pellucida but fails to penetrate due to either spermal antibodies or antibodies to zona pellucida.
- No or weak binding of sperm to zona. This may be caused because of receptor defect on the zona, enzyme digestive defect or defective sperm motility.
- Oligospermia and asthenospermia.

Zona drilling (ZD) to allow spermal penetration has not been successful.

Partial zonal dissection (PZD) or puncture followed by insemination has produced pregnancies, but polygamy and abnormal embryos have occurred.

Subzonal insemination (SUZI) into perivitelline space is useful if the sperms are immotile or have reduced motility.

ICSI is indicated and proved successful in case of immotile sperms and sperm count less than 5 million/mL with a pregnancy rate of 30–40%. A single sperm is injected into the cytoplasm of the oocyte, which is then incubated overnight.

Indications for ICSI are as follows:

- Sperm count less than 5 million/mL.
- Absent or reduced sperm motility.
- Abnormal sperm morphology.
- Previous IVF has failed.
- Unexplained infertility.
- Failure to penetrate zona by sperm as seen in IVF.

Epididymal or testicular aspiration or biopsy. This is the latest technology employed in azoospermia caused by blocked vas. The former can be done under local anaesthesia, but testicular biopsy requires general anaesthesia.

Cryopreservation of semen of the husband and embryos for future fertility is required if the man has to undergo radiation or chemotherapy for malignancy. Alternately, epididymal or testicular aspiration technique is employed. In the latter situation, repeat aspiration can be avoided and sperms cryopreserved. ICSI now supersedes zonal techniques because:

- It is more successful in improving fertility.
- Spermatozoa as well as spermatids can be employed.
- Histopathology and karyotype study is possible.
- Cryopreservation saves cost and stress of repeated performance in each cycle.

The low success rate is attributed to older age of the woman undergoing the procedure. Because of the cost and stress of the procedure, women opt for these only if other methods fail.

Epididymal aspiration can be done under local anaesthesia, but testicular biopsy requires general anaesthesia.

We have come a long way in male infertility from initial donor insemination, artificial insemination of washed semen to IVF and ICSI with improved success.

Psychological Considerations. The discovery of infertility or sterility can create shock, fear and depression in the couple. Some feel inadequacy and shame of not being able to reproduce (Figure 19.7). Some lose their self-esteem and feel the social disadvantage. To add to this, the strain of investigations and treatment increase the financial burden not affordable to all. Sympathetic and respectful attitude by the medical personnel will help in dealing with the infertile couple during their consultation.

Impotence caused by fatigue, drugs, multiple sclerosis and diabetes needs correction. Similarly premature ejaculation needs physiotherapy and psychological counselling.

Erectile failure can be improved by the following methods:

1. Local injection of Alprostadil (prostaglandin) into the penile vessel. Erection occurs in 10 min and lasts for

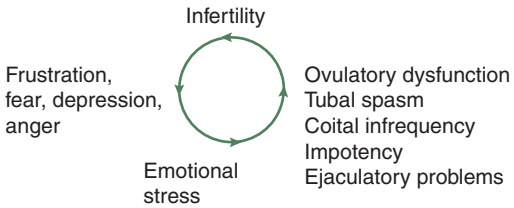

Figure 19.7 Psychological problems in infertility.

half an hour. This is painful, causes infection and fibrosis, besides being clinically impracticable.
2. Vacuum pump is applied to the tip of the penis to draw blood into it.
3. Prostaglandin pellets are inserted in the urethra and the penis is massaged.
4. Silicon cylinder prosthesis is implanted into the penis.

Compared to the above methods, consuming Viagra is easy, bearing in mind its side effects and contraindications.

Female Infertility

Age over 35 years, longer duration of infertility and primary rather than secondary infertility have adverse prognosis.

Aetiology

The causes of female infertility are attributed to (Figure 19.8):

1. Dyspareunia and vaginal causes.
2. Congenital defects in the genital tract.
3. Infection in the lower genital tract.
4. Cervical factors.
5. Uterine causes.
6. Tubal factors.
7. Ovaries.
8. Peritoneal causes—adhesions, endometriosis.
9. Chronic ill health—especially thyroid dysfunction.
10. Hormonal—pituitary gland dysfunction, hyperprolactinaemia and hypothalamic disorders.

Dyspareunia. Causes of dyspareunia have already been discussed. The important organic causes are fixed retroversion with prolapsed ovaries, inflamed adnexal disease and pelvic endometriosis. These conditions are often associated with blocked fallopian tubes. Dyspareunia alone can reduce the coital frequency.

Congenital defects in the genital tract. Absent or septate vagina, hypoplasia and absent uterus are the obvious causes leading to sterility.

Infection in the vagina and cervix. Although mild infection may not prevent sperms fast getting into the cervical canal, it is prudent to clear the infection before any therapeutic measures are applied in treatment of infertility.

Chlamydial cervicitis is now understood to impair spermal functions (fragmentation) besides causing blocked tubes due to PID.

Cervical mucus. As mentioned earlier, cervical factor can be assessed by the postcoital test. The test also provides the opportunity to assess sperm–mucus interaction and whether satisfactory coitus occurs or not.

- The finding of leucocytes in the mucus is suggestive of infection commonly due to cervicitis. Cultures for gonorrhoea, *Chlamydia trachomatis* and *Ureaplasma urealyticum* may help in selecting the proper antibiotic for the treatment of cervicitis. Large erosions are treated with electrocautery/cryocautery. Posttreatment repeat postcoital test often shows marked improvement.
- Nonmotile, nonprogressively motile sperms showing a 'shaking' pattern are highly suspicious of the presence of sperm antibodies and an immunological cause. If an immunological cause is suspected, the patient's serum and cervical mucus can be examined for the presence of antisperm antibodies. If the cervical mucus is found to contain spermal antibodies, the couple is advised to use a condom or a diaphragm as a barrier method for 3 months. During this period, the antibodies gradually disappear, and once the mucus is found to be normal, conception is attempted. The presence of serum antibodies has a poor prognosis, and IUI, IVF or GIFT technique is offered.

Cervical factors. The cervix has an active role in the physiology of conception. The position of the cervix and patency of the cervical canal facilitate the entry of sperms into the uterine cavity. The cervical canal functions as a sperm reservoir, and capacitation of sperms occurs here. The cervical mucus is alkaline and is suited for the semen. The ciliated endocervical cells actively select the normal motile sperms and sieve out the abnormal ones by phagocytosis, so that only the healthy fertilizable sperms enter the upper genital tract. The cervical mucus at ovulation exhibits characteristic changes which help in easy sperm penetration. These cervical factors are responsible for about 5% of infertility.

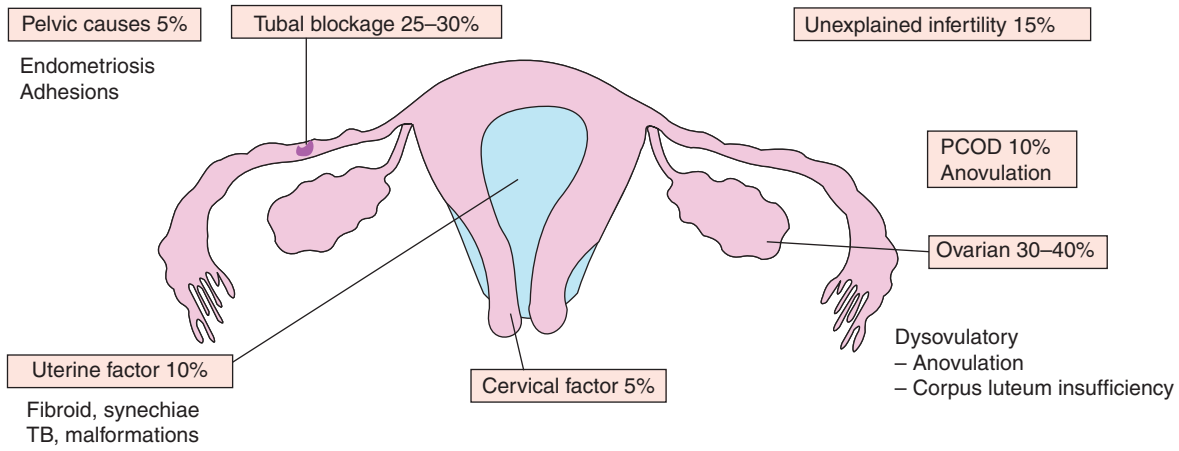

Figure 19.8 Causes of female infertility.

Uterine causes. Hypoplasia, malformed uterus and incompetent os cause habitual abortion more than infertility. In pelvic tuberculosis, blockage of tubes and endometrial tuberculosis causing Asherman's syndrome (adhesions) are responsible. Asherman's syndrome may also result from other infections, vigorous curettage, postabortal and puerperal infection, as well as packing the uterine cavity to control postpartum haemorrhage.

Asherman syndrome is classified as:

- Minimal—<25% adhesion involves the uterine cavity, flimsy adhesions involving the fundus and tubal ostia.
- Moderate—25–70% adhesion of the endometrial surfaces, but no agglutination of the uterine wall.
- Severe >75% adhesions with agglutination and thick adhesions.

The uterine fibroids which account for infertility are a cornual fibroid blocking the medial end of the fallopian tube, submucous fibroid and cervical fibroid distorting the passage of the sperms and preventing implantation.

Pregnancy rate of 30–40% following myomectomy proves that other factors may be involved apart from the presence of a fibroid.

Dyschrony between the glandular and stromal growth in endometrium or endometrium unreceptive to ovarian hormones can prevent implantation.

Tubal factors. One of the most important and common causes of infertility is salpingitis, when as a result of inflammation, adhesions form around the abdominal ostium, while within the lumen of the tube, the plicae become adherent, blocking the passage in the tube. Gonorrhoea and chlamydial infections or salpingitis following septic abortion and puerperal infections are amongst the common causes of blockage of the fallopian tubes. Tuberculosis has already been mentioned, and endometrial biopsy shows that 5% asymptomatic infertile women suffer from genital tuberculosis. Apart from tubal blockage, peritubal adhesions and fimbrial end blockage can cause infertility.

Westorm observed that one episode of tubal infection leads to tubal blockage in 12% cases. The incidence increases to 23% after two episodes of PID and 54% following three episodes.

Ovaries. Nonovulation due to endocrine disorders, polycystic ovarian disease (PCOD) and corpus luteal phase defects (LPDs) are some of the important causes of infertility. Peri-ovarian adhesion in pelvic infection and luteinized unruptured follicular (LUF) syndrome in 9% cases are also responsible. Resistant ovarian syndrome causes nonovulation.

Corpus LPDs either due to deficient progesterone or shorter duration of luteal phase occur in 3–4% of infertile women. This defect is also seen in in vitro fertilization programme, pituitary hormone deficiency (defective folliculogenesis), hyperprolactinaemia, excess luteolysis, clomiphene therapy and hypothyroidism.

Corpus LPD also occurs with low oestrogen and progesterone levels. Oestrogen is responsible for progesterone receptors in the endometrium, so low oestrogen will not develop secretory endometrium adequately. Corpus LPD means failure of endometrium to exist in the right phase at the right time. In luteal phase defect, histology of endometrium lags behind the day of menstruation by 2 days or more. Retrieval of ova in IVF by puncture can disrupt the granulosa cells. *Duphaston (dydrogesterone) is effective in corpus LPD without causing any adverse effect on ovulation.*

Subendothelial layer. A subendothelial layer in the endometrium can be recognized on ultrasound scanning and MRI, and this layer has increased nuclear content and vascularity and is under the influence of ovarian hormones.

Before menarche and after menopause, this zone is indistinct, so also in oral combined pill users and GnRH therapy. It is prominent in a menopausal woman on hormone replacement therapy (HRT).

In a conceptional cycle, peristalsis of this zone is upwards from cervix to fundus during preovulatory phase and may help in sperm migration. This zone becomes indistinct in the postovulatory period and quiescent and may help in implantation.

In IVF programme, increased activity of this zone may be responsible for failure as well as occurrence of an ectopic pregnancy.

Peritoneal causes. Peritubal and intratubal adhesions by kinking the fallopian tubes cause blockage of the tubes. More importantly, these adhesions form part and parcel of PID. These adhesions can also impair the peristaltic movements of the fallopian tubes. In pelvic endometriosis, macrophages in the peritoneal fluid may engulf the ovum and sperms, preventing fertilization.

Chronic ill health. Hypothalamic and pituitary disease, hypothyroidism and adrenal cortical dysfunction are the important causes of nonovulation. Diabetes and tuberculosis may lead to infertility. Smoking is known to impair ovarian function and prevent embryo implantation into the endometrium.

Investigations

Investigations comprise the following:

- History.
- Examination.
- Special investigations.

History. Age of the woman, past obstetric history in secondary infertility regarding puerperal infection, coital difficulty and menstrual history give clues to the possible cause. History of tuberculosis and previous pelvic infection is important. History of diabetes and thyroid dysfunction may be evident. The duration of infertility and previous use of contraceptive and the type may be linked to infertility.

Examination. This includes height and weight of the woman; blood pressure should be checked. Hirsutism, palpation of thyroid and lymph nodes, palpation of the breasts and presence of secretion suggest hormonal dysfunction.

An abdominal swelling may be due to uterine fibroid. Bimanual pelvic examination will reveal an obvious gynaecological cause for infertility.

Tests for Tubal Patency. A mere patency of the tubal lumen is not the only criteria to affect fertility. The normal physiological function of the fallopian tube is essential for pregnancy to occur. The endosalpinx is lined by ciliated epithelial cells and the secretory cells. The cilia help in propulsion of the fertilized egg towards the uterine cavity. The secretory cells provide nutrition to the sperms as well as the ovum during their passage across the tube. The peristaltic movements of the fallopian tube are under the influence of oestrogen, progesterone and prostaglandins, and synchronized movements help in propulsion of sperms and the fertilized egg in either direction. The ovarian fimbriae are spread over the ovary at ovulation and bring the ovum into the fimbrial end. The loss of any of these functions could prevent conception.

The testing of tubal patency and detecting tubal pathology are done in the preovulatory phase of the menstrual cycle. If performed in the postovulatory period, insufflation might disturb a fertilized or implanted ovum and may also cause pelvic endometriosis.

Hysterosalpingography (HSG). Visualization of the uterine cavity and the fallopian tubes should be carried out by screening with the use of an image intensifier in an X-ray room using a Foley catheter, Rubin cannula (Figure 19.9) or Leech-Wilkinson cannula for insufflation. The investigation is performed between the end of the menstrual period and ovulation (usually the ninth or tenth day of the cycle). After thoroughly cleaning the lower genital tract and with full aseptic precautions, a radiopaque dye is injected through the cannula into the uterine cavity under direct vision with a fluoroscopic screen; 15 mL of the medium is usually adequate to visualize the uterine cavity and the tubes. If the tubes are patent, the medium will be seen to spill out of the abdominal ostia and smear the adjacent bowel. A hydrosalpinx will show as a large confined mass of dye without peritoneal spill. If either tube is blocked, the site will be shown. At any stage of examination, radiographic pictures are taken for permanent record of the result. A viscous water-soluble solution, 50% iodine with 6% polyvinyl alcohol in water, is the medium usually employed for HSG. It is rapidly absorbed, and the risk of tissue reaction and adhesion formation in the pelvis is minimal; even when intravasated into the uterine venous system, it is harmless. Although an oil-soluble medium gives a sharper and clearer picture and may have improved therapeutic effect, it is not preferred because of the occurrence of oil granuloma, peritoneal reaction, formation of pelvic adhesions and the need for a delayed film to be taken for detecting peritoneal spill (Figures 19.10–19.14). Besides, it causes pain. The pregnancy rate is slightly better than that with water-soluble dye.

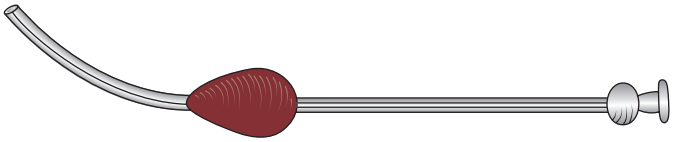

Figure 19.9 Rubin's cannula. It is used in hysterosalpingogram recording: while the dye is instilled into the uterine cavity, the cone prevents retrograde spill into the vagina.

Blockage of tube may be due to fibrotic block (stricture), spasms or inspissated amorphous material plugging the lumen.

Bilateral cornual block with extravasation of the dye is highly suggestive of tubercular salpingitis. Other hysterosalpingographic findings in tuberculosis are described in Chapter 14.

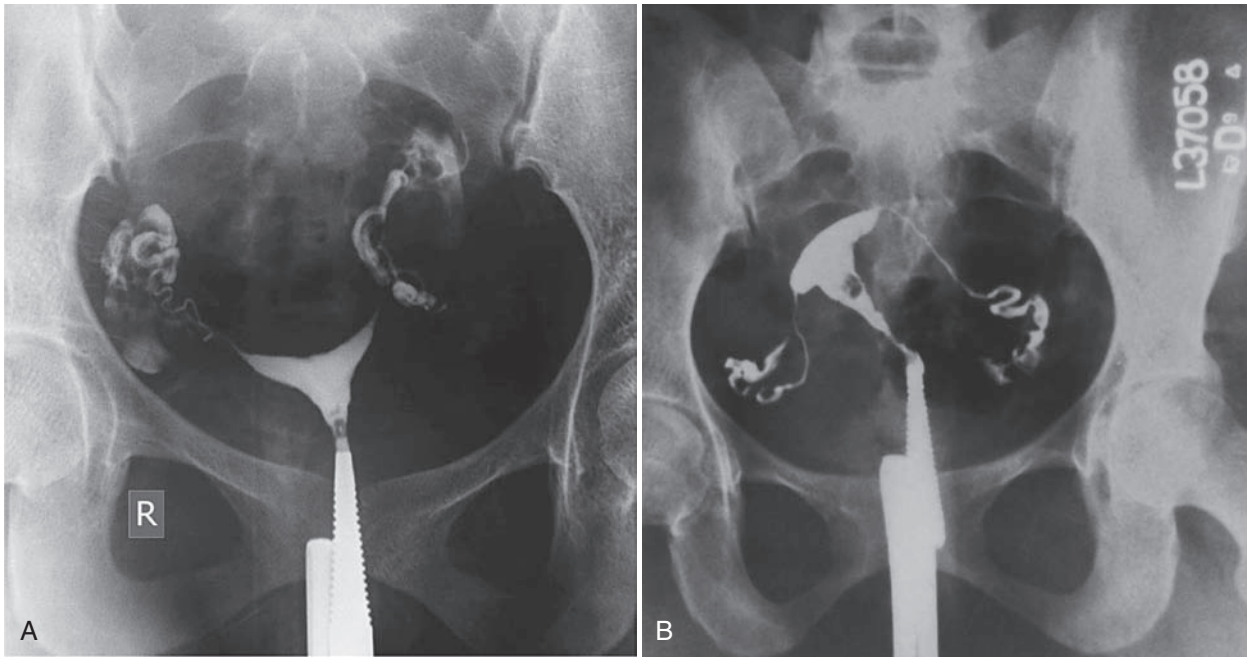

Figure 19.10 **(A)** Normal hysterosalpingogram. Note both the fallopian tubes are patent with spill into the peritoneal cavity. **(B)** HSG showing a filling defect in the uterine cavity which represent a polyp or fibroid. (Courtesy: Dr K K Saxena, New Delhi.)

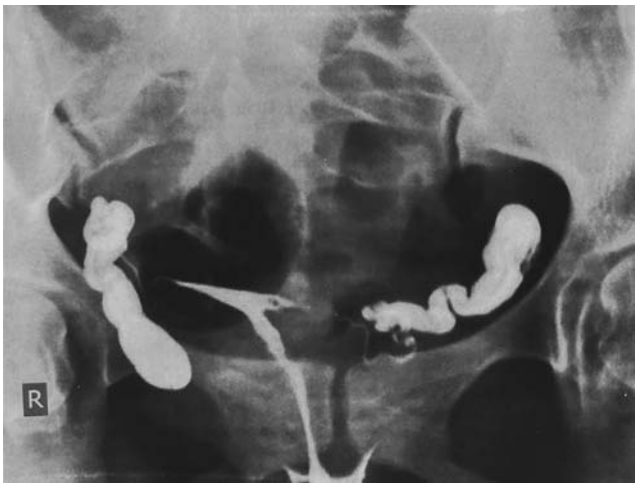

Figure 19.11 HSG showing bilateral dilated fallopian tubes with no free spill suggestive of bilateral hydrosalpinx (Courtesy: Dr K K Saxena, New Delhi.)

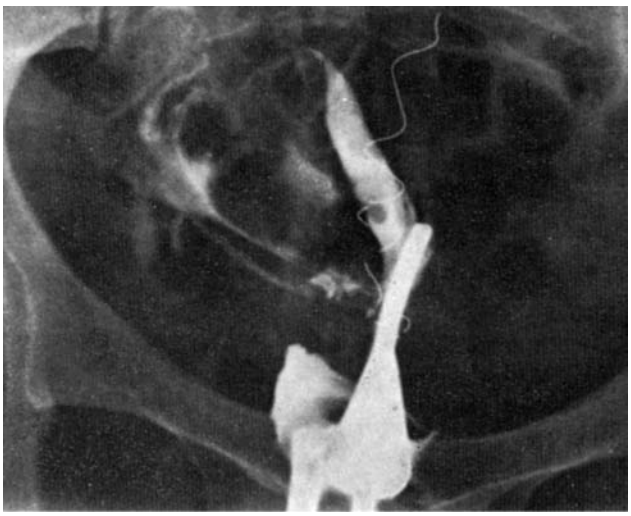

Figure 19.12 Hysterosalpingogram showing unicornuate uterus. The fallopian tube is patent and dye is seen in the peritoneal cavity.

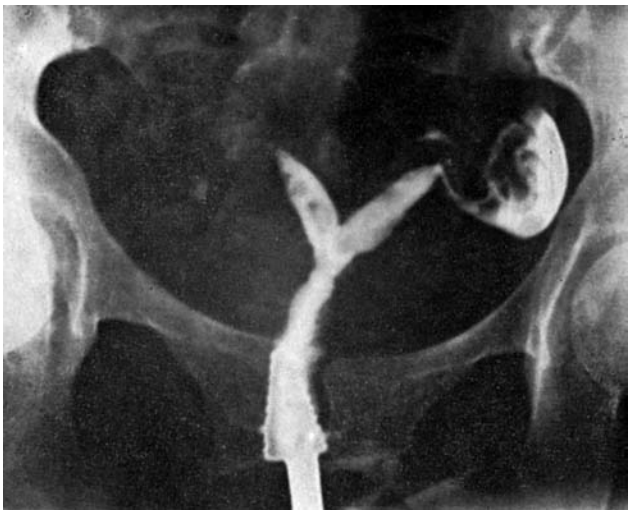

Figure 19.13 Hysterosalpingogram demonstrating a bicornuate uterus. The dye which is present in the peritoneal cavity demonstrates patency of the left fallopian tube.

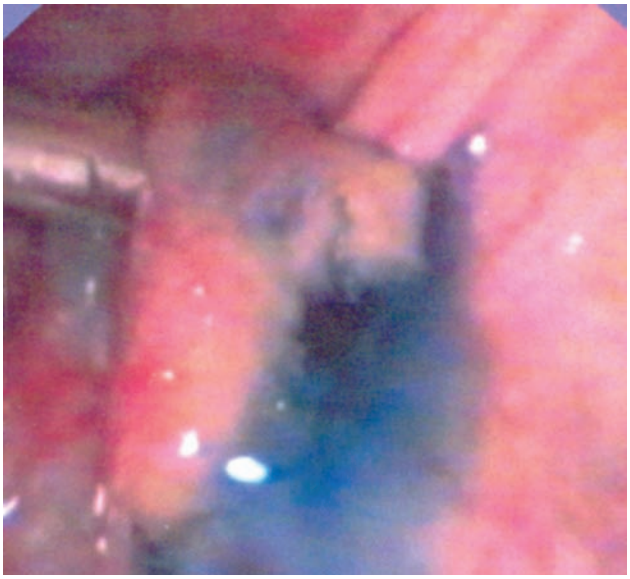

Figure 19.14 Diagnostic laparoscopy and chromopertubation with methylene blue dye showing free spill of the dye at the fimbrial end, indicative of a patent tube.

Apart fromtubal anatomy, this examination excludes congenital abnormalities of the uterus, such as uterus bicornis, arcuate, septate uterus and fibroids. HSG has the advantage that it gives a permanent record and shows the site of tubal blockage. Among its complications are (i) pelvic infection, (ii) pain and collapse which can however be avoided by injecting atropine half an hour before the procedure and (iii) allergic reaction. HSG should not be performed (i) in the postovulatory period, (ii) in the presence of genital infection and suspected genital tuberculosis and (iii) if the patient is sensitive to iodine. HSG yields 25–30% salvage value and this enhancement of fertility is attributed to flushing and dislodgement of amorphous material that sometimes blocks its lumen. The amorphous material is an aggregate of histiocytes. *HSG is not required in severe male infertility when IVF is decided upon, or any indication for IVF.*

Laparoscopic chromotubation. Laparoscopic visualization of the pelvis, fallopian tubes and ovaries and injection of methylene blue through the cervix to visualize the free spill or absence of spill are indicated in infertility to establish patency of the fallopian tubes and to verify the findings when HSG has shown blocked tubes (Figure 19.15). Apart from visualization of the tubal patency, peritubal adhesions and unsuspected endometriosis can be diagnosed. The laparoscopic study is indicated in patients with blocked fallopian tubes prior to undertaking tubal microsurgery. In such cases, planning of appropriate surgery can be chalked out and correct surgical prognosis offered to the couple. Laparoscopy demonstrates the external condition of the fallopian tubes as well as the patency. It is, however, an invasive procedure and requires hospitalization. The greatest advantage of laparoscopy today is that one can proceed with the therapeutic procedure if adhesions or fimbrial block is recognized. For this reason, the endoscopist alone should undertake this procedure.

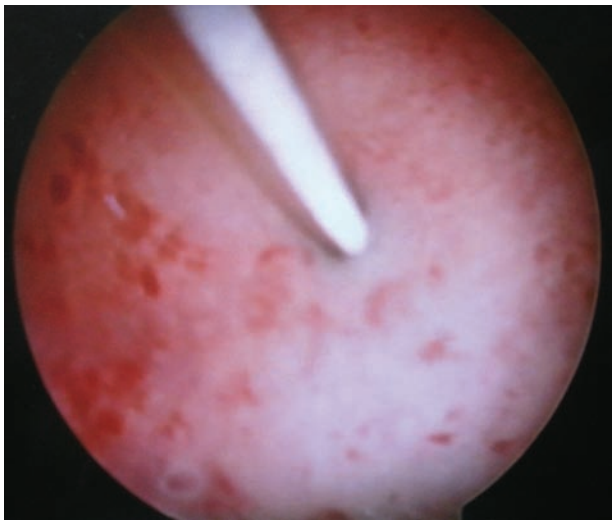

Figure 19.15 Hysteroscopic cannulation of the fallopian tube.

It is now well established that the toxic fluid in the hydrosalpinx reduces conception rate in IVF programme. Most believe in performing laparoscopic removal of hydrosalpinx prior to the IVF procedure. Similarly, endometrioma should be excised prior to IVF reproduction.

Indications for laparoscopy:

- HSG showing abnormal findings.
- Prior to planning tuboplasty.
- Prior to IUI.
- Prior to induction of ovulation.
- Removal of hydrosalpinx prior to IVF.
- PCOD to puncture the cysts to improve the pregnancy rate of assisted reproduction and avoid hyperstimulation syndrome.
- Suspected cases of endometriosis.

Sonosalpingography (SSG). It is a safe and practical method of evaluating tubal patency and to study the uterine cavity. Under ultrasound scanning, a slow and deliberate injection of about 200 mL of physiological saline into the uterine cavity is accomplished via a Foley catheter, the inflated bulb of which lies above the internal os and prevents leakage. It is possible to visualize the flow of saline along the tube and observe it issuing out as a shower at the fimbrial end. The ultrasound scan also shows the presence of free fluid in the pouch of Douglas if the tubes are patent. Injecting a small amount of air facilitates the visualization of air-bubble movement in each fallopian tube.

Sonosalpingography is also a very good technique of detecting submucous fibroid polyp and intrauterine lesions. Because of the side effects of the dye in HSG, many prefer sonosalpingography to HSG. Also known as saline sonohysterography, it is now employed in:

1. Abnormal uterine bleeding to study the endometrium and detect polypi.
2. Amenorrhoea due to Asherman's syndrome.
3. Part of infertility investigation.
4. Repeat pregnancy losses for uterine anomalies.
   - Prior to IVF.
   - It is done in the preovulatory phase as in HSG. Contraindications and complications are similar to HSG, but no allergic reaction as with the dye.

Newer Modalities. Tubal pathology can be assessed by newer diagnostic techniques. These are as follows:

Hysteroscopy and falloscopy. When HSG shows a cornual block, this may be due to tubal spasm (25%, avoided by prior atropine injection), mucus or inspissated material (25%), polyp (10%), synechiae or isthmica nodosa. The interstitial end of the fallopian tube is studied by falloscopy via the hysteroscope.

The mucus plug or inspissated material can be flushed and patency restored. Polypus can be removed. To break synechiae, a soft pliable cannula is passed through hysteroscope and its tip directed at the tubal ostium and gradually advanced while breaking the flimsy adhesions, and the fallopian tube flushed. *Dense adhesions cannot be dealt with in this way* (Figure 19.16).

Ampullary and fimbrial salpingoscopy (Figure 19.16). Salpingoscopy can be utilized to study the mucosa of the fallopian tube in deciding between tubal microsurgery and IVF in an individual case. Colour Doppler ultrasound for assessing tubal pathology is under study.

Descending test using starch is injected into the pouch of Douglas. The presence of starch in the cervical mucus 24 h later indicates patency of one or both tubes.

Laparoscopy is now combined with hysteroscopy as a comprehensive one-stop infertility work up, to detect the cause of infertility and treat the cause in one go. This is now considered the gold standard in the investigation of tubal infertility. To avoid the abdominal route, a few have attempted a vaginal laparoscopy through the pouch of Douglas to view the pelvic organs.

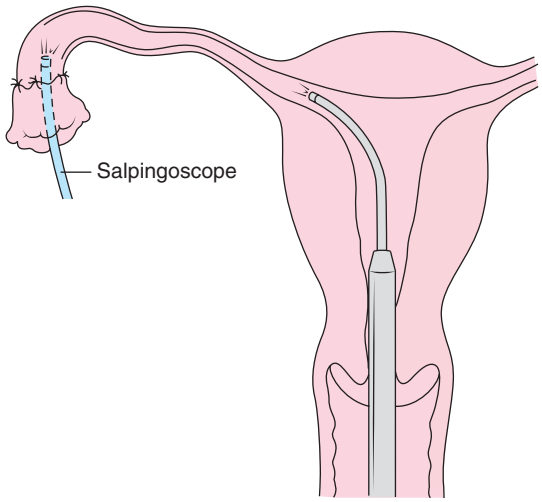

Figure 19.16 Falloposcopy and salpingoscopy. The flexible falloposcope is inserted via a channel in an operating hysteroscope, while salpingoscopy (usually rigid) is performed transabdominally during laparoscopic evaluation of the pelvis.

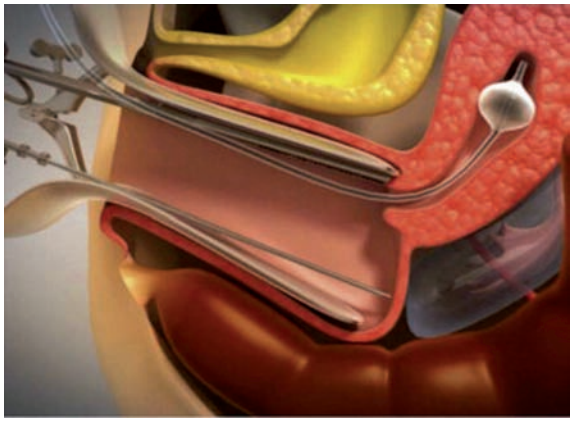

Figure 19.17 Principles of fertiloscopy: Introduction of Veress needle into the pouch of Douglas to study the tubes. (From Figure 2. Watrelot A and Chauvin G: Current practice in tubal surgery and adhesion management: a review. Reproductive BioMedicine Online 23, 53–62, 2011.)

Fertiloscopy (Figure 19.17). Following the initial work by Gordts, fertiloscopy is now introduced as a combined technique parallel to hydropelviscopy, and other methods in infertility work up. It can be done under local or general anaesthesia.

Fertiloscope consists of two introducers, one for uterine cavity and the second to study the genital organs through the pouch of Douglas. The uterine introducer is provided with a balloon for a good seal in the dye test and the vaginal fertiloscopy has three channels.

Prerequisites:

1. Preparation of colon by enema to avoid rectal perforation.
2. Pouch of Douglas should be clear of any mass or endometriosis.

Hydroperitoneum is necessary. Therapeutic procedures such as drilling of ovarian cyst and adhesiolysis have been attempted.

Procedure:

- HSG is the first line of investigation in assessing tubal function and anatomy.
- In presence of abnormal HSG findings. Fertiloscopy is recommended as the next step in infertility work-up and it may even replace laparoscopic chromotubation in future. In an elderly woman over 35 years, it may be prudent to straight go for fertiloscopy without preliminary HSG.

Indications:

- Diagnosis of pelvic pathology and testing of tubal patency.
- Assess the exact pathology of infertility and decide between surgery and assisted reproduction.
- Therapeutic—to perform adhesiolysis, ovarian drilling for PCOD, and lysis of endometriosis.

4) Second look fertiloscopy—for follow-up after the surgical procedures.

Advantages of fertiloscopy over laparoscopy:

- No Trendelenburg position—only lithotomy position.
- No trocar needed—trauma avoided.
- No CO_2—Hydroperitoneum with saline.
- Good view of the posterior surface of the ovary and genital organs.
- Peritoneal spill can be seen.

Complications:

- Failure of technique and visualization of pelvic organs.
- Bleeding at the site of puncture in posterior fornix.
- Infection.
- Perforation of the colon.
- False route with Veress needle for hydroperitoneum.

Technique:

1. Lithotomy position.
2. Local/general anaesthesia.
3. Insertion of Veress needle and creation of hydroperitoneum with saline.
4. Insertion of two fertiloscopes.
5. Chromotubation.
6. Inspection of organs.
7. Therapeutic, if it is needed.

Management of Tubal Infertility

Tuboplasty

Tubal microsurgery (Figure 19.18). It is advocated in tubal blockage. Depending upon the site of block, varieties of

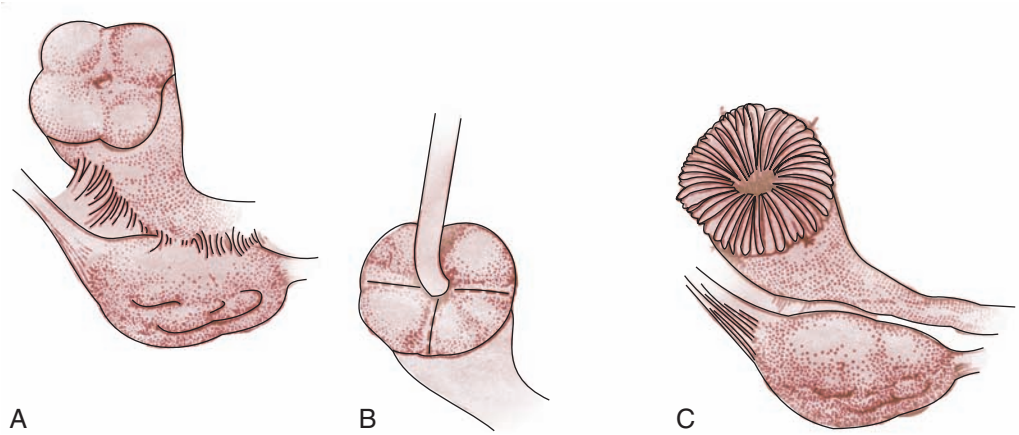

Figure 19.18 Tubal surgery at the fimbrial end (fimbrioplasty).

tuboplasty surgery have been performed with successful pregnancy rates varying from 27% for fimbrial surgery to 50–60% for isthmic blockage. The success of tuboplasty can be improved with (i) gentle handling of tissues; (ii) use of magnification; (iii) avoiding mopping or rubbing of the tissues but using continuous irrigation and suction to remove the clots, and prevent desiccation of tissues; (iv) haemostasis secured by cautery or laser; (v) use of fine suture material (Vicryl, Proline) and (vi) use of Heparin solution for hydroflotation to prevent postoperative adhesions. Restoration of latency of the fallopian tube should be checked by HSG 3 months later.

The risks of tuboplasty are (i) anaesthetic complications, (ii) postoperative wound infection, chest infection and embolism, (iii) failure and (iv) an ectopic pregnancy. Other indications for surgery are reversal of tubectomy, conservative ectopic pregnancy and salpingitis isthmica nodosa.

Advantages of tuboplasty:

- One-time therapy.
- Low cost compared to IVF.
- Saves time of repeated visits to IVF centre.
- Subsequent spontaneous pregnancies possible if surgery is successful.
- No risk of IVF, i.e. ovarian hyperstimulation syndrome, multiple pregnancies.

Laparoscopic tubal adhesiolysis, fimbrioplasty and tubal surgery have yielded good results.

IVF. Today, IVF (in vitro fertilization) and ET (embryo transfer) are offered to women in whom tuboplasty has failed or to women with extensive and irreparable tubal damage. The overall success rate of 20–30% is obtained. This is a very expensive therapy which few can afford. *Contraindications* to IVF are extensive pelvic adhesions and inaccessible ovaries due to adhesions—ova retrieval in such cases may be impossible or dangerous to the bowels. Laparoscopic adhesiolysis followed by IVF may be possible. Normally, three trials are given and if IVF fails, other MAF (micro-assisted fertilisation) processes offered.

Extra embryos can be cryopreserved for subsequent cycles.

Balloon tuboplasty and cannulation are done with a hysteroscope through transcervical route for medial end block.

This only breaks flimsy adhesions and dislodges plugs of mucus and inspissated material, but does not break the dense adhesions. The complications are:

1. Infection
2. Perforation of the tube
3. Ectopic pregnancy

Tubal cannulation restores patency in 75% cases, and pregnancy rate of 40% is reported if tubal blockage is due to flimsy adhesions.

Medial end tubal blockage is seen in 10–15% cases of HSG

Aetiology:

- Amorphous material organized as a plug
- Inflammatory exudates
- Tubal spasm
- Polypus
- Fibrosis by PID, endometriosis, isthmica nodosa

Treatment:

- Tubal cannulation
- Balloon tuboplasty
- Surgery—tuboplasty
- IVF

Pregnancy rate of 20% is reported.
Lateral end block can be rectified by:

- Fimbrioplasty—50–60% success
- Salpingostomy—20–30% success
- Adhesiolysis of external adhesions

Uterine causes, such as a septum, Asherman's syndrome and a fibroid need surgical correction.

Tests of Ovulation

Basal Body Temperature

It is established that the basal body temperature (BBT) falls at the time of ovulation by about 1/2°F. Subsequently, during the progestational half of the cycle, the temperature is slightly raised above the preovulatory level, and the rise is of the order of 1/2°F to 1°F. Moreover, if the patient conceives, the temperature remains at this level and does not fall as it normally would with the onset of menstruation. This phenomenon is due to the thermogenic action of progesterone, and is therefore presumptive evidence of the presence of a functioning corpus luteum and hence ovulation. Accurate recordings will therefore indicate whether the ovarian cycle is ovulatory or not and will also denote the timing of ovulation. The patient must be capable of reading the thermometer to 1/10th degree. Oral temperatures are accurate, provided the patient does not take hot or cold drinks before taking the temperature, and this should be done first thing after waking up in the morning. The patient must be instructed to record the temperatures on a graph (Figure 19.19). BBT is retrospective and does not indicate impending ovulation and is not useful in IVF. It, however, does reveal corpus luteal phase insufficiency and defective folliculogenesis.

BBT has now become obsolete because of:

1. Tedious daily recording.
2. Not very accurate.
3. Retrospective diagnosis and not useful therapeutically.
4. Better modalities of ovarian monitoring by ultrasound being available.

Endometrial Biopsy

Endometrial biopsy consists of curetting small pieces of the endometrium from the uterus with a small endometrial biopsy curette, preferably 1 or 2 days before the onset of menstruation. The material removed should be fixed immediately in formalin saline and submitted to histological scrutiny. Secretory changes prove that the cycle has been

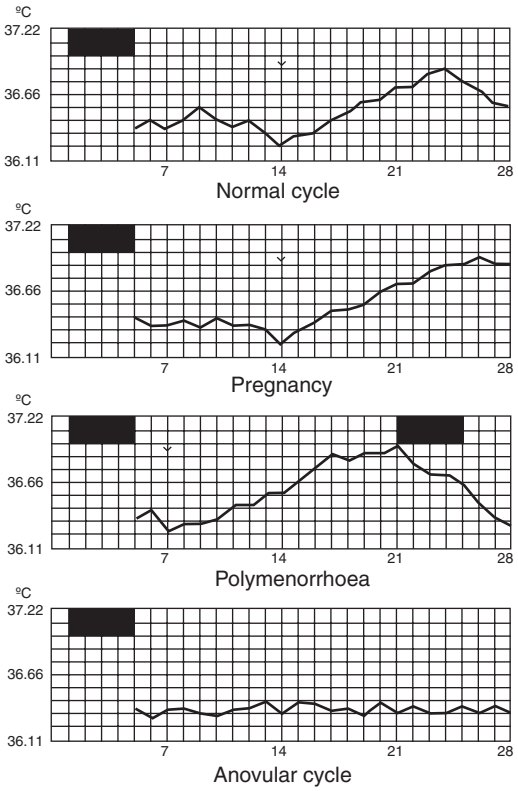

Figure 19.19 Specimen charts of BBT recordings. Arrows indicate ovulation time; the dark zones indicate the days of menstrual bleeding.

ovulatory. The incidence of anovulation varies between 10 and 25%, and only 4% are habitually anovulatory. Endometrium should be subjected to culture, PCR and staining to rule out genital tuberculosis, which is present in 5–10% of Indian women complaining of sterility. Corpus LPD can also be diagnosed by endometrial biopsy, which shows a lag of 2–3 days between the calendar and histological dating of the specimen. Today, endometrial biopsy is omitted as a routine investigation of infertility and ovulation best monitored by serial ultrasound scanning. *Endometrial biopsy is taken only in suspected tubercular endometritis, and the tissue is subjected to a PCR test instead of culture.*

Fern Test

A specimen of cervical mucus obtained using a platinum loop or pipette is spread on a clean glass slide and allowed to dry. When viewed under the low-power microscope, it shows, during the oestrogenic phase, a characteristic pattern of fern formation (Figures 19.20 and 19.21). This ferning disappears after ovulation, and if previously present its disappearance is presumptive evidence of corpus luteum activity. The ferning is due to the presence of sodium chloride in the mucus secreted under oestrogen effect. The physical character of cervical mucus also alters with the date of the cycle. At the time of ovulation, the cervical mucus is thin and profuse that the patient may notice a clear discharge, the so-called normal ovulation cascade. This ovulation mucus has the property of great elasticity and will withstand stretching up to 10 cm. This

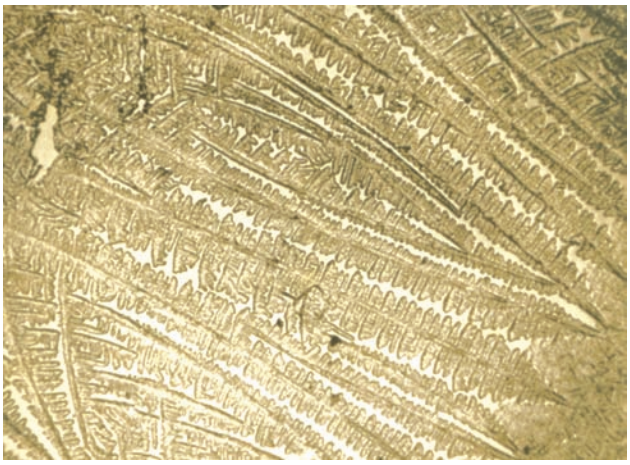

Figure 19.20 Dried cervical mucus showing ferning at the time of impending ovulation.

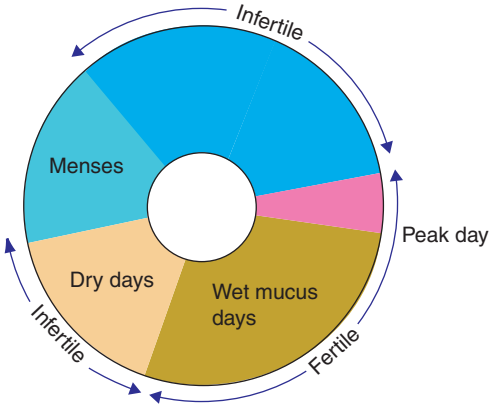

Figure 19.21 Mucus secretion during a menstrual cycle.

phenomenon is called spinnbarkeit or the thread test for oestrogen activity. During the secretory phase, the cervical mucus becomes tenacious and its viscosity increases so that it loses the property of spinnbarkeit and fractures when put under tension. This property is called tack. The observation of this change in the cervical mucus pattern in a menstrual cycle is another evidence of ovulation (Figure 19.21). Insler devised a scoring system which takes into account the various cervical mucus properties such as the amount, spinnbarkeit, ferning, viscosity and cellularity. The maximum score is 15 and a score of less than 10 is considered unfavourable. Cervical infection, if any, needs to be treated prior to performing this test. Postcoital test and detection of antibodies in the cervical mucus can be integrated with this test into one composite study.

Ultrasound

Ultrasound has now become the standard and indispensable procedure for monitoring maturation of the Graafian follicle and in detecting imminent ovulation in IVF, IUI and in timing intercourse. This requires daily ultrasonic visualization of ovaries from the 10th to 16th day of the menstrual cycle. It is noninvasive, accurate and safe. Apart from follicular study for ovulation, pelvic pathology if any can be picked up and

endometrial thickness measured. The follicle grows at the rate of 1–2 mm daily to reach 20 mm or more when follicular rupture and ovulation occur at midcycle. The sudden disappearance of the follicle, presence of free fluid in the pouch of Douglas and growth of corpus luteum are evident. Endometrial thickness of 8–10 mm is the normal response of endometrium to progesterone. A lesser thickness indicates corpus luteal phase deficiency (CLPD).

Other ultrasonic findings relevant to infertility are:

- Tubo-ovarian mass.
- Undiagnosed uterine fibroid—uterine abnormalities.
- PCOD.
- Endometrial volume and its blood supply into the basal layer.
- 3-layered endometrial echogenicity.
- Endomyometrial junction upwards peristalsis—three is seen during the late proliferative phase.

Ultrasound is extensively used in therapeutic procedures; Doppler ultrasound and 3D ultrasound are now in vogue.

Hormonal Study

Plasma progesterone. Plasma concentration of progesterone rises after ovulation and reaches the peak of 15 ng/mL at mid-luteal phase (22–23rd day) and then declines as the corpus luteum degenerates. A low level of the plasma progesterone below 5 ng/mL at mid-luteal phase, suggests corpus LPD and prompts hormonal therapy. Use of daily progesterone suppository in the luteal phase or administration of hCG 5000–10,000 IU weekly will help to improve the chances of conception. Oral micronized progesterone 100 mg bid or 300 mg vaginal pessary twice daily is useful in corpus LPD. Weekly proluton injection (500 mg) and oral dydrogesterone are also used.

Corpus luteal phase deficiency
Aetiology:

- Hypopituitarism with low FSH, LH
- Poor follicular development.
- Hyperprolactinaemia.
- Clomiphene citrate (CC) ovulation induction.
- Retrieval of egg in IVF. CLPD is seen in postmenarchal and premenopause period.
- Poor response of endometrium to endogenous progesterone.

Diagnosis:

- BBT.
- Mid-luteal progesterone estimation (normal 15 ng/mL).
- Endometrial biopsy.

Treatment: Administration of progestogen or HCG administration IM weekly.

LH. LH surge from the anterior pituitary gland occurs about 24 h prior to ovulation. Radioimmunoassay of the morning sample of urine and blood give the LH results in 3 h. Not only does the LH surge help in predicting ovulation, but the approximate time of ovulation can be gauged and coitus around this time can improve the chances of conception. Gauging the time of ovulation has therapeutic applications in IVF and in artificial insemination. LH kits are now available.

Hyperprolactinaemia is seen in pituitary adenoma, hyperplasia, hypothyroidism and with the usage of drugs, i.e., metoclopramide, cimetidine, methyldopa. Hyperprolactinaemia (more than 25 ng/mL) will require X-ray of pituitary fossa or CT scan, and a fundus examination to exclude a neoplasm. Macroadenomas may require surgery. Microadenomas and hyperprolactinaemia respond to bromocriptine and allied drugs (see chapter on Hormonal therapy).

FSH. Raised FSH level is seen in ovarian failure. Low FSH level indicates pituitary dysfunction and anovulation. Normal FSH level in the preovulatory phase is 1–8 mIU/mL, and LH level at ovulation is 1–5 mIU/mL. FSH level >25 IU/mL clomiphene on day 3 fails ovulation.

Thyroid tests. These should be done especially in case of hyperprolactinaemia. Hypothyroidism with raised TSH level is related to hyperprolactinaemia.

Ovarian reserve or premature failure includes both qualitative and quantitative estimation of FSH/LH.

Aetiology of premature ovarian failure:

- Poor migration of premature eggs from the yolk sac during embryogenesis.
- Early or increased apoptosis of eggs.
- Radiotherapy.
- Hysterectomy—deprives blood supply to the ovaries (Kinking or obliteration).
- Ovarian hyperstimulation.

Diagnosis:

- Day 3 serum FSH should be 10–15 IU/L or more for the diagnosis.
- LH <10 IU/L or
- Day 3 serum E_2 should be 60–80 pg/mL or less.
- Anti-Müllerian hormone is low (normal 0.2–0.7 ng/mL).
- Inhibin B is low <40 pg/mL.
- Antral follicular count measuring 2–9 mm in both the ovaries and number of follicles and size. Count less than 4–5 on day 2–5 denotes poor response to hormones.
- Ultrasound ovarian volume low.
- Progesterone on 21st/22nd day >15 ng/mL.

Management of Anovulation

Anovulation is a common problem encountered in infertility. Several endocrine disturbances contribute to its occurrence; hence, different drug combinations are required to obtain optimal results.

Clomiphene citrate. Ovulation should be induced with CC, with a dose of 50 mg/day starting from day 2 to day 6 of the cycle for 5 days. Ovulation is monitored by serial ultrasound monitoring of the follicular size, and occurrence of ovulation. If the response to 50 mg CC is not satisfactory, the dose of CC should be increased to 100 mg/day from day 2 to day 6. Further increase in dosage dose of CC, if required, should be undertaken in an infertility set-up, where monitoring facilities by sonography and hormone estimation are easily available. If clomiphene therapy fails following 6–8 cycles,

FSH and hCG therapy is recommended. Since, this regime requires constant monitoring; the treatment should be initiated in special infertility clinics. The risk of multiple ovulations and multiple pregnancies with this regime is around 10%. In hypothalamic disorder, GnRH is given to stimulate the pituitary FSH and LH and the folliculogenesis monitored. The pituitary and hypothalamic stimulation is often employed in in vitro and GIFT techniques. To avoid peripheral suppressive oestrogen action on cervical mucus and endometrium by clomiphene, and to improve the fertility rate, Letrozole 2.5 mg (nonsteroidal aromatase inhibitor) is found superior to clomiphene, which has no such adverse action.

Prolonged clomiphene and letrozole therapy beyond 8 months can cause oestrogen deficiency with menopausal symptoms of hot flushes and osteoporosis (reversible).

With letrozole, ovulation occurs in 90% cases and with a pregnancy rate of 40–50%. Letrozole is given 2.5 mg daily for 5 days starting on the second day of the cycle or 20 mg single dose on day 3.

Letrozole has no adverse peripheral action on endometrium and cervical mucus as with clomiphene (antioestrogen action). It, however, causes drowsiness (no driving). Half-life is 50 h. *However, it is banned by the Government of India for use in infertility.*

It is contraindicated in severe hepatic dysfunction. It enhances the action of FSH, the dose of which is therefore reduced by 50%. At present it is an off-label drug and banned in India.

In case of clomiphene failure, some have tried clomiphene 50 mg with 20 mg tamoxifen (double dose if necessary) in anovulatory infertility. Tamoxifen, unlike clomiphene, has no anti-oestrogenic action on endometrium and cervical mucus.

PCOD. The first line of treatment is medical. If this fails, laparoscopic drilling of follicles is done by monopolar cautery or laser.

Octreotide is a peptide (somatostatin analogue) secreted by the hypothalamus; it inhibits the growth hormone and insulin. It enhances the effect of clomiphene and reduces the risk of ovarian hyperstimulation syndrome.

In PCOD with insulin resistance, pregnancy rate can be improved by administering metformin 500 mg daily at night for 1 week, and gradually increasing the dose twice a day up to three times a day for 6 months. This avoids vomiting. Progesterone or hCG can be added for pregnancy support.

Combination of CC + hMG. In PCOD, ovulation is ideally induced with a combination of CC and hMG. The patient is advised CC 50–100 mg/day from day 2 to day 6 of the cycle for 5 days. Injecting hMG 75 units intramuscularly is added on day 3, 5 and 7, and more if so required.

Anovulatory women who fail to respond to CC + hMG treatment as well as amenorrhoeic women with low oestrogen levels need to be treated with hMG + hCG as detailed below.

Combination of hMG + hCG

1. Perform baseline oestradiol assay and ultrasound scanning.
2. Administer hMG, two ampoules (75 IU each) per day for 3 days.
3. Repeat oestradiol. If it is doubled, monitor hMG dosage; if not, increase hMG dosage by 50% for 3 days.
4. Repeat step 3 until oestradiol doubles.
5. Perform ultrasound scan every 2–3 days until the dominant follicle is ≥14 mm. Thereafter, daily monitoring till size 20 mm is reached.
6. Administer IM injection of hCG 5000 IU. Recommend artificial insemination, otherwise advise natural intercourse.
7. Administer injection of hCG 3000 IU 7 days later.
8. Await onset of menses or perform urine pregnancy test.

GnRH In hypothalamic dysfunction. This is also used as an alternative to administration of hMG. Since GnRH is a decapeptide, it cannot be administered orally. Because continuous administration of GnRH will saturate the receptors and thus inhibit gonadotropin release, GnRH is administered in a pulsatile fashion preferably subcutaneously. Ovulation rates of 75–85% have been reported and pregnancy rates of 25–30%. One advantage of GnRH is that the risk of hyperstimulation is greatly reduced (1%) as compared to hMG (20–25%); hence, less monitoring is required. The drug is very expensive (Figure 19.22).

Prednisolone. In women with anovulation and increased androstenedione, the administration of 5.0 mg prednisolone at night + 2.5 mg every morning is advised until spontaneous ovulation sets in. In case this treatment does not succeed, this can be combined with any other ovulation induction regime.

INFERTILITY

COMPONENTS OF A TYPICAL ART CYCLE

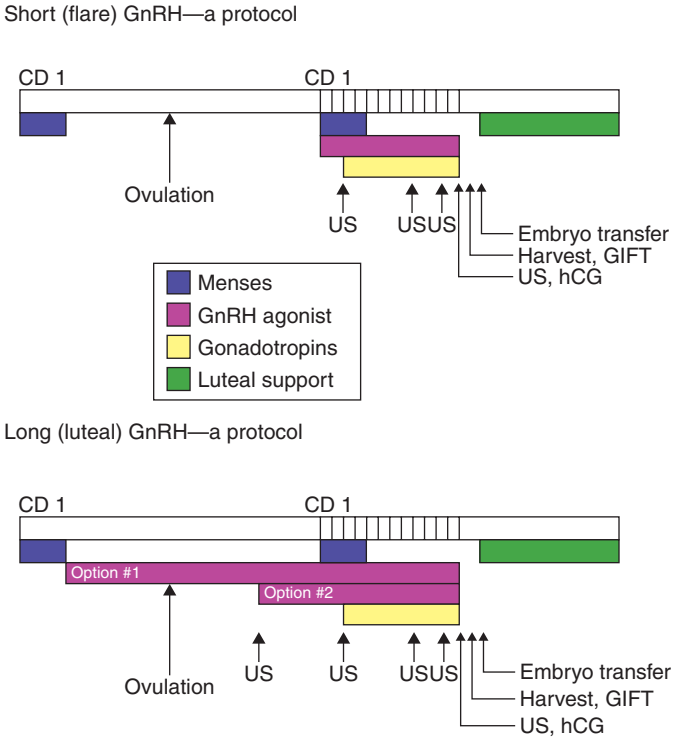

Figure 19.22 GnRH protocols.

Hyperprolactinaemia is treated with bromocriptine 1.25 mg at bedtime daily for 7 days, dose increments of 1.25 mg per week is recommended until the hyperprolactinaemia gets corrected when spontaneous ovulation is likely to occur and pregnancy often follows.

Laparoscopic ovarian drilling. In women with PCOD in whom induction of ovulation with medical line of treatment fails, laparoscopic ovarian drilling of follicles with monopolar cautery/laser has yielded satisfactory results.

Corpus LPD is treated either with intramuscular progesterone 100 mg or micronized 300–600 mg vaginal tablet daily in the postovulatory phase. Oral micronized progesterone tablets are not recommended. They cause drowsiness, poor absorption and bypass effect in the liver. HCG is also employed.

Poor response to induction of ovulation is indicated by:

- Less than five follicles on day 5.
- Estradiol level less than 300 pg/mL.

In such cases, testosterone patches or DHEA have shown improved oocyte quality in IVF programme; 25 mg t.i.d. is given for 6 months followed by ovarian stimulation. DHEA in poor responders:

1. Improves the number of follicles.
2. Improves ovulation and yield.
3. Increases insulin growth factor 1.
4. Decreases pregnancy loss.
5. Reduces age related aneuploidy.

Peritoneal Disorders

Peritoneal disorders include peritubal adhesions and endometriosis, and are diagnosed on laparoscopy.

Therapy consists of operative laparoscopy for adhesiolysis, ablation of endometriosis, incising the chocolate cyst and removing its lining at laparoscopy. Dilatation of fimbrial phimosis, opening of the terminal end of a hydrosalpinx and microsurgery for restoring tubal patency are also possible with laparoscopic methods.

Endometriosis

Endometriosis, associated with infertility, is treated medically, surgically or as a combination of the two.

Luteinized Unruptured Follicular Syndrome

LUF syndrome is seen in 9% cases of infertility and is diagnosed only on ultrasound scanning. Micronized progesterone or hCG is needed in these cases (Table 19.2).

Unexplained Infertility

Many a time, infertility is unexplained, but this could be attributed to inadequate or inefficient investigations and inability to detect biological capability of the sperms to fertilize an ovum.

Sperm dysfunction and its biological function are now detected on computer-assisted semen analysis (CASA). Abnormal acrosome reaction and sperm–oocyte fusion defects have been identified by CASA and male infertility problems better understood.

It has been observed that 20% of such unexplained infertile couples succeed in having a baby in due course of waiting. Perhaps newer and advanced technology in this field may yield a better pregnancy rate of 40–50% in future, albeit at a high cost.

TABLE 19.2 Female infertility: Causes, investigations and management

Aetiology	Investigations	Management
Tubal cause	• Hysterosalpingography or sonosalpingography • Falloscopy • Salpingography • Laparoscopic chemotubation	• Adhesiolysis (Lap.) • Tuboplasty • Hysteroscopic cannulation and balloonoplasty ↓ If failed or not feasible ↓ IVF/Gif+
Ovulation	• Ovulation monitoring by ultrasound (BBT, BBI) EB for tuberculosis ↓ Abnormal ↓ Hormonal study • FSH, LH, Prolactin • E_2, P level • Thyroid and diabetes	• Clomiphene, letrozole ↓ Failed ↓ FSH, LH, GnRH ↓ Positive, No response ↓ Response ↓ if failed IVF Donor egg ↓ Adoption
Other causes	Ultrasound, MRI, SSG, hysteroscopy	Treat the cause

When all fail, and the couple is desperate to have a baby, adoption is recommended.

Lately, aspirin 75 mg orally daily in the premenstrual phase has shown to improve implantation rate and to improve pregnancy rate. Assuming implantation may be at fault; this treatment is recommended in unexplained infertility.

Assisted Reproductive Technology: An Overview

Assisted reproductive technology (ART) comprises a group of procedures that have in common the handling of oocytes and sperms outside of the body. The gametes or embryos are replaced into the uterine cavity to establish pregnancy.

These procedures, although benefited many infertile couples (20–40% pregnancies), are stressful and very expensive with complications such as hyperstimulation syndrome, multiple pregnancy, abortion and ectopic pregnancies. Although no gross fetal malformations have yet been reported, long-term study is required to detect subtle and late complications.

Definition

ART refers to any fertility treatment in which the gametes (sperms and ova) are manipulated. Accordingly, ART procedures involve surgical removal of eggs known as *egg retrieval.* IVF is the most common ART procedure. It was first successfully used by Steptoe and Edwards leading to the birth of Louise Brown in 1978. Since then many births have been achieved, with the world over using this and other related ART procedures.

Indications

The common indications for ART procedures include the following:

- Abnormal fallopian tubes: Blocked tubes or absent tubes (surgical removal).
- Endometriosis adversely affecting tubo-ovarian pick-up function, or distorting the tubes.
- Idiopathic or unexplained infertility.
- Male subfertility.
- Immunologic infertility.
- Failure of ovulation—donor ovum. Bilateral oophorectomy for diseased ovaries, i.e. endometriosis and ovarian cancer.

Investigations Prior to ART

- Thyroid function tests, diabetes.
- Serum FSH on day 3 of cycle. FSH >25 mIU/mL indicates poor prognosis.
- Serum oestradiol on day 3 of cycle. Serum oestradiol >75 pg/mL indicates poor prognosis.
- Maternal age more than 40 years. Success rate drops. Prior to considering ART, assess 'ovarian reserve', or use donor eggs.
- Test for ovarian reserve: This is indicated in women over 35 years of age, smokers, presence of only one ovary and unexplained infertility. It involves standard day 3 laboratory tests as mentioned above, along with administration of 100 mg CC from day 5 to day 9, repeat FSH on day 10. FSH values must be the same as on day 3 of the cycle.
- Serologic evidence of chlamydial infection is associated with reduced birth rates and increased perinatal loss.
- Zona-free hamster oocyte penetration test to asses fertilizing capacity of sperm (optional).
- Enhanced sperm penetration test using TEST-yolk buffer.
- Testing both partners for antisperm antibodies.
- Assess uterine cavity—HSG/hysteroscopy/transvaginal sonography. Hydrosalpinx reduces IVF success rates by 50%. Success rate increases to expected rates after surgical tying off or excision of hydrosalpinx. Tying the medial end of the tube also reduces the risk of ectopic pregnancy.
- Complete seminogram and treatment of male partner prior to ART procedure.
- Diagnostic laparoscopy to assess tubal patency and treat any subtle causes of infertility such as lysis of adhesions, treatment of endometriosis etc. Excision of hydrosalpinx or ligation of medial end of the tube.

Types of ART Procedures in Practice

1. **IVF.** This involves ovulation induction, oocyte retrieval and fertilization of the oocytes in the laboratory; embryos are then cultured for 3–5 days followed by subsequent transfer of selected fertilized oocytes transcervically under ultrasound guidance into the uterine cavity. Genetic study of polar body or embryonic cells may be required in a few cases.

   Low-cost IVF: In developing countries, low-cost technique of IVF called intravaginal culture (IVC) also called INVO (intravaginal culture of oocyte) fertilized is being developed. Oocyte fertilization and early development of embryo are achieved within a gas permeable air-free plastic device placed in the vaginal cavity for incubation. The vaginal cavity replaces the in vitro incubation. Clinical pregnancy of 20% is reported. It is done with ovarian stimulation.
2. **GIFT.** This involves ovarian stimulation and egg retrieval, followed by laparoscopically guided transfer of a mixture of two ova and 50,000 sperms into each of the fallopian tubes.
3. **Zygote intrafallopian transfer (ZIFT).** This involves the laparoscopic transfer of day 1 fertilized eggs (zygotes) into the fallopian tube.
4. **Intracytoplasmic sperm injection (ICSI).** This technique was developed in the early 1990s. It aims at helping couples with severe male factor infertility. One sperm is directly injected into each mature egg prior to intrauterine transfer of the fertilized eggs. The method yields 50–70% successful fertilization rates.

Indications of ICSI in male infertility comprise:

- Sperm count less than 5 million/mL.
- Decreased or absent motility of sperms.
- Many abnormal sperms.
- Previous failed IVF.
- Unexplained infertility.

The sperms are obtained by one of the following sources:

- Semen washing in a normal male.
- Testicular sperm aspiration (TESA).
- Percutaneous epididymal aspiration. However, a decreased number of sperms are available (PESA) with this technique. This technique can also cause trauma to the epididymis.
- Microsurgical epididymal sperm aspiration (MESA)—the tissue can be cryopreserved for future cycles or future pregnancy.
- Lately spermatids have been matured in vitro and utilized in ICSI.

Other techniques of IVF:

1. Zonal drilling and injecting the sperm—results are poor.
2. Subzonal injection.
3. Intracytoplasmic injection of a single sperm yields the best results as of today.

   Cryopreservation avoids repeat aspirations, reduces the cost of the procedure and can be used in subsequent cycles as well as for further pregnancies. Cryopreservation is also useful in young men who have to undergo surgery, radiotherapy or chemotherapy for cancer, or are frequent travellers.

   How to improve the pregnancy rate in ART?

   With great advances in the ART, it is possible that surgery may take a back seat both in a female and a male, and performed only if ART fails. Improvement in ART is possible as follows:
   - Strict monitoring of multiple ovulations and improving the quality of ova.
   - Avoiding multiple pregnancies. European countries practice one-ET. In India, most women who seek IVF are elderly over the age of 35 years (they try spontaneous pregnancies for many years), and the chances of IVF is as such reduced due to age. Most gynaecologists prefer to transfer two embryos in each cycle, and some continue with more.
   - Avoiding ectopic pregnancy and heterotropic pregnancy by ligating the medial ends of the fallopian tubes prior to IVF.
   - By excising hydrosalpinx prior to IVF, as fluid in the hydrosalpinx has shown to reduce implantation rate.
   - Cryopreservation of ova, sperms, embryos and testicular tissue.
   - Feticide if multiple pregnancies occur.
4. **Ovum donation.** Donor eggs are offered to women with poor egg numbers or quality and elderly women. An egg donor is screened for HIV and other diseases. She is then subjected to stimulation protocol for inducing superovulation, followed by standard egg retrieval. These eggs are fertilized by the sperms of the patient's male partner and the embryos transferred to the patient's uterus which has been simultaneously prepared as per the standard IVF protocol. Ovum donation is also required if both ovaries are removed or radiated.
5. Ovarian transplant is a possibility in future.
6. **Surrogacy and posthumous reproduction** are extensions of ART procedures. However, ethical, legal, religious and social issues of these procedures need clarification and understanding. There are grey areas to be cautious about until legal procedures have been drawn. Hysterectomised woman needs surrogacy.
7. Stem cell culture agar is a future goal in infertility.
8. **Adoption.** Considering the cost of ART and the stress involved, adoption can be a suitable alternative for infertile couples. Many, however, prefer to have their own genetic babies and resort to adoption when all other measures fail.

Brief Points in IVF

1. Minimal investigations:
   - Male—semen examination.
   - Ultrasound—ovulation. Monitoring, uterine morphology, endometrial thickness. Doppler study of endometrium.
   - Hysteroscopy and laparoscopy are lately included prior to IVF.
2. GnRH antagonists instead of GnRH agonists are preferred, as they act fast and are cost effective.
3. Oocyte collection—antibiotics and progesterone given 2 days prior to oocyte collection to prevent infection and for better implantation. Vaginal saline washing but not Betadine as it affects the quality of ova. One- to two-ET is in vogue.

IVF Complications
Short Term:

- Failure.
- Oocyte retrieval can cause bleeding trauma, infection, pain, pelvic abscess.
- Ectopic and heterotropic pregnancy 0.4%.
- Multiple pregnancies and its complications.
- Abortion, IUGR.
- Hyperstimulation syndrome.
- Cost.

Long-term complications:

- Premature ovarian failure.
- Ovarian cancer—due to hyperstimulation.
- Breast cancer.

Surrogacy required in:

- Absent uterus, diseased uterus.
- General condition of the woman precludes pregnancy.
- Repeated pregnancy loss.
- Hereditary disease.
- Failed IVF.

Key Points

- Increased information related to biological process of fertilization and implantation has evolved newer technologies in assisted reproduction and has improved the fertility rate.
- Andrology has expanded into extensive male investigations, study of the morphology and functions of the sperm. This has given hope by adopting techniques such as semen wash and intrauterine insemination, MAF and MESA, IVF and lately effective testicular biopsy and testicular retrieval of sperms.
- ICSI if the sperms are immobile or possess antibodies yields considerable success rate in male infertility.
- Although several factors are responsible for female infertility, the most common causes are tubal blockage, ovarian dysfunction and anovulation.
- Ovulation is now monitored by ultrasound scan, and hormone profile study is reserved in abnormal findings and when a woman is given pituitary hormones for induction of ovulation.
- Tubal patency and morphology of endosalpinx can be extensively studied, apart from HSG and laparoscopic chromotubation, by falloscopy, salpingoscopy and hysteroscopic cannulation; hysteroscopy not only reveals uterine abnormalities but deals with any abnormality surgically.
- Ovulation induction, tubal microsurgery, balloon tuboplasty and hysteroscopic cannulation are the added armamentarium in the treatment of female infertility, which are yielding better results.
- Laparoscopy combined with hysteroscopy forms 'one sitting' investigation to detect the cause of female infertility. This is cost effective and saves time.
- We have come a long way from donor semen and IUI to picking up just one healthy sperm in ICSI in male infertility.
- Cryopreservation of sperms, ova and embryos is one big step forward in the field of infertility. It avoids repeated aspirations and other procedures, and thereby reduces the costs. It also permits donation of eggs as well as of sperms to couples whose husband is azoospermic or wife is incapable of ovulation.
- Stem cell therapy holds promise for future generations.

Self-Assessment

1. Discuss the causes and management of male infertility.
2. A 28-year-old woman presents with irregular menstrual cycles and primary infertility. How will you investigate this case?
3. A 23-year-old woman presents with primary sterility, hirsutism and oligomenorrhoea. How will you investigate and manage this case?
4. A 32-year-old woman presents with secondary infertility, regular cycles, last delivery was 6 years ago. How will you manage this case?
5. A 36-year-old woman married for 3 years presents with primary infertility. How will you manage this case?
6. How will you investigate and manage a case of tubal infertility?

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Chapter

20

Birth Control and Medical Termination of Pregnancy

CHAPTER OUTLINE

Birth Control

Today, as ever, there is a pressing need for limiting the family size at a personal level and for the control of population at a national level. The need of birth control at a personal level has arisen through increased cost of living, scarcity of accommodation, a desire for better education of children in the present competitive world, and an overall desire for an improved standard of living.

The population in India has been growing rapidly. The socio-economic problems of overpopulation are too well known to be discussed here. World population is also a major problem with more than 6.3 billion living on this earth and 26 children born every second.

Reproductive health and medical grounds are now the other considerations for birth control. It is reckoned that a woman below 20 years is not physically grown to produce a child. If she does reproduce, she becomes a high-risk case during pregnancy and labour, and is likely to deliver a low birth weight (LBW) newborn. Spacing birth, 3 years apart, is considered beneficial for both the mother and the child. *Birth control is thus seen as a woman's health measure*. A multiparous woman from a low-income group generally suffers from malnutrition and is also predisposed to prolapse, stress incontinence, chronic cervicitis and cancer of the cervix. The spacing of childbirth and limiting the number of pregnancies are strongly desirable for this reason. The previous two caesarean sections is indication of a repeat caesarean section in a subsequent pregnancy which exposes the woman to further surgical risks. In India, it is customary to suggest sterilization operation at the time of the third caesarean section, and sometimes during the second caesarean section. Other indications for sterilization include the mentally retarded woman and the one suffering from serious psychiatric disorders like schizophrenia. A woman who has given birth to a child with a genetic disorder needs genetic counselling and may be advised against future pregnancy.

There are following three types of preventing population control:

- Contraceptives—prevent fertilization
- Emergency contraception—prevents implantation
- Medical termination of pregnancy (MTP)—abortion

Definition of Contraception

A method or a system which allows intercourse and yet prevents conception is called a contraceptive method. This contraception may be temporary when the effect of preventing pregnancy lasts while the couple uses the method but the fertility returns immediately or within a few months of its discontinuation. The permanent contraceptive methods are surgical: tubectomy in a woman and vasectomy in a man. Whichever method selected, it should be effective as well as safe.

Unfortunately, no contraception has proved perfect and its effectiveness, safety and techniques vary. This therefore requires counselling, screening of the couple and offering the best method suited to the couple. It also requires monitoring while the woman uses any contraception.

The choice of contraception depends upon the following:

- Availability, cost.
- Age and parity of the couple.
- Reliability (failure rate).
- Side effects, contraindications to a particular method.

- Advantages and disadvantages.
- Requirement of follow-up.
- Counselling and allowing the couple to make a suitable choice. The couple may need to change one contraception to another from time to time during the reproductive period. Personal, medical and social factors should be taken into consideration during counselling.

Methods of Contraception

1. Natural methods:
   - Abstinence during the fertile phase.
   - Withdrawal (coitus interruptus).
   - Breastfeeding.
2. Barrier contraceptives:
   - Use of condoms by male.
   - Use of spermicidal agents.
   - Use of diaphragm, or the cervical cap in the vagina, use of female condom.
   - Use of hormones which alter the cervical mucus and prevent entry of sperms into the cervical canal.
3. Intrauterine contraceptive devices (IUCDs).
4. Suppression of spermatogenesis.
5. Suppression of ovulation with hormones—hormonal contraceptives.
6. Interceptive agents (postcoital contraception).
7. Immunological methods.
8. Surgical sterilization.

Failure rate of any contraceptive method is described in terms of pregnancy rate per 100 woman years (Pearl index).

Ideal contraceptive methods should be effective, long acting, safe, coital-independent and reversible. Besides, they should be available and affordable with minimal side effects.

Refer to Figure 20.1 for various sites of action of contraceptive techniques.

Contraceptives are:

- Long acting:
  - Three-monthly oral tablets
  - Three-monthly IM injections
  - Implants
  - IUCD
  - Surgical methods
- Medium acting:
  - Weekly
  - Monthly injections
- Short acting:
  - Condoms, barrier methods
  - Postcoital
  - Daily pills
  - Skin patches

Medical history and physical examination will pick up the high risk method for a particular case. After the elimination of high risk method, decision is taken amongst the remainder methods based on couple's choice, effectiveness, convenience as well as the duration of contraception required.

Natural Methods of Family Planning

Abstinence during the Fertile Phase. 'Fertility awareness' means the woman learns to know when the fertile time starts and when it ends. The fertile phase of the menstrual cycle can be predicted in various ways.

THE CALENDAR METHOD OR THE RHYTHM METHOD. This depends upon the avoidance of sexual intercourse around ovulation. In a 28-day cycle, ovulation normally occurs on the 14th day of the cycle, but may occur anytime between the 12th and 16th day. Spermatozoa deposited in

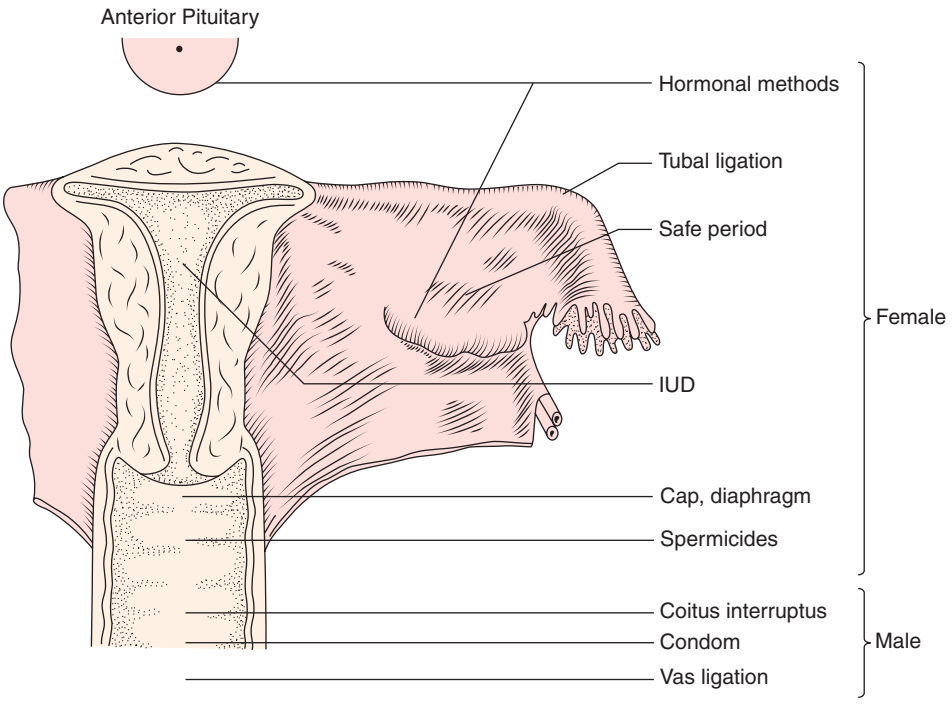

Figure 20.1 Sites of action of modern contraceptive techniques.

the female genital tract may survive for 24 h. The ovum itself may live for 12–24 h so that intercourse between the 11th and 17th day may result in a pregnancy. The safe period is, therefore, calculated from the first day of the menstrual period until the 10th day of the cycle and from the 18th to the 28th day. An alternative method is to calculate the risk period, which is from 3 days before ovulation to 3 days after ovulation. In a 35-day menstrual cycle, therefore, ovulation will occur on the 21st day (that is 14 days before the next period) so that the risk period is from day 18 to day 24.

CALENDAR METHOD. In Knaus–Ogino method, the fertile period is determined by subtracting 18 days from the shortest cycle and 10 days from the longest cycle which gives the first and the last day of fertile period, respectively.

This method will result in approximately 25 pregnancies per 100 woman years. The failure results from irregular ovulation or from irregular menstrual cycles. Some couples prefer this method on religious grounds or because they find other methods unacceptable. The methods of predicting ovulation have been described in Chapter on Infertility and Sterility.

MUCUS METHOD (BILLINGS OR OVULATION METHOD). The properties of the cervical mucus change under the influence of the ovarian hormones on different days of the menstrual cycle. The woman attempts to predict the fertile period by feeling the cervical mucus. Under oestrogen influence, the mucus increases in quantity and becomes progressively more slippery and elastic until a peak is reached. Thereafter, the mucus becomes thicker, scanty and dry under the influence of progesterone until the onset of menses. Intercourse is considered safe during the 'dry days' immediately after the menses until mucus is detected. Thereafter, the couple must abstain until the fourth day after the 'peak day' (Figure 19.21).

TEMPERATURE METHOD. Progesterone is known to exert a thermogenic effect on the body. Therefore, if the woman records her basal body temperature (BBT) daily on awakening in the morning and plots the readings graphically, the BBT chart will be biphasic in an ovulatory cycle (Figures 19.19 and 20.2). The day of temperature shift indicates the time of ovulation. Avoidance of intercourse during the fertile days can prevent an unwanted pregnancy. This is a cumbersome method, hardly practised.

SYMPTOTHERMAL METHOD. This combination method is more effective. The first day of abstinence is predicted either from the calendar, by subtracting 21 from the length of the shortest menstrual cycle in the preceding 6 months, or the first day mucus is detected, whichever comes first. The end of the fertile period is predicted by use of the 'BBT' chart. The woman resumes intercourse 3 days after the thermal shift. Apart from the long periods of abstinence required, this method is not reliable if the woman is lactating or has irregular cycles or develops fever.

Withdrawal Method (Coitus Interruptus). Coitus interruptus is a common practice. Coitus takes place in a normal manner but the penis is withdrawn immediately before ejaculation. The unreliability of this method is obvious, but it has the advantage that it costs nothing and it requires no device. Nevertheless, it has a pregnancy rate of approximately 25 per 100 woman years. The main cause of the failure is not that ejaculation occurs inside the vagina but that prostatic fluid secreted prior to ejaculation, frequently contains active spermatozoa. This practice imposes a great strain upon the husband and can cause considerable anxiety. It is also a cause of failure in the wife to enjoy intercourse fully. Some couples seem to prefer this method and make no complaints of suffering from strain or anxiety.

ADVANTAGES. *Advantages* of fertility awareness methods are: (i) no cost, (ii) no contraindications, (iii) no systemic side effects and (iv) no effect on lactation.

DISADVANTAGES. *Disadvantages* are: (i) failure rate is high, (ii) requires motivation and (iii) no protection against HIV and STD.

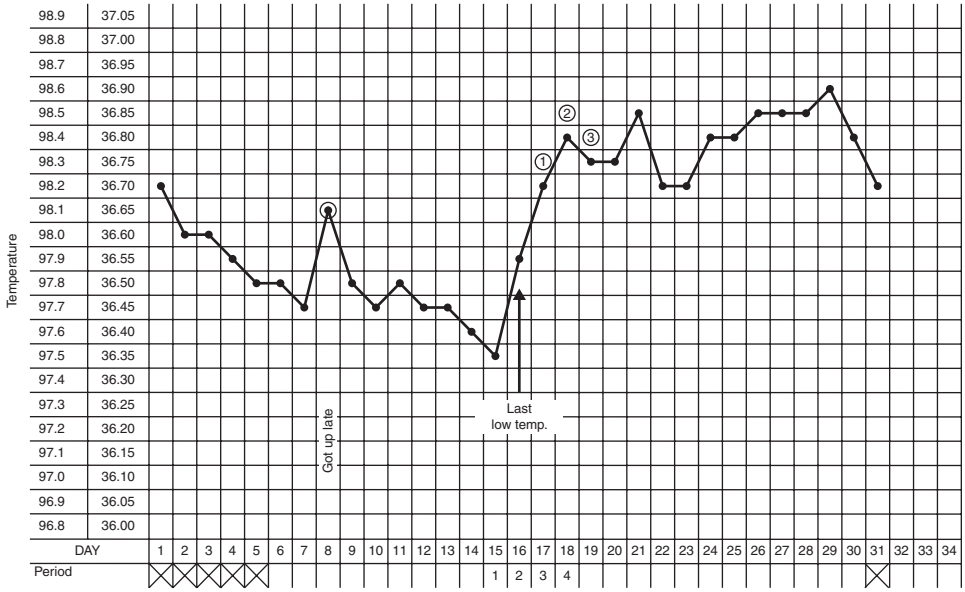

Figure 20.2 Basal body temperature chart.

Breastfeeding. Regular breastfeeding with at least one feed at night is shown to prevent pregnancy for 6 months, with a failure rate of only 0.5–1.5%. This occurs due to prolactin preventing LH surge and ovulation. Thereafter, the protective effect wears off. Apart from the beneficial effects of lactation on the newborn, it is emphasized as the natural method of family planning in the first 6 months puerperium. Beyond 6 months of breastfeeding, prolactin level falls and ovulation can occur. It is the frequency rather than the duration of feed that decides nonovulation in a nursing mother. Breastfeeding is contraindicated in an HIV woman and one on certain drugs.

Persona

This is a microcomputer attached to a micro-laboratory. It measures the levels of oestrone-3 glucuronide and LH in the morning urine by dipping a test stick in the urine 'green light' shows conception unlikely and 'red light' shows fertile period and warns the probable ovulation and conception. The failure rate with this technique is approximately 6 per 100 women year.

Barrier Methods

Condoms. In this method, the erectile penis is completely covered by a very thin rubber (condom) which is used only once. It is desirable to use a condom with a water-based spermicidal agent to improve the efficacy of the method (Figure 20.3).

Condoms are made of latex which can be damaged by oil-based spermicidal agents; therefore, water-based spermicides should be used. Because of irritation by latex in some women, nonlatex polyurethane condoms are available. They, however, slip and break easily and are more costly than the latex condoms. The condoms prevent sexually transmitted diseases (STD) and HIV, but are less protective against STD transmitted from skin-to-skin contact such as human papilloma virus and herpes virus.

ADVANTAGES. It is easily available, cheap, easy to carry, free from side effects and requires no instruction. It emphasizes the male involvement in contraceptive effort and is immediately effective. It prevents sperm allergy. It has no adverse effect on pregnancy, should the method fail. *Nirodh* brand is distributed free of cost in the government hospitals in India. Condoms also prevent transmission of STDs from one partner to the other. The occurrence of cancer of the cervix is low amongst women whose partners use condom because sexual transmission of the viral infection causing this disease is prevented. Condom has also a place in checking the spread of the dreaded AIDS infection. It can be used along with other contraceptive methods to enhance the contraceptive efficiency.

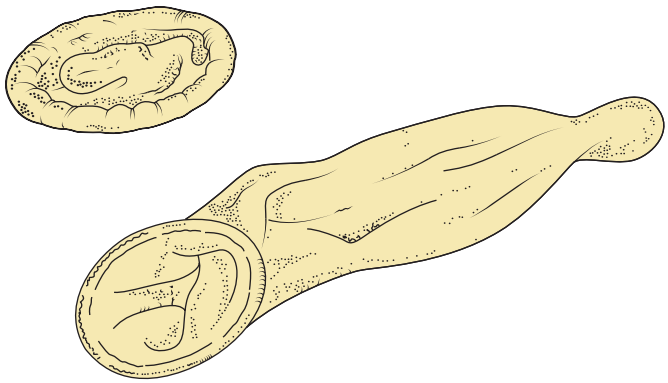

Figure 20.3 Condoms rolled and unrolled.

DISADVANTAGES. The method is only partially reliable, having a pregnancy rate of 10–14 per 100 woman years. This is partly due to bursting of the condom or slipping and partly due to noncompliance. Occasionally, a woman develops vaginal irritation to the latex. Some couples dislike the method because they do not obtain full sexual satisfaction. This method is coitus-dependent. To avoid allergy to latex rubber, polyurethane condoms and Tactylon material are manufactured which are slightly more expensive.

Other uses of condoms are:

- For 12 ejaculation following vasectomy, as these ejaculations may contain sperms from the ejaculatory duct.
- For 3 months, condom use is advocated, if sperm antibodies are the cause of infertility. The antibodies clear by end of this period.
- To prevent transmission of gonococcal, chlamydia, syphilis, trichomonad and fungal infection. Especially, it has an important role in transmission of HIV from one partner to the other.

The risk of transmission of infection after one intercourse from male to female is 60–80%, but reduced to 40% with condom use. The transmission from female to male is only 20% and reduced by 75% with use of condom.

Spermicidal Agents. The spermicidal agents kill the sperms before the latter gain access to the cervical canal. These chemical contraceptive agents contain surfactants, such as nonoxynol-9, octoxynol and menfegol and enzyme-inhibiting agents, and are available as foam tablets, soluble pessaries, creams, jellies, or as films along with other contraceptives such as the diaphragm, occlusive cervical cap and condom. Used alone, failure rate is high, approximately 30 per 100 woman years. When used in conjunction with a mechanical barrier, they give a reliable contraceptive effect. The spermicidal agent remains effective for 1–2 h after the application.

By causing irritation and abrasions in chronic use, they can cause vaginal ulceration and perhaps increase the risk of HIV spread rather than prevent it. Therefore, the spermicidal agents should not be recommended to HIV couples. A new spermicidal cream, Tenofovir, prevents viral attachment to the vaginal mucosa and is nonirritant and is under development.

The use of condoms with spermicidal agents and postcoital agents as back-up technique is effective in avoiding pregnancy.

Praneem from neem is spermicidal and prevents transmission of sexually transmitted infections. This is under trial.

Occlusive Diaphragms. These provide a barrier in the vagina against direct insemination. The diaphragm is

effective when used in conjunction with a chemical spermicide in the form of a jelly or cream, and when sufficient time is allowed for complete destruction of the sperms before the diaphragm is removed. In practice, the diaphragm liberally covered with spermicide can be inserted at any convenient time and is left in position for a minimum of 8 h after coitus. It causes no discomfort and no douching is required when these precautions are observed.

Alterations in the size and type of diaphragm may be required as a result of changes in weight, illness, delivery and prolapse so that routine checking is advisable at suitable intervals, usually 6 months to 1 year. A refitting of the diaphragm is always required after childbirth, and this can be done about 6–8 weeks after confinement.

The woman needs initial training in insertion and removal of diaphragm.

TYPES

1. *The Dutch cap or diaphragm*. This consists of a dome-shaped diaphragm of thin rubber, with a rubber-covered metal rim which may be either a watch spring or spiral spring. The diaphragm is made in a wide range of sizes varying from 50 to 95 mm diameter (the ones in common use range between 65 and 80 mm) and fit obliquely in the vagina, stretching from just behind the pubic ramus into the posterior fornix, thus covering the cervix. It is held in position by the tension of the spring rim. It is the easiest type of cap for the patient to use, fits in the majority of cases, causes no discomfort to either partner when correctly fitted (Figure 20.4).Contraindications to use of diaphragm are: (i) prolapse, cystocele, rectocele because accurate fitting is not possible; (ii) recurrent urinary tract infection and (iii) allergy to rubber or spermicidal agent. Toxic shock syndrome (TSS) may occur if the diaphragm is left in the vagina for a long period. TSS is caused by staphylococcal pyogenic infection. The failure rate of the Dutch cap is about 4–6 per 100 woman years and is nearly always associated with poor fitting and noncompliance.
2. *The cervical cap*. This is a cup-shaped rubber somewhat like a thimble, with a solid rolled rubber rim. It fits closely to the cervix and is suitable where the cervix is long and firm. When a woman has a prolapse of uterus and vagina, a cervical cap is preferred to the vaginal diaphragm. Chronic cervicitis, erosion and cervical laceration contraindicate its use. The cervical caps are available in four sizes, varying from 22 to 31 mm (Figure 20.5).
3. *Dumas cap*. It is a cup-shaped rubber with a thickened rim which fits well into the vault of the vagina so that it encloses the cervix. The size varies from 55 to 75 mm diameter.
4. *Femshield (female condom)*. It is known as 'FEM' or Femidom. It is a newly developed female barrier contraceptive and is woman oriented. It is a loose-fitting 15–17 cm long sheath made of polyurethane prelubricated. It has a polyurethane ring at the closed end of the sheath, serving as an insertion and anchoring device, and the second end is open and lies outside the vagina after insertion. It has the combined features of a diaphragm and a condom (Figure 20.6). It covers the entire vagina, cervix as well as the external genitalia. It is highly protective against spread of STDs, and AIDS in particular. It can be removed immediately after intercourse. The advantages of the Femshield are: (i) it is coital-independent and can be worn well in advance of the sexual act; (ii) it does not slip off easily, and the failure rate is expected to be low; (iii) it is stronger than the condom and does not

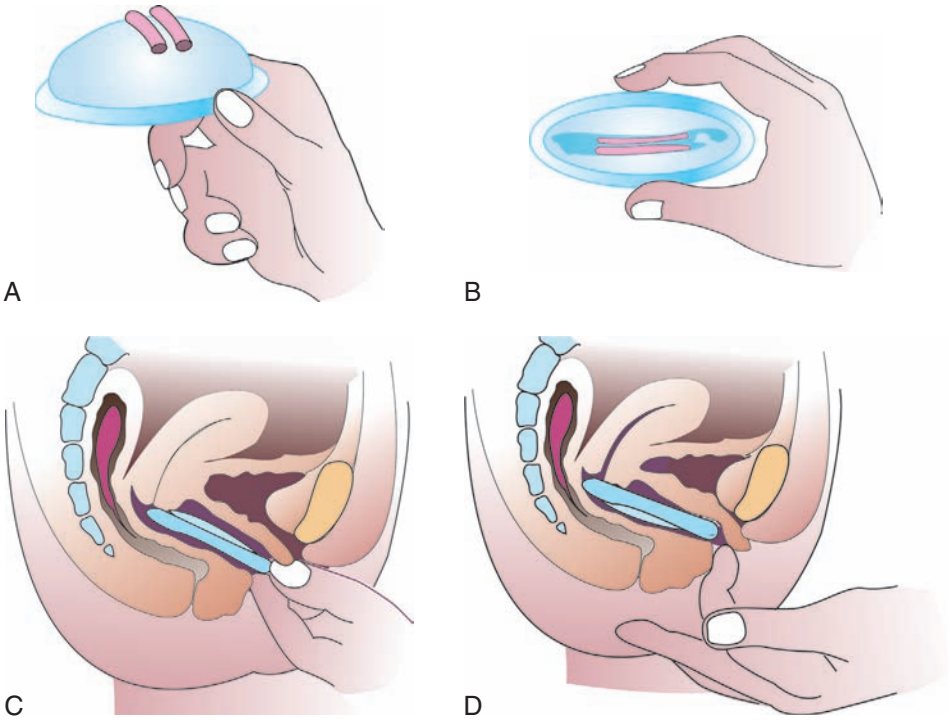

Figure 20.4 **(A)** Two strips of contraceptive paste are placed over the dome of the cap. **(B)** The rim is squeezed together so as to enclose the paste. **(C)** Insertion of Dutch cap—first stage. **(D)** Insertion of Dutch cap—second stage. The anterior rim is pushed up well behind the symphysis pubis.

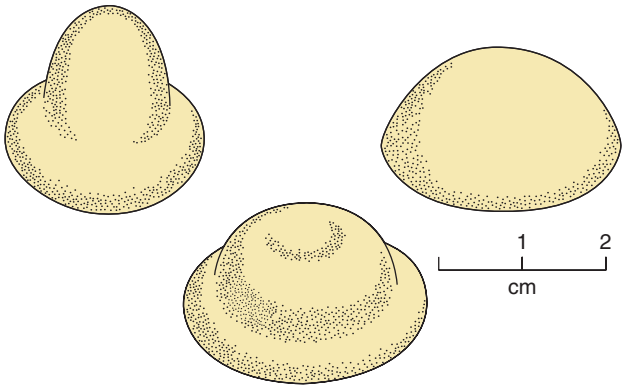

Figure 20.5 Types of cervical caps.

burst easily and (iv) it can be worn during the puerperal period unlike the diaphragm. Failure rate is 5–15 per 100 woman years. The Femshield is expensive, costing 2–3 dollars per piece. Besides, its reuse more than once has not yet been recommended.

5. *Today*. It is a mushroom-shaped polyurethane disposal sponge, 2 inches in diameter, 1.25 inches thick and contains 1 g of nonoxynol-9 (Figure 20.7). It is provided with a loop for its easy removal. It should be placed high up in the vagina with the concave side covering the cervix. It can remain effective for 24 h. It is used only once. It acts as a mechanical barrier and prevents entry of sperms into the cervical canal, absorbs semen and contains a spermicidal agent.

Failure rate is similar to those of other barrier methods and spermicidal agents (9–30 per 100 woman years). It is however expensive, coital-dependent, and may cause TSS if left over a long period.

Occlusive diaphragms are cheap and easy to use. One diaphragm can be used for over a year if it is washed, dried and kept properly after each use. Like the condom, the diaphragm prevents transmission of STDs from one partner to another and the incidence of cancer of the cervix is low in women using this contraceptive. It does not, however, prevent transmission of HIV, because it allows vaginal secretion to mix with semen. The lack of bathroom facilities and of privacy in low socio-economic groups prevents its wider use in India. An occasional woman develops vaginal irritation to latex.

New nonsclerotic occlusive copolymer of styrene maleic anhydride (SMA)—lowers PH of semen and alters sperm transportation and morphological changes in the sperms.

Advantages

- Instant infertility
- Reversible in 2–4 months
- No toxicity
- No decreased libido

Disadvantage

Scrotal swelling is sometimes reported.

Altering Cervical Mucus by Progestogen

Low-dose progestogen-only pill (POP), called 'minipill', is administered daily. Under the influence of progestogen, the cervical mucus becomes viscid and prevents penetration of sperms into the cervical canal. In addition, the pill inhibits ovulation in 40% and reduces fertility. Minipill is described later in this chapter.

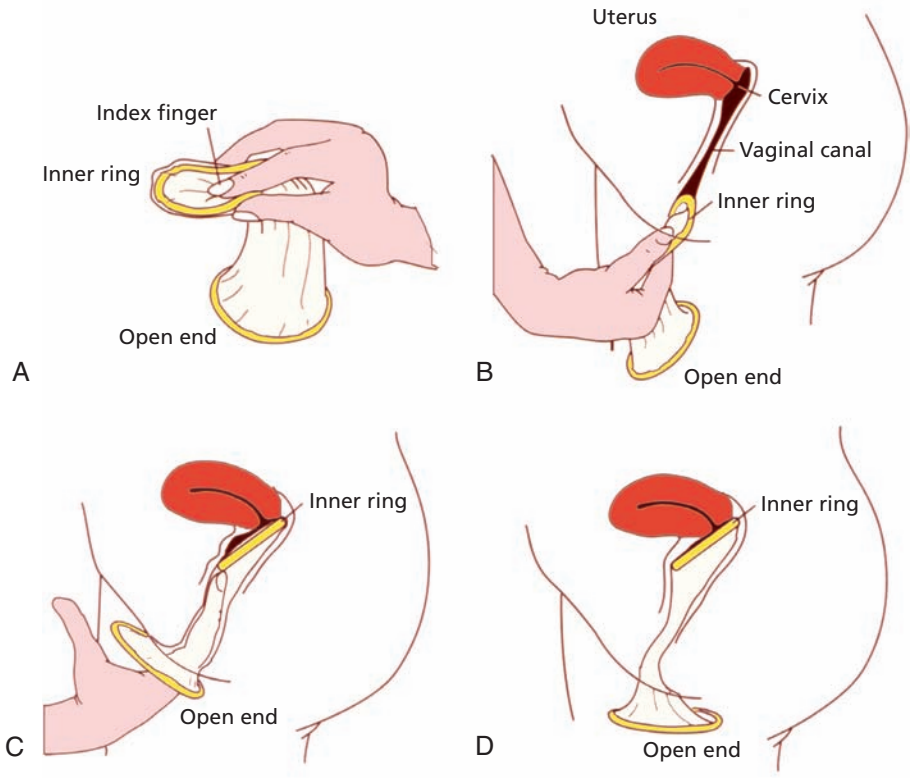

Figure 20.6 Femshield or female condom.

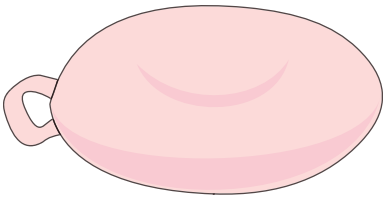

Figure 20.7 'Today' vaginal sponge.

Intrauterine Contraceptive Devices

IUCD is an effective, reversible and long-term method of contraception, which does not require replacement for long periods and does not interfere with sexual activity. The device is commonly made of polyethylene which is impregnated with barium sulphate to render it radiopaque so that the presence or absence of the device in the pelvis can be easily detected by radiograph or ultrasound. Medicated devices which contain copper, progesterone hormone and other pharmacologic agents have been introduced. The plastic devices are flexible so that they can be straightened and loaded into an introducer by which they are passed through the cervical canal and gently released within the uterine cavity to take up their original shape. Each device has a nylon thread attached to its lower end and this thread protrudes through the cervical canal into the vagina, where it can be felt by the patient herself and by the doctor, and can be removed by pulling it with the forceps.

Classification of the Commonly Used IUCDs (Figure 20. 8)

1. **Copper-carrying devices**. In these, copper wire of surface area 200 to 250 mm is wrapped round the vertical stem of a polypropylene frame. Among these devices are Copper T 200, Copper 7, Multiload Copper 250, Copper T 380, Copper T 220 and Nova T. The copper devices are more expensive than inert devices but are reported to exert a better contraceptive effect, with fewer side effects. They have an effective life of about 3–5 years. It is estimated that about 50 mcg of copper is eluted daily in the uterus. Copper T 380A, known as Paraguard, has a lifespan of 10 years. Nova T has silver added to the copper wire, thereby increasing its lifespan to 5 years.
2. **Progestasert and levonova**. Progestasert is a T-shaped device carrying 38 mg of progesterone in silicon oil reservoir in the vertical stem. It releases 65 mcg of the hormone per day. The hormone released in the uterus forms a thick plug of mucus at the cervical os which prevents penetration by the sperms and thus exerts an added contraceptive effect. Menstrual problems like menorrhagia and dysmenorrhoea noticed with Copper T are less with this device (40% reduction). It is expensive and requires yearly replacement. A new device, levonova, contains 60 mg of levonorgestrel (LNG) and releases the hormone in very low doses (20 mcg/day). It is thus longer acting (5 years) and has a low pregnancy rate of 0–3 per 100 woman years. However, the incidence of ectopic pregnancy is sixfold to ninefold higher in women who do become pregnant with progestogen IUCD as compared to failures amongst Copper T users. It can be safely recommended for nursing mothers.

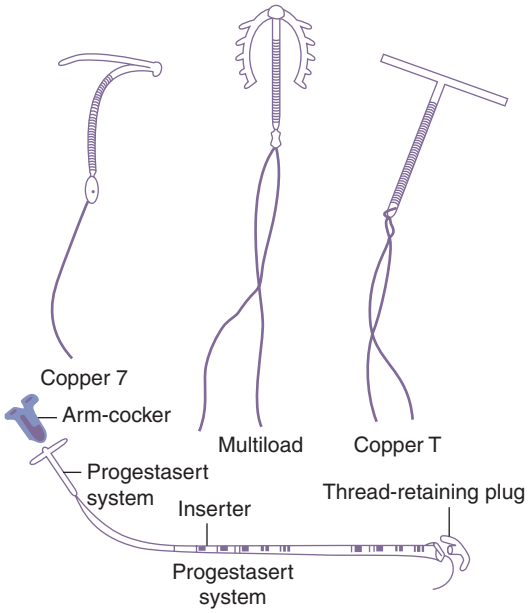

Figure 20.8 IUCDs in common use.

Mirena (32 × 32 mm) contains 52 mg LNG, eluting 20 mcg daily (Ch. 24). It can be retained for 5 years, with a failure rate of 0.1–0.4 per 100 woman years. Hormone containing IUCD combines the best of properties of IUCD and hormonal contraceptive, and eliminates some of the problems of IUCDs, i.e. dysmenorrhoea and menorrhagia. It does not affect ovarian function, but acts locally, prevents implantation.

Frameless IUCD and fibroplast releasing 14 mcg progestogen daily for 3 years are under trial. Gyneflex is 3–4 cm long, 1.2 mm in width, and adapts to the shape of the uterine cavity. Because it is small in size, complications such as pain, bleeding, ectopic pregnancy and expulsion are less reported. It contains 6 copper beads on a monofilament polypropylene thread. The thread is knotted at one end which is fixed to the fundus. Frameless IUCD contains several copper cylinders tied together on a string, and it is anchored 1 cm deep into fundus (Figure 20.9).

Essure device within the intramural portion of the fallopian tube is a new IUCD under trial (Figure 20.10).

Patient Selection. IUCDs are a good contraceptive choice for the following groups of women:

- Low risk of STD
- Multiparous woman
- Monogamous relationship
- Desirous of long-term reversible method of contraception, but not yet desirous of permanent sterilization
- Unhappy or unreliable users of oral contraception or barrier contraception

Uses of IUCD

- As a contraceptive
- Postcoital contraception (emergency contraception)

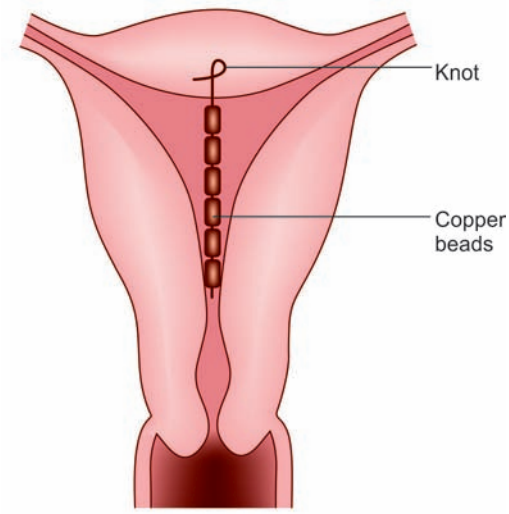

Figure 20.9 Frameless IUCD.

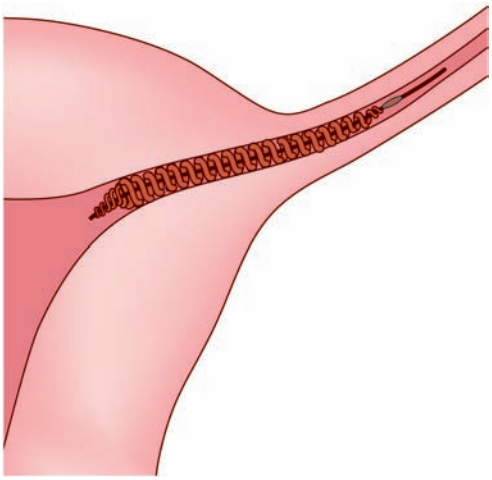

Figure 20.10 Essure device.

- Following excision of uterine septum, Asherman syndrome
- Hormonal IUCD (Mirena) in menorrhagia and dysmenorrhoea, and hormonal replacement therapy in menopausal women
- In a woman on tamoxifen for breast cancer, MIRENA can be used to counteract endometrial hyperplasia

Contraindications

- Suspected pregnancy
- Pelvic inflammatory disease (PID), lower genital tract infection
- Presence of fibroids—because of misfit
- Menorrhagia and dysmenorrhoea, if Copper T is used
- Severe anaemia
- Diabetic women who are not well controlled—because of slight increase in pelvic infection
- Heart disease—risk of infection
- Previous ectopic pregnancy
- Scarred uterus
- Preferably avoid its use in unmarried and nulliparous patients because of the risk of PID and subsequent tubal infertility
- LNG IUCD in breast cancer
- Abnormally shaped uterus, septate uterus

Technique of Insertion. The insertion of an IUCD is relatively simple and easy. However, the person who is going to insert a device requires some training in accurate pelvic examination and in gentle insertion of the device. A thorough pelvic examination is performed to determine the position and size of the uterus. The presence of any uterine, tubal or ovarian pathology precludes the insertion of the device. The vagina and cervix are inspected by means of a speculum. Any vaginal or cervical infection must be treated and cured before a device is inserted. The cervix is grasped with a vulsellum or Allis forceps. The device with the introducer is available in a presterilized pack. The device is mounted into the introducer, and the stop on the introducer is adjusted to the length of the uterine cavity. The introducer is then passed through the cervical canal and the plunger is pressed home. This is known as 'push-in technique'. The better method is 'withdrawal technique' with less chance of uterine perforation. In this, the rod containing IUCD is inserted up to the fundus. The outer rod is withdrawn followed by inner rod (multiload). The device uncoils within the uterine cavity (Figure 20.11). The nylon thread is cut to the required length. The forceps and the speculum are removed and the patient is then instructed to examine herself and feel for the thread every week. The acceptance rate of the IUCDs varies. The removal rate at the end of 1 year, because of pain, discomfort, continuous or heavy bleeding or vaginal discharge, is reported to be about 15–20%. The pregnancy rate varies from 2 to 6 per 100 woman years. It is advisable to insert IUCD during or soon after menstruation and after abortion or MTP. *Lately, immediate postpartum insertion within 10 min of placental expulsion or within 24 h of delivery is practiced and is found effective.* This saves the woman second visit to the clinic. There is no clinical evidence of increase in perforation, expulsion. The failure rate is less than 1%. Progestogen-containing IUCDs having a thicker vertical stem require cervical dilatation in a few cases.

Mechanism of Action. Several mechanisms are responsible for the contraceptive effect of an IUCD.

- The presence of a foreign body in the uterine cavity renders the migration of spermatozoa difficult.
- A foreign body within the uterus provokes uterine contractility through prostaglandin release and increases the tubal peristalsis so that the fertilized egg is propelled down the fallopian tube more rapidly than in normal and it reaches the uterine cavity before the development of chorionic villi and thus is unable to implant.
- The device in situ causes leucocytic infiltration in the endometrium. The macrophages engulf the fertilized egg if it enters the endometrial tissue.

- Copper T elutes copper which brings about certain enzymatic and metabolic changes in the endometrial tissue which are inimical to the implantation of the fertilized ovum.
- Progestogen-carrying device causes alteration in the cervical mucus which prevents penetration of sperm, in addition to its local action. It also causes endometrial atrophy. It prevents ovulation in about 40%.

Complications. With improvements in the new devices, the acceptability and compliance have improved. The complications of an IUCD are:

Immediate
- Difficulty in insertion
- Vasovagal attack
- Uterine cramps

Early
- Expulsion (2–5%)
- Perforation (1–2%)
- Spotting, menorrhagia (2–10%)
- Dysmenorrhoea (2–10%)
- Vaginal infection
- Actinomycosis

Late
- PID—2–5%. IUCD does not prevent transmission of HIV
- Pregnancy—1–3 per 100 woman years (failure rate)
- Ectopic pregnancy
- Perforation
- Menorrhagia
- Dysmenorrhoea

IUCD can be inserted in HIV-positive woman on medication.

Long-term follow-up of women wearing IUCD has shown no ill effects on systemic diseases. There is no evidence that the device predisposes to either cervical or endometrial cancer.

Perforation can occur at the time of insertion, particularly during puerperium. Its incidence is 1–3 per 100 insertions, lately reduced with improved devices. Perforation is rare with withdrawal than push-in technique. Menorrhagia is controlled with NSAID drugs.

Expulsion may occur in 5–15% and is due to small size of IUCD. It is common during the puerperal period or following MTP of a large gestation size.

PID occurs usually in the 4 weeks of insertion and may be due to existing unrecognized vaginal infection, or the tail of IUCD causing ascending infection. Actinomycosis is an infection commonly associated with IUCD.

IUCD is removed by grasping the thread with an artery forceps and gently pulling it out.

Misplaced IUCD. It is defined as the condition when the tail of the IUCD is not seen through the os. The causes are: (i) uterus has enlarged through pregnancy, (ii) thread has curled inside the uterus, (iii) perforation has occurred or the IUCD is buried in the myometrium and (iv) it has been expelled (Figure 20.12).

A plain radiograph or pelvic ultrasound will show whether the IUCD is still inside or has been expelled. If it is inside, the uterine sound or another IUCD inserted in the uterine cavity will show on radiograph its proximity to the misplaced IUCD and perforation can be diagnosed (Figure 20.12). Abnormal shape or location of IUCD on radiograph indicates likely perforation. Hysteroscopy is useful not only to locate it but also for its retrieval. If the IUCD is in the uterine cavity, it can be retrieved with Shirodkar's hook, a curette or through a hysteroscope and ultrasonic guidance. In case of perforation, a laparotomy is needed, because Copper T causes adhesions to the omentum or a gut and cannot be retrieved easily through a laparoscope.

PREGNANCY. *Pregnancy* occurs with IUCD in situ in 1–3 per 100 woman years. If this happens, it is important to do

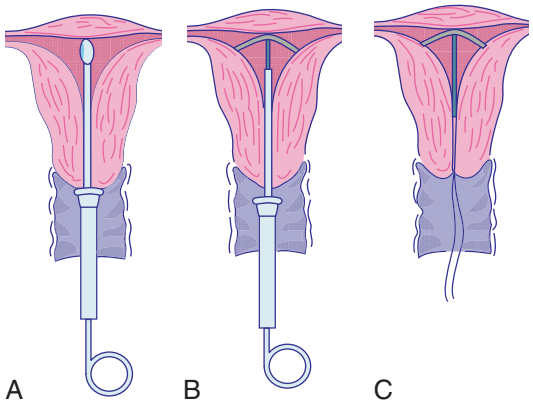

Figure 20.11 **(A)** IUCD inserted. **(B)** Inserter withdrawn. **(C)** IUCD released.

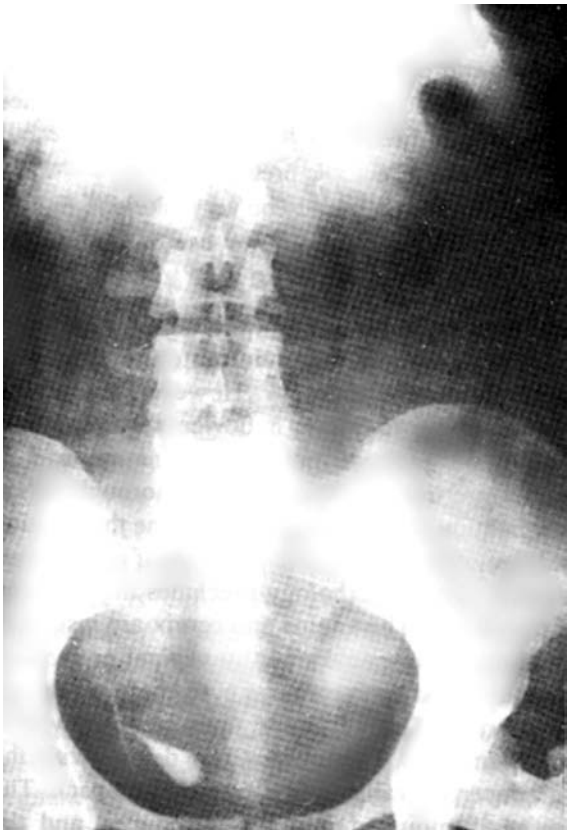

Figure 20.12A Displaced Copper T with calcium deposition at tip of T.

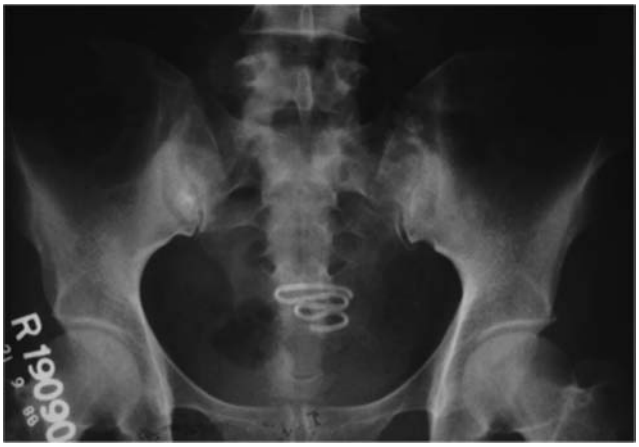

Figure 20.12B Pelvic radiograph showing Lipples loop in the pelvic cavity (Courtesy: Dr K K Saxena, New Delhi.)

ultrasound and rule out ectopic pregnancy. The uterine pregnancy can cause severe infection. It is therefore mandatory to remove the IUCD if the tail is visible through the os. While doing so, the risk of abortion should be explained to the woman. If the thread of the IUCD is not seen, termination of pregnancy is offered, not because IUCD has any teratogenic effect but because the risk of uterine infection is considerable. Alternatively, the pregnancy is continued after counselling and explaining the risk.

ECTOPIC PREGNANCY. It occurs in 1:30 pregnancies in woman wearing IUCD. This is because IUCD has a local contraceptive action on the uterus and prevents a uterine pregnancy but does not protect against tubal or ovarian pregnancy. Progestasert has the highest incidence of ectopic pregnancy (six to nine times more than Copper T). PID caused by IUCD also contributes to the occurrence of an ectopic pregnancy.

Advantages of IUCD

- It is coital-independent.
- One-time insertion gives continuous protection for a long period. It is cost effective.
- It is highly effective, newer IUCDs being as effective as oral contraceptives. Three per cent failure rate at the end of 1 year is reduced to less than 1% at the end of 5 years. There is no user failure.
- There is no evidence of reduced fertility following its removal. About 75% women conceive within 6 months of its removal and almost 90% conceive within a year.
- There are no systemic ill effects, unlike oral contraceptives. No adverse effect on lactation is observed.

Copper T is inserted free of cost in government hospitals in India.

Disadvantages of IUCD

- A medical or paramedical personnel is required to screen and insert an IUCD.
- Certain complications have been mentioned.

Mirena IUCD. It is 32 × 32 mm IUCD with the vertical rod containing 52 mg LNG progestogen in a silastic reservoir in its vertical arm: 20 mcg hormone is eluted in 15 min after its insertion, and the peak level reaches in a few hours. The hormone does not get absorbed into the general circulation (or minimal amount) so the side effects of systemic administrations are not seen. It does not suppress ovulation, and its effect is mainly on the endometrium and cervical mucus. Because of this, Mirena is also used in abnormal uterine bleeding (AUB), endometrial hyperplasia, in HRT and in a woman on tamoxifen for breast cancer to combat hyperplasia of endometrium caused by oestrogen. It may cause irregular bleeding during the first 3–6 months. The pregnancy rate is 0.5 per 100 woman years (equal to that of tubectomy).

- Teratogenic, if pregnancy occurs with Mirena in situ due to progestogen.
- Incidence of ectopic pregnancy 0.02%.
- 20 mcg hormone is daily eluted.

As compared to tubectomy, Mirena is an effective contraceptive, reversible and reduces dysmenorrhoea and menorrhagia unlike tubectomy. Mirena, since it cures menorrhagia and is as effective as tubectomy, is expected to reduce the number of hysterectomies and tubectomy operations in future. It is safe. Continuation rate of 80% is reported at the end of 1 year.

Advantages of Mirena

1. One-time insertion
2. Effective for 5 years
3. Compliance
4. Reduces menorrhagia and dysmenorrhoea

Fibroplant: Is a frameless LNG IUCD; releases 14 mcg LNG daily, and is under clinical development.

Suppression of Spermatogenesis

Gossypol. Its use as a male contraceptive was discovered in China. Gossypol is a yellow pigment isolated from cottonseed oil. It is administered orally 10–20 mg daily for 3 months and thereafter 20 mg twice weekly. The action is directly on the seminiferous tubules inhibiting spermatogenesis without altering FSH and LH levels. The side effects such as weakness, hypokalaemia and permanent sterility in 20% cases limit its use.

Testosterone Enanthate

- Testosterone enanthate 200 mg injection weekly causes azoospermia in 6–12 months. Testosterone buciclate 600 mg 3-monthly is also effective through negative feedback mechanism without loss of libido.
- Instead of weekly injection, testosterone decanoate 1000 mg IM followed by 500 mg 4-weekly is more convenient.
- Four implants of 200 mg each of testosterone every 4–6 months with 300 mg medroxyprogesterone 3-monthly is successful in 96% cases with count less than 1 million/mL.

Side effects—osteopenia, liver and lipid metabolism dysfunction, prostate enlargement.

GnRH. The continuous administration of analogues of gonadotropin-releasing hormone (GnRH) causes a fall in the sperm count and sperm motility. The level of testosterone also falls. The loss of libido and osteoporosis makes this regime unacceptable over a long period. Besides, it is very expensive and needs to be given subcutaneously.

Medroxyprogesterone Acetate. Medroxyprogesterone acetate 250 mg intramuscularly with 200 mg norethisterone given as weekly injections is reported to suppress spermatogenesis with 97% success.

Desogestrel. It has androgenic property. 75–300 mcg daily with subcutaneous pellets of testosterone 300 mcg causes oligospermia, without altering the level of HDL.

The hormonal suppression of spermatogenesis causes loss of libido and is toxic in high doses. Besides, the injection of hormones is inconvenient to administer regularly. The acne, weight gain and decreased HDL are other side effects. Immunological methods of suppressing spermatogenesis have not yet been successful.

Synthetic hormone—MENT used as substitute of testosterone—no side effects.

Suppression of Ovulation (Hormonal Contraceptive Agents) (Table 20.1)

Hormonal contraception is one of the most effective contraceptive methods available today. Since 1956, when Pincus first brought out an oral contraceptive drug, more than 30 millions of women have used this method in one form or the other. A wide variety of hormonal preparations are now available for contraceptive use alone. The mode of action depends upon the hormone used, the mode of delivery and the time of administration.

There are three types of hormonal oral contraceptives, viz. monophasic combined oral pills (Table 20.2), triphasic combined pills and minipills.

TABLE 20.1 Hormonal contraceptives

Oral	Insertions	Injections
	• Vaginal ring • IUCD Mirena	• Monthly • 3 monthly 2 monthly • Combined
COC, POP Combined pills • Oral daily	• Implants	E_2 + P injection monthly
3 weeks cyclically • 3 monthly • Yearly • Triphasic • Emergency pills	• Testosterone implants in male	Progestogen patch • Subdermal self-administration injection of DMPA on trial • Testosterone injections in males

TABLE 20.2 Types of monophasic combined oral pills

1st generation	Ethinyl oestradiol	Norethindrone
2nd generation	Ethinyl oestradiol	Norgestrel, LNG
3rd generation	Ethinyl oestradiol	Desogestrel, gestodene norgestimate
4th generation (Yasmin)	Ethinyl oestradiol	Drospirenone

Combined Oral Pills (OC). Combined oral pills contain a mixture of ethinyloestradiol (EE_2) in a dose of 20–30 mcg and an orally active progestogen. Mala-D contains 0.5 mg of d-norgestrel and Mala-N contains 1 mg norethisterone; these are available free of cost in India. The tablets are taken starting on the second day of the cycle for 21 days (now started on 1st day). A new course of tablets should be commenced 7 days after the cessation of the previous course. They should be taken at a fixed time of the day, preferably after a meal.

The combined oral pill suppresses pituitary hormones, FSH and LH peak and through their suppression prevents ovulation. At the same time, progestogen causes atrophic changes in the endometrium and prevents nidation. Progestogen also acts on the cervical mucus making it thick and tenacious and impenetrable by sperms.

It also increases the tubal motility, so the fertilized egg reaches the uterine cavity before the endometrium is receptive for implantation.

Pregnancy rate with combined oral pill is 0.1 per 100 woman years, which is the lowest of all contraceptives in use today. During the first cycle of use, ovulation may not be suppressed and the patient is advised to use an additional method to prevent pregnancy. Lately, starting the pill on the first day of the cycle has reduced the failure rate and the need to take the additional precaution in the first cycle. If she forgets to take a tablet, she should take two tablets the following day. If she forgets to take the tablet more than once in a cycle, she is no longer adequately protected and must use a barrier method during that cycle. The majority of failures with oral combined pills are due to the failure to take the pills regularly. With proper compliance, most women have regular 28-day menstrual cycles. The bleeding is less in amount and shorter in duration than a normal menstrual period. In a nonlactating woman, OC can be started after 3 weeks of delivery, but can be given soon after an abortion, MTP or an ectopic pregnancy. Following hydatid mole, one should start on OC only after serum β-hCG is negative. HIV antiviral drugs reduce effectiveness of OC but when combined with condoms, OC pills are protective against pregnancy.

BENEFITS OF COMBINED PILLS

- It effectively controls fertility.
- As it causes regular and scanty menstruation, it is useful in menorrhagia and polymenorrhoea. By virtue of nonovulation, it can relieve dysmenorrhoea and premenstrual tension.

- It prevents anaemia by reducing the menstrual loss.
- It has proved to lower the incidence of benign breast neoplasia such as fibrocystic disease.
- It reduces the incidence of functional ovarian cyst (50%) and ovarian and uterine malignancy. The incidence of ovarian cancer is reduced by 40% and uterine malignancy by 50% if taken for 1 year, and this effect lasts as long as 10 years after stoppage. The risk decreases with duration of its use.
- The incidence of PID is reduced, though it does not reach the same low level as seen with the barrier method. This effect is due to the thick cervical mucus caused by progestogen, preventing the organisms entering into the uterine cavity.
- Reduced incidence of ectopic pregnancy is due to suppression of ovulation and reduction in PID.
- It protects against rheumatoid arthritis.
- Reduces the risk of anorectal cancer by 30–40%.
- It is useful in acne, PCOD and endometriosis.

SIDE EFFECTS AND CONTRAINDICATIONS

- Intermenstrual spotting is common in the first 3 months of the start of the pills but it gradually disappears. Heavy spotting can be stopped by increasing the dose for a few months.
- Menstrual bleeding can become very scanty and occasionally a woman becomes amenorrhoeic causing undue fear of pregnancy. Amenorrhoea of 6 months requires investigations. Postpill amenorrhoea is not related to the type, dose or duration of pill intake. Those with previous menstrual irregularity (oligomenorrhoea) are likely to suffer amenorrhoea.
- Genital tract. Oral pills are associated with monilial vaginitis. Carcinoma of the endocervix has been reported if used for more than 5 years but dysplasia is more frequent. No adverse effect is noted on uterine fibroids, and it is oestrogen singly that increases their size.
- Breast. The combined pills should not be offered to a woman suffering from cancer of the breast. Some have reported the breast cancer in a nulliparous woman (25%) who has taken oral contraceptive pills before the age of 24 years for over a period of 4 years. This should be considered while prescribing oral pills to a young nulliparous woman. Lately, OC is proved to increase the risk of breast cancer in a high-risk woman. Progestogen component has a high potential for breast cancer. However, if breast cancer develops, it is well differentiated with good prognosis. The risk of malignancy disappears after 10 years of stoppage.
- Pituitary adenoma was attributed to the use of the pill but its exact role in its development is not clear and doubtful.
- Lactation is suppressed with combined pills. The combined pills are therefore contraindicated in a lactating mother. Besides, the risk of thromboembolism is high during puerperium.
- Libido varies and may not be related to the pills.
- Nausea and vomiting are mainly due to oestrogen. It can be avoided by taking the pills at bedtime. If vomiting occurs within 1 h of taking pill, repeat dose.
- Liver. Adenomas have been reported and though they are benign, rupture of a hepatoma can be fatal. Because the hormones are metabolized in the liver, chronic liver diseases and recent jaundice contraindicate the use of pills.
- Gall bladder function may be adversely affected.
- Carbohydrate metabolism. Carbohydrate tolerance may be reduced. Therefore, combined oral pills are contraindicated or cautiously given to a diabetic woman.
- Lipid metabolism. Oestrogen increases the high-density lipoprotein (HDL) and lowers low-density lipoprotein (LDL). Some progestogens have a reverse effect and the overall effect on the myocardial and lipid depends upon the combined effect of both the hormones. The incidence of myocardial infarct therefore depends upon the type of pill used.
- Rifampicin, an antibiotic prescribed for a tubercular patient, reduces the absorption of the pill; hence, it is contraindicated in a tubercular patient on rifampicin. Other drugs interfering with OC are tetracycline and anticonvulsants, antifungal, cephalosporin and phenobarb. Ritonavir for HIV also interferes with absorption of OC.
- Headache, migraine, depression, irritability, increased weight and lethargy can occur due to progestogen.
- Thromboembolic disorders. Pulmonary embolism and cerebral thrombosis, both venous and arterial, are 7 to 10 times more frequent in the pill users than in the nonusers in the first year of use. This is due to increased clotting mechanism (platelet aggregation and increased fibrinogen factor VII, VIII and decreased fibrinolysis) caused by the oestrogen component of the pill. The effect is dose-dependent, and the reduction of the oestrogen content of the pill from the original 100–30 mcg, and presently a newer oral pill (Femilon) which contains 20 mcg EE_2 reveals an improved safety and tolerance profile, and at the same time retains its contraceptive efficacy. The incidence of thromboembolic disorders has thus dropped without diminishing the efficacy of the pill. A woman over 40 years, a woman with stroke, heavy smoker, a cardiac and hypertensive patient, a woman with familial hyperlipoproteinaemia are all high-risk cases for this complication. The pills containing desogestrel and gestodene (third generation) carry a higher risk of venous thromboembolism than the pills containing LNG.
- Sickle cell anaemia can cause thrombosis and crisis.
- A woman who wears contact lenses should be warned of oedema and irritation of eyes (thrombosis of optic vessels)—it is a relative contraindication. Combined oral contraceptive (COC) pill does not protect a woman against HIV and sexually transmitted infections. This is important while counselling a woman at a high risk for these infections. Barrier methods alone reduce the risk of transmission of infection. Dual methods of barrier contraceptive with OC are recommended.
- No adverse effects on thyroid.

Pills are therefore contraindicated in:

- Cardiac disease, hypertension, smoker over 35 years.
- Diabetes.
- History of thrombosis, myocardial infarct, sickle cell anaemia, severe migraine.
- Chronic liver diseases such as cholestatic jaundice of pregnancy, cirrhosis of liver, adenoma, porphyrias.
- Breast cancer, gall bladder disease.
- Gross obesity.
- Patient on enzyme-inducing drugs like rifampicin, and antiepileptic except sodium valproate.
- 4–6 weeks prior to planned surgery.
- Lactating woman.
- Monilial vaginitis.

The woman can take OC for several years up to the age of 35, and thereafter until 45 years if she is healthy, slim and nonsmoker; however, she should remain under the supervision of the doctor and have Pap smear done regularly to check on cervical dysplasia.

RETURN OF MENSTRUATION AND FERTILITY. Ninety-nine per cent of women will have normal menstrual cycles within 6 months of stopping OC but return of fertility may be slightly delayed due to delayed return of ovulation. There is no evidence of fetal malformation or increased rate of abortion in those who conceive while on pills. Ninety per cent ovulate within 3 months of stopping the drug.

Triphasic Combined Pills. The triphasic preparations of EE_2 and LNG contain during the first 6 days of the cycle 30 mcg EE_2 plus 50 mcg LNG, for the next 5 days 40 mcg EE_2 plus 75 mcg LNG, and during the last 10 days 30 mcg EE_2 and 125 mcg LNG, followed by one medication-free week. These pills have no adverse effect on carbohydrate and lipid metabolism; therefore, they can be prescribed to diabetic women and without expecting any increased risk of myocardial infarct. They are as effective as the monophasic oral pills but not recommended in menorrhagia and for other indications.

TO MAINTAIN GOOD COMPLIANCE OF ORAL PILLS. New ORAL PILLS are now manufactured and available (though more expensive). These are the following:

- Three-monthly course of 'seasonal' which contains EE_2 plus levonorgestrel. The packet contains 84 tablets (with a gap of 7 days), one daily, which means only four menstrual cycles in a year, and has been attractive to many women. Some, however, face the problem of prolonged breakthrough bleeding initially. Yearly continuous pills is under trial (one period a year)—Lybrel effective for 1 year.
- OC containing only 10 mcg EE_2. (Low dose pill)
- Once-a-month pill contains 3 mg quinestrol and 12 mg megestrol acetate, popular in China and Latin America. Two tablets in first month are followed by one tablet monthly.
- EE_2 + drospirenone (Yasmin, Tarana, Janya) contain 21 tablets in a packet, but Janya contains 24 tablets (gap of four tablets in a cycle), and contains 20 mcg EE_2.
- EE_2 + cyproterone acetate (Dianette) 35 mcg EE_2.
- Quadriphasic pill containing E2 + dienogest, daily—no pill-free days, better tolerated, good control of menses.
- Chewable tablets contain 35 mcg EE_2 and 0.4 mg norethidrone.
- Lybrel-continuous daily use for 1 year contains 20 mcg EE_2 + 90 mcg LNG in a tablet.

Drospirenone is an analogue of spirinone (3 mg drospirenone is equivalent to 25 mg of latter), is antimineral, corticocoid and with antiandrogenic activity. It inhibits ovulation, cures acne and hirsutism. It reduces fluid and sodium retention, and has no adverse effect on bone mineral density. It also prevents obesity and maintains good lipid profile. Because of this and cure of acne, it is also known as 'beauty pill'.

Side effects are:

- Potassium retention. It is contraindicated in renal and liver disease and in a woman with previous thromboembolism.

Different generations of oral pills:

- First generation contained norethindrone.
- Second generation contained LNG.
- Third generation contained gestodene, desogestrel, norgestimate.
- Fourth generation contains spironolactone and cyproterone acetate.
- Janya contains 24 tablets, each containing 20 mcg EE_2 and 3 mcg drospirenone.
- Yasmin contains 30 mcg EE_2 3 mg drospirenon.
- DIAN-35 contains cyproterone acetate.

PROGESTOGENS. Progestogens are available as oral pills (mini pills), intramuscular injections, implants, patches, vaginal ring and Mirena IUCD.

Minipill/Progestogen-Only Pill (POP). The low-dose POP (norethisterone 350 mcg, norgestrel 75 mcg or LNG 30 mcg) have been introduced to avoid the side effects of oestrogen in the combined pills. The tablet is taken daily without a break. The pill should be started within 5–7 days of the menstruation and taken at the same time with a leeway of 3 h on either side of the fixed time each day. If this regime is not observed any day, the woman continues with POP but observes extra precaution for 48 h. The mode of action of progestogen has already been discussed earlier.

POP is started 21 days postpartum and soon after abortion. The woman needs to take precaution in the first 48 h in the first cycle.

Minipill does not have some of the major side effects of the combined pill and *it is well suited for lactating women*; some progestogens, in fact, increase milk secretion. However, it has a pregnancy rate of 2–3 per 100 woman years which is higher than that of the combined pill though comparable to an IUCD and is higher in obese women. Strict daily compliance is a drawback. Other drawbacks are irregular bleeding (20%), amenorrhoea, depression,

headache, migraine and weight gain, ectopic pregnancy, functional ovarian cysts besides a higher failure rate.

The use of newer generation of synthetic progestogen, namely desogestrel, has been encouraging. It has no androgenic effect, no adverse effect on carbohydrate and lipid metabolism, and is considered to be safe, especially for lactating women. *However, the incidence of thromboembolism is higher with these progestogens*.

CONTRAINDICATIONS. Contraindications to POP are previous ectopic pregnancy, ovarian cyst, breast and genital cancers, abnormal vaginal bleeding, active liver and arterial disease, porphyria, liver tumour, valproate, spironolactone and meprobamate. *Because of osteopenia, it is contraindicated in adolescents and young women.*

ADVANTAGES. Advantages of POP are that they can be recommended to:

- Lactating women
- Women over 35 years
- Those with focal migraine
- Those intolerant to oestrogen or oestrogen contraindicated
- Diabetic, hypertensive woman, sickle cell anaemia. As regards to return of fertility, it is faster than in COC users because ovulation is not suppressed in all cases (suppressed in 40%)

Mode of Action of Mini-Pills

- Cerazette suppresses ovulation in 97–100%, whereas other progesterone only pills suppress ovulation in only 40%.
- It forms a thick plug of mucus in the cervical canal and acts as a barrier to sperms.
- It increases tubal peristalsis and fertilized egg reaches the uterine cavity too early for implantation.

Cerazette containing 75 mcg desogestrel has the following advantages over other POPs:

- Stringent time compliance not necessary, as it suppresses ovulation in 97%, through pituitary hormone suppression.
- No androgenic effects like acne.
- No ectopic pregnancy, no effect on carbohydrate or lipid metabolism.
- Failure rate only 0.21 per 100 woman years. It acts through metabolite etonogestrel which binds to progesterone receptors

Complications of desogestrel are:

- Deep venous thrombosis
- Pulmonary embolism, breast cancer, liver disease apart from common other complications of progestogens

Side effects: (1) weight gain, (2) irregular menstrual bleeding, (3) depression, (4) breast cancer and (5) thromboembolism.

Depot Injections. To overcome the inconvenience of daily compliance, depot injections of progestogens have been developed. Depot medroxyprogesterone acetate (DMPA) is given in microcrystalline aqueous suspension and norethisterone enanthate (NETO) in castor oil solution, both by deep intramuscular injection (not subcutaneous). A monthly injection of DMPA 25–50 mg, combined with 5 mg oestradiol is considered to be effective. Other preparations in use are the DMPA 150 mg 3-monthly, DMPA 300 mg 6-monthly and NETO 200 mg 2-monthly. After stoppage, the contraceptive effect of DMPA lasts longer than that of NETO. Menstrual irregularity is accepted by puerperal woman as physiological. The injection should be started within a month of delivery in a nonlactating woman and during the third month in a lactating woman because ovulation is delayed up to at least 10 weeks in lactating mothers. Pregnancy rate is 0.4 per 100 woman years for DMPA and 0.6 per 100 woman years for NETO.

The injection should be administered within 7 days of menstruation with grace period of 2 weeks for DMPA and 1 week for NETO (12–14 weeks of first injection for DMPA and 8–9 weeks for NETO).

Three monthly DMPA is also used in endometriosis.

ADVANTAGES

- Injections are easy to administer and there is no worry over 'missing pill'. Long-acting, reversible.
- The compliance is good and the woman remains under regular medical supervision.
- The side effects of lipid and carbohydrate metabolism are avoided. DMPA is least androgenic.
- It is suited to lactating women.
- The incidence of PID, ectopic pregnancy and functional ovarian cysts is low, so also endometrial cancer.
- Avoids oestrogenic side effects.
- Can be given to a woman with sickle cell anaemia.
- Return of fertility is slightly delayed in DMPA group compared to NET, but 80% conceive in 1 year (5 months for DMPA and 3–4 months for NETO).
- Coital independent.

DISADVANTAGES

- Once administered, the side effects, if any, need to be tolerated until the progestogenic effect of the injection is over.
- Menstrual irregularity occurs and amenorrhoea is reported in 20–50% at the end of 1 year, more with DMPA than NET. Heavy bleeding is reported in 1–2% users.
- Do not prevent STD and HIV.
- There is a delay in return of fertility but 80% are expected to conceive by end of 1 year. With DMPA, ovulation returns in 5 months, and with NETO, within 3 months of the last injection.
- The side effects of weight gain, depression, bloated feeling and mastalgia can occur with injectable progestogen.
- The women are clinic-dependent.
- Prolonged DMPA use, by virtue of antioestrogenic action, may reduce bone density mass and induce osteopenia.
- Contraindicated in breast cancer.
- It does increase LDL but does not adversely affect the blood pressure.
- Decreases libido, causes dry vagina.

Because of risk of osteopenia, this contraceptive is contraindicated in adolescents, and should not be used for more than 2 years in others. Lately, subcutaneous injections are under development to enable self-administration by the woman.

ONCE-A-MONTH INJECTIONS. Once-a-month intramuscular deep injection of combined oestrogen and progestogen are available in some countries.

These are:

- Mesigyna (1/2 mL containing NET 50 mg with oestradiol valerate 5 mg) is given by deep intramuscular injection once a month with ±3 days. The low failure rate of 0.4% at the end of 1 year is encouraging.
- Cyclofem and Lunelle (1/2 mL contains 25 mg DMPA and oestradiol cypionate 5 mg). The failure rate is 0.2% at the end of 1 year. The menstrual irregularity is less than with progestogen-alone injections.
- Marvelon (Desogestrel 150 mcg with EE_2 30 mcg).
- Femovan—gestodene 75 mcg with EE_2 35 mcg.
- Anafertin—dihydroprogesterone + 150 mg testosterone enanthate 5 mg.

It should be remembered that the first menstrual period comes 10–15 days after the first injection but thereafter every 30 days and lasts for 5 days. Failure rate of 0.1–0.4% is reported. Ovulation returns in 6 months.

Subdermal Implants. There was a need to explore the other routes of progestogen delivery into general circulation with slow, sustained release, long-acting and with reduced side effects.

The subdermal implant has no 'nuisance value' of continuous compliance which often adversely affects motivation. Besides, nonoral system avoids 'hepatic first pass effect and systemic side effects'.

To reduce the frequent visits to the clinics, ensure an even release of the hormone and reduce the side effects while maintaining the efficacy; implants containing various amounts of progestogen have been used subdermally.

NORPLANT I. **Norplant I** (Figures 20.13–20.15) containing six silastic capsules has been withdrawn and replaced by a single rod implant.

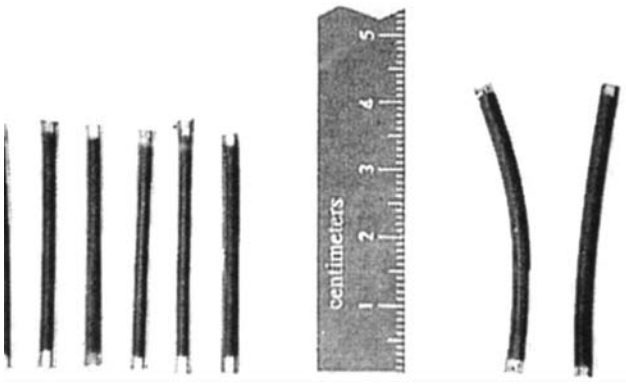

Figure 20.13 Norplant I and Norplant II.

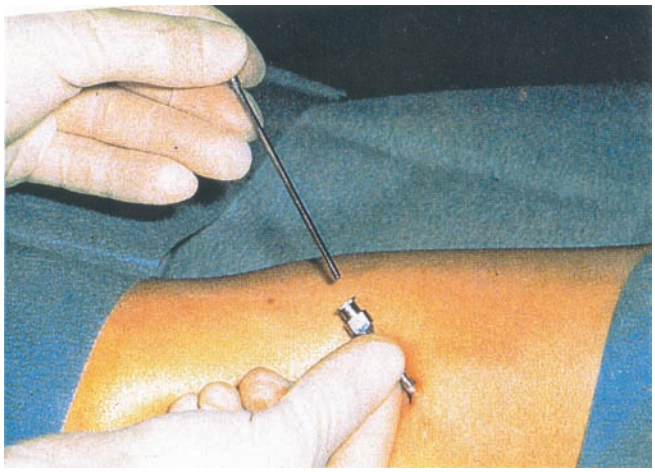

Figure 20.14 Insertion of Norplant.

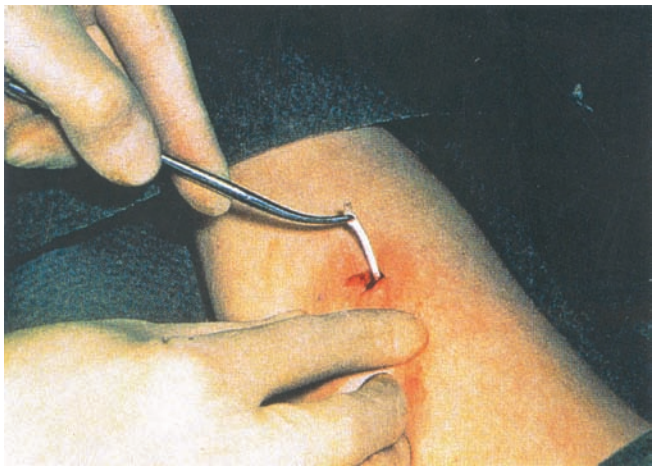

Figure 20.15 Removal of Norplant.

Norplant II (Jadelle) consists of two rods each containing 70 mg LNG. The daily release of hormone is 50 mcg and provides contraception for 3–5 years.

The implants suppress ovulation in 50% but the main action is suppressing endometrium.

The implants are inserted on the first day of the menstrual cycle, within 5 days of abortion, and 3 weeks after the delivery. The woman needs to use barrier contraception or abstain in the first 7 days of insertion.

It takes 5–10 min to insert under local anaesthesia. It is best inserted on the medial aspect of the upper arm. Since the capsules are nonbiodegradable, they need removal at the end of its use or earlier, if side effects are intolerable.

The insertion and removal is made easier by using a single rod, Implanon (40 × 2 mm), which contains 67 mg desogestrel and does not require an incision to insert. It elutes 30 mcg of the hormone daily and the effect lasts 3 years. There has been no failure to date. It prevents ovulation and is reversible within 1 month of removal.

Implanon—Amenorrhoea is common at the end of 1 year. Acne is reduced and no osteoporosis.

ADVANTAGES. The advantages of implants are:

- They are long-acting with sustained effect—compliance is good.
- Coital-independent with no 'nuisance' of daily oral or frequent injections.
- Pregnancy rate—varies between 0.2 and 1.3 per 100 woman years. The failure rate is higher in obese women weighing more than 70-kg.
- Systemic side effects are few and first pass effect on the liver avoided.
- Return of fertility has been mentioned.
- Can be used by lactating mothers and over the age 40.

DISADVANTAGES

- Breakthrough bleeding, irregular cycles, amenorrhoea occur as with other progestogenic contraceptives.
- Other side effects of progestogens exist.
- Ectopic pregnancy is reported in 1.3%.
- Local infection may occur.
- Requires insertion and removal with nonbiodegradable capsules, which are however minor surgical procedures.
- Failure rate (pregnancy) has been mentioned above.
- The implants are expensive and cost Rupee 10,000.
- Infertility is seen in a few cases.

Silastic Vaginal Rings (SVR). In an attempt to reduce the side effects of systemic hormonal contraception and the surgical method of insertion of implants, silastic vaginal rings carrying different progestogens in different doses have been tried. The ring is 50–75 mm in diameter and 5–9 mm thick. The latest SVR found effective contains LNG releasing 20 mcg of hormone daily and 15 mcg EE_2. The contraceptive effect is mainly on the cervical mucus. The hormone is safe as it gets absorbed through the vaginal mucosa and bypasses the liver. It is kept in situ for 3 weeks and removed for a week, thus bringing about regular menstrual cycles; failure rate is 1.8/100 woman years.

Recently, some progestin-containing rings (3-keto desogestrel 10 mg) have been left in for 3 months at a time. The pregnancy rate with this is reported to be 3.5 per 100 woman years (WHO, 1985). A ring releasing 30 mcg EE_2 with either 120 mcg desogestrel or 650 mcg norethisterone is under trial. Nestorone ring releases 150 mcg progestogen plus 15 mcg oestradiol daily—one ring remains effective for 1 year.

Nuvaring contains 2.7 mg EE_2 + 11.7 mg etonogestrel used continuously for 3 weeks and removed for 1 week.

Other rings are:

1. Nuvaring—120 mcg etonogestrel + 15 mcg EE_2 daily release can be removed during intercourse but not for more than 3 h at a time.
2. Nestorone—150 mcg progesterone +15 mcg EE_2, effective for 1 year; failure rate is 1.2/100 woman years.

ADVANTAGES

- Self-insertion and removal, good compliance.
- Other advantages of progestogen contraceptives.
- Quick reversibility.

DISADVANTAGES

- Expensive Rupees 700 per ring per cycle.
- Local irritation is felt by few, vaginitis 5%.
- Expulsion can occur.
- Pregnancy rate has been mentioned.
- Systemic side effects of progestogens have been noted in a few women.

IUCD impregnated with progestogens are Progestasert and Mirena. Mirena contains 52 mg LNG in the vertical arm of T device and elutes 20 mcg daily. The effect lasts for 5 years.

The failure rate is 0.1% similar to oral combined pills.

Though primarily used in AUB, its contraceptive benefit is also appreciated.

The menstrual irregularity in the first 3 months settles down to normal cycles and dysmenorrhoea is also cured. The incidence of PID and ectopic pregnancy is reduced.

The insertion is however difficult due to the thick vertical stem. Amenorrhoea is reported in about 20% at the end of 1 year. Mirena costs Rupee 7000.

Skin Patches

HORMONAL PATCH (ORTHO-EVRA). Hormonal patch Elutes 150 mcg of norelgestromin and 20 mcg EE_2 daily and the hormone lasts for 7 days. Three patches are required each cycle followed by 1 week patch-free interval. The patch should be applied within 5 days of menses over the buttocks, abdomen but not over the breasts.

The failure rate is 1–2.8 per 100 woman years. Compliance of 90% is reported. The breakthrough bleeding (18%) and skin reaction (20%) breast discomfort are the side effects. The other symptoms are headache, nausea and mastalgia. The site of patch should be changed often and is contraindicated in obese women.

GnRH, given continuously, suppresses FSH and LH and thereby ovulation. However, the drug is very expensive and long-term use causes osteoporosis.

Combined long-acting norgestrel 12 mg with 3 mg quinestrol, two tablets in the first month followed by one tablet each month is under trial.

PERCUTANEOUS GEL. Three grams daily of percutaneous gel of oestradiol with cyclical progestogen is easy to apply. One should wait for 1 h for the gel to dry up and not to be in contact with other members. It should not be applied over the breasts.

Centchroman (ORM ELOXIFEN). Centchroman is a synthetic nonsteroidal contraceptive taken as a 30 mg tablet, started on the first day of menses and taken twice weekly for 12 weeks and weekly thereafter (half-life is 170 h). It does not prevent ovulation. It prevents implantation through endometrial changes. It exhibits a strong antioestrogenic and a weak oestrogenic action peripherally at the receptor

level. The return of fertility occurs soon after stoppage of the drug (within 6 months).

Centchroman is not teratogenic or carcinogenic, exerts no pharmacological effect on other organs. The only side effect noted is prolonged cycles and oligomenorrhoea in 8% cases. This is due to prolonged proliferative phase. Pregnancy rate is 1.83 per 100 woman years. The drug can also be used as a postcoital pill, given in 60 mg dose within 24 h of coitus (two tablets repeated 12 h later with failure rate of 1%). It has been developed by Central Drug Research Institute, Lucknow, and has been released in India under the name of *Saheli.*

SIDE EFFECTS

- Headache, nausea, vomiting.
- Gain in weight.
- Does not protect against HIV and STD.
- Some delay in return of fertility (up to 6 months).
- Prolonged use—hyperplasia and atypical endometrium.

CONTRAINDICATIONS

- During 6 months of lactation.
- PCOD, hepatic dysfunction, cervical dysplasia, allergy to the drug.

Postcoital Contraception (Interceptives)

Postcoital contraceptive agent interferes with postovulatory events leading to pregnancy and is therefore known as interceptive. It is also known as 'emergency contraception' method used to prevent pregnancy after an unprotected intercourse. Emergency contraception is used following rape, unprotected intercourse or accidental rupture of a condom during coitus taking place around ovulation. It is used in misplaced IUCD and missed pill. These postcoital methods should be used mainly as 'back-up' methods in these conditions and not as a regular contraceptive technique as an ongoing method following every act of sexual intercourse. The preparations available include:

Two tablets of relatively high doses of combined pill (Ovran/Eugynon 50), containing 100 mcg EE_2 and 1 mg norethisterone, or 500 mcg LNG, taken within 72 h of intercourse followed by two tablets taken 12 h later (Yuzpe and Lancee, 1977). Failure rate—3.2 per 100 woman years.

Mode of action. The hormones may delay ovulation if taken soon after intercourse, cause corpus luteolysis, and bring about cervical mucus changes and endometrial atrophy.

Levonorgestrel (LNG). Prostinar tablet contains 0.75 mg LNG. One tablet should be taken within 72 h of unprotected intercourse and another 12 h later. Alternately, two tablets can be taken as a single dose. The failure rate is 1.1%. The tablets can be offered up to 120 h but its efficacy decreases with the longer coital-drug interval. LNG prevents ovulation and causes desynchronization of endometrium through its receptors (luteal phase deficiency). The period may come earlier or delayed.

Side effects are those of progestogens. The hormone is not teratogenic in case pregnancy does occur but risk of ectopic pregnancy remains.

ADVANTAGES

- It has no oestrogen and its associated side effects.
- It can be offered to hypertensive, cardiac and diabetic woman.
- It can be offered to a lactating woman.
- It can be given as late as 120 h after the unprotected intercourse.
- Single-dose therapy is an advantage.

Contraindicated in liver disease, contains lactate, so allergy to galactose. The drug is also contraindicated in a woman with history of thrombophlebitis and migraine.

RU 486 (Mifepristone)

RU 486 is a steroid with an affinity for progesterone receptors. It does not prevent fertilization but by blocking the action of progesterone on the endometrium, it causes sloughing and shedding of decidua and prevents implantation. It is not teratogenic.

A single dose of 25–50 mg is effective in preventing pregnancy in 99.1% cases (failure rate 0.9%). It causes delayed menstruation. Ectopic pregnancy is not avoided. The drug is expensive as compared to LNG.

Ulipristal. Ulipristal is a synthetic progesterone hormone receptor modular, attaches to progesterone receptor and prevents/delays ovulation and suppresses endometrium, prevents implantation. A 30 mg tablet should be taken within 5 days. Two per cent pregnancy rate is reported. Side effects are headache and mood changes.

Centchroman. Two tablets (60 mg) taken twice in 24 h within 24 h of intercourse can prevent implantation in 99% women.

GnRH Agonists. Daily administration of GnRH agonist (buserelin) prevents ovulation. The drug is on trial for its contraceptive effect. Very expensive—has to be given by subcutaneous injection.

Prostaglandin

Self-administered vaginal suppository containing prostaglandin following an unprotected intercourse, by virtue of its luteolytic effect on the ovary and its increased motility effect on fallopian tubes and the uterus, prevents implantation and brings about menstruation. Its specific role as contraceptive is however yet to be established.

Copper T IUCD. Inserted within 5 days of intercourse can prevent implantation of a fertilized ovum. Advantages of Copper T as emergency contraception are:

- It can be inserted as late as 5 days after the unprotected intercourse.
- It is cheap.
- Failure rate is 0.1%.
- It can remain as ongoing contraceptive method for 3–5 years.

The contraindications and complications of IUCD have already been mentioned.

Methods of contraceptions are explained in Table 20.3.

Immunological Methods

Immunological approach to family planning is still in a developmental stage. Should immunology prove successful, family planning efforts will be simplified and will be more acceptable to the couples. The antigens which are being experimented upon are:

- β-hCG subunit (300 mcg) IM six-weekly × 3 doses evokes specific antibodies and thereby produces temporary sterility for 1 year.
- Zona pellucida plays an important role in fertility. The zona pellucida antibodies can either prevent penetration of ovum by the sperm or prevent shedding of zona after fertilization so that implantation is impossible.
- Antibodies to sperm antigens. These trials have not yet proved successful in human beings.
- AntiFSH vaccine (inhibin) is also under trial.

Surgical Sterilization

The sterilization operation is undertaken with the primary objective of preventing further pregnancy permanently. Sterilization is suited to those couples who have completed their families and do not want to bear the inconvenience or cost of the other methods of contraception, and when the other methods are contraindicated.

An ideal method of sterilization should have the following criteria:

- It should be an outpatient procedure.
- The anaesthesia should be local or short general anaesthesia, so that the woman or man can return home in a few hours.
- The surgical technique should be simple and quick.
- The instruments should be inexpensive.
- Minimal scar is desirable.
- The method should be 100% effective.
- Cost-effective.
- The complications and sequelae of surgery should be minimal.
- The technique should be surgically reversible in case of unexpected disaster like death of children.

Male Sterilization

Vasectomy

Vasectomy consists of dividing the vas deferens and disrupting the passage of sperms. It is done through a small incision in the scrotum, under local anaesthesia. The sterility is not immediate. The sperms are stored in the reproductive tract for up to 3 months. The couple must therefore abstain from intercourse during this period or use other methods of contraception. Approximately, 20 ejaculates clear the semen of all sperms. Two semen analysis reports must confirm the absence of sperms before the man can be declared sterile. No-scalpel technique has been now adopted. One single incision is made with a special forceps and skin stitch is not required. Clips and plugs can be applied over the vas instead of cutting. Vasectomy is cheaper than tubectomy (Figure 20.16).

Reversible inhibition of sperm under guidance (RISUG) is experimented by All India Institute of Medical Sciences and Indian Institute of Technology in India. A polymer gel is injected into the vas. Reversibility is possible by flushing the vas with sodium bicarbonate. This technique is under trial.

TABLE 20.3 Methods of contraceptions

Methods	Advantages	Disadvantages
Barrier	1. Prevents STD, HIV 2. incidence of Ca cervix reduced 3. Effective if used properly 4. No contraindication use	• Cumbersome • Coital dependent • Short term • High failure rate
Lactation	• Beneficial to the new born • Contraceptive action (nonovulation) 6 months	• Short-term benefit
IUCD	• Long-term use • Effective • Coital independent	• Side effects • Failure rate 1–3% • Contraindicated in few
Hormones	• Effective 99–100% long-term use beneficial effects of OC coital independent	• Side effects • Not used during lactation • Contraindicated in few • Requires surgery for implantation
Surgery	Permanent and effective	• Surgical complications surgery required. • Not suited in low parity women
Postcoital	Effective 95–98% short-term use	Failure in 1–5% Not used as contraceptives

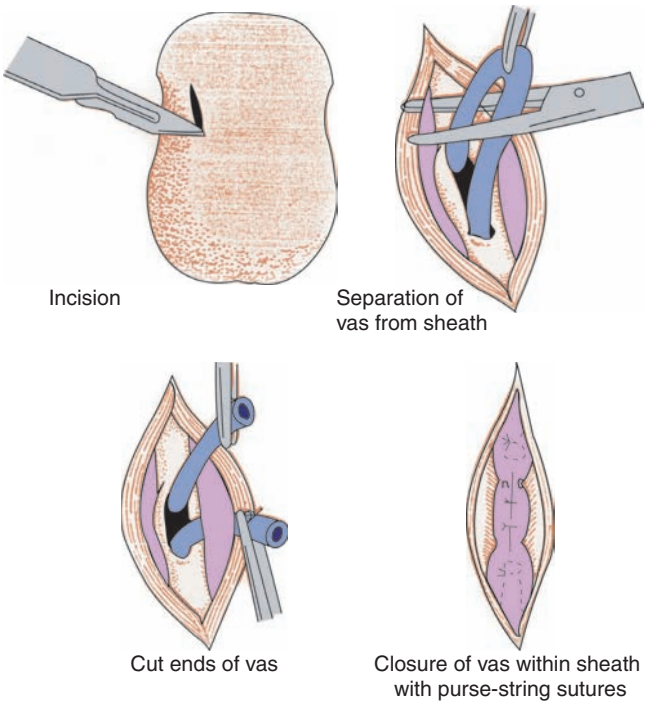

Figure 20.16 Vasectomy operation.

Complications of Vasectomy:

- Local pain, skin discolouration, bleeding, haematoma formation (1–2%).
- Infection (1%), trauma to the testicular artery causing gangrene, rare.
- Antibody formation and autoimmune disease (40%).
- Failure rate of 0.15/100 woman years at the end of 1 year.
- Granuloma formation in 0.1–3% cases.
- Spontaneous recanalization.
- Formation of spermatocele.
- Decreased libido or impotency are mainly psychological in origin and occur in men who were not properly motivated.
- Does not prevent HIV, STD.

Advantages

- It is an outpatient procedure.
- Local anaesthesia is adequate.
- It is a minor surgical procedure and the man can resume duty after rest of 1 or 2 days.
- Libido not affected. No evidence of prostate cancer.

Newer Techniques

Chemical sclerosing agents such as 90% ethanol, 3.6% formaldehyde, silver nitrate, hydrogen peroxide, acetic acid can eliminate the need of surgery, are effective and easily administered. However, the consequence of intravascular injection and excessive destruction of the vas by even a slight increase of instillation can be disastrous and the procedure irreversible.

Occlusive plugs and intravasal devices are still in the experimental stage.

Plugs. A device called 'SHUG' consists of two flexible silicon plugs connected by a nylon thread which lies outside the vas. This thread prevents migration of plugs and allows easy removal through a small incision.

Contraindications to vasectomy are:

- Local skin infection
- Varicocele, hernia
- Undescended testis

Female Sterilization

Tubal ligation can be done at any convenient time to the patient (Figure 20.17). Postpartum sterilization is done within the first week of delivery when the patient is already

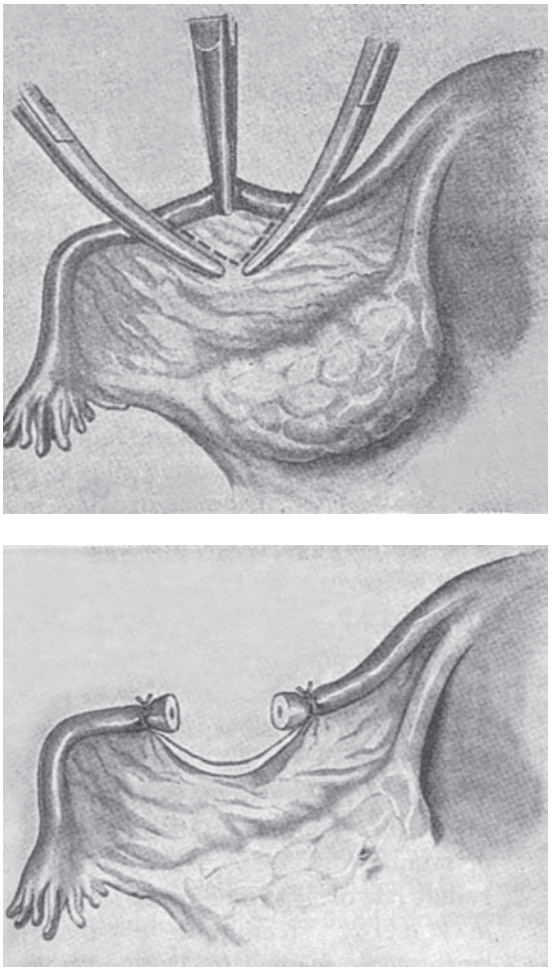

Figure 20.17 Operation for sterilization. The fallopian tube is drawn up with dissecting forceps in a position where the broad ligament is relatively bloodless and curved clamps are placed in position on each side. The tissue enclosed by the two clamps is then excised with a scalpel. Subsequently the tissue enclosed in the clamps is ligatured. No effort is made to bury the cut ends of the fallopian tube. Although the operation is simple, it gives excellent results and subsequent adhesions have been shown to cause no trouble. (From: Shaw's Textbook of Operative Gynaecology, Elsevier.)

hospitalized. Interval sterilization is done when the woman is not pregnant or any time after 6 weeks of delivery. It can be combined with caesarean section.

Indications

Apart from multiparity and the need of permanent method of family planning, sterilization may be advisable in women with medical diseases. Indications are:

- Multiparity
- Obstetrics—three caesarean deliveries
- Medical diseases at high risk of pregnancy
- Psychiatric problems
- Breast cancer
- Eugenic conditions—repeat fetal malformations such as haemophilia, Rh incompatibility, Wilson's disease, Tay–Sachs disease and Marfan syndrome.

The interval surgery should preferably be done in the preovulatory phase to avoid the potential risk of pregnancy in the postovulatory period.

Contraindications

1. Young woman less than 25 years (as dictated by the Government of India).
2. Parity less than two children (as per the Government rule).
3. Local infection.
4. Prolapse—tubectomy can be done at the time of repair surgery.

Methods of Sterilization (Figures 20.17–20.19)

1. Laparotomy
   - Pomeroy method
   - Madlener method
   - Irving method
   - Aldridge method
   - Cornual resection
   - Uchida method
   - Fimbriectomy
2. Minilaparotomy
   - Pomeroy
   - Madlener
   - Aldridge
   - Uchida
   - Fimbriectomy
3. Vaginal route
4. Laparoscopy
5. Hysteroscopy

Laparotomy. Laparotomy sterilization is performed when the abdominal incision extends well over 5 cm and is done during caesarean section and during gynaecological surgery.

Minilaparotomy. The operation is performed through a small suprapubic incision (Figure 20.18).

POMEROY METHOD. The most popular technique of tubal ligation is the Pomeroy operation. The fallopian tube is identified on each side, brought out through the incision, and the middle portion is formed into a loop which is tied at the base with catgut and excised. The failure rate is only 0.4% and it is mainly due to spontaneous canalization. The operation is simple, requires short hospitalization, does not require sophisticated and expensive equipment like a laparoscope, and can be performed in primary health centre by a doctor trained in this procedure. It is surgically reversible.

MADLENER OPERATION. A loop of the tube is crushed and ligated with a nonabsorbable suture. Failure rate of 7% and occurrence of ectopic pregnancy are unacceptable, though it is a simple procedure to perform.

IRVING. The mid-portion of the tube is ligated and the intervening portion excised. The proximal end is buried in the myometrium and the distal end is buried in the broad

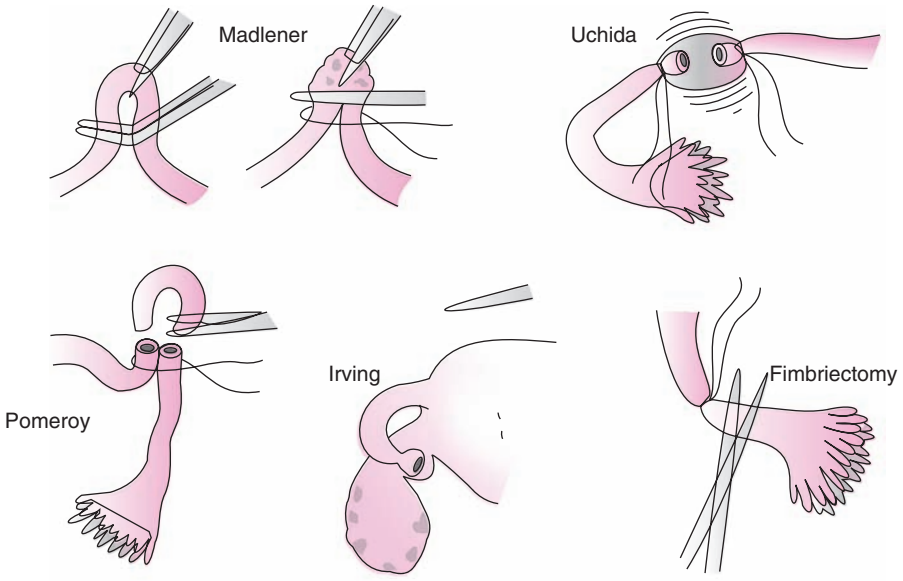

Figure 20.18 Different surgical techniques of sterilization.

ligament. It is a reliable method but irreversible and may require a laparotomy incision.

ALDRIDGE METHOD. A hole is made in the anterior leaf of the broad ligament and the fimbrial end is buried into this. The high failure rate is due to the fimbrial end popping out and restoring the patency of the tube.

CORNUAL RESECTION. The cornual portion of the tube is resected between clamps. The technique is complicated and the uterine end tends to bleed heavily. This may also require a laparotomy incision.

UCHIDA METHOD. The tubal serosa is stripped off the muscular layer in the midsegment of the tube, which is then excised. The proximal end is ligated and buried in the broad ligament. The minimal excision of the tube preserves the potential for tuboplasty.

FIMBRIECTOMY. Excision of fimbria results in permanent sterilization and leaves no potential for reversibility.

Vaginal Tube Ligation. Vaginal tube ligation is not popular because of higher morbidity and mortality associated with infection, higher failure rate, and it is more difficult to perform. It is mainly combined with the Manchester repair operation for prolapse.

Laparoscopic Sterilization. Laparoscopic sterilization is carried out under local or general anaesthesia. A small subumbilical incision is made and pneumoperitoneum created by inserting a Veress needle and introducing CO_2. CO_2 is safer than air and nitrous oxide which can cause air embolism and accidental explosion, respectively. With the patient in the head low position, the trocar and cannula are inserted through the incision and an operating laparoscope introduced after removing the trocar. The illumination of the pelvic organs for visualization is by fibreoptic light. The uterus is manipulated from below by an assistant so that the fallopian tubes are moved to the centre of the operating field. Each fallopian tube is picked up near the isthmic end (2–3 cm away) and it clipped/banded (silastic bands) (Filshie, Hulka band, silastic ring) or divided after cauterization of a segment of the tube with a bipolar cautery. The gas is allowed to escape and the instruments are removed. A subcuticular skin stitch with catgut completes the operation. The failure rate with this technique is 0.6 per 100 woman years.

The earlier cauterization technique has now been replaced by the silastic Falope ring, Hulka clip and Filshie clip, which are safer (Figure 20.19). Monopolar cauterization is liable to cause accidental intestinal burns and destroy a considerable part of the tubal structure, a disadvantage if recanalization is required at a later date. The Falope silastic ring destroys 2–3 cm of the fallopian tube. The Hulka and Filshie clips destroy a smaller segment (3–4 mm), thus preserving the potential for successful reversal surgery. The failure rate varies between 0.2% and 1.5%.

Falope ring, introduced by Yoon in 1974, is a silastic band with 3.6 mm and 1 mm outer and inner ring diameter, respectively, and is 2.2 mm thick. It is impregnated with barium sulphate for radiological visualization.

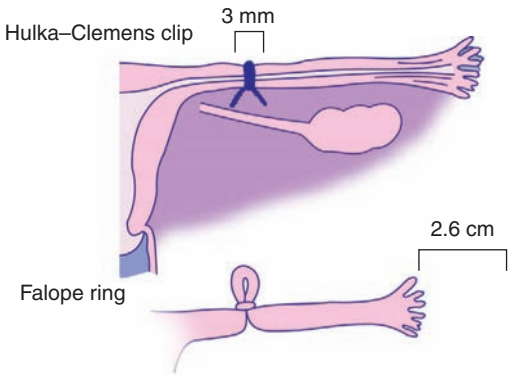

Figure 20.19 Application of Hulka–Clemens clip and Falope ring.

ADVANTAGES. Laparoscopic sterilization is gaining popularity all over the world as it has a number of advantages:

- Subumbilical scar is small and nearly invisible.
- It can be done under local anaesthesia in the out-patient department.
- It is highly reversible, with a success rate of 70% or more.

DISADVANTAGES

- The equipment is expensive and maintenance is not easy.
- Experienced personnel are required to perform this operation.
- Mortality of 1–2 per 100,000 and is now very low with experience.

COMPLICATIONS. Complications are uncommon but when they do occur, they are usually in the hands of inexperienced personnel:

- Abdominal wall emphysema due to wrong placement of the needle.
- Bleeding from superior epigastric vessel by trocar injury.
- Tearing of the mesosalpinx and bleeding.
- Uterine perforation.
- Wrong application of the ring, e.g. putting the ring on round ligament/meso salpinx/utero-ovarian ligament, will cause operation failure.
- Failure rate varies between 0.4 and 2.5%. Whereas cauterization carries a failure of 0.8%, Hulka clip has a failure rate of 2.3% and Falope ring 0.8%. Most failures occur within 2 years of operation. At the end of 10 years, failure is reported in 1.8% cases.
- Spontaneous recanalization occurs if cauterization is incomplete.
- Ectopic pregnancy is reported in 0.2–0.3%.
- Hydrosalpinx formation if the tube is occluded at two places some distance apart.

CONTRAINDICATIONS. The contraindications are not many:

- In a patient with a cardiac or pulmonary disease, head low position and CO_2 are contraindicated.
- Previous abdominal surgery exposes the patient to the risk of intestinal trauma in case parietal adhesions are present.

- Puerperal cases. The fallopian tubes are oedematous and vascular and may easily get torn. The uterus is soft and can get easily perforated with the uterine manipulator.
- Extreme obesity, diaphragmatic or umbilical hernia. The increased risk of interstitial injury in these cases.
- In PID, fallopian tubes may not be easily visible amongst the adhesions.

Due to associated morbidity, the Government of India has forbidden laparoscopic sterilization combined with MTP and in the puerperal period.

- Skin infection, anaemia, thrombophlebitis.

Hysteroscopic Sterilization. This technique of using sclerosing agents and quinacrine has been abandoned because of high failure rate, and other complications of uterine perforation, burn injury and infection.

Essure permanent device

The latest technique of 'Essure permanent device' is a dynamically expanding micro-inserter consisting of a flexible inner coil made of stainless steel and a dynamic outer coil made of nickel titanium alloy (nitinol). The device is 4 cm long with inner 0.8 mm diameter. Running along and through the inner coil is a layer of polyethylene terephthalate (PET) fibres, which initiate a benign local fibrous tissue growth responsible for the occlusion of the fallopian tube. The guide wire guides the device into the fallopian tube.

During the insertion, the outer coil is wound down to keep it in a low-profile position. Upon release, the outer coil expands to 1.5–2 mm from 0.8 mm and anchors tissue device firmly in the fallopian tube. It takes 3 months to occlude the tube, during which period other contraceptive is required to protect against pregnancy. This is an irreversible and permanent technique. Hysterosalpingography 3 months later should confirm tubal blockage.

Kerin devised this technique. PET fibres are effective and unlike liquid sclerosing agents, don't cause chemical peritonitis.

Buscopan and NSAID are required to prevent tubal spasm and facilitate proper insertion via hysteroscope. Failure rate of 3.5% is reported.

Optimal placement of Essure device at the proximal fallopian tube allows the device to span the utero-tubal junction. The device is placed far enough to allow the tubal block while a portion of the device trails into the uterine cavity (4–8 coils).

Disadvantages:

- Hysteroscopy is required.
- Cost and expertise required.
- Permanent method.
- HCG to confirm blockage.
- 3 months waiting.
- Bilateral insertion difficult due to spasm in 15% cases.
- Tuboplasty for reversal not possible.
- Perforation of the tube

Advantage:

No abdominal scar and can be done under local anaesthesia.

Adiana

Adiana is controlled thermal damage destroying only 1 cm of the medial end of the fallopian tube via hysteroscope using radiofrequency energy is under trial.

Occlusion takes 3 months as with Essure. A porous matrix is left in the tube following thermal damage.

Complications and Sequelae of Sterilization

- Anaesthetic complications.
- Mortality of 4 per 100,000 procedures is due to haemorrhage, sepsis and embolism, and anaesthetic risks.
- Morbidity is due to postoperative lung infection, abdominal wound sepsis, peritonitis.
- Trauma to the bladder, bowel may occur with laparoscopic technique.
- Thrombophlebitis and embolism is rare, but may complicate puerperal sterilization.
- Pelvic adhesions.
- Failure rate of sterilization varies from 0.4% in Pomeroy technique, 0.3–0.6% by laparoscopic method to 7% by Madlener method. Pregnancy occurs either because of undiagnosed corpus luteal phase pregnancy, faulty technique or due to spontaneous recanalization.
- Ectopic pregnancy. Partial spontaneous recanalization may result in ectopic pregnancy, and estimated rate is 0.6 per 1000 sterilized women.
- AUB following sterilization is seen in 15% cases but the exact aetiology is not known.
- Regret and depression may ensue especially when death of a child follows sterilization. Request for tuboplasty is made when a child dies or a change of partner occurs as in remarriage. The success of tuboplasty is 70–80%. Libido is not usually affected.

Mirena versus Tubectomy (Table 20.4)

Lately, Mirena is emerging as a better alternative to tubectomy in a young woman who may want to retain fertility and avoid a permanent method.

Mirena is used in:

1. Mainly in AUB.
2. Dysmenorrhoea—by reducing uterine blood flow.

TABLE 20.4 Comparison of Mirena and tubectomy

Mirena	Tubectomy
• Effective	Effective
• Reversible	Surgically reversible—success 70%
• Bleeding, dysmenorrhoea less	May increase in 15%
• Cheaper than surgery	Costly
• Nonsurgery, anaesthesia complications avoided	Surgery, anaesthesia required
• Ectopic pregnancy (0.2/1000)	Same
• Ovarian function not compromised	May be compromised

3. Pelvic endometriosis, adenomyosis, myoma other than submucous.
4. HRT—oral oestrogen + Mirena instead of oral progestogens.
5. A woman on tamoxifen.
6. Contraceptive for 5 years.

Mirena causes local decidualization of endometrial stroma and atrophy of glands. The ovulation is not suppressed, no menopausal symptoms even if the woman develops amenorrhoea.

Contraception for Adolescents

In India, many girls get married at an early age and become mothers. They need counselling regarding spacing and delaying the birth of the next child. Unmarried adolescents are exposed to the risk of unwanted pregnancy and unsafe abortion, as well as the possibility of acquiring AIDS and sexually transmitted infections.

Family planning and contraception become important health care issues amongst adolescents. Whereas sex education will provide benefit, many will require contraceptive guidance and provision of a suitable contraception.

Barrier Method

It is the best method in young girls. Apart from providing contraceptive method, it can prevent transmission of infections from one partner to the other.

If the man refuses to use condoms, a married woman can use *Today* sponge with spermicidal cream. A recently married woman may find barrier method cumbersome in the initial stages.

The adolescent should receive informed knowledge on 'unsafe period' when ovulation occurs, and be provided with emergency contraception such as LNG, two tablets. This is because periodic abstinence is difficult amongst the young couples.

IUCD

While IUCD may not be a suitable contraceptive device in the unmarried and recently married nulliparous women, it is a long-term coital-independent method suited to young parous women, provided no contraindication exists for its use. It is one of the best methods for spacing childbirth. Progesterone copper device is recommended if the woman has heavy periods with dysmenorrhoea.

Hormonal Contraceptives

COC pills can be safely prescribed to adolescents. One must remember the possibility of breast cancer at a later date if the young nulliparous woman below 24 years of age takes COC for more than 4 years.

POPs are not preferred over COC, because of the irregular bleeding, amenorrhoea, a higher failure rate and osteopenia.

Three-monthly injections or implants, skin patches and vaginal rings may be acceptable to young married adolescents, and side effects tolerated. Occasional failure may be backed up with MTP facilities.

Sterilization should not be offered to young couples. Government of India has passed a law that the surgical procedure should not be performed in a woman less than 25 years with two or less children and the youngest child less than 2 years old.

MTP and emergency contraception should form the back-up procedures in these girls.

Parous Women

A multiparous woman may be counselled on sterilization or vasectomy. This is done any time after 24 h of delivery, so the woman need not return to the hospital for tubectomy later, and this is cost effective and convenient. Minilaparotomy is a simple and a quick procedure done under local or a short general anaesthesia.

Because of the possible risk of thrombosis and embolism, many prefer to avoid tubectomy until 6 weeks after delivery.

COC pills are contraindicated in the puerperium, both because of its adverse effect on milk secretion in a lactating woman and increased risk of thromboembolic episode. COC can be prescribed to a nonlactating woman 3 weeks after delivery.

POP is safe in a lactating woman and can be started 6 weeks onwards. LNG is safer than desogestrel and gestagen from thrombosis point of view.

Intramuscular and progestogen implants can be prescribed 6 weeks after delivery.

Lately, IUCD insertion within 10 min of expulsion of placenta or within 24 h of delivery is proved safe and effective.

Regarding the barrier methods, female condoms and Today sponge may not be reliable with a patulous vagina and laxity of the perineum. Male condoms with spermicides are safe.

Lactating Woman

Regular lactation with one feed at night delays ovulation and pregnancy for up to 6 months, provided she remains amenorrhoeic. After 6 months, lactation has no bearing on ovulation and pregnancy can occur, despite amenorrhoea. Thereafter, the woman needs some form of contraceptive precaution.

POP does not suppress lactation or alter the quantity and quality of milk. It can be started after 6 weeks of delivery. Irregular periods during this period is taken as puerperal event and accepted by the woman. Instead of oral pills, implants and injection are other alternatives.

Oral combined pill in a lactating woman is contraindicated because:

- It reduces the quality and quantity of milk.
- Hormone secreted in the milk may be harmful to the infant.
- There is increased risk of thromboembolism.

IUCD can be inserted immediately after the delivery.

- Male condoms are safe and effective.

A Woman with AIDS or Positive HIV

Condoms are the best in prevention of transmission of infection from one partner to the other. Female barrier methods are not as effective as male condoms, except Femshield.

Since, the failure rate with condom is high, dual method of using hormonal contraceptives (COC) or IUCD is desirable. IUCD can be inserted provided the woman has not suffered from PID and is on medication. The screening for other STD becomes part of screening procedures before inserting an IUCD. Surgical procedures are not contraindicated in these women.

Contraception for Women Over the Age of 35 Years

Women over the age of 35 years constitute 20% of the contraceptive users, and selection of the proper contraception is an essential component of family planning counselling. A woman after 35 years may become obese, hypertensive and diabetic. She is likely to suffer AUB.

Sterilization

When considering a permanent method of sterilization, one should weigh the risk of surgical procedure against the number of years a woman needs contraceptive protection. In a woman nearer the menopause with a fewer years of fertility, surgical procedure may not be a wise proposition, and temporary methods will be cost-effective as well as safe, with emergency contraception and MTP as a back-up method.

Low-dose COC pills are safe, if the woman is thin, nonsmoker without any medical disease up to the age of 45 years.

Whereas POPs may be safer than COC, its adverse effect on bone density and occurrence of osteoporosis must be borne in mind if given over a prolonged period. Besides, they cause irregular bleeding, and the risk of breast cancer increases.

IUCD may be suitable and effective. *If the woman suffers from menorrhagia, Mirena may be inserted and is effective for 5 years.*

Desogestrel and gestodene cause thromboembolism and are contraindicated in elderly women.

A Woman with Medical Disease

The risk of pregnancy should be weighed against the risk of any contraception in a woman with medical disorder. While prescribing a family planning method, *due consideration and counselling related to side effects is necessary*.

If the risk is negligible, sterilization provides the permanent method to prevent a pregnancy. Vasectomy would be ideal, with no risk to the woman.

IUCD is carefully considered in cardiac and diabetic women, because of the possibility of pelvic infection.

COC is contraindicated in a hypertensive, cardiac and diabetic women, as well as a woman with breast cancer, liver disease and previous thromboembolism. An epileptic woman and a woman on antitubercular drugs like rifamycin may face a higher failure rate due to interaction with rifamycin and antiepileptic drugs except sodium valproate.

Similarly POP is contraindicated in liver diseases, vascular disorders and breast cancer. It is safe in sickle cell anaemia.

Emergency contraception (LNT tablets) is safe in a woman with medical disorders.

Psychiatric Disorders

If a woman is considered unfit to bear children, and permanent method considered, a written opinion regarding psychiatric problem should be obtained. The written consent should be obtained from the husband or guardian, as the psychiatric patient may not be mentally aware of the nature of sterilization.

Emergency contraception is no bar to a woman with a medical disorder, as only two tablets are given in 24 h.

Medical Termination of Pregnancy

Wilful termination of pregnancy prior to the age of fetal viability has been controversial at all times. However, many governments the world over have liberalized 'Abortion Laws' in keeping with changing times, accepting the recognition of the right of the individual to bear a child at her chosen time and helping to curb the malpractices accompanying illegal abortions. In India, the MTP Act was adopted as a health measure way back in 1972 to avoid death due to criminal abortions.

Definition

The Indian Act permits the wilful termination of pregnancy before the age of fetal viability (20-weeks' gestation) for well-defined indications. It has to be performed by recognized medical practitioners in a recognized place approved by the competent authority under the Act.

Incidence

It has been estimated that the total number of abortions performed globally is approximately 46 million annually; of these, 26 million take place in countries where abortions are legalized. In India, 6.7 million MTPs take place; 40% pregnancies are unplanned and 25% are unwanted. Despite the law, 40–50% abortions are unsafe terminations of pregnancy done by a less qualified person under unhygienic conditions.

Grounds for Performing MTP

Medical Grounds

Medical grounds when the continuation of pregnancy is likely to: (i) endanger the life of the pregnant women or (ii) cause grievous injury to her physical and/or mental

health, as in cases of severe hypertension, cardiac disease, diabetes, psychiatric illnesses, genital and breast cancer.

Eugenic Grounds

Eugenic grounds when ultrasound shows malformed embryo or fetus or there is a substantial risk of the child being born with serious physical or mental abnormalities. For example, hereditary disorders, congenital malformation in previous offspring with high risk of recurrence in subsequent childbirth/Rh-isoimmunization, teratogenic drugs and maternal rubella posing risk of anomalies in the fetus. Chorion villus biopsy, cordocentesis and sonographic evaluation of the fetus have contributed significantly in identifying the fetuses at risk.

Humanitarian Grounds

Humanitarian grounds when the pregnancy is caused by rape or incest.

Social Grounds

Social grounds when: (i) in the actual or reasonably foreseeable future, her environment (social or economic) might lead to risk of injury to her health or (ii) pregnancy resulting from failure of contraceptive device or method.

The written consent of the patient on specially prescribed form is necessary prior to undertaking the procedure. The written consent of the legal guardian must be obtained in case the woman is under the age of 18 years or she is a lunatic, even if she is older than 18 years.

Indications of MTP are:

- Maternal medical disorders
- Fetal conditions
- Rape, incest
- Failure of contraceptives
- Social grounds

The Place for Performing MTP

The Act stipulates that no MTP can be performed at any place other than: (i) a hospital established and maintained by the government, (ii) a place recognized and approved by the government, under this Act.

Abortion services are provided under this Act at these centres under strict confidentiality.

The identity of the person is treated as a statutory personal matter.

Ultrasonic scanning plays an important role in confirming uterine pregnancy, estimating gestational age detecting malformed embryo and sometimes in performing MTP under ultrasonic guidance.

How to Comply with the Indian MTP Act and Ensure Quality Care

- Ensure proper case selection: Document meticulously the patient' age, gestational maturity and indication for MTP.
- Essential investigations performed such as haemoglobin, urine routine, blood group and Rh factor; sonography whenever in doubt.
- Opinion of one medical practitioner for first-trimester MTP, and opinions of two medical practitioners for second-trimester MTP.
- MTP to be performed by a registered medical practitioner approved for undertaking MTP in a place recognized under the Act.
- Documents to be maintained: Form I, Form II and admission register.

Implications of the MTP Act

In countries with liberal abortion laws, maternal morbidity and mortality have declined, and women have been motivated to accept birth control measures. Deaths due to illegal abortions (500 per 1 lakh) are due to haemorrhage (20%), sepsis and embolism (20–25%), anaemia and gut injury. Mortality and morbidity increases with each week of gestation, and is fivefold to tenfold in the second trimester as compared to the first.

Repeated abortions are not conducive to a woman's health, hence, MTP should not be considered as a birth control measure and should not replace prevailing methods of contraception. Even in the best of circumstances, there is a small inherent risk in the procedure of MTP. This should serve as a warning that MTP can never be as safe as efficient contraception. The woman undergoing MTP should be educated to accept contraception.

Thus, MTP can indirectly promote family planning and population control.

Methods of MTP

Methods of MTP can be broadly classified as follows:

Methods of first-trimester MTP

- Menstrual regulation
- Dilatation and suction evacuation
- Cervical softening prior to dilatation and suction evacuation
- Medical methods

Methods of second-trimester MTP

- Surgical evacuation
- Extraovular instillation of drugs
- Extrauterine methods

The above methods are used singly or in combination. The oxytocic drugs stimulate myometrial activity and shorten the induction–abortion interval in the second trimester. Similarly, the use of prostaglandins (gel, suppository) a few hours prior to the procedure helps to attain a gradual softening and atraumatic dilatation of the cervix, facilitating further dilatation and evacuation procedures.

First-Trimester MTP

Surgical Methods

Menstrual Regulation. Menstrual regulation consists of aspiration of the contents of the uterine cavity by means of a plastic cannula (Karman's cannula). It has a plastic 50 mL syringe capable of creating a vacuum of of 65 cm Hg (Figure 20.20). It has a simple thumb-operated pressure control valve and piston locking handle. It is independent of electricity, is portable and washable. It is carried out effectively within 42 days of the beginning of the last menstrual period (LMP). A paracervical local anaesthetic block or preoperative sedative alone usually suffices but sometimes in an apprehensive patient, general anaesthesia with intravenous thiopentone sodium may be necessary. This procedure can be performed in an office set-up, outpatient clinic, or day-care centre. Since 1972, this method has been extensively evaluated and found to be efficient, safe, and easy to use in terminating early pregnancy. It is a good practice to examine the products of conception. The occasional complications encountered include failure to evacuate leading to continuation of pregnancy, incomplete evacuation, haemorrhage, cervical laceration, perforation, infection and anaesthetic complications.

A failure to evacuate is due to:

1. Too early pregnancy.
2. Ectopic pregnancy.
3. Uterus bicornuate, aspiration being carried out in non-pregnant horn. Sometimes, tip of the cannula breaks but comes out in the next menstrual bleeding—and it may not be necessary to retrieve it.

RH anti-D globulin 100 mcg IM should be given to a RH negative nonimmunized woman.

Vacuum Evacuation. Vacuum evacuation is the most efficient method of terminating pregnancy up to 12 weeks of gestation. It has gained rapid worldwide acceptance. The operation can be generally undertaken under local anaesthetic, paracervical block, coupled with some sedation if necessary. Apprehensive patients may need general anaesthesia. The procedure involves examination of the patient in the operation theatre observing full aseptic precautions. The gestation size and the position of the uterus are carefully assessed. After administering a paracervical block, the cervix is held with an Allis forceps and dilated by means of specially designed dilators with a guard, until adequate dilation is achieved to permit introduction of the suction cannula of the appropriate size (diameter corresponding to the weeks of gestation) into the uterine cavity (Figure 20.21). A standard negative suction of 650 mm (65 cm) of Hg is applied and the products are aspirated. When the procedure is completed, a grating sensation is felt all around the uterine cavity, no further tissue is aspirated, and the internal os begins to grip the Karman cannula which reveals a blood-stained froth. There is no need to follow this up with a check curettage with a sharp curette, as this step can be traumatic and lead to complications like perforation, synechiae (Asherman syndrome), and predispose to placenta accreta in a future pregnancy. In case the pregnancy exceeds 8-weeks gestation size, the patient is nulliparous, or there is presence of a uterine scar, general anaesthesia may be preferred.

In case of large uterus of 10- to 12-week gestation size, or nulliparous cervix, priming the cervix with prostaglandin gel or suppository, at least 4 h earlier, helps to soften the cervix so that it yields more easily and undue force is avoided during cervical dilatation. This precaution safeguards against complications like cervical tear, lacerations, and injury to the internal os leading to incompetent cervix; 200–400 mcg misoprostol pessary is inserted in the vagina (prostaglandin E_1).

Vacuum aspiration as a method of MTP has a very low failure rate (less than 1%). Complications like incomplete evacuation, infection, uterine perforation and excessive bleeding occur in less than 2% of cases. The mortality is less than 2 per 100,000 procedures. Nonimmunized Rh-negative mothers must receive 100 mcg of anti-D immunoglobulin after undergoing MTP. Failure to end pregnancy is due to a very early pregnancy, unrecognized ectopic pregnancy and pregnancy in a rudimentary horn. Preoperative ultrasound is useful in preventing these complications.

Medical Methods

Prostaglandins and RU 486 have been extensively used as medical methods of MTP in early pregnancy. Acting

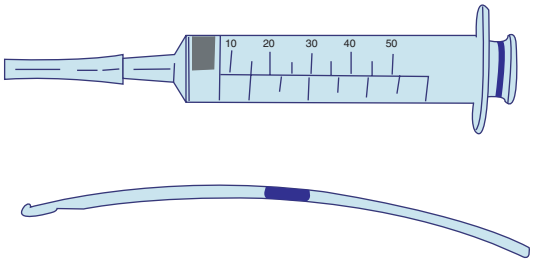

Figure 20.20 Menstrual regulation syringe with Karman cannula.

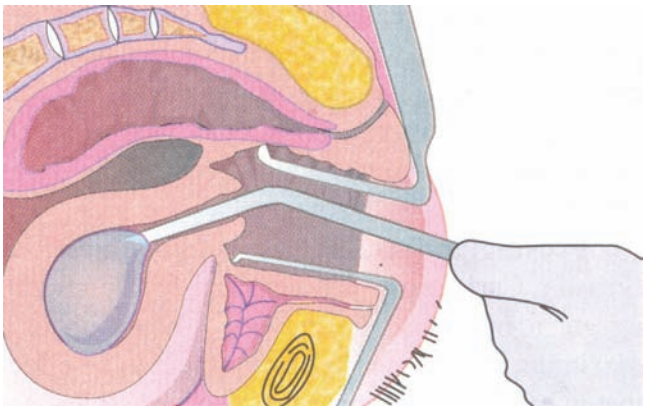

Figure 20.21 Suction evacuation—aspiration of the products of conception.

singly, they are not as effective as when used in combination. The medical method avoids hospitalization but the prolonged observation, occasional need of surgical termination (failure) and the cost of the drugs are some of the disadvantages. Medical method is permissible up to 9 weeks of gestation (63 days).

Prostaglandins. Prostaglandin Injections (Prostin, Carboprost-prostaglandin $F_{2\alpha}$) 250 mcg given intramuscularly every 3 h up to a maximum of 10 doses has been found to be effective in initiating the process of abortion. It has not been popular in the first trimester because of an unacceptably high incidence of incomplete abortion (20%) requiring surgical intervention to complete the procedure, and the high rate of unpleasant side effects like nausea, vomiting diarrhoea, cramping abdominal pain, bronchospasm and mild fever at times.

Mifepristone (Mifegest–RU 486). First invented in France 1980, RU stands for Roussel Uclaf 486 (laboratory number)

It is a synthetic steroid, a derivative of 19-nortestosterone, with antiprogestogenic effect. It also has antiglucocorticoid and weak antiandrogenic action. By competing with progesterone receptors it reduces the endometrial glandular activity, accelerates degenerative changes and increases stromal action, thereby causing sloughing of endometrium. It thus prevents or disturbs implantation of the fertilized ovum through luteolysis.

It also causes uterine contractions, softens and slightly dilates the cervix.

Used singly, it is effective in only 83%, causes incomplete abortion in 10–20% cases. Adding prostaglandin yields a success rate of 95% in pregnancies less than 63 days duration, with 4% incomplete abortion and continuation of pregnancy in 1% cases.

The protocol is as follows:

- Written consent for MTP is required.
- Blood group RH, Hb% urine
- Ultrasound is done to confirm uterine pregnancy and duration, and exclude ectopic pregnancy.

  Day 1: 200 mg of mifepristone given as a single dose—the woman is observed for half an hour and then allowed home. Anti-D globulin to RH negative woman.

  Day 3: 400 mcg of oral misoprostol (prostaglandin) is administered (two tablets) unless abortion has occurred. Sublingual or vaginal prostaglandin is also used but stronger action of sublingual route can cause uterine rupture in a scarred uterus. Pulse BP is observed for 2 h, if all well—allow home.

  Nowadays, misoprostol (PGE_1) vaginal tablet of 400 mcg is inserted instead of oral tablet.

  Day 14: Follow-up to confirm abortion has occurred; if not, surgical MTP is done.

  The bleeding usually starts within few hours of taking mifepristone, and abortion occurs in about a week.

Contraindications to mifepristone are:

- IUCD in situ—IUCD should be removed prior to medical termination to avoid the risk of perforation.
- Suspected ectopic pregnancy—ultrasound should be done before termination.
- Hypertension, anaemia, glaucoma, cardiovascular disease, smoker, asthmatic.
- A woman on anticoagulant (coagulopathy) and glucocorticoid therapy. Allergy, porphyria, seizures (adrenal failure)
- Previous uterine scar—scar rupture can occur with misoprostol. Fibroid uterus.
- Lactating woman—the drug is secreted in the milk or lactation stopped temporarily. Infant gets diarrhoea.
- Gestation period should not exceed 63 days (preferably 49 day).

Advantages of Misoprostol

- Easily stored in room temperature
- Shelf life 3 years
- Cheap
- Easy administration

No cardiovascular or asthma complications.

Complications

- Adrenal failure
- Headache, malaise, skin rash, fever, nausea vomiting, diarrhoea
- Failure to abort, 1%
- *Misoprostol causes Möbius syndrome in the fetus* (congenital facial palsy, limb defects, bladder extrophy, hydrocephalus). *Therefore, termination of pregnancy is strongly recommended if medical termination fails.*
- It takes longer time for termination compared to surgical termination and longer follow-up of 2 weeks is necessary.
- Surgery is required in case of failure or is incomplete. In case the woman starts bleeding profusely, emergency surgical evacuation is required. Emergency surgical backup is a must.
- The subsequent menstruation may be delayed by 10–14 days.
- Sublingual misoprostol is as effective as vaginal pessary but side effects are more severe than with oral tablets and vaginal pessaries.
- If vomiting occurs soon after oral misoprostol repeat the dose. Vaginal pessary is safe.

Alternative protocols used are:

- 200 mg of oral mifepristone followed by 800 mcg vaginal misoprostol on the third day.
- 200 mg mifepristone and 1 mg tablet of prostaglandin E_1 analogue, gemeprost vaginally—pregnancy failure is reported in 0.2–2.3% cases.
- Methotrexate 50 mg intramuscular or oral followed 5–7 days later by 800 mcg vaginal misoprostol (repeat misoprostol 24 h later if required).
- Epostane—A progesterone-blocking agent is administered in doses of 200 mcg every 6 h for 7 days.

*Choice between medical and surgical termination of early pregnancy***.** There is not much difference in terms of safety and efficacy in two methods. It is mainly the contraindications prevailing and the choice of the woman that decides which method is chosen. If the endometrium is more than 15 mm thick, the risk of incomplete evacuation favours surgical method.

Second-Trimester MTP

The incidence of second-trimester MTP has dropped with the passage of time, from about 30% of all MTPs performed two decades ago to about 10% in the present times, and is mostly performed for fetal malformations.

Surgical Methods

Dilatation and Evacuation. In some western countries, MTP up to 16 weeks is accomplished by slow and deliberate dilatation of the cervix with laminaria tents, prostaglandin gel or pessary, prior to evacuation of the uterine contents using either vacuum aspiration or aspirotomy with ovum forceps. Complications such as cervical trauma, uterine perforation or tear, incomplete evacuation, haemorrhage and infection are more common with second-trimester MTP than first–trisemester MTP.

Aspirotomy. Aspirotomy involves suction aspiration of the liquor amnii, followed by evacuation of the fetal parts in pieces with the help of a specially designed instrument called the aspirotomy forceps. The procedure is carried out in the operation theatre observing full surgical asepsis. The cervix is exposed under a good light with the help of a Sims' vaginal speculum and an anterior vaginal wall retractor. A paracervical block given with a local anaesthetic agent such as 1% Xylocaine is followed by intracervical infiltration of the cervix and uterine isthmus with Xylocaine with adrenaline to help alleviate pain, facilitate cervical dilatation, and reduce bleeding during the procedure. The cervix is dilated up to Hegar size 12–14, and the amniotic fluid is drained with the help of a large-bore suction cannula. With aspirotomy forceps, the fetus is dismembered, crushed and extracted through the dilated cervix. The extracted mass is assembled to ensure that the fetus has been totally extracted. It is desirable to have an oxytocin infusion running throughout the procedure to reduce the risk of uterine perforation and bleeding. Performed by technically competent experts, the procedure is safe, the blood loss is reduced, and permits discharge of the patient from the hospital within 8 h, thus reducing hospital stay and cost. *Slow cervical dilatation with misoprostol prior to aspiration reduces cervical trauma***.**

Medical Methods of MTP

Medical methods use of abortifacient drugs to accomplish pregnancy termination.

Extraovular Instillation of Drugs. Several drugs such as ethacridine lactate, hypertonic saline and prostaglandins have been successfully used in the past, but the drug of choice has been ethacridine lactate.

ETHACRIDINE LACTATE**.** Ethacridine lactate is available as Emcredil. The advantage is that extraovular instillation can be easily performed in second trimester with low failure rate.

The procedure should be undertaken in the operation theatre. After steadying the anterior lip of the cervix, a Foley catheter is introduced transcervically into the extraovular space. The bulb of the Foley catheter is inflated with 10–20 mL of distilled water to seal off the internal os. Ethacridine lactate 0.1% pre-prepared solution is instilled into the extraovular space in a dose of 10 mL/week of gestation up to a maximum of 150 mL. The catheter is left in place for 6 h, whereupon it gets gradually expelled spontaneously. Alternatively, the Foley catheter bulb is deflated and the catheter removed. Uterine activity usually begins within 12–18 h. The mean induction–abortion interval varies between 24 and 36 h. About 30% of the abortions are incomplete and require oxytocin infusion and occasionally blunt curettage to remove the retained placental tissue. In the event of failure to initiate uterine activity within 24 h, an augmenting oxytocin drip is desirable. In case of failure in 72 h, reinstillation of ethacridine may be tried or some other method of MTP resorted to.

Supplementation with prostaglandins helps to hasten the process of abortion. Amongst the methods tried, the following merit mention: (i) instillation of 1 mL of carboprost or Prostodin injection diluted in 10 mL of distilled water into the extraovular space just before removing the Foley catheter, (ii) addition of 0.5 mg prostaglandin E_2 gel (Cerviprime gel, Prostodin tablet) to the Emcredil solution prior to its instillation into the extraovular space, (iii) Inj. prostaglandin $F_{2\alpha}$ 250 mcg intramuscularly every 3 h, commencing from the time of removal of the catheter. In all such cases the induction–abortion interval is reduced to 12–18 h. A 75–80% success rate is reported.

Intracervical or Extraovular Instillation of Cerviprime (PGE_2). PGE_2 induces uterine contractions within a few hours of insertion. If the uterine contractions are weak or fail to occur, Syntocinon drip is started 6 h later. Ninety per cent abort in 24 h.

Contraindications to the use of prostaglandins are cardiac, renal disease, hypertension, bronchial asthma and previous caesarean scar.

Mifepristone and Misoprostol. Oral mifepristone (200 mg) followed 36–48 h later by 600 mcg of vaginal misoprostol and then 400 mcg of vaginal misoprostol every 3 hourly with a maximum of five doses or 200–600 mcg of vaginal misoprostol every 12 hourly. *Oral misoprostol is not effective after 49 days of amenorrhoea*; misoprostol alone 400 mcg 8 hourly for five doses is less effective than combined drugs.

Postoperatively woman receives antibiotics, pain killer and RH anti-D globin in an RH negative nonimmunized woman.

Prostaglandins. Prostaglandin $F_{2\alpha}$ is available as Inj. prostodin 1 mL ampoule (Astra-IDL) containing 0.25 mg of the drug, for parenteral use. It has been used in doses of 250 mcg (1 mL) intramuscularly every 3 h, for a maximum of 10 doses. Compared to natural prostaglandins, their synthetic analogues have the advantage of being long-acting. Prostaglandins have also been used instead of laminaria tents to soften the cervix prior to undertaking dilatation and evacuation.

COMBINED METHODS. These involve the use of several methods in combination to take advantage of their synergistic effects on myometrial activity, thereby hasten the abortion process, and minimize complications. Amongst the popular combinations in use are: (i) Emcredil plus PG, (ii) PG and laminaria tent, (iii) Emcredil and oxytocin.

In a primigravida, ethacridine is more effective than misoprostol. Manual removal of the placenta under anaesthesia may be required if placenta is not expelled in 4 h. The fetus is dead and should be disposed off in a proper manner.

Late Sequelae of MTP

Late sequelae of MTP include:

- PID—chronic pelvic pain.
- Infertility caused by tubal infection and blockage.
- Incompetent os following trauma to the cervix; this may lead to preterm births and habitual mid-trimester abortions.
- Adherent placenta in the subsequent pregnancy.
- Asherman syndrome.
- Ectopic pregnancy following PID.
- Cervical ectopic pregnancy caused by trauma.
- IUGR.
- Rh-isoimmunization if anti-D has not been administered after the MTP to nonimmunized Rh-negative mothers.
- Psychiatric disorders, if MTP was done without proper counselling, and feeling of regret, especially if infertility follows the procedure.

Although MTP is restricted to 20 weeks of pregnancy, a gross fetal malformation is sometimes detected later than 20 weeks. It is desirable to terminate such a pregnancy instead of allowing it to continue to term. However, Government of India does not permit abortion beyond 20 weeks under any circumstances as of today.

Indian Experience with MTP

- Nearly 15 million MTPs are taking place in India; of these, 10 million are performed by unrecognized providers. Nearly 15,000–20,000 women die annually as a result of complications of unsafe illegal abortions.
- Vacuum aspiration for the first-trimester MTP has been proved effective in 98.6% cases and it can be accomplished in 94.8% under paracervical block anaesthesia with or without sedation.
- The ICMR investigating the sequelae of induced abortions reported an incidence of minor complications in 3.13% procedures and major complications in 0.21%.
- Administration of two tablets of 100 mcg each of misoprostol inserted into the posterior fornix of the vagina 3 h prior to suction evacuation brings about softening of the cervix and dilation, thus facilitating cervical dilatation and reducing the time of surgery as well as its accompanying blood loss.
- Second-trimester MTP with ethacridine lactate can be facilitated with the addition of prostaglandins to the instillation fluid and setting up oxytocin drip.
- Termination of pregnancy is legally restricted to 20 weeks.

Key Points

Birth Control

- Family planning and contraceptions have gained momentum world over with an urgent need to control the world population as well as to promote 'woman's health care'.
- This has prompted continuous effort to discover new methods and new modes of delivery with optimal effectiveness but with minimal side effects.
- Barrier methods, both male and female, apart from their contraceptive effect, have the advantages of preventing transmission of STDs , HIV and reducing the incidence of cancer of the cervix by preventing viral transmission. A high failure rate of barrier methods can be improved by back-up method on the use of emergency contraception if unprotected intercourse occurs around ovulation. These advantages along with the low cost and excellent reversibility can enhance the use of this method in preventing an unwanted pregnancy.
- Low dose E_2, starting on first day of the cycle has reduced the failure rate and side effects of oral contraceptive pills.
- IUCD is an established method of female contraception in India on account of one-time insertion, low cost and prolonged coital-free use. Progesterone-impregnated IUCD has an added advantage of reducing menstrual bleeding, but it is expensive. The removal rate of 5–10% on account of side effects is acceptable.
- Hormonal contraceptives are not new but newer drugs and newer delivery systems are continuously on trial, and the advantages, disadvantages, effectiveness and reversibility are being studied.
- The beneficial effects of COC are well established and are emphasized when recommending to the woman.
- POPs are particularly useful when oestrogen is contraindicated or its side effects are intolerable. POP is as effective as IUCD but less effective than COC. It can be used by the lactating woman, unlike COC.
- Centchroman is manufactured in India. It is cheap and easy to take.
- Vasectomy and tubectomy are the surgical methods offered only when a permanent method is desired by the couple.

- Emergency contraceptive also known as postcoital contraceptive is an innovative technique of preventing conception if rape or unprotected intercourse occurs around ovulation. This method yields 95–98% success and avoids MTP.
- LNG is now available in India as a tablet containing 0.75 mg LNG. One tablet taken within 72 h of intercourse and another 12 h later is 98.9% successful. The tablets can be taken up to 120 h but its efficacy decreases with the longer coital drug interval.
- RU 486 (Mifepristone) 25 mg single dose is effective in 99.1% as postcoital drug. Other drug is prostaglandin and insertion of Copper T.
- A wide range of contraceptives allow a wider selection of choice to the couples and improves the acceptability of one or more methods.
- MTP service is available in India as a health measure to avoid criminal abortion and not as a contraceptive technique. Its indications are clearly defined by the government and should be abided by the gynaecologists.
- First-trimester MTP by suction evacuation is safer than second-trimester termination.
- Medical method of using mifepristone and misoprostol has proved successful, but the drugs are expensive and requires 2-weeks follow-up. The surgical method may still be required in failed cases.
- The choice between medical and surgical methods of termination of pregnancy depends upon the choice of the woman and contraindications of a method.
- Newer progestogens have fewer side effects.
- Availability of short-acting and long-acting contraceptives allow the couple to choose a method of their need and convenience.

Self-Assessment

1. Discuss the advantages and disadvantages of oral combined contraceptive pills.
2. What are the contraindications to oral combined pills?
3. What is the role of mini-pills in contraception?
4. Discuss the complications and contraindications of intra-uterine device.
5. Write short notes on:
   - Hormonal implants
   - Vasectomy
   - Barrier contraceptives
6. Discuss the methods of termination of pregnancy in the first trimester.
7. Discuss the uses of Mirena and Copper T.

Suggested Reading

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Chapter 21 Ectopic Gestation

CHAPTER OUTLINE

Fertilization takes place in the distal portion of the fallopian tube and the ovum is subsequently transported by the contractions of the tube into the uterine cavity, aided by the fluid current imparted by the ciliated epithelium. The journey takes 3 to 4 days. During this period, the developing ovum is nourished by the cells of the corona radiata and the secretion of the cells lining the fallopian tube. In pathological conditions, implantation may occur anywhere outside the normal uterine cavity, the subsequent gestation being called ectopic. In about 95% such cases, ectopic gestation occurs in the fallopian tube, when it is called tubal pregnancy. In rare cases, it occurs in the ovary, the rudimentary horn of a bicornuate uterus and the cervix. Lately, ectopic pregnancy over the caesarean scar has been reported. Primary abdominal pregnancy is indeed a very rare phenomenon but secondary abdominal pregnancies have been reported.

Types of Ectopic Gestation

Extrauterine

- Tubal (90–95%)
- Ovarian (1%)
- Abdominal (1–2%)—rare now

Uterine but ectopic location in the uterus

- Interstitial (2%)
- Rudimentary horn of a bicornuate uterus
- Cervical (0.5%)
- Caesarean scar
- Heterotopic pregnancy

Epidemiology

1. Ectopic pregnancy constitutes one of the leading causes of pregnancy-related maternal deaths and accounts for about 10% of maternal mortality.
2. The incidence has quadrupled over the past two decades.
3. Increasing incidence of pelvic inflammatory disease (PID) in the community, the use of intrauterine contraceptive devices (IUCD) and the wider use of assisted reproductive technology (ART) have contributed significantly to this rising incidence.

Incidence

The incidence of ectopic pregnancy has been increasing over the past two decades. It has risen from 1:150 pregnancies to about 1:40–1:25 pregnancies in present times. Goldner et al. (1993) reported a fivefold increase in its incidence in USA. Racial, genetic and environmental factors have been implicated. Promiscuity, rising incidence of sexually transmitted infections and the practice of resorting to induced abortions have contributed to this increased incidence. Social and lifestyle changes such as late marriage and older age at the time of childbearing amongst career women have become a common practice. Those women who seek postponement of pregnancy have adopted the use of contraceptives, especially in urban areas. Modern technology today offers hope to many infertile couples in the form of ART procedures. However, their widespread use in clinical practice has been accompanied by a 5% increase in the incidence of ectopic pregnancies. A few early ectopic pregnancies resolve spontaneously and are not recognized. Therefore, the exact prevalence of ectopic pregnancy is difficult to estimate. Repeat ectopic pregnancies are reported in 13–15% cases.

Aetiology (Table 21.1)

Tubal pregnancy occurs either because the fallopian tube offers the fertilized egg a congenial environment for implantation or because a delay in the ovum transport across the fallopian tube cause the fertilized egg to implant in the tube itself. The risk factors predisposing ectopic tubal implantation include—previous salpingitis, previous ectopic pregnancy, tubal damage following genital tuberculosis, previous tubal surgery like tubectomy (especially Madlener) or tubal reanastomosis, presence of IUCD, prolonged infertility and following ART procedures in infertile women.

TABLE 21.1 Aetiology of tubal ectopic pregnancy

- Previous pelvic inflammatory diseases
- Genital tuberculosis
- Endometriosis in the pelvis causing distortion of the fallopian tube
- Previous ectopic pregnancy
- Pelvic adhesions
- Congenital elongation, accessory ostia, diverticula
- Transmigration
- Previous tubal surgery, tubectomy
- IVF programme
- IUCD, progesterone containing IUCD
- Progestogen-only pills (POP)

The commonest causes of PID include sexually transmitted infections like chlamydia trachomatis and gonorrhoea. Other leading causes of salpingitis are septic abortion, postabortal sepsis and puerperal sepsis common in developing countries. With reduction in the incidence of gonococcal infection, chlamydial infection predominates and causes extensive and more damage than that caused by gonococcal infection. Barlow et al. evidenced the presence of chlamydial infection in 50% women presenting with ectopic pregnancy. By treating chlamydial infected women for the infection, a Sweden study showed a drop in the incidence of ectopic pregnancy by 45%.

Almost 40% of women suffering from ectopic pregnancy reveal evidence of PID. Westrom reported that following one episode of salpingitis, 12.8% of the affected women showed partial or complete tubal blockage; this figure rose to 30% following two episodes of salpingitis and 75% after three episodes. He reported a sevenfold increase in the incidence of ectopic pregnancy amongst women proved laparoscopically to have the stigma of PID. The incidence of ectopic pregnancy following one episode of PID rises from 1:150 pregnancies to about 1:25. The incidence also rises in women who have undergone induced abortion and who have suffered genital tuberculosis, which is not uncommon in India. The pelvic adhesions following appendicitis and endometriosis may kink or deform the fallopian tube so as to interfere with ovum transport. Endometriosis in the lining of the fallopian tube may attract premature implantation of the fertilized egg. Acute salpingitis leads to congestion and oedema of the tubal wall and exfoliation of tubal epithelium during the healing process. Often the tubal musculature is also involved in fibrosis following PID, thus causing partial blockage of its lumen, impaired tubal peristaltic activity and delay in the transport of the fertilized egg.

Pathogenesis

Situations favouring delay in tubal transport of the fertilized egg, or those contributing to its tubal implantation, are discussed below:

- Congenital defects in the fallopian tubes such as accessory ostia, diverticula, partial stenosis and polyp may

entrap the fertilized egg and prevent it from reaching the uterine cavity. A cornual fibroid, by narrowing the tubal lumen, can cause tubal pregnancy.

- Transperitoneal migration of the ovum from one ovary to the opposite fallopian tube has been established by demonstrating the presence of the corpus luteum in one ovary and an ectopic pregnancy in the opposite fallopian tube. Berlind observed this migration in 8% cases of ectopic pregnancies.
- Delayed transport of the fertilized ovum along the tube may result from impaired ciliary and peristaltic activity in the fallopian tube as a consequence of injury or inflammation. Hormonal contraceptives, mainly progestogen-only pills, are known to reduce tubal motility and thereby favour an ectopic pregnancy.
- Pelvic adhesions and endometriosis may distort the tube and cause kinking. Following the surgical procedure of ventrosuspension, kinking at the isthmic portion of the tube may contribute to ectopic pregnancy.
- Surgical procedures like tubectomy (especially Madlener—7%), by virtue of spontaneous reanastomosis, and tuboplasty may end up in partial stenosis at the anastomosis site favouring ectopic pregnancy. Conservative surgery for an ectopic pregnancy is reported to cause repeat tubal pregnancy in 15% cases.
- Laparoscopic cauterization in sterilization operation may lead to the formation of a fistulous opening in its medial end permitting the sperms to reach the ovary. The fertilized egg however is large and gets entrapped in the distal segment causing ectopic pregnancy as seen in 75% cases. Wolf et al. reported that 7.4% of ectopic pregnancies occurred in previously sterilized women. The incidence is now reduced by using clips instead of cauterization.
- In vitro fertilization (IVF) favours occurrence of ectopic pregnancy on account of fundal insertion of two or more eggs during embryo transfer. The number of eggs and the quantity of fluid medium inserted during embryo transfer may flush an egg into the tubal lumen. This explains the occurrence of heterotopic pregnancy in 1–2% of IVF cases.
- In some cases, it is probable that the ovum itself is at fault. The rapid development of trophoblast may favour premature implantation in the fallopian tube. In contrast, delayed trophoblastic development may end up as a cervical pregnancy.
- Extraneous causes such as appendicitis and pelvic endometriosis may involve the fallopian tubes in adhesions, impair its mobility or cause kinking. This partly explains a higher incidence on the right side.
- About 4% of pregnancies with IUCD are ectopic pregnancies because of its ineffectiveness in preventing extrauterine pregnancy. Progestogen-containing IUCDs and progestogen-only contraceptive pills delay tubal peristalsis and thereby contribute to the occurrence of an ectopic pregnancy.
- Induction of ovulation with gonadotropins may increase the risk of ectopic pregnancy because of multiple ovulation and multiple pregnancy.
- In older women, the risk of defective embryogenesis increases, thereby the incidence of ectopic pregnancy also increases.

Pathological Anatomy

Tubal Pregnancy

Tubal pregnancy accounts for 90–95% of all ectopic pregnancies. In a tubal pregnancy, the most frequent implantation site is the ampulla (80%) because the plicae are most numerous in this situation and previous salpingitis is more likely to produce crypts here than elsewhere along the fallopian tube. If the ovum is attached to the antimesenteric border, the trophoblast eventually erodes through the peritoneal surface of the tube and leads to intraperitoneal haemorrhage. If attached caudally, erosion of the trophoblast leads to formation of a broad ligament haematoma.

The decidual reaction of the tissues of the plicae of the tube is both scanty and incomplete. The muscle wall of the tube is also thin, and there is therefore little resistance to the eroding action of the trophoblast of the embedded ovum. Erosion of tubal vessels causes bleeding. The trophoblast is also less vascular as compared to one in normal pregnancy due to poor decidualization.

In favourable cases, the haemorrhage is slow and slight blood clot around the trophoblast dislodges the ovum and produces a tubal mole. The size of the mole depends partly on the extent of the haemorrhage and partly upon the stage of pregnancy so that a tubal mole may vary from the size of a cherry to a swelling of 10 cm in diameter. This mole may remain within the tube and gradually get absorbed. More often, it gets expelled through the abdominal ostium into the peritoneal cavity—tubal abortion. The blood may form a clot around the rupture site or near the fimbrial end—peritubal haematocele. A profuse haemorrhage causes blood to collect in the pouch of Douglas to form a pelvic haematocele (Figure 21.1). The worst form of haemorrhage results when the trophoblast of the ovum erodes through all the layers of the tube causing tubal rupture (Figures 21.2–21.6). A rare rupture into the broad ligament forms a broad ligament haematoma (Figures 21.7 and 21.8).

Location

While the ampullary portion is the site of ectopic pregnancy in 80%, fimbrial ends is the site in 6%, isthmus in 12% and interstitial in 2%.

Ovarian Pregnancy

Ovarian pregnancy is relatively more prevalent now because of the increased use of IUCDs. Although IUCD prevents implantation of conceptus in the uterus and in the medial half of the tube, it has no contraceptive effect on the distal end of the tube and on ovarian pregnancy. As the

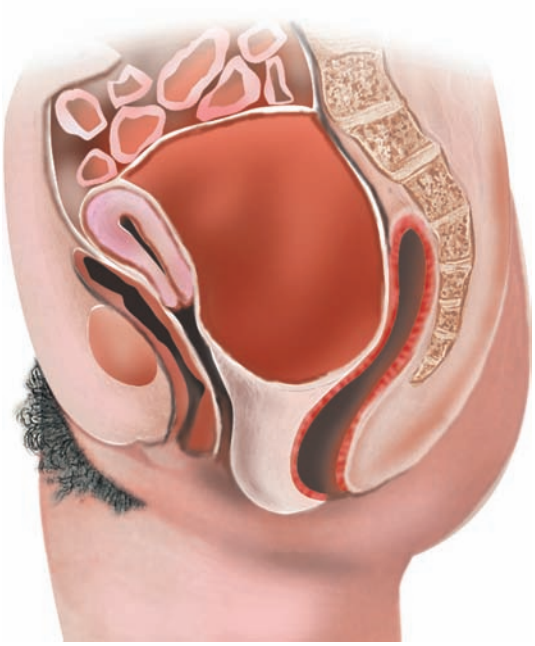


Figure 21.1 A large pelvic haematocele from a case of a ruptured tubal gestation. Note how the swelling pushes the uterus forwards, and how retention of urine may develop from elongation of the urethra. Note the close relation to the rectum.

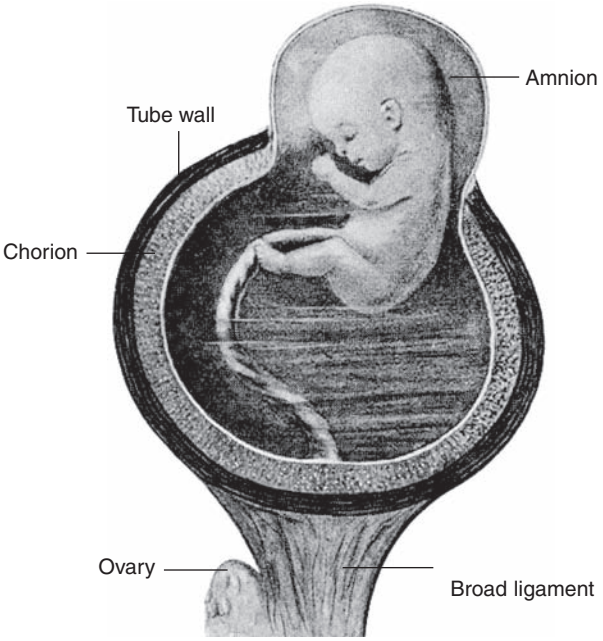


Figure 21.2 Tubal rupture with intact gestational sac—a rare event. Compare with Figure 21.3.

fertilized egg lodges in the corpus luteum, ovarian pregnancy gives the appearance of a corpus luteal haematoma. Histological examination will establish the diagnosis. Ovarian pregnancy accounts for 20 to 30% of all ectopies in IUCD users and 0.5 to 3% of all ectopic pregnancies.

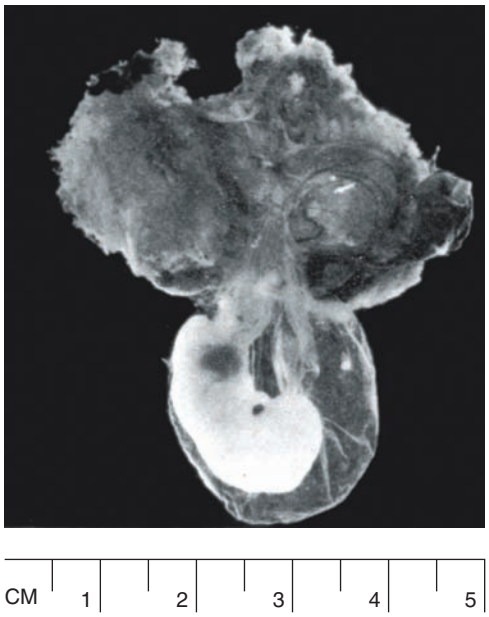


Figure 21.3 Actual specimen removed at operation, illustrating the exact situation of Figure 21.2.

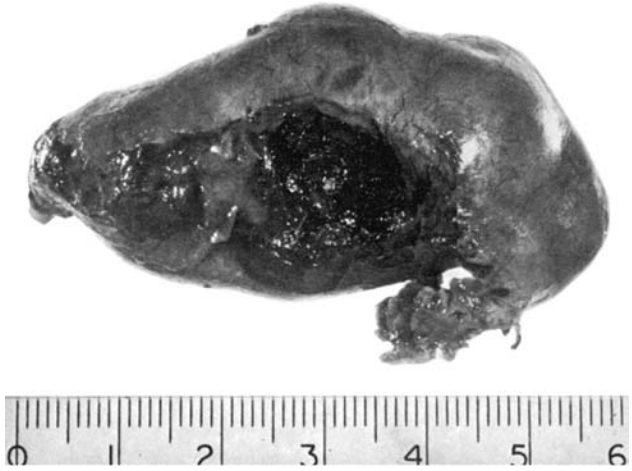


Figure 21.4 Fallopian tube containing ectopic gestation on point of rupture, removed intact at operation. In the lower half of the picture, the point of erosion is shown by a blood clot.

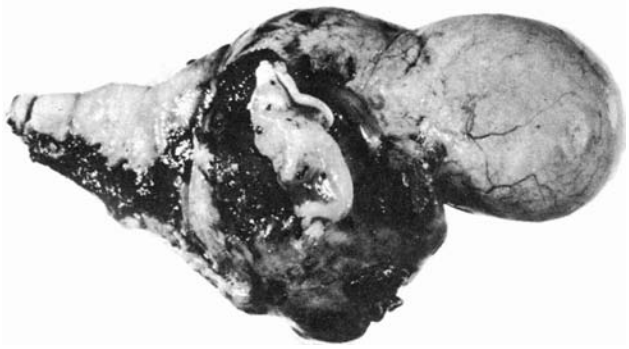


Figure 21.5 Ruptured tubal pregnancy. Note the fetus surrounded by a haematoma being extruded through the wall of the distended tube.

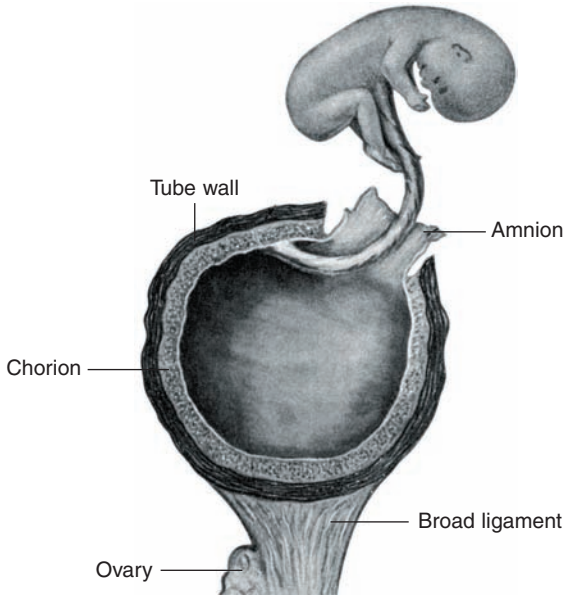


Figure 21.6 Tubal rupture with rupture of gestational sac—the more common event.

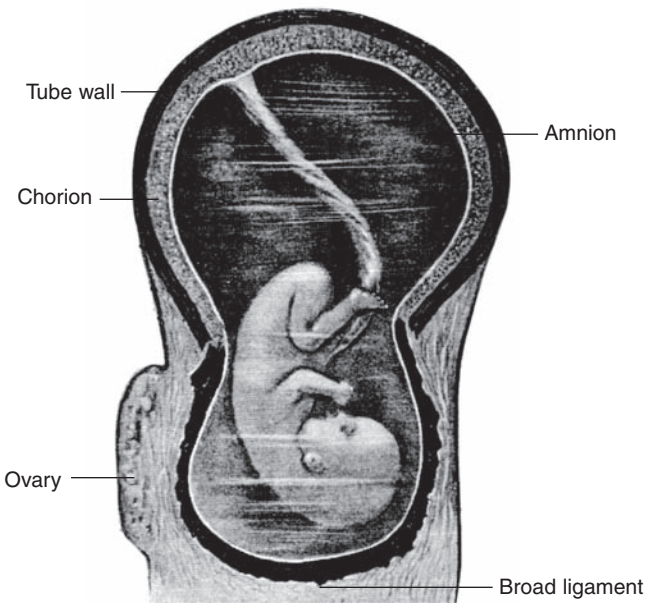


Figure 21.7 Intra-ligamentary rupture of tube. Gestational sac intact.

Spiegelberg laid down the following criteria to diagnose ovarian pregnancy:

- Both fallopian tubes must be anatomically normal at laparotomy.
- The gestational sac must occupy the ovary in depth, not just be superficially adherent to it.
- The wall of the gestational sac should consist of recognizable ovarian elements on histological examination. Chorionic tissue should also be identifiable in the ovarian mass.

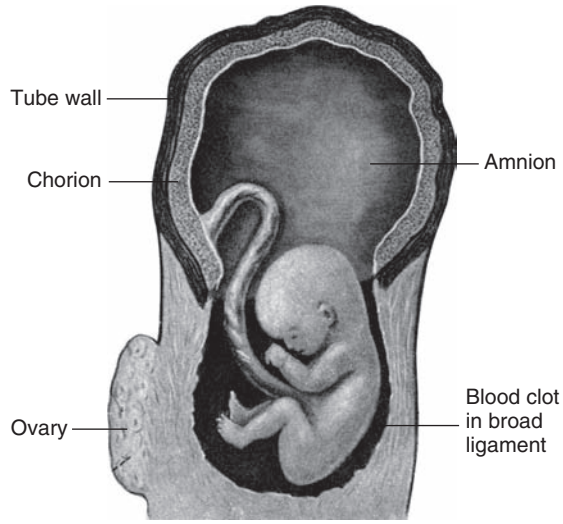


Figure 21.8 Same as Figure 21.7, but with the gestational sac ruptured.

- The gestational sac should be attached to the uterus by the ovarian ligament and to the pelvic wall by the infundibulopelvic ligament.

Primary Abdominal Pregnancy

This condition is so rare that it probably does not exist, and little is known of the method of implantation. It is possible that the ovum is implanted in areas of ectopic decidua.

Secondary Abdominal Pregnancy

With routine ultrasonic scanning in early pregnancy, it is very unlikely that secondary abdominal pregnancy can be missed and pregnancy need not proceed to term. A rare unbooked case from rural areas may present at term with advanced secondary abdominal pregnancy. In the present scenario, it is very unlikely to encounter a secondary abdominal pregnancy booked for hospital delivery.

A woman may suffer mild abdominal pain and threatened abortion in the early weeks but pregnancy proceeds with abdominal discomfort throughout pregnancy. At term, the woman goes into spurious labour but fails to deliver spontaneously or with syntocinon drip.

Ultrasound or radiograph reveals an abnormal and high position of a malformed or a dead fetus outside the uterus. Rarely, a normal live fetus is seen. The uterus is normal in size. Long-standing abdominal pregnancy causes calcification and shrinkage of the fetus which is then called a lithopaedion.

Interstitial Pregnancy

Interstitial pregnancy is a very rare form of ectopic gestation, when the ovum is implanted in the interstitial portion of the tube (2%). Usually a muscular septum intervenes between the gestational sac and the cavity of the uterus.

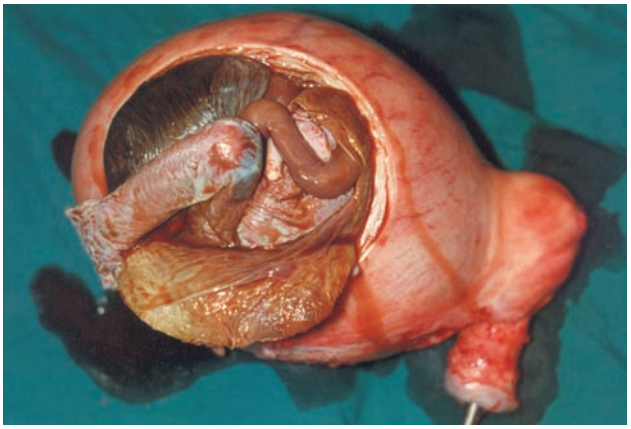


Figure 21.9 Ectopic tubal pregnancy—fetus expelled from the fallopian tube.

Interstitial pregnancy usually terminates by rupture into the peritoneal cavity during the third month of pregnancy (Figure 21.9).

Pregnancy in an Accessory Horn (Figure 21.10)

The fate of pregnancy in a duplicated uterus depends upon the degree of development of the horn. In uterus didelphys or when both horns are well developed, pregnancy usually proceeds to term or near-term, and parturition may be normal. If one horn is ill-developed, the muscle wall becomes thinned out and may rupture during pregnancy. This complication usually develops during the fourth month and causes severe internal bleeding. At operation, the type of gestation is recognized from the position of attachment of the round ligament, which in uterine pregnancy passes from the lateral end of the gestational sac to the internal abdominal ring, whereas in a tubal pregnancy, the round ligament lies medial to the gestational sac. Pregnancy in an accessory cornu has been recorded when the corpus luteum was present in the opposite ovary, with the accessory cornu shut off from the cavity of the uterus. This occurrence is explained by transperitoneal migration of the fertilized ovum.

Multiple Pregnancy and Ectopic Gestation (Heterotopic)

The association of multiple pregnancy with ectopic gestation is not uncommon, especially now with the introduction of IVF and multiple embryo transfer. Combined uterine and extrauterine pregnancy is reported in 1 to 3% of successful IVFs. In a spontaneous pregnancy, the incidence of combined pregnancies is as low as 1:4000 to 1:30,000 pregnancies. A tubal gestation is occasionally a twin pregnancy and one instance of quintuplets in a tubal pregnancy has been recorded. Authentic cases of bilateral tubal pregnancies have also been recorded. It is not unusual, however, in cases of ectopic gestation for the opposite fallopian tube to be distended with blood by regurgitation from the cavity of the uterus into the tube, the abdominal ostium of which is closed by adhesions from previous salpingitis. The diagnosis of bilateral tubal pregnancy must not be made unless chorionic villi can be demonstrated in both tubes. *The importance of examining both tubes when operating on a case of ectopic gestation must be emphasized.*

Another important feature of tubal gestation is the frequency with which a subsequent ectopic gestation develops in the opposite tube. If a woman conceives after having had an extrauterine gestation, the chances are 1 in 7 that she will develop an ectopic pregnancy in the other tube (15%).

Caesarean scar ectopic pregnancy is recently recognized as a rare variety of an ectopic pregnancy, when the

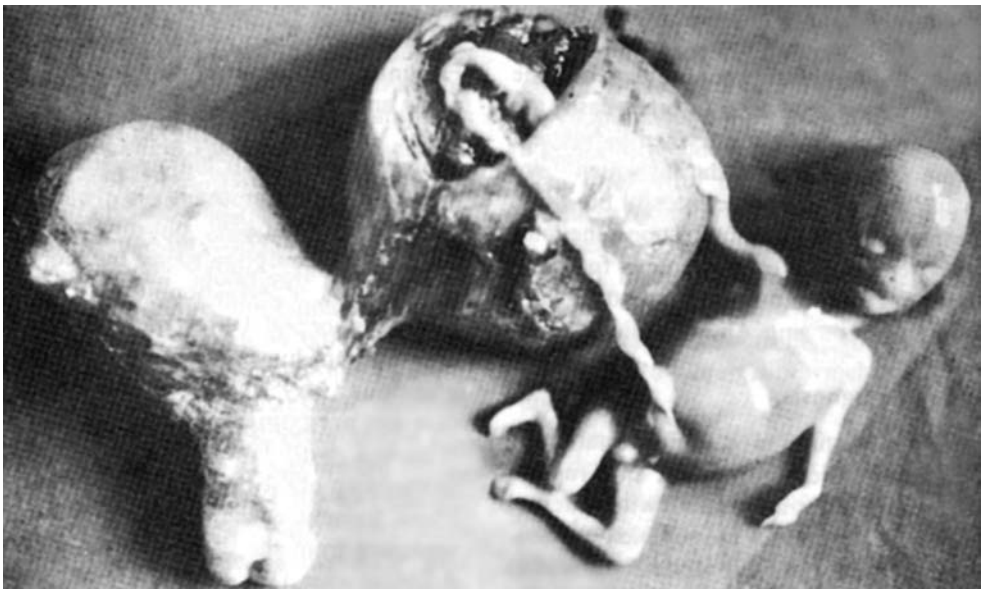


Figure 21.10 Accessory horn pregnancy in a multiparous patient. (Courtesy: Dr Narayan M Patel, Ahmedabad.)

gestational sac is seen embedded and surrounded by myometrium and fibrosis of the caesarean scar.

Fate of the Ovum

In the majority of cases, the haemorrhages produced around the ovum separate the chorionic villi from their attachment so that the ovum is forcibly dislodged either into the lumen of the tube or, in case of tubal rupture, into the peritoneal cavity. In other cases, the ovum, though not completely dislodged from the tube, may be separated to a degree sufficient to deprive it of its nutrition so that it dies and forms a tubal mole.

On rare occasions, the dislodgement may be partial so that the ovum continues to develop. Two types of such cases can be recognized. In the first group, the trophoblast is attached to the caudal aspect of the tube, adjacent to the broad ligament, so that the ovum grows cranially. In almost all cases, the cranial surface of the gestational sac erodes through the tube, at first becoming surrounded by blood clot and later forming adhesions to the omentum and intestine. In the second group, the attachment of the trophoblast is to the cranial aspect of the tube, and the ovum grows downwards in the broad ligament. Such a pregnancy is referred to as broad ligament pregnancy or secondary abdominal pregnancy. The subsequent fate of such secondary pregnancies is variable. There is always a danger of further internal haemorrhage from erosion of maternal vessels, or the trophoblast may become detached so that the fetus dies. In other cases, the pregnancy may proceed to term, when the patient experiences a spurious labour during which there is again a further risk of severe internal bleeding. If the patient survives these complications, the fetus dies and may remain inside the abdomen for many years undergoing mummification and calcification and becomes a lithopaedion. It is extremely rare that a live fetus is delivered by laparotomy.

Symptoms and Diagnosis

Accurate diagnosis based on symptoms and clinical signs is possible in only 50% cases. *One should therefore consider the possibility of an ectopic pregnancy when a woman presents with bizarre clinical features.*

The key to a successful outcome is an early diagnosis of ectopic pregnancy.

The clinical picture in ectopic gestation is related to the pathological anatomy. A tubal rupture is an acute emergency associated with internal bleeding and shock. This is acute ectopic gestation. A tubal mole, with peritubal and paratubal haematocele, causes abdominal pain and irregular vaginal bleeding. This is a less urgent condition and is called the subacute or chronic ectopic gestation. The subacute ectopic pregnancy may eventually rupture and become an acute emergency.

With routine ultrasonic scanning in early pregnancy, unruptured ectopic pregnancy can be detected before the clinical features develop.

Amenorrhoea

About 75% patients present with a history of amenorrhoea of less than 6 weeks duration. If the ectopic gestation ruptures in the early weeks, there is no history of amenorrhoea, bleeding and pain having started around the expected period. In a rare case of abdominal pregnancy, amenorrhoea may proceed into the third trimester or even beyond 9 months. Persistent failed induction necessitates further investigations to find the true nature of the pregnancy. Amenorrhoea lasts 3 to 4 months in case of interstitial and cornual pregnancies. Early bleeding simulating uterine abortion is seen in caesarean scar ectopic pregnancy.

Pain

Abdominal pain, generally severe, is a consistent feature of ectopic pregnancy in 95% cases. Most severe pain is caused by tubal rupture and also due to discharge of large quantity of blood into the peritoneal cavity. When internal haemorrhage floods the peritoneal cavity and irritates the undersurface of the diaphragm and phrenic nerve, the patient complains of shoulder and epigastric pain. If a patient is brought in a condition of shock complaining of abdominal as well as shoulder pain, the diagnosis of ectopic pregnancy is more certain. In a subacute variety, the patient complains of pain but signs of shock are absent and the diagnosis may at first be missed. Fortunately, these are not emergency cases and there is ample time for further investigations. Pain is often absent in unruptured ectopic pregnancy.

Vaginal Bleeding

Vaginal bleeding is almost always small but persistent and consists either of dark altered and fluid blood or of dark coagulated blood. The bleeding may come as a trickle from the fallopian tube but more commonly it originates in the endometrium of the uterus. Under the hormonal effect of the ectopic pregnancy, the endometrium hypertrophies and is converted into a decidua, very similar to that seen in a normal uterine pregnancy. When the pregnancy is disturbed, withdrawal of the hormonal effect results in shedding of the decidua in the form of a vaginal bleed. Sometimes, the whole of the uterine decidua separates from the uterus and is discharged as a decidual cast (Figure 21.11). Decidual cast has a smooth glistening inner surface and shaggy maternal surface. The chorionic villi are conspicuously absent. The passage of a decidual cast is pathognomonic of ectopic gestation. The presence of chorionic villi in the cast indicates uterine pregnancy. If a young woman with a short period of amenorrhoea complains of continuous or intermittent but slight vaginal bleeding, ectopic pregnancy should be considered even

Figure 21.11 Complete decidual cast extruded from the uterus in a patient operated for ectopic gestation.

if the abdominal pain may be slight or might have been short-lived and almost forgotten. Vaginal bleeding and pain are absent in early unruptured ectopic pregnancy. Very early bleeding occurs in cervical and caesarean scar ectopic pregnancies.

Asymptomatic unruptured ectopic pregnancy which may resolve spontaneously is diagnosed by high-resolution ultrasound complemented by β-hCG estimation and laparoscopy.

Retention of Urine

In a subacute variety of ectopic pregnancy, the blood collects in the pouch of Douglas to form a pelvic haematocele. This haematocele forms an irregular mass of differing consistency due to a mixture of clot and blood, and bulges forwards displacing the cervix against the bladder neck leading to retention of urine.

Fever

If the pelvic haematocele gets secondarily infected, the patient develops slight fever. It is rare to find high-grade fever as seen in pelvic infection.

Physical Signs

The physical signs vary according to whether the patient is suffering from acute intraperitoneal bleeding or from localized intraperitoneal haemorrhage.

Acute Ectopic Pregnancy

A patient with acute intraperitoneal haemorrhage presents with pallor and two other signs of internal haemorrhage, viz., restlessness and air hunger. The patient is cold, the skin is clammy, the temperature subnormal and the pulse thready with marked tachycardia. Blood pressure will be low. Breast signs of pregnancy may or may not be present depending upon the duration of pregnancy. The abdomen is slightly distended and its movements restricted. The distension is not always due to free intraperitoneal blood but to an associated localized ileus of gut caused by blood. An extreme tenderness can be elicited in the lower abdomen but rigidity is not so well marked. Signs of free fluid in the abdomen are present in case of profuse internal haemorrhage. The bluish discolouration of the cervix is rarely seen at this early stage of gestation. Similarly, the cervix may or may not be soft. Cervical movement causes severe pain. Abdominal tenderness may prevent an accurate bimanual examination of the uterus but if the uterus can be felt, it is found to be normal or slightly enlarged and softened. It is difficult to feel any pelvic mass but pelvic haematocele may be felt as a tender bulge in the posterior fornix.

Clinical features of various ectopic pregnancies is explained in Table 21.2.

Differential Diagnosis

- Splenic rupture produces a similar clinical picture but amenorrhoea is absent.
- Perforated gastric and duodenal ulcer produce acute abdomen pain but signs of internal haemorrhage are absent. Abdominal palpation reveals board-like rigidity which is absent in ectopic pregnancy. Air may be seen under the diaphragm in gastric perforation.

TABLE 21.2 Clinical features of ectopic pregnancy

Acute ectopic pregnancy	Haemorrhagic shock
	Acute pain in the abdomen
	Amenorrhoea
	Vaginal bleed
	Abdominal tenderness
Subacute ectopic pregnancy and chronic ectopic pregnancy	Amenorrhoea
	Abdominal pain
	Vaginal bleeding
	Retention of urine
	Abdominal mass and tenderness
	Ultrasound
	β-hCG level laparoscopy
Abdominal pregnancy	Amenorrhoea
	Colicky pain
	Postmaturity
	Failed induction
	Ultrasound: Abdominal fetal position—Malformed, dead

- Perforated appendix and acute pancreatitis will demonstrate high fever and signs of peritonitis.
- Rupture of a corpus luteal haematoma simulates ectopic gestation both in the history and clinical findings. With a history of short period amenorrhoea, pain, vaginal bleeding and a tender mass with internal haemorrhage, it is impossible to be sure of the pelvic condition. Ultrasound gives an identical finding in both. The treatment is immediate laparotomy in both these conditions.
- Myocardial infarct has occasionally been considered when the patient complains of epigastric pain and collapses. Normal ECG and the gynaecological history will lead to accurate diagnosis.
- The diagnosis may be much more difficult with ruptured secondary abdominal pregnancy as the differential diagnosis of ruptured uterus and concealed accidental haemorrhage have to be considered.

Localized Intraperitoneal Haemorrhage (Subacute and Chronic)

In this condition, there may be some degree of constitutional disturbance as a result of the local intraperitoneal bleeding but the dominant features are recurrent abdominal pain and vaginal bleeding. Retention of urine may occur due to pelvic haematocele.

The pulse rate is raised in proportion to the severity of the bleeding. It is exceptional for the temperature to be raised to more than 99.48°F. The absence of severe pyrexia may be of some service in distinguishing between ectopic gestation and pyosalpinx. The breasts may show signs of early activity. On examination of the abdomen, tenderness in one or other iliac fossa is invariable, and sometimes, the haematocele can be palpated, arising from the pelvis as a tender, firm swelling. Distension and rigidity are not characteristic of localized pelvic haematocele.

The most important physical signs are found on vaginal examination because accurate bimanual examination is usually possible. The peculiar brownish uterine haemorrhage can be recognized; the cervix is found to be soft and the uterus slightly enlarged. The other physical signs vary with the type of case. With pelvic haematocele, an irregular swelling can be felt through the posterior fornix in the pouch of Douglas. It has a peculiar consistency which is almost pathognomonic, for it has no definite outline, is neither fluid nor solid, and its consistency varies in different areas. Occasionally the haematocele is extremely tender. It pushes the uterus forwards and upwards, and on occasions, produces retention of urine. Very occasionally, it may extend upwards into the abdomen and is palpable on abdominal examination. A tubal mole and the haematosalpinx form a retort-shaped swelling which is tense, firm but smooth, and which pushes the uterus to the opposite side of the pelvis. Peritubal haematoceles form firm swellings which may be mistaken for subperitoneal myomas. Firmness, tenderness and smoothness are characteristics of the localized haematomas of ectopic gestation. One danger of vaginal examination is it is possible to disturb a quiescent ectopic which has stopped bleeding and cause a further severe haemorrhage. For this reason, if an ectopic gestation is strongly suspected, vaginal examination should be performed gently, keeping the operation theatre ready for surgery. *If facility prevails, ultrasound diagnosis should replace clinical examination.*

The diagnosis of ectopic gestation presents great difficulty and it is usually missed because it is not suspected. *During the childbearing period of life, a woman complaining of pain in the lower abdomen associated with continuous vaginal bleeding should be suspected of ectopic gestation.*

Differential Diagnosis

Clinical diagnosis remains a challenge as the condition may simulate other conditions. *Think of ectopic pregnancy when the woman presents with atypical features in early pregnancy.*

Pyosalpinx

In acute pyosalpinx, the temperature is raised and the patient may complain of vaginal discharge. The signs of internal haemorrhage are absent; so also the history of amenorrhoea, though slight irregular vaginal bleeding may be reported in a pyosalpinx. In chronic pyosalpinx, the patient may be afebrile, pain and tenderness is mild, and the pelvic mass is often bilateral. In tubercular pyosalpinx, a history of amenorrhoea, pain and a pelvic mass may resemble chronic ectopic pregnancy; it mandates certain investigations such as laparoscopy and endometrial PCR staining to establish an accurate diagnosis.

Septic Abortion

A history of amenorrhoea, pain and bleeding is similar to that of ectopic gestation. Fever however is high with leucocytosis in septic abortion. Offensive vaginal discharge goes in favour of septic abortion.

Pelvic Abscess

Pelvic haematocele may be mistaken for pelvic abscess, especially if the patient has fever. Culdocentesis reveals the true nature of the swelling.

Retroverted Gravid Uterus

Retroverted gravid uterus can be mistaken for a pelvic haematocele when retention of urine occurs. In the case of a haematocele, vaginal examination will reveal the uterus separate from an ill-defined mass of the pelvic haematocele, with the cervix merely pushed forward by this mass. Retroverted gravid uterus, on the other hand, causes the cervix to be pushed forward and pressed against the bladder neck; the mass in the posterior fornix is identified as a well-defined soft uterus corresponding to a period of amenorrhoea. Ultrasound will further confirm the findings.

Twisted Ovarian Cyst

Twisted ovarian cyst causes acute abdominal pain and sometimes slight vaginal bleeding but amenorrhoea is absent; so also signs of internal haemorrhage.

Rupture of a Chocolate Cyst

Rupture of a chocolate cyst causes shock and collapse, with acute abdominal pain. Amenorrhoea as well as signs of internal haemorrhage are absent.

Uterine Fibroid

At times, a pelvic haematocele forms a firm swelling adherent to the uterus giving the latter the feeling of an irregular uterine swelling of a fibroid. In such cases, history is more reliable than the pelvic findings. Ultrasound can make a correct diagnosis.

Corpus Luteal Haematoma

Corpus luteal haematoma also presents with a short period of amenorrhoea, acute abdominal pain, vaginal bleeding and shock due to haemorrhage. The pelvic findings resemble that of an ectopic gestation. Fortunately, the treatment in both conditions is immediate surgery.

Acute Appendicitis

The patient has fever with leucocytosis and vomiting. There is no history of amenorrhoea and vaginal bleeding. Tenderness is felt high up in the right fornix.

High-risk cases for an ectopic pregnancy are those with:

- Previous PID
- Pelvic tuberculosis
- IUCD and POP users
- Previous tubal surgery
- IVF—gamete intrafallopian transfer (GIFT) technique
- Previous ectopic pregnancy.

Diagnostic Investigations (Table 21.3)

In the management of acute ectopic gestation, when the patient is obviously ill from severe internal bleeding, there is no need and no time for any investigation other than haemoglobin count, blood grouping, cross-matching and immediate laparotomy. In the subacute variety, the condition is not desperate and certain investigations may be required to confirm the diagnosis.

TABLE 21.3 Investigations

- Pregnancy test
- Serum β-hCG level; repeat every 2 days
- Ultrasound—MRI
- Culdocentesis
- Laparoscopy

Hormonal Tests

A negative pregnancy test is of no value in ruling out an ectopic pregnancy. If the test is positive and the uterus is empty as seen on ultrasound, it is suggestive of ectopic pregnancy. Serum β-hCG level less than 6500 mIU/L is seen in ectopic pregnancy and missed abortion. A slow rise in serum hCG level is also of diagnostic value in suspected ectopic pregnancy.

Unlike earlier latex agglutination inhibition assays, there is no need to test strictly morning urine sample if radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA) techniques are used.

β-hCG

β-hCG is detected in the serum 9 days (5–10 mIU/mL) and in the urine 13 days after ovulation, around the time of implantation and before the missed period. The level doubles every 2 days in a normal pregnancy. Therefore, in case of doubt and if the condition of the woman remains stable, serial study and doubling time study are useful. If the level does not rise or rises by less than 66% from the previous reading, ectopic pregnancy or missed abortion should be suspected (Kadar et al.). If the hCG level is over 6500 mIU/L, the ultrasound invariably reveals a uterine pregnancy in 95% cases. At 6 weeks, 85% of ectopic pregnancies reveal a low level of β-hCG or a slow rise subsequently.

Ratio of hCG at 48 h/HCG at 0 h: Ratio of less than 2 is more or less diagnostic of an ectopic pregnancy. In ectopic pregnancy, the doubling rate of β-hCG is slow with less than 66% increase over 48 h.

Rapid bedside qualitative hCG test with a sensitivity of 25–50 mIU/L should be used, if available, in an acute emergency case (takes 1 h). Progesterone level less than 20 ng/mL also suggests abnormal pregnancy but this hormone test has a limited value and takes time (24 h). It is not done in a routine work-up. It has a sensitivity of only 80%.

Culdocentesis or Aspiration of Pouch of Douglas

Culdocentesis or aspiration of pouch of Douglas is helpful if free blood can be aspirated. A positive finding of microclots in the blood justifies laparotomy; a negative result obligates further investigations.

Ultrasound

In an ectopic pregnancy, the uterus appears empty and a mass can be located in one of the lateral fornices. The

gestational sac is however identified only in 5 to 15% cases in early ectopic pregnancy. β-hCG in the urine and serum, empty uterus, adnexal mass and free fluid in the peritoneal cavity is pathognomonic of an ectopic pregnancy. The ultrasonic findings alone may resemble that of PID and endometriosis (Figures 21.12 and 21.13). The advantage of transvaginal sonography is the early detection of a uterine pregnancy at fifth week of gestation when the serum β-hCG reaches 1000 mIU/L. In a normal uterine pregnancy, the gestational sac with a yolk sac is slightly asymmetrically placed attached to one wall of the uterus.

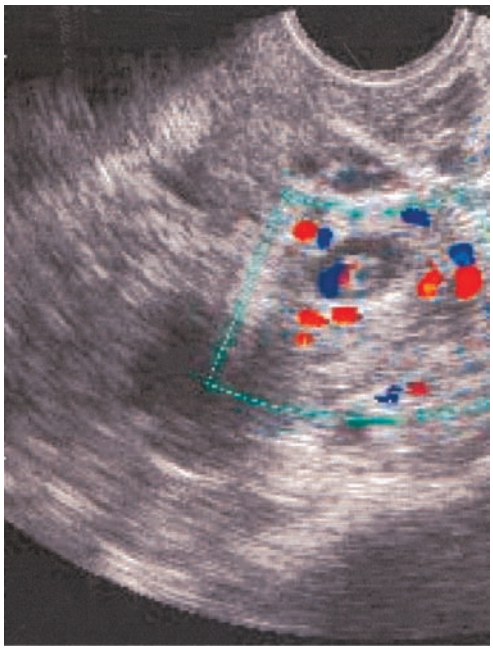


Figure 21.12 Ultrasonography: Adnexal mass showing ectopic pregnancy.

In an ectopic pregnancy, a pseudosac or an empty sac without yolk is formed by decidual thickening and therefore is central in location.

Other ultrasonic features are 'blob' sign and 'bagel sign'. A blood clot with trophoblastic tissue is known as blob sign. An empty gestational sac in the fallopian tube is known as bagel sign. Corpus luteal haemorrhage shows spider-web like contents with haemorrhagic areas. Doppler reveals increased vascularity over the corpus luteal cyst.

Transvaginal ultrasound (TVS) detects uterine gestational sac 1 week earlier than transabdominal probe (TAS) and gives a clearer image because of its proximity to the pelvic organs. Pregnancy can be detected by TVS approximately 14 days after pregnancy detection by serum hCG at 1000 mIU/L level (fifth week of gestation). Pulsed Doppler ultrasound can add further information regarding the vascularity of the peritrophoblastic structure and reduce false-positive findings (Figure 21.14). Transabdominal ultrasound detects uterine pregnancy at serum β-hCG of 1800 mIU/L.

In a cervical pregnancy, the uterus is empty but a gestational sac occupies the cervical canal. In a caesarean scar pregnancy, the uterus as well as the cervix is empty and the sac is located over the isthmus.

The threshold hCG level at which a gestation sac is always seen has fallen from 6500 mIU/mL with TAS to about 1000 mIU/mL with TVS.

Other Hormonal Studies

Placental proteins, especially PP14 (placental protein 14), are reduced in ectopic pregnancy and their diagnostic value appears to be useful. Schwangerschafts protein-1 (SP1) and pregnancy-associated plasma protein-A (PAPP-A 1) appear

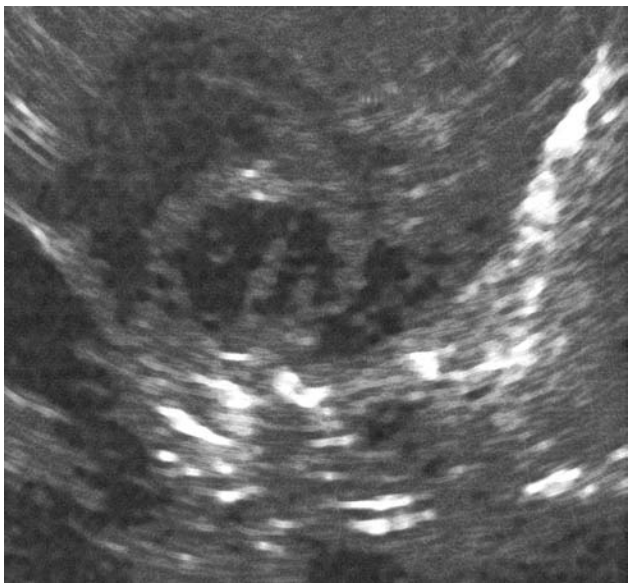


Figure 21.13 Ultrasonography: Ectopic pregnancy with free fluid (blood) in the peritoneal cavity.

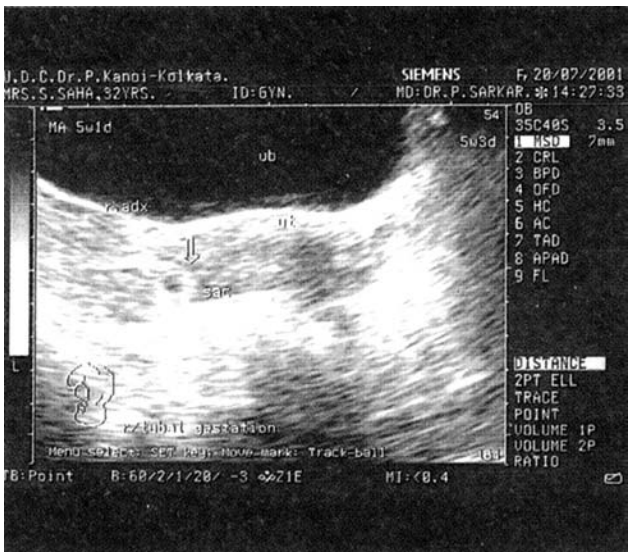


Figure 21.14 Ultrasonography showing ectopic pregnancy with free fluid in the pouch of Douglas.

late, after 6 weeks of gestation; therefore, their value in the early diagnosis of ectopic pregnancy remains doubtful. Normal progesterone level in early pregnancy is 25 ng/mL. Less than 20 ng/mL is seen in ectopic pregnancy but its use in clinical practice in limited at present as it takes 24 h to perform.

Laparoscopy

When an ectopic pregnancy is suspected, but the diagnosis cannot be confirmed because of equivocal findings of hormonal tests and ultrasound, one should proceed with laparoscopic visualization of the pelvis. It is important to note *that the laparoscopist should be competent to perform therapeutic procedure if so required in the same sitting*.

Treatment

Initially, surgery (laparotomy) was the only lifesaving management of an ectopic pregnancy. Then followed conservative fertility-retaining procedures and laparoscopically performed conservative surgeries. With the possibility of diagnosing a very early, unruptured pregnancy by routine ultrasonic screening, more cases are now treated with medical treatment with equally good outcome, without added surgical morbidities.

Medical Management

Methotrexate Therapy

The principle for its use is based on the fact that methotrexate (mTX) is a folate antagonist that inactivates dihydrofolate reductase enzyme, leading to a fall in tetrahydrofolate (essential cofactor in the synthesis of DNA and RNA during cell division). A single dose of mTX therapy comprises parenteral administration (IM) of mTX in a dose of 50 mg/m^2 (approximately 1 mg/kg body weight).

This form of therapy meets with close to 90% success rate (Tanaka), although about 4% may require more than one course of treatment for persistent trophoblastic tissue as recognized by hCG level or the failure of treatment, which is defined as failure of hCG to fall below 15% in the first week (4–7 days). A higher failure rate (18.6%, Lipscomb 2004) has been reported in women with previous ectopic pregnancy. Eighty per cent conceive but repeat ectopic pregnancy is observed in 15% cases. Eighty-five per cent of these cases reveal patent fallopian tubes during the follow-up. Five per cent require surgery for failed medical treatment.

- Injection mTX 25–50 mg injected into the gestation sac under ultrasound/laparoscopic guidance has also shown similar success rate but these procedures are invasive and require hospitalization; they have no advantage over intramuscular injection.
- Lately, hysteroscopic transcervical administration has also been attempted. Further trial is required to prove its effectivity.
- mTX with alternate folinic acid as in trophoblastic disease is also done by a few practitioners, with similar outcome.

Indications. For consideration of suitability of a patient with ectopic pregnancy for mTX therapy, the following criteria should be met:

- The women should be haemodynamically stable.
- Ectopic pregnancy should be unruptured.
- Serum β-hCG level should not exceed 6500–10,000 mIU/mL.
- The size of the gestation sac should not exceed 3–5 cm in its longest diameter.
- Fetal cardiac activity should be absent.
- The patient should be willing to come for follow-up.
- There should be no contra-indication to mTX (liver disease, anaemia).
- The patient should be desirous of future fertility.
- Hb%, WCC and liver function should be normal

Side Effects of Methotrexate.

- Anaemia: Hb% should be at least 9 gm%
- Leucopenia: WCC should be at least 4000 cmm
- Agranulocytosis: Platelet count 100000 cumm
- Liver functions: normal
- Kidney functions: normal
- Nausea, vomiting, gastric haemorrhage
- Alopecia

Contraindications. The following should be noted:

- Serum creatinine level >1.3 mg%, liver function tests, serum SGOT and SGPT >50 IU/L, low Hb and platelet count contraindicate its use
- Chronic alcoholism and liver disease
- Pre-existing blood dyscrasias
- Acute pulmonary disease
- Peptic ulcer
- Immunodeficiency disease
- Breast feeding
- Known drug sensitivity or presence of allergic diathesis
- Gestational sac >3.5 cm
- Presence of fetal cardiac activity
- Cervical caesarean scar and interstitial pregnancy.

Other Surgically Administered Medical (SAM) Drugs
These include:

- Mifepristone
- Prostaglandins
- 20% KCl solution
- Glucose solution—all injected into the gestation sac under ultrasound/laparoscopic control

Of all these, mTX has proved most effective.

Postmedication Management. Postmedication management comprises:

- No alcohol, no folic acid.
- Avoid pregnancy until ectopic pregnancy resolves and serum hCG is undetected. Use barrier method consistently during the follow up.

Following mTX, a fall in the level of hCG to 15% or below the initial level is considered satisfactory resolution of trophoblastic tissue. It is important however to note that there may be initial rise in serum hCG level in the first 4–7 days before the decline, increase in the size of the gestation sac and abdominal pain due to release of hCG, and slight bleeding during resolution. Ultrasound scanning therefore should be delayed until after a week. Follow up with hCG and ultrasound is mandatory. Serum hCG should be done weekly until the hormone is undetected.

The disadvantage of medical treatment lies in the prolonged follow-up and resorting to surgery in failed cases (5%).

Surgical Treatment

All patients with acute ectopic pregnancy should be operated upon at the earliest once the diagnosis is made. The operation essentially consists of open laparotomy, identifying the affected tube, clamping the mesosalpinx and performing salpingectomy as described by Lawson Tait in 1884. The pedicles are transfixed and the collected blood is removed. Occasionally, it takes time to identify the gestation sac as the contralateral tube is also distended with haematosalpinx. Adhesions may cause difficulty in delivering the gestation sac. The woman may require blood transfusion. The recovery is rapid and uneventful. Some pyrexia and jaundice, noted in a few cases, resolve spontaneously. It is very important to inspect the contralateral tube for two reasons.

1. Bilateral tubal pregnancy is rarely encountered.
2. Condition of the tube need to be assessed to check the prognosis of future pregnancy.

The controversy as to whether the ovary on the affected side should be removed or conserved is theoretical. If the ovary is separate from the gestation sac, it should be preserved. This will help if future IVF is planned.

If it is buried in the mass, salpingo-oophorectomy is performed. The blood in the peritoneal cavity is fit to be used in autotransfusion provided it is fresh and not clotted. The advantages of autotransfusion are that blood is available in plenty, there is no need to cross-match the blood and there is no fear of transmission of HIV, malaria and hepatitis B.

In subacute ectopic pregnancy, there is not the same urgency as in the acute form. However, the earlier the patient is operated upon the better, and it avoids the risk of tubal rupture. During surgery, one should be gentle in removing the clots because they may be adherent to organs and cause tear if not careful.

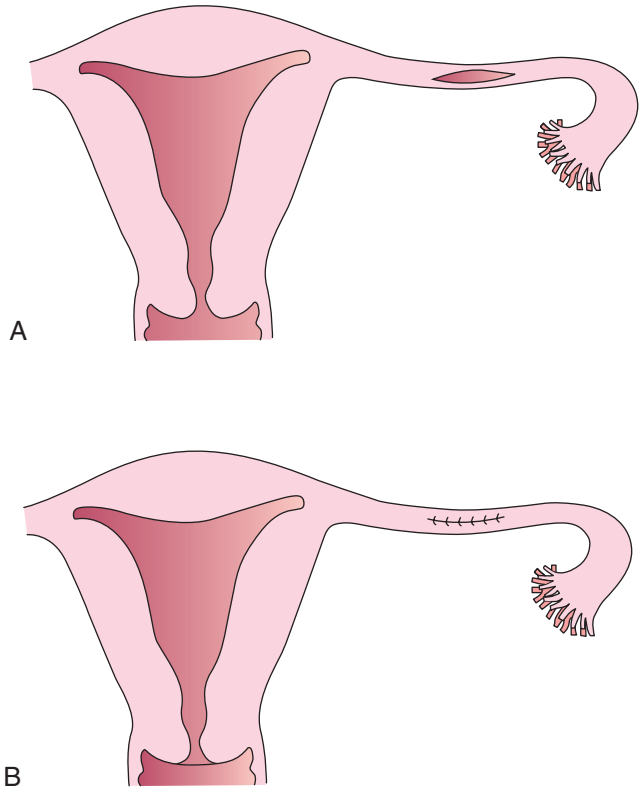


Figure 21.15 **(A)** Salpingostomy. **(B)** Salpingotomy.

Types of Surgery

Treatment comprises salpingectomy, partial salpingectomy, salpingostomy and milking of the tube (Figure 21.15).

- Salpingectomy if the gestation sac is >4 cm, most of the tube is damaged and the other tube is healthy (Figure 21.18).
- Partial salpingectomy if more than 6 cm of the tube can be preserved. Later, tubal anastomosis can be performed (Figures 21.16 and 21.17).

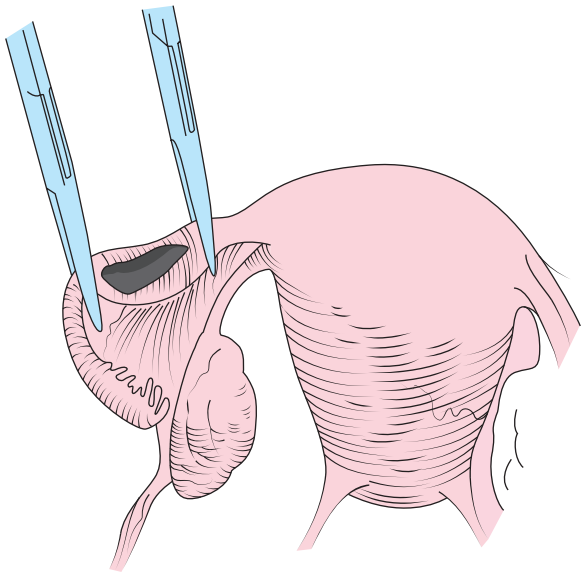


Figure 21.16 Partial salpingectomy for a tubal pregnancy.

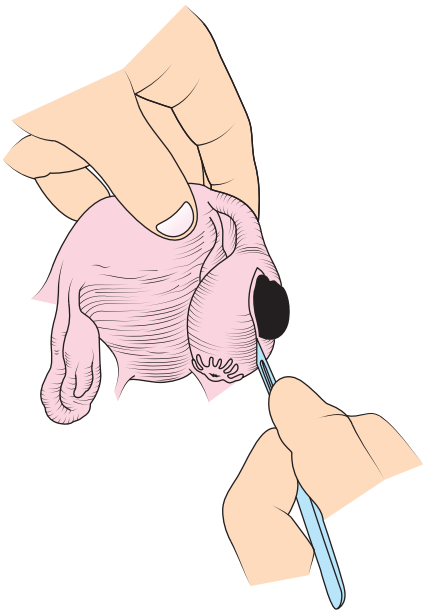


Figure 21.17 Removing an ampullary tubal pregnancy with conservation of tube.

- Salpingostomy—Antimesenteric border is incised, conceptus removed, haemostasis secured and the wound left open for secondary healing. The pregnancy rate is better than with salpingotomy (Figure 21.15) and repeat ectopic pregnancy is low. Salpingotomy—The wound is closed with Vicryl sutures.
- Milking of the tube is possible with fimbrial pregnancy but prolonged bleeding and persistent trophoblastic tissue as well as increased risk of recurrent ectopic pregnancy do not favour this technique.

With improved technique, laparoscopically performed above-mentioned procedures have become the gold standard in the treatment, with early recovery, less pain and short hospital stay. The future outcome is similar to that of laparotomy.

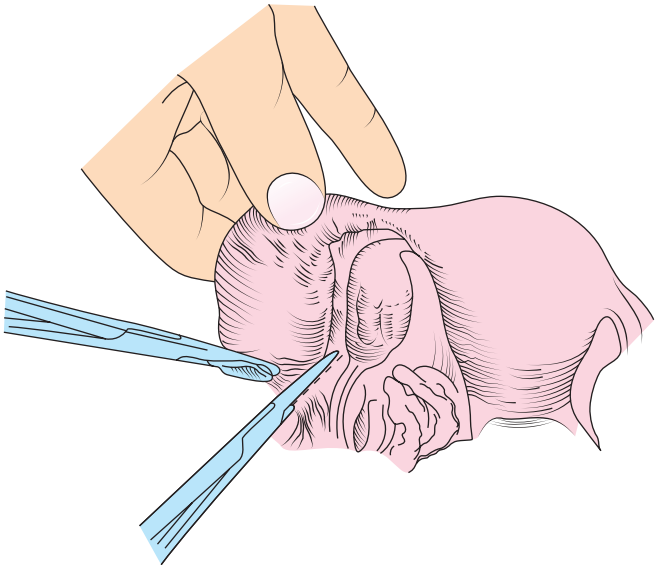


Figure 21.18 Total salpingectomy for a tubal pregnancy.

Conservative tubal surgery is justifiable only if the contralateral tube has already been removed or is diseased, because this type of surgery exposes the woman to a recurrent ectopic pregnancy.

Fifty per cent women undergoing conservative surgery conceive and have uterine pregnancy.

With improved awareness and screening procedures, life-threatening ectopic pregnancy has changed to a benign condition, especially in the case of an asymptomatic woman in stable condition at the time of diagnosis (unruptured ectopic). Conservative medical treatment then applied is safe and cost effective. It also improves the subsequent pregnancy outcome.

The treatment of secondary abdominal pregnancy includes performing a laparotomy and removing the fetus and placenta. If the placenta is adherent to a vascular organ, it may be safer to clamp the cord close to the placenta, leave the latter in situ and close the abdomen without a drainage. Hreschchyshyn et al. (1965) proposed administration of methotrexate to resolve the placental tissue. Ultrasonic monitoring and estimating serum β-hCG level is mandatory in such a situation.

Hysterectomy is the appropriate treatment for interstitial and cornual pregnancy.

Interstitial Pregnancy

Treatment

Hysterectomy is indicated in ruptured interstitial pregnancy. In unruptured pregnancy, conservative management may be possible. Incision and emptying the gestational sac following ligation of the ipsilateral uterine artery, ovarian and round ligament is followed by suturing the muscular layer. The risk of uterine rupture in subsequent pregnancy mandates careful antenatal monitoring and caesarean delivery. Recently, hysteroscopic removal of the sac has been attempted.

When a pregnancy is advanced to more than 8 weeks of gestation, it is advisable to administer 100 µg anti-D gamma globulin to the Rh-negative patient to safeguard against isoimmunization in a subsequent pregnancy. *Early interstitial pregnancy is now managed with local or intramuscular mTX injection and a follow-up until serum β-hCG disappears.*

Prognosis

Ten per cent deaths in ectopic gestation are primarily due to haemorrhage. Following treatment, 50–80% of the cases conceive and of these 30% to 50% have live births and 15% have repeat ectopic pregnancy. The rest remain infertile, due to tubal damage.

Unruptured Ectopic Gestation

Recent advances in immunoassays to detect hCG and high-resolution ultrasound have made radical progress in the diagnosis and management of early unruptured ectopic pregnancy and before significant haemorrhage has occurred. In these cases, there has been a shift from ablative surgery to conservative fertility-preserving therapy. Schenker observed that 15% of ectopic cases suffer recurrent ectopic pregnancies and 60% to 70% have fertility problems. To improve future fertility, and to avoid catastrophic haemorrhage, it is necessary to make a diagnosis before the ectopic sac ruptures. *This is possible with routine ultrasonic scanning in early pregnancy. Early diagnosis is the key to conservative management.*

If a woman in the reproductive age complains of amenorrhoea, mild abdominal pain and abnormal uterine bleeding, she should be suspected of having either genital tuberculosis or an ectopic pregnancy.

Pelvic examination will reveal a normal-sized firm uterus. An adnexal mass may or may not be palpable. Tenderness may be minimal at this stage or may not even be elicited.

The investigations include a pregnancy test (Figure 21.19), serum quantitative β-hCG estimation, ultrasound and laparoscopic inspection of pelvic organs. Pregnancy test is usually positive in the unruptured stage but β-hCG does not rise as in a normal pregnancy. If the pregnancy test is positive but ultrasound reveals an empty uterus with a small adnexal mass, an ectopic pregnancy is suspected. In case of equivocal findings, laparoscopic visualization should be performed and pelvic organs inspected, and therapeutic procedure done as required (Figure 21.20).

Early diagnosis of ectopic pregnancy allows laparoscopic conservative surgery or medical therapy. This not only reduces mortality and morbidity due to haemorrhage but also improves subsequent fertility in some cases.

Prognosis

Conservative medical treatment and minimal invasive surgery yield better fertility rate than radical surgery. However, recurrent ectopic pregnancy still occurs in about 15% at the end of 2 years. Recurrence in the methotrexate group is on account of the damage to the fallopian tubes and adhesion formation.

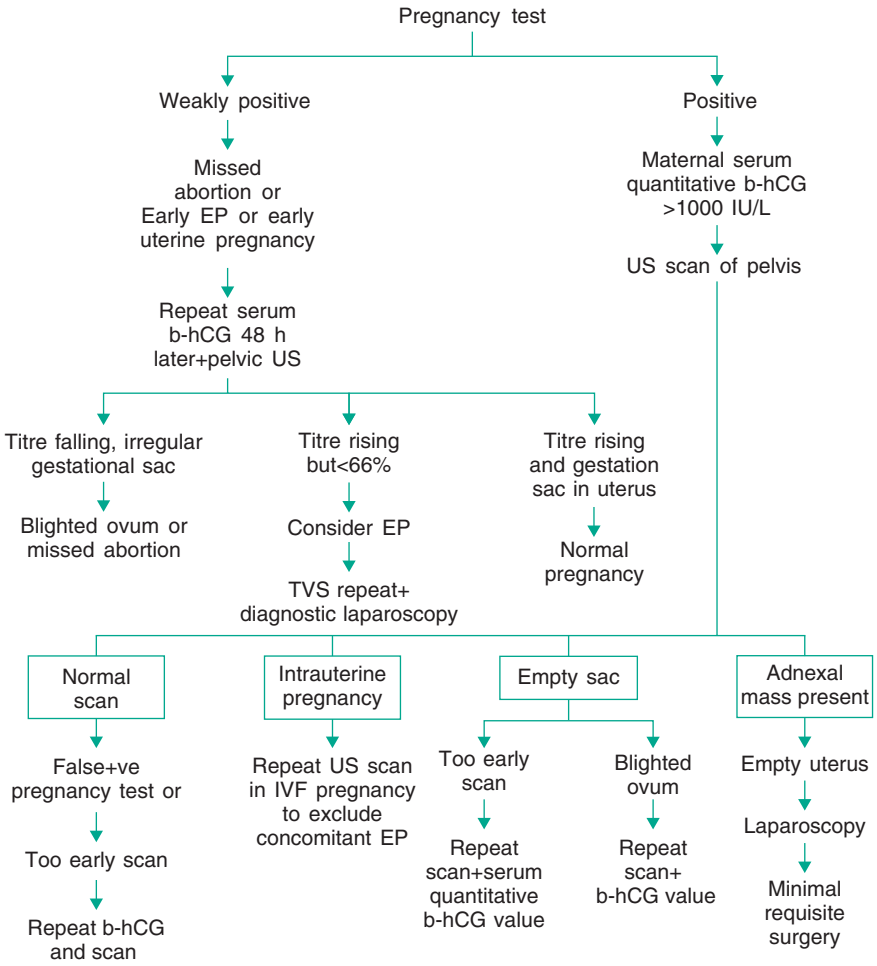
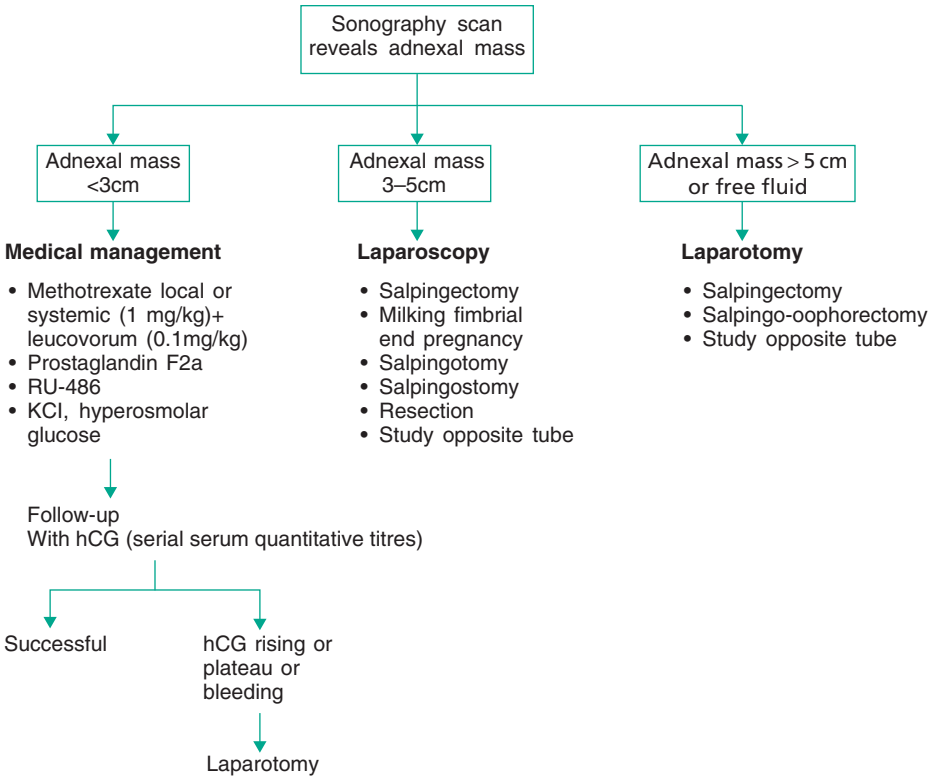


Figure 21.19 Positive pregnancy test: Features suggestive of ectopic pregnancy (EP).



In laparoscopic salpingectomy, the ectopic tube is removed using a tissue removal bag. Before removal, endo-loop is slipped into the mesosalpinx and tightened.

Diathermy knife or laser can be used in salpingotomy and salpingostomy to cut and secure haemostasis.

Figure 21.20 Treatment of ectopic tubal pregnancy (ETP).

The *advantages* of drug management are avoidance of general anaesthesia, a short hospital stay, less cost and improved fertility. The *disadvantages* are puncture of viscera and blood vessels through the transvaginal route, if injected locally, long follow-up and failure which requires surgery with added morbidity in 4–5%.

mTX (1 mg/kg) intramuscularly as prophylaxis against persistent or residual ectopic pregnancy given within 24 h of salpingostomy reduces the period of follow-up with hCG, provided Hb%, liver and renal functions are normal. Persistent ectopic pregnancy (PEP) is defined as a rise in hCG level or decline of less than 15% between two consecutive measurements taken 3 days apart. Seifer et al. (1993) and Vermesh et al. (1988) reported 16% incidence of PEP following laparoscopic salpingostomy as compared to 1% with laparotomy. With 50 mg methotrexate, most ectopics regress in 2–3 weeks.

Expectant Treatment (Figure 21.20)

Expectant treatment comprising follow-up with hCG levels and ultrasound scanning is only possible if the gestational sac is less than 2 cm and hCG level is not high (<2000 mIU/mL) and haemoperitoneum is <50 mL. Most resolve without any surgery or medical treatment. The uncertainty and prolonged follow-up however is not practical in most cases.

Ovarian Pregnancy

Ovarian pregnancy constitute 0.5–1% of all ectopic pregnancies. Treatment is oophorectomy.

Cervical Pregnancy

Cervical pregnancy is extremely rare (0.5–1%), though in Japan, the incidence is 1/1000 pregnancies and it is the second most common variety of ectopic pregnancy (Shinagawa et al.). The woman presents with profuse painless bleeding following a short period of amenorrhoea. Pelvic examination reveals a patulous external os and products of conception in the cervical canal; the internal os is closed and the uterus is firm and normal in size. Ultrasound helps in correct diagnosis; clinically, the diagnosis of inevitable abortion is initially made. Doppler blood flow mapping and MRI improve the diagnostic accuracy.

The risk factors are previous endocervical curettage and Asherman syndrome.

Ultrasound

Ultrasound in cervical pregnancy shows:

- An empty uterus.
- The gestational sac is located below the internal os.
- The cervix is barrel shaped.
- The blood flow in the cervix is increased.
- Absence of sliding sign—the pressure over the cervix causes sliding down of the gestational sac in a miscarriage, whereas the cervical pregnancy remains static, since it is attached to the cervix.

Treatment

Treatment consists of ligating the uterine vessel vaginally, suction evacuation and tamponade by inserting a distended Foley catheter in the cervical canal for 24 h. In case of profuse haemorrhage, hysterectomy may be needed. Hysteroscopic resection of the cervical pregnancy using resectoscope has been described by Ash and Farroll in the US. mTX has also been injected locally, followed if necessary a week later with suction evacuation. Unlike in tubal pregnancy, IM methotrexate inj. 50 mg may have to be repeated weekly until β-hCG level disappears. This entails a prolonged follow-up.

Uterine artery embolization has been attempted to reduce blood loss, prior to evacuation of cervical and caesarean scar pregnancy; this controls the bleeding.

Heterotopic Pregnancy

Heterotopic pregnancy, i.e. combined uterine and ectopic tubal pregnancy, is very rare in spontaneous conception cycles; the incidence is not more than 1:4000 to 1:7000 pregnancies. The incidence is however higher in IVF programmes because of the higher number of embryo transfer, with one embryo migrating to the tube. The incidence is also related to the amount of fluid injected with the embryo. At present, IVF centres present an incidence of 1–3% of heterotopic pregnancy.

The diagnosis is not easy. The serum β-hCG may not be proportionately high. Ultrasound can visualize multiple pregnancy in early pregnancy. *It is therefore mandatory to search for adnexal mass when pregnancy occurs in ART.*

Treatment

Medical treatment with mTX, mifepristone and prostaglandin are contraindicated because of their adverse effects on the normal uterine pregnancy. Glucose and KCl may be used or surgery performed. The treatment is preferably laparoscopic minimal invasive surgery, allowing uterine pregnancy to grow.

In IVF programme, the following prophylactic measures have been suggested:

- Bilateral tubectomy prior to IVF.
- Transfer of not more than two embryos.
- A small amount of fluid medium to be transferred.
- A routine ultrasound scanning in early pregnancy, in case conception follows.

Caesarean Scar Ectopic Pregnancy

Caesarean scar ectopic pregnancy is recently reported in 6% of ectopic pregnancies. The ultrasound shows an empty uterus and cervix and the gestational sac is attached low to the lower segment caesarean scar. Doppler imaging confirms the diagnosis. The woman presents with clinical features of threatened or inevitable abortion.

The gestation sac is embedded in the myometrium and fibrosis of the caesarean scar. MRI is diagnostic.

Ultrasound

Ultrasound shows:

- Gestational sac located over the lower anterior uterine segment.
- Absence of sliding sign.
- Increased blood flow over the lower uterine segment.

Treatment

- Methotrexate injection.
- Surgery—Suction curettage may be risky even under ultrasonic guidance and the risk of caesarean scar rupture remains.
- Hysterectomy is recommended in a multiparous woman. In a young woman desirous of childbearing, resection and suturing of scar can be done but the risk of scar rupture in subsequent pregnancy is considerable. There is an increased risk of repeat scar ectopic pregnancy as well as placenta accreta.

Persistent Ectopic Pregnancy (PEP)

PEP complicates conservative therapy, especially milking of the tube, when a portion of the conception products is left behind. Following laparoscopic salpingostomy, PEP is reported in 16% against 1% who follow laparotomy.

Persistence in the level of serum β-hCG is diagnostic. A single injection of mTX resolves most of PEP.

Recurrent Ectopic Pregnancy

Recurrent ectopic pregnancy is seen in about 15% cases, whatever the method of previous treatment for ectopic pregnancy. This is obvious from the cause (PID) which leads to an ectopic pregnancy in the first instance.

When a woman suffers from a recurrent ectopic pregnancy, it may be prudent to perform salpingectomy and offer IVF and embryo transfer if the cost permits.

Mortality and Morbidity

Ectopic pregnancy is responsible for 11.5% maternal mortality. In general population, 10–15% mortality is mainly due to haemorrhage. Early diagnosis and management can avoid maternal death.

Morbidity includes:

- Infertility
- Recurrent ectopic pregnancy
- Pelvic adhesions and chronic pelvic pain.
- Psychological morbidity and fear of future pregnancy outcome.

Routine early ultrasonic scanning in the first trimester and early diagnosis have reduced morbidity.

Cornual Pregnancy

Cornual pregnancy in a rudimentary horn is treated either by hysterectomy, excision of the horn, hysteroscopically guided suction curettage if the communication with the cervix is patent, or by mTX depending upon the age of the woman and size of the gravid horn.

Key Points

- Of all the ectopics, tubal pregnancy is the most common and its aetiological factors are well defined. Pelvic inflammatory disease and IUCD are the most common causes.
- While an acute ectopic pregnancy is life-threatening and requires an emergency surgery, subacute and chronic ectopic pregnancy require investigations to confirm the diagnosis.
- It is now possible to detect an early unruptured ectopic pregnancy by ultrasound, aided by serum β-hCG level, and at times by laparoscopy.
- Conservative surgery and medical therapy can salvage the fallopian tube for future fertility. However, 15% do develop recurrent ectopic pregnancy.
- Cervical pregnancy, pregnancy in a rudimentary horn, caesarean scar pregnancy and abdominal pregnancy are rare.
- Heterotopic pregnancy is gaining importance with successful assisted reproductive technology and its management requires conservation of uterine pregnancy.
- Caesarean scar ectopic pregnancy has been recently recognized.
- Recurrent pregnancy remains a threat to a woman with one ectopic pregnancy, and she needs good monitoring in subsequent pregnancies.
- Early diagnosis is the key to successful medical and minimal conservative surgery; it reduces mortality.
- Ectopic pregnancy has to be considered when a patient presents with bizarre clinical picture.
- Persistent trophoblastic residual tissue and recurrent ectopic pregnancy requires further improvement in conservative management.
- Ultrasound, MRI enable early diagnosis of ectopic pregnancy.
- With greater awareness in high-risk cases and better screening procedures, life-threatening ectopic pregnancy has changed to a benign condition in asymptomatic women, allowing conservative management and improving subsequent fertility outcome.

Self-Assessment

1. What are the causes of ectopic pregnancy?
2. Discuss the symptoms and signs of chronic ectopic pregnancy. How will you investigate a case?
3. A 24-year-old woman presents with 2 months amenorrhoea. Pregnancy test is positive, but ultrasound shows an empty uterus. How will you manage this case?
4. A young primigravida presents with 2 months amenorrhoea, slight abdominal pain and vaginal bleeding. Discuss the management.
5. A woman presents with 3 months amenorrhoea, with fainting attacks and acute abdominal pain. Discuss the management.

Suggested Reading

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Chapter

22

Gestational Trophoblastic Diseases

CHAPTER OUTLINE

Gestational trophoblastic diseases (GTDs) comprise a variety of biologically interrelated conditions which form a clinical spectrum from a benign partial hydatidiform mole at the one end to the highly malignant choriocarcinoma at the other without any precise line of demarcation. This spectrum extends from a very early pregnancy (H. mole) to years after the pregnancy is over (choriocarcinoma).

Trophoblastic tumours may be categorized into three broad groups (Table 22.1):

1. **Benign hydatidiform mole:** It may be a complete or a partial mole. The tumour sometimes invades the wall of the uterus and the surrounding structures, when it is called an invasive mole.
2. **Persistent trophoblastic disease (PTD)** also known as residual trophoblastic disease (RTD) includes the invasive mole.
3. **Choriocarcinoma:** This is truly a malignant tumour. It could be a nonmetastatic (NMTD) or a metastatic (MTD) trophoblastic disease.

Metastatic tumour may be of low or high risk.

Hydatidiform Mole

Incidence and Aetiology

The incidence of the disease is higher in the eastern countries than in the West. Its geographical distribution is as follows: UK and USA 1:2000 to 1:3000, India and the Middle-East 1:160 to 1:500, China 1:150, Philippines 1:173, Indonesia and Taiwan 1:82 pregnancies. Likewise, the malignant potential of this disease is higher in Southeast Asia, where it is as high as 10–15% compared to 2–4% in the western countries. Some immigrants from Southeast Asia to a developed country lose the potential to develop hydatidiform mole once they settle down in the new environment. This proves that the condition is not racial, but may be related to geographical and environmental influences.

Vitamin A, β-carotene and folic acid deficiency in the diet are also implicated in the occurrence of trophoblastic disease.

Women belonging to blood group A are susceptible to this disease, but the reason is not known. Very young and women over 40 years are prone to it. Repeat molar pregnancy occurs in 2–10% cases. In contrast to a complete mole, maternal age and nutrition do not appear to influence the incidence of a partial mole.

The diagnosis of complete and partial mole is based on morphological, histological and karyotype findings (Table 22.2).

Morbid Anatomy

A complete hydatidiform mole resembles bunches of grape-like vesicles, pearly white in colour and translucent, containing watery fluid (Figures 22.1 and 22.2). The vesicles vary in size from a few millimetres up to 2–3 cm in diameter and are attached to the main stalk by thin pedicles. A few haemorrhagic areas are seen in between the bunches. The fetus, amniotic sac and the placenta are conspicuously absent. The size of the mole depends on the duration of pregnancy and degeneration.

Histologically, the disease is characterized by (i) hydropic degeneration and swelling of the villous stroma, (ii) absence of villous blood vessels and (iii) proliferation of both the trophoblastic epithelia to a varying degree. The vesicle demonstrates irregular proliferation and pleomorphism of

TABLE 22.1 Classification of trophoblastic diseases

1. Molar pregnancy (benign)
   - Partial
   - Complete
2. Persistent or residual mole
   - Invasive
   - Placental site
3. Choriocarcinoma
   - Nonmetastatic
   - Metastatic: Liver, lungs, brain

TABLE 22.2 Features of complete and partial mole

S. no.	Features	Complete Mole	Partial Mole
1.	Fetus	Absent	Present, malformed or IUGR
2.	Fetal vessels	Absent	Present
3.	Hydropic changes	Diffuse and placenta not present	Focal
4.	Trophoblastic hyperplasia	Marked	Mild to moderate
5.	β-hCG level	Very high	Comparatively low
6.	Karyotype	46 XX mostly and paternally derived	69 XXY
7.	Malignant potential	15–20%	Rare

epithelial cells whose nuclei are hyperchromatic and actively mitotic. The villous structure is, however, well preserved and identifiable. Irrespective of trophoblastic cell proliferation, it is the preservation of a villous structure that determines the benign nature of the trophoblastic disease (Figure 22.3).

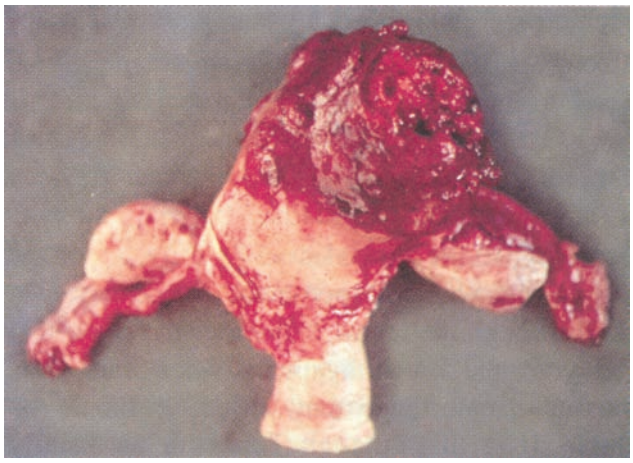

Figure 22.2 Perforation of uterus by hydatidiform mole.

In a very early pregnancy, it is difficult to differentiate between a molar pregnancy and a missed abortion. Histology of products of conception alone can identify molar pregnancy. Karyotype is 46XX.

A partial mole resembles the placenta, but contains a few vesicles on its maternal surface. A fetus is identifiable in this case. One of the twins may be a mole and another a normal fetus. Even an ectopic pregnancy has been reported to contain a molar pregnancy. In a partial mole, some or most of the villi appear normal. The fetus most often shows gross malformation, intrauterine growth retardation and in utero death. Very few live babies are born through a partial mole. The fetal blood vessels are seen on ultrasound scan. Karyotype is 69XXY.

The average gestational age when a partial mole is diagnosed is at a later date than a complete mole, around 24–26 weeks of pregnancy. The undue enlargement seen in a complete mole is rarely observed in a partial mole, and it may be of a normal size or smaller for the gestational period on account of intrauterine fetal growth retardation. It

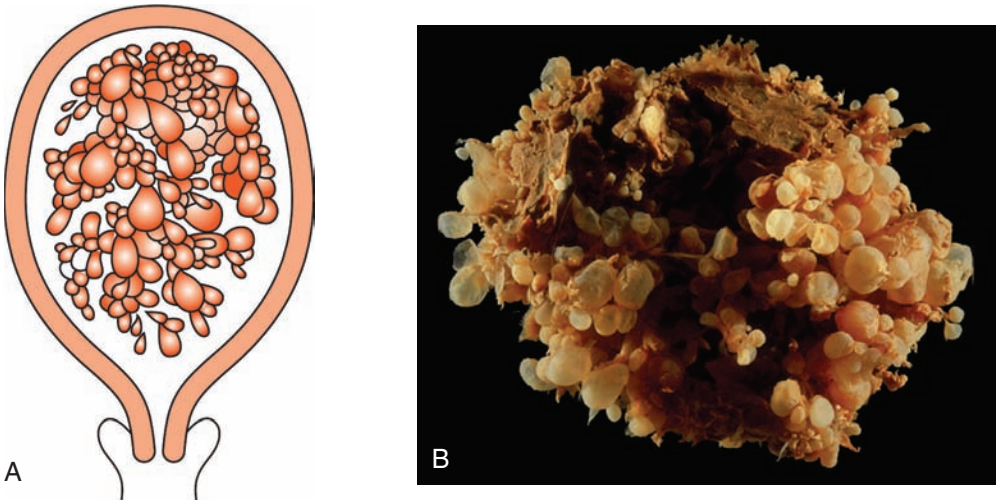

Figure 22.1 **(A)** Hydatidiform mole. (From Figure 31-2. Physiology in Childbearing Elsevier, 2005.) **(B)** Hydatidiform mole (43-year-old). (From Figure 16-22. Nicholas Vardaxis: A Textbook of Pathology. Elsevier, 2010.)

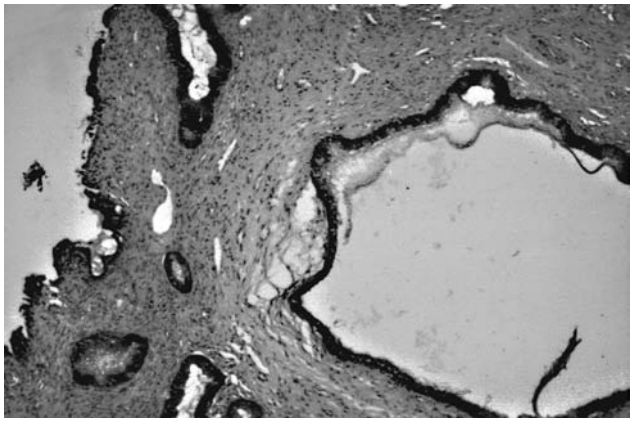

Figure 22.3 Histology of a molar pregnancy.

rarely metastasizes and does not require prophylactic chemotherapy, as the level of human chorionic gonadotropin is comparatively low (<10,000 IU). Despite this, follow-up is necessary, as choriocarcinoma may, in rare cases, follow a partial mole.

The uterine wall is hypertrophied in a hydatidiform mole as in a pregnancy and is lined by a thick decidua. The ovaries contain enlarged granulosa lutein cysts in 60% cases, and the cysts may grow to the maximum size of a fetal head. Rare complications of a torsion of this ovarian cyst and haemorrhage into the cyst necessitating laparotomy have been reported.

Features of complete and partial mole have been discussed in Table 22.2.

Invasive Mole (Persistent or Residual)

Some hydatidiform moles (about 5–10%) are invasive moles that erode the wall of the uterus, burrow into the myometrium and, in some cases, even burst through the uterus into either the peritoneal cavity or the broad ligament when dangerous internal haemorrhage may ensue. It should be emphasized that, though behaving as locally malignant, the invasive mole does not kill by distal metastasis and, therefore, cannot be considered a cancer. The relative proportion of invasive moles to the benign noninvasive type is in the region of 1:12. The invasive mole occupies an intermediate position between a benign hydatidiform mole and a choriocarcinoma.

An invasive mole is very likely to be mistaken for a choriocarcinoma, but there is one distinguishing feature—an invasive mole will show evidence of chorionic villi whereas in a choriocarcinoma, all evidence of villous formation is lost. Trophoblastic tumour following a full-term pregnancy is always choriocarcinoma, whereas it may be either an invasive mole or a choriocarcinoma if it follows an abortion or a molar pregnancy. Trophoblastic tumour diagnosed up to 6 months following an abortion or a mole is often an invasive mole, but tumour diagnosed later than 6 months is usually a choriocarcinoma. Eighty per cent of hydatidiform moles resolve by treatment, 15% persist as persistent or residual mole and 5% develop into choriocarcinoma.

Invasive or persistent mole is diagnosed clinically by persistent vaginal bleeding and pain following evacuation of a hydatidiform mole, but more often by follow-up with ultrasound scan and serial β-human chorionic gonadotropin (β-hCG) levels (persistently raised level). Chemotherapy is usually effective, but hysterectomy may be required to control bleeding if perforation occurs.

Placental Site Trophoblastic Tumour

It constitutes 1% of all trophoblastic diseases. Placental site trophoblastic tumour arises from the placental bed trophoblast and invades the myometrium. It follows a full-term normal delivery in 95%, though in rare cases, one follows a mole (5%). hCG levels are lower than that observed in choriocarcinoma, and rarely exceed 2000–3000 IU/L. Most of these tumours run a benign course, malignancy being rare. This tumour contains mainly cytotrophoblasts with few or no syncytiotrophoblasts. For this reason, β-hCG level is low and serum human placental lactogen (HPL) level high.

Aetiology

The disease usually occurs in young women below the age of 20 or in multiparous women aged 40 and above. The incidence is higher amongst the low socioeconomic group subsisting on a poor rice diet and vitamin deficiency. Dietary deficiency in protein, folic acid and iron, and environmental factors are incriminated in the aetiology. Folic acid is essential for the cellular metabolism of rapidly growing cells, and it is hypothesized that its deficiency in the diet predisposes to abnormal trophoblastic proliferation.

The cytogenic study of a hydatidiform mole displays typical chromosome patterns. A complete mole is composed of 46 XX, and all the chromosomes are of paternal origin. The phenomenon is known as androgenesis, in which the empty ovum is fertilized by a haploid sperm which then duplicates after meiosis to produce 46 XX. The chromosomes in the ovum are either absent or inactivated. Infrequently, when 46 XY chromosome pattern is detected, it is hypothesized that two sperms have fertilized an empty ovum which itself is lacking chromosomes. The partial mole demonstrates triploid karyotype (69 chromosomes XXY).

Classification (Figure 22.4)

Histological features are not reliable guides to future clinical behaviour of the tumour as well as therapeutic decisions. In persistent invasive tumour, the tissue may not be available for histology, as previous surgical management by hysterectomy is now replaced by chemotherapy. WHO has therefore

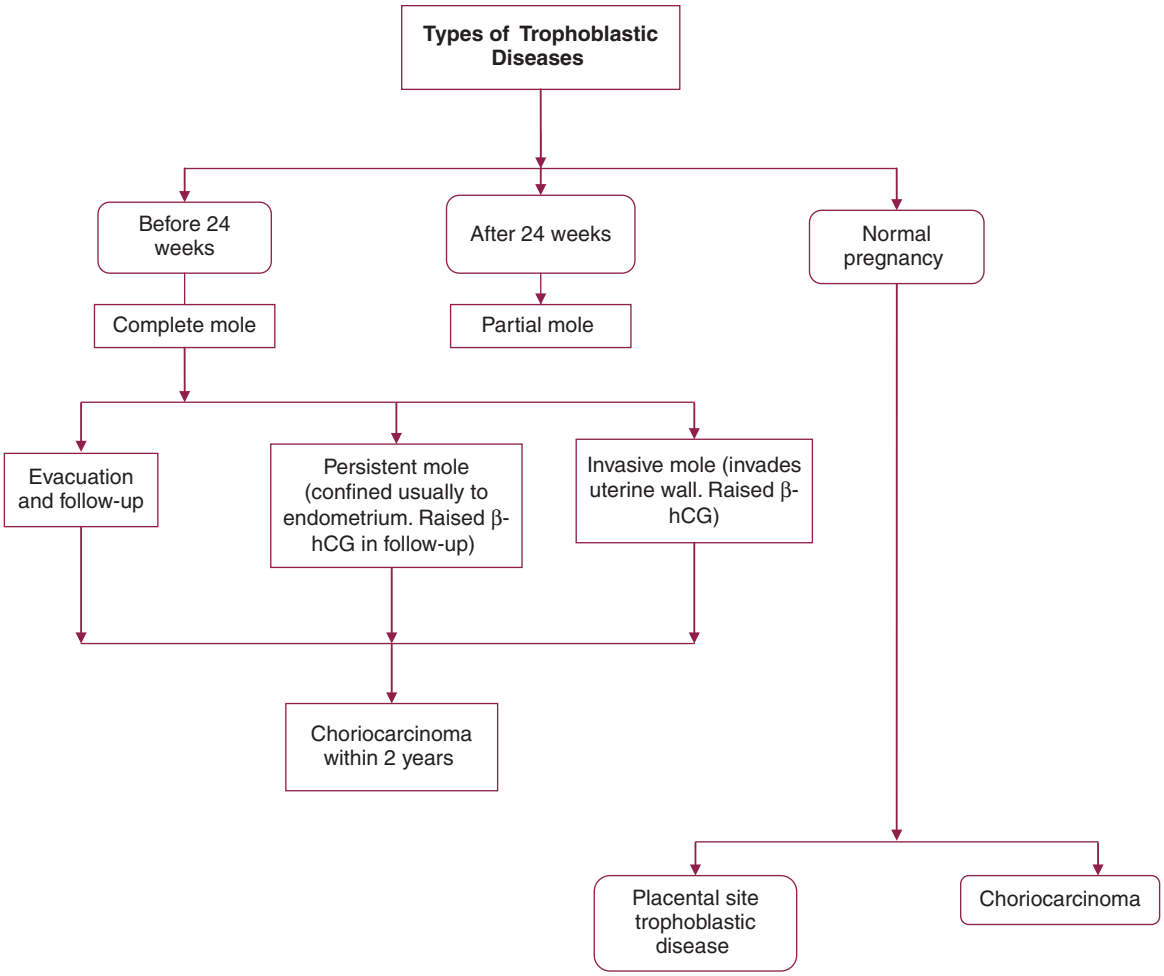

Figure 22.4 Types of trophoblastic diseases.

recommended the clinical classification of gestational trophoblastic neoplasia (GTN) as follows:

I. **Benign GTN**
   A. *Hydatidiform mole*
      - Complete
      - Partial
   B.
      - Placental site trophoblastic disease.
      - Invasive and persistent trophoblastic disease.

II. **Nonmetastatic malignant GTD**. Choriocarcinoma.

III. **Metastatic malignant GTD**
   A. *Good prognosis*
      - Duration of disease from termination of pregnancy to initiation of chemotherapy is less than 4 months.
      - Pretreatment urine hCG level less than 1000 IU/24 h or serum β-hCG 40,000–50,000 mIU/mL.
      - Metastatic disease limited to the pelvis or lungs.
      - No significant prior chemotherapy.
   B. *Poor prognosis*
      - Duration of the disease from termination of pregnancy to initiation of chemotherapy more than 6 months.
      - High serum hCG level—50,000 mIU/mL or more.
      - Brain, liver metastasis.
      - Metastatic choriocarcinoma following a term pregnancy.

Symptoms and Signs

A woman with a complete mole presents with amenorrhoea of less than 24 weeks gestation, usually 3–4 months. A history of vaginal bleeding and abdominal pain is present in 70% cases. The vaginal bleeding may be slight and intermittent or prolonged. Profuse haemorrhage occurs usually with the onset of spontaneous abortion, but brisk haemorrhage without abortion is not unknown. The passage of vesicles is rarely observed except when the woman is aborting. Prolonged or heavy bleeding leads to anaemia. The abdominal pain is due to abortion, concealed haemorrhage, sudden distension of the uterus or, in rare cases, perforation. Hyperemesis is reported in about 30% cases. Pregnancy-induced hypertension (PIH) before 24 weeks is noted in one-third of the cases. Thyrotoxicosis resulting in supraventricular tachycardia, dyspnoea and raised T_3 and T_4 levels is seen in 3% cases and is due to the fact that subunits of both thyroid-stimulating hormone (TSH) and hCG share a similar structure. One per cent women are asymptomatic and the condition is suspected by palpating an undue enlarged uterus. Lately, with routine ultrasound screening performed

in early pregnancy, more asymptomatic cases are being diagnosed and treated before bleeding starts.

The symptomatic patient may look pale and ill, and she may be febrile. The uterus is larger than would be expected from the calculated date of gestation in 70% cases. In 15% of the cases, the uterine height corresponds to the period of gestation, and in the remaining 15%, it is smaller than expected due to missed abortion or a partial mole. The uterus feels doughy in consistency due to the absence of amniotic fluid. External and internal ballottement cannot be elicited and the fetal heart cannot be heard on the Doppler. Ovarian granulosa lutein cysts more than 6 cm and bilateral are present, but may be difficult to feel because the enlarged uterus occupies most of the pelvis. The cervix feels soft as in a normal pregnancy. Serum hCG level is raised. Hydatidiform mole usually leads to abortion between the third and sixth month of pregnancy. A partial mole often presents with oligohydramnios, intrauterine growth retarded fetus or malformed fetus as detected on ultrasound scanning, during the second trimester. Few vesicles may be revealed in the placenta on ultrasound scanning.

Differential Diagnosis

Mistaken Date

Undue enlargement of the uterus may be due to the patient stating the wrong date of her last menstrual period (LMP). The fetal parts are palpable. Ultrasound scan reveals a fetal shadow and ultrasonic fetal maturity corresponds to uterine size.

Multiple Pregnancy

Ultrasound scanning can identify multiple fetuses.

Acute Hydramnios

Acute pain, sudden enlargement of the uterus and slight haemorrhage may simulate a hydatidiform mole with concealed haemorrhage. Ultrasound scan will reveal hydramnios, a fetal shadow and perhaps multiple pregnancy with which acute hydramnios is commonly associated.

Fibroid in Pregnancy

A uterine fibroid may contribute to undue enlargement of the uterus in pregnancy. The presence of fetal parts and fetal heart establishes the diagnosis of a normal pregnancy. Ultrasound scan will show a fibroid in addition to a fetus.

Threatened Abortion

Ultrasonic study distinguishes a normal pregnancy from a molar one.

Complications

- Hyperemesis gravidarum, pregnancy-induced hypertension.
- Haemorrhage, anaemia.
- Infection.
- Thyroid storm—3%.
- Embolization with acute pulmonary insufficiency and coagulation failure—2%.
- Uterine perforation—spontaneous but more commonly during suction evacuation.
- Delayed—recurrent mole and choriocarcinoma.

Investigations

Doppler

The auscultation of fetal heart by Doppler can rule out a complete molar pregnancy. The absence of a fetal heart goes in favour of a molar pregnancy.

Ultrasound

Ultrasound examination shows the 'snow storm' appearance in the uterus and the absence of fetal shadow in a complete molar pregnancy (Figure 22.5). In a partial mole, the fetus (malformed or intrauterine growth retardation (IUGR)) and placenta are visualized. The placenta shows scattered cysts.

Ultrasound scanning is also required during the follow-up to see if the corpus luteum cysts diminish in size and disappear, and to detect persistent mole, invasive mole and choriocarcinoma. The metastasis in the liver can be picked up on ultrasound scan. Doppler ultrasound shows abnormal vascularization.

Serum β-hCG

Serum β-hCG level is very high in a complete mole, but is not very much raised in a partial mole. A serum level of more than 40,000 m IU/mL as determined by radio-immunoassay is reported. For diagnostic purpose, ultrasound scan alone is confirmative, quick and a safe procedure. Hormonal assays are now mainly confined to postmolar and postchemotherapy follow-up. Human placental lactogen is low in a complete

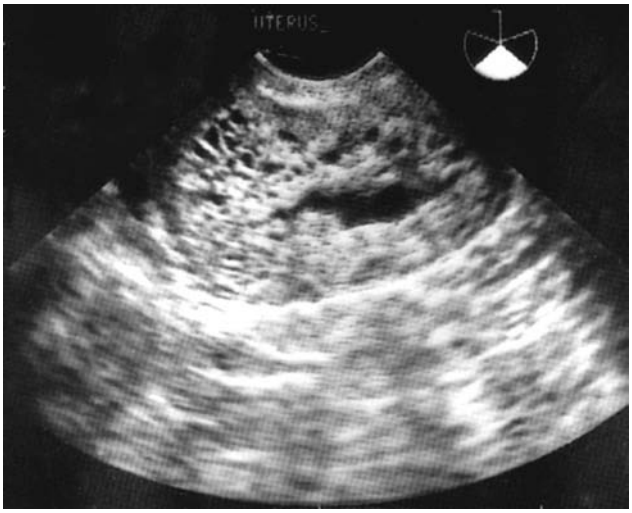

Figure 22.5 Ultrasound scan shows 'snow storm' appearance of a mole.

mole, but raised in a partial mole, pulmonary metastasis and placental site tumour.

X-ray chest is done to rule out lung metastasis. CT scan is required in liver and brain metastasis and sometimes to detect pulmonary metastasis if X-ray chest is normal.

In the early stage of pregnancy, combined ultrasound scanning and serum β-hCG estimation improves the diagnostic accuracy.

Treatment

When a woman comes in the process of abortion, vesicles can be identified amongst the products passed. Blood should be transfused if required and intravenous oxytocin drip of 10–20 units or more in 500 mL of 5% glucose should be set up. Surgical evacuation with a suction evacuation machine (as in medical termination of pregnancy (MTP)), using No. 10–12 Karman cannula reduces the blood loss in the spontaneous abortion of a mole. A digital exploration or a gentle curettage will remove any remnants of chorionic tissue. The evacuation can be assisted by administration of intravenous Methergine 0.2 mg. Digital exploration of the uterine cavity is preferred to curettage because of the risk of perforation with the latter. The operation can be very messy and bloody, but by fast evacuation with an oxytocin drip running and IV Methergine, the evacuation can be completed with minimal blood loss.

With the availability of ultrasonic facilities and routine screening in early pregnancy, a molar pregnancy is now diagnosed before a spontaneous abortion begins. In such cases, termination of hydatidiform mole should be done under a planned and controlled situation using a suction evacuation machine. An incomplete evacuation of chorionic tissue will cause the hCG levels to remain elevated and interfere with the proper follow-up of the patient. Besides, it will cause continuous bleeding. *Today, many prefer to evacuate a mole under ultrasonic guidance to ensure complete evacuation and to avoid uterine perforation*. This also avoids a repeat check curettage 7–10 days later, as was practised earlier. 100 μg Rh anti-D globin should be given to an unimmunized Rh-negative woman to prevent isoimmunization in subsequent pregnancies.

Induction of abortion of a molar pregnancy with prostaglandin is effective in dilating the cervix prior to evacuation. Prostaglandin vaginal pessary (400–600 μg) for ripening the cervix or cervical gel (Cerviprime containing 0.5 mg dinoprostone, PGE_2) may be warranted in a few cases in whom cervical dilation with a metal dilator may be undesirable or difficult due to a tight cervical os. A sudden unexplained collapse during evacuation is attributed to massive disseminated intravascular coagulation (DIC) or to massive pulmonary embolization by the molar tissue leading to acute pulmonary hypertension and cardiac failure. Hysterectomy is generally not required except for its prophylactic value in preventing choriocarcinoma in patients over 40 years of age and who have completed their family. It must be remembered, however, that hysterectomy, while preventing development of local choriocarcinoma, does not obviate the need for careful follow-up because a metastatic tumour can still develop in the distal organ. Under modern treatment, the mortality due to a molar pregnancy is very low. Death is invariably associated with profuse haemorrhage. Hyperthyroidism and congestive cardiac failure are seen in 3% cases. The patient may recover from a molar pregnancy but develop metastasis in the lungs, brain and liver at a later date. Whether it is a benign or a malignant metastatic lesion, haemorrhage in this lesion can cause sudden death. Postabortal anaemia and sepsis are not uncommon. Choriocarcinoma develops in 2–10% cases. As the dread of malignancy stays once a woman suffers a molar pregnancy, she requires careful follow-up.

Medical termination with prostaglandin alone is not desirable because of the risk of pulmonary embolization, and surgical evacuation is needed following cervical dilatation. In a partial mole, however, medical termination is the method of choice.

Follow-Up (Figure 22.6)

There is no marker to decide which molar pregnancy will proceed to choriocarcinoma. Histological features alone do not provide a reliable clue to the future behaviour of the mole and its progression to carcinoma. Therefore, the therapeutic decision in the follow-up should not be influenced by histology. However, fibrinoid deposition in the tissue does suggest host's favourable immunological response. *Follow-up for 2 years remains the only option for detecting early choriocarcinoma*.

All patients should be kept under careful observation for 2 years because choriocarcinoma, if it occurs, develops within this period of evacuation of the mole.

A method of detecting persistent moles and development of choriocarcinoma is by estimating the hCG level in the serum and urine. Normally, the test becomes negative in about 6–8 weeks' time following evacuation of a molar

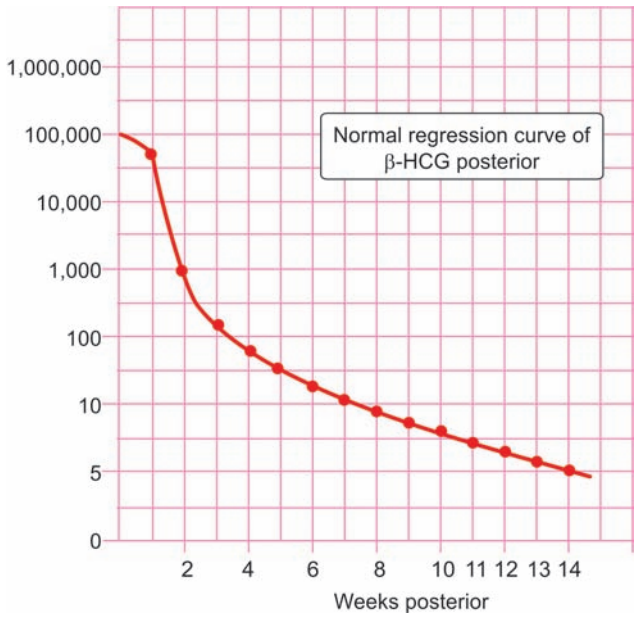

Figure 22.6 Postmolar follow-up showing normal β-HCG curve.

pregnancy. The patient is called at weekly intervals for this test. Once the test becomes negative, the patient is followed up monthly and 3 monthly in the first year and 6 monthly in the second year. Radioimmunoassay techniques have revolutionized the follow-up of patients with molar pregnancy (Figure 22.7).

Pelvic examination is done to rule out any vulval and vaginal metastasis, and the uterine size is recorded. The size of any ovarian cyst and reduction in its size are noted. A radiograph of the chest is taken to detect lung metastasis. Persistent uterine bleeding calls for a curettage, and the curettings are sent for histopathological examination to detect choriocarcinoma. Pelvic ultrasound scan can detect residual or locally invasive tumour as well as an ovarian cyst.

Pregnancy should be avoided preferably by barrier methods for at least 1 year (preferably 2 years) as a fresh pregnancy would interfere with the hCG levels. Intrauterine device and progestogen-only pills cause irregular bleeding and are best avoided. Combined oral pills can be offered once the β-hCG level becomes undetected. Oral combined pills lower the luteinizing hormone (LH) level and thereby, the hCG level and can cause misinterpretation of results.

Pregnancy should also be avoided for 1 year after stoppage of chemotherapy because of the teratogenic effect of drugs.

Because histopathology of molar tissue does not give a clue as to which molar tissue will progress to choriocarcinoma, prophylactic chemotherapy is indicated in the following conditions in 20% cases:

- High-risk case, i.e. a very young woman and a multiparous woman above age 40 who refuses hysterectomy.
- A patient with an initial very high level of hCG or a patient in whom the level of hCG persists or does not regress satisfactorily or there is a rise in the hormone. Patients with urine hCG level more than 30,000 IU/24 h after 6 weeks or more than 24,000 IU/24 h at 10 weeks after evacuation and patients with serum hCG level more than 20,000 mIU/mL if the serum β-hCG

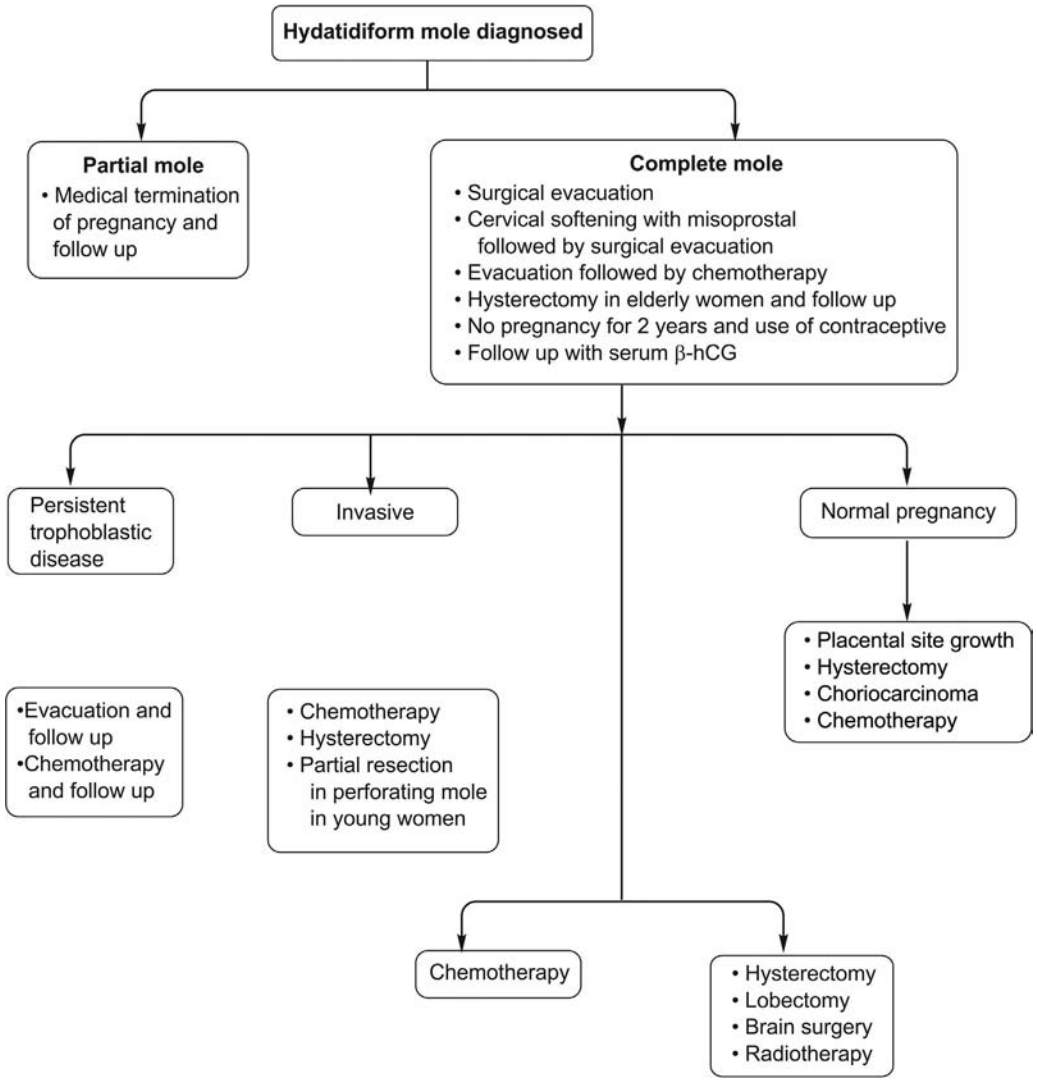

Figure 22.7 Management of hydatiform mole.

level plateaus over 4 weeks or rises over 3 consecutive weeks also need prophylactic therapy.
- If a woman cannot come for the follow-up, prophylactic chemotherapy is better than no follow-up.

A partial mole has a very low malignant potential and does not require chemotherapy. All the same, the woman needs a follow-up in the same manner as a complete mole. The hCG level should return to normal within 6–8 weeks.

Prophylactic chemotherapy comprises administration of methotrexate 5 mg five times a day for 5 days, and three courses repeated at the interval of 7–10 days, provided haemoglobin percentage and white cell count remain above critical levels (see later), so also liver functions.

Routine prophylactic chemotherapy in all patients is not advocated because 80% molar pregnancies resolve following evacuation. If chemotherapy is prescribed for all molar pregnancies, 80% would be exposed to unnecessary morbidity and toxicity of the drugs.

Some recommend chemotherapy during surgical evacuation of a molar pregnancy and it is discussed below:

- Actinomycin-D IV 12 μg/kg daily for 3 days prior to evacuation and 2 days after.
- Methotrexate 15 mg orally daily for 3 days prior to planned evacuation and 2 days after.
- During evacuation, 50 mg methotrexate IV drip lasting for 3–4 h.

This is expected to reduce the risk of pulmonary emboli and dissemination.

Prophylactic hysterectomy is not recommended today, because (i) it is not often required, (ii) it does not avoid follow-up and (iii) follow-up with β-hCG levels is effective and decides the course of subsequent management.

Because of 2–10% incidence of recurrent mole, it is necessary to perform an ultrasound scan in subsequent early pregnancies.

Persistent Trophoblastic Disease

Persistent trophoblastic disease (PTD) is diagnosed when at least three follow-up shows persistence of β-hCG level or a rise. Up to 20% of women with a hydatidiform mole show persistence of the tumour in the uterus following surgical evacuation. An enlarged cyst and continued vaginal bleeding, with static or raised level of hCG in serum and urine during the follow-up, are suggestive of the persistence of chorionic tissue. The International Federation of Gynecology and Obstetrics (FIGO) 2002 criteria of persistent trophoblastic disease are:

- The plateau of hCG levels of four readings over three weeks.
- A rise in hCG level of 10% or more over 3 weeks.
- Detection of hCG at 6 months
- Persistence of irregular vaginal bleeding.

Careful follow-up and hCG monitoring are the keys to identifying PTD:

- Pelvic ultrasound scan will detect PTD in the genital tract.
- Chest X-ray, brain CT scan and liver scan will pick up metastatic growth. Negative chest X-ray mandates CT scan of the lungs. CT scan can detect an occult lesion in the lung.

Once diagnosed, treatment is chemotherapy:

- Methotrexate 0.5 mg/kg IV or IM daily for 5 days—repeated every 2 weeks until hCG is undetectable. Or
- Methotrexate 1.0–1.5 mg/kg IM or IV on day 1, 3, 5 with folinic acid 0.1–0.15 mg/kg IM on alternate days. The course is repeated every 2 weeks as long as required.
- Actinomycin-D 10–12 μg/kg IM daily for 5 days every 2 weeks if methotrexate is contraindicated (liver damage) or fails, and in high-risk cases.
- Etoposide (VP-16)—200 mg/m^2 daily for 5 days orally every 2 weeks in high-risk group or IV over 3 h.

Haemoglobin percentage should not fall below 8 g%, white cell count not less than 3000/cu mm and platelet not less than 100,000/cu mm. Blood transfusion will be required if the blood profile falls below the critical levels. Raised serum glutamic pyruvate transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT) and alkaline phosphatase levels indicate liver dysfunction.

Perforating Mole

Perforating mole was treated by hysterectomy in the past. In a young woman wishing to conserve fertility, partial resection of the uterus and newer techniques to control bleeding by occlusive instruments and ligation of uterine/internal iliac ligation has now been successfully done. However, the risk of uterine rupture should be watched during subsequent pregnancy, and elective caesarean section is often advocated. Postsurgical chemotherapy may also be required for a residual tumour.

Recurrent Molar Pregnancy

Recurrent molar pregnancy is reported in 2–10% cases, with as many as nine consecutive molar pregnancies as reported by WHO in 1973. Following two molar pregnancies, the risk of recurrent mole rises to 28%. A woman with one molar pregnancy faces 20 times the risk of suffering another molar pregnancy and choriocarcinoma. *It is therefore mandatory to perform an ultrasonic screening in this woman in subsequent early pregnancy.*

In a rare case with recurrent molar pregnancies, pregnancy with her husband should be avoided. Instead, in vitro fertilization with a donor sperm is the option to avoid not only subsequent molar pregnancy, but also the risk of choriocarcinoma.

Coexisting Molar Pregnancy

Coexisting molar pregnancy with another uterine pregnancy is reported in 1:10,000 to 100,000 pregnancies. In the majority, the fetus shows gross structural and genetic anomalies, and 30% terminate in intrauterine fetal death. Termination of pregnancy is therefore recommended. In rare cases, if the fetus proves normal by ultrasonic scanning and genetic study, pregnancy may be allowed to continue, but hCG monitoring has no value during pregnancy. Vaginal delivery is possible. Placental site tumour does not respond to chemotherapy and requires hysterectomy.

Key Points

- Trophoblastic diseases comprise a spectrum of clinical features varying from partial hydatidiform mole to malignant choriocarcinoma.
- Hydatidiform mole is more prevalent in Southeast Asia, diagnosed clinically and confirmed by ultrasound scan and raised β-hCG levels.
- Treatment of hydatidiform mole is surgical evacuation. Two-year monitoring is required to detect persistent moles and development of choriocarcinoma. Pregnancy during this period should be avoided. Prophylactic chemotherapy is beneficial in selective cases.
- Ultrasound scan and serum hCG level are key markers in follow-up.
- Histology is not able to indicate the potential of molar pregnancy for malignancy. Therefore, follow-up with serum β-hCG is necessary for 2 years. Thereafter, the risk of malignancy is negligible.
- Persistent trophoblastic disease and choriocarcinoma are treated effectively by chemotherapy. Surgery is rarely required.
- Choriocarcinoma and metastatic growths developing several years after pregnancy render the diagnosis difficult.
- Placental site trophoblastic disease with low hCG but raised HPL level fails to respond to chemotherapy and requires hysterectomy.
- Following molar pregnancy, the woman needs counselling regarding recurrent mole and choriocarcinoma, and should be persuaded for follow-up.
- Prognosis has greatly improved because of specific hCG marker and effective chemotherapy.

Self-Assessment

1. A 25-year-old woman presents with 3 months amenorrhoea, abdominal pain and vaginal bleeding. The uterus is 20 weeks size. How will you investigate the case?
2. How will you manage a case of hydatidiform mole at 16 weeks pregnancy?
3. What are the complications of hydatidiform mole? How will you prevent them?

Suggested Reading

1. Dalya Alhamdan, Tommaso Bignardi, George Condous. Recognising gestational trophoblastic disease. In: Best Practice and Research: Clinical Obstetrics and Gynaecology, Vol 20(5): 565–573, Elsevier, 2006.
2. Ma HK, Wong LC, Ngan JYS. In: The modern management of trophoblastic disease. Bonnar J. In: Recent Advances in Obstetrics and Gynaecology. Vol 16: 1–23, Churchill Livingstone, London, 1990.

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Chapter 23

Disorders of Menstruation—Amenorrhoea

CHAPTER OUTLINE

Menstrual Cycle Irregularities

Menstruation is the end point in a series of events which begin in the cerebral cortex and hypothalamus and ends at the uterus in the hypothalamic–pituitary–ovarian–uterine axis. Any break in this axis creates menstrual problems.

Excessive or inappropriately timed menstruation and amenorrhoea are the most common complaints for which women seek advice from medical healthcare providers.

As described in Chapter 3, normal menstruation requires integration of the hypothalamic–pituitary–ovarian axis with a functional uterus, a patent lower genital outflow tract and a normal genetic karyotype of 46XX.

Abnormal menstruation can be a harbinger of a sinister pelvic pathology or denote a relatively minor problem; therefore, a thorough investigation into the problem is called for in every patient presenting with this complaint.

In normal healthy women, menarche occurs between the ages 10 and 16 years, mean age of menarche being around 12.5 years. Cyclic menstruation persists throughout the reproductive era of life with an average rhythm of 28 ± 7 days, inclusive of 4–6 days of bleeding (except pregnancy lactation). It is not uncommon for minor variations to occur from time to time.

Definitions of Menstrual Cycle Irregularities

These terms are descriptive of the nature of cyclic disturbance, but not related to specific causes.

- **Amenorrhoea** indicates the absence of menstruation. It is a symptom and not a disease entity.
- **Oligomenorrhoea** denotes infrequent, irregularly timed episodes of bleeding usually occurring at intervals of more than 35 days.
- **Polymenorrhoea** denotes frequent episodes of menstruation, usually occurring at intervals of 21 days or less.
- **Menorrhagia** denotes regularly timed episodes of bleeding that are excessive in amount (>80 mL) and/or duration of flow (>5 days).
- **Metrorrhagia** refers to irregularly timed episodes of bleeding superimposed on normal cyclical bleeding.
- **Menometrorrhagia** means excessive, prolonged bleeding that occurs at irregularly timed and frequent intervals.
- **Hypomenorrhoea** refers to regularly timed but scanty episodes of bleeding.
- **Intermenstrual** bleeding refers to bleeding (usually not excessive) that occurs between otherwise normal menstrual cycles.
- **Precocious** menstruation denotes the occurrence of menstruation before the age of 10 years.
- **Postcoital bleeding** denotes vaginal bleeding after sexual intercourse.

Amenorrhoea

Initiation of menstruation is an important milestone in the reproductive lives of women.

Amenorrhoea denotes absence of menstruation. It may be *physiological* or *pathological*.

Its onset may be *primary* or *secondary*.

Physiological amenorrhoea naturally prevails prior to the onset of puberty, during pregnancy and lactation and after menopause.

Pathological amenorrhoea is the result of genetic factors, systemic diseases, endocrinopathies, disturbance of the hypothalamic–pituitary–ovarian–uterine axis, gynatresia, nutritional factors, drug usage, psychological factors and other rarer causes.

Primary amenorrhoea refers to the failure of onset of menstruation beyond the age of 16 years regardless of development of secondary sexual characters.

Secondary amenorrhoea refers to the failure of occurrence of menstruation for 6 months or longer in women who have previously menstruated.

Primary Amenorrhoea

Primary amenorrhoea at the age of 14 years behoves the clinician to undertake investigations for the cause of failure of occurrence, and institute timely therapy. However, in the presence of well-developed secondary sexual characteristics, investigations may be delayed until the age of 16 years with the hope that spontaneous menstruation will eventually ensue in due course of time. *This occurs in delayed puberty*.

In the vast majority of cases, a detailed evaluation of growth charts, height and weight records, chronology of development of secondary sexual characteristics, body habitus, history of cyclic abdominal pain, administration of drugs, history of illnesses like tuberculosis, thyroid disease, juvenile diabetes, mumps and any previous surgery may be important in revealing the possible aetiological cause. Physical examination should include documentation of the height–weight ratio, stature, Tanner evaluation for maturation status of the secondary sexual characteristics and observation of any genetic or endocrine stigmata. The presence of the uterus and vagina must be established by ultrasound scanning of the pelvis. In all patients presenting with primary amenorrhoea, estimation of the levels of serum follicle-stimulating hormone (FSH), oestradiol and prolactin are important. Serum FSH levels help to differentiate between central nervous system (CNS) aetiologies and gonadal failure. A baseline radiological evaluation of bone age and a simple skull film or CT to exclude pituitary macroadenoma should precede further investigations. Genetic karyotyping is strongly indicated in all subjects revealing serum FSH levels elevated above 40 mIU/mL. A few selective investigations like thyroid function profile, renal function tests and androgen estimation must be done when indicated.

Classification

The spectrum of diagnosis presenting clinically as primary amenorrhoea can be conveniently classified according to the status of her serum FSH levels into hypergonadotropic (FSH > 40 mIU/mL), eugonadotropic or hypogonadotropic (Table 23.1).

TABLE 23.1 Classification of primary amenorrhoea

Secondary sexual characteristics normal
- Imperforate hymen
- Transverse vaginal septum
- Absent vagina and functioning uterus
- Absent vagina and nonfunctioning uterus (Mayer–Rokitansky–Küster–Hauser syndrome. [MRKH])
- XY female—androgen insensitivity
- Resistant ovary syndrome
- Constitutional delay

Early PCOD (polycystic ovarian disease)

Secondary sexual characteristics absent
- Normal stature
  - Hypogonadotrophic hypogonadism
    - Congenital
      - Isolated gonadotrophin-releasing hormone deficiency
      - Olfacto–genital syndrome
    - Acquired
      - Weight loss/anorexia
      - Excessive exercise
      - Hyperprolactinaemia
  - Hypergonadotrophic hypogonadism
    - Gonadal agenesis
    - Chromosomal aberrations resulting from XX-agenesis
  - Gonadal dysgenesis
    - Turner's mosaic
    - Other X deletions or mosaics
    - XY enzymatic failure
    - Ovarian failure
    - Galactosaemia
- Short stature
  - Hypogonadotrophic hypogonadism
    - Congenital
      - Hydrocephalus
    - Acquired
      - Trauma
      - Empty sella syndrome
- Tumours
  - Hypergonadotrophic hypogonadism
    - Turner's syndrome
    - Other X deletions or mosaics

Heterosexual development
- Congenital adrenal hyperplasia
- Androgen-secreting tumour
- 5α-reductase deficiency
- Partial androgen receptor deficiency
- True hermaphrodite
- Absent Müllerian inhibitor

Hypergonadotropic Primary Amenorrhoea.
- Gonadal dysgenesis: 45 OX (Turner's syndrome) mosaics, abnormal X.
- 46 XX pure gonadal dysgenesis.
- 46 XY gonadal dysgenesis—Swyer syndrome, testicular feminizing syndrome.
- Gonadotropin-resistant ovary syndrome—Savage syndrome.

Eugonadotropic primary amenorrhoea.

A. Absence of Müllerian development:
- Androgen insensitivity syndrome (testicular feminization).
- Müllerian agenesis—absence of uterus/vagina. Rokitansky–Küster–Hauser syndrome.

B. Normal Müllerian development:
   - Female or true intersex.
   - Polycystic ovary syndrome.
   - Adrenal or thyroid diseases.

C. Cryptomenorrhoea—imperforate hymen, vaginal septum, cervical atresia.
D. Tubercular endometritis.
E. Constitutional delay – Nutrition.

Hypogonadotropic Primary Amenorrhoea.

A. Hypothalamic causes:
   - Delayed menarche and puberty.
   - Hypothalamic hypogonadism (Kallmann syndrome). GnRh deficiency syndrome.
   - Psychogenic causes, weight loss, stress, anorexia nervosa and malnutrition.

B. Pituitary causes:
   - Pituitarism causes short stature, obesity, genital dystrophy, mental retardation, polydactyly and retinitis pigmentosa.
   - Neoplasms—prolactinomas, craniopharyngiomas, adenomas and empty sella turcica.
   - Hypopituitary states—Simmond's disease, Chiari–Frommel syndrome, Forbes–Albright syndrome and pineal gland tumour.

C. Severe systemic diseases like tuberculosis, syphilis.
D. Other endocrinal disorders—thyroid or adrenal gland.

Aetiology

According to the location of cause of amenorrhoea:

- Delayed puberty.
- Pregnancy before menarche is extremely rare, but not impossible.
- Cerebral cortex—stress, emotional disturbances, infection, trauma, tumour.
- Hypothalamus—Kallmann syndrome, vigorous exercise, weight loss.
- Pituitary gland—empty sella turcica, Fröhlich syndrome, Laurence–Moon–Biedl syndrome, Cushing's disease, pineal tumour, prolactinaemia, galactosaemia.
- Ovary—Turner's syndrome, primary ovarian failure (Savage syndrome), polycystic ovarian disease (PCOD), 17-hydroxylase deficiency.
- Genital tract—absent uterus, (Mayer–Rokitansky–Kuster–Hauser syndrome. Testicular feminizing syndrome), refractory endometrium, obstruction in the lower genital tract, genital tuberculosis.
- Chromosomal—intersex, Turner's syndrome, testicular feminizing syndrome, Swyer syndrome.
- Other endocrine glands—Juvenile diabetes, thyroid, adrenal glands.
- Drugs—tranquillizers, antihypertensives, antidepressants, metoclopramide, oestrogen.
- Nutrition—overweight, weight loss, tuberculosis, malnutrition.

Anorexia Nervosa. Anorexia nervosa is a psychological somatic self-imposed eating disorder mainly affecting adolescents and young women more than men. It is the failure to maintain body weight for age and height. For menstruation to occur, minimal fat should constitute 22% of body weight. Loss of weight >15% causes amenorrhoea. Leptin in the fat initiates gonadotropin-releasing hormone (GnRH) secretion. When weight reduction falls below required body fat, GnRH and gonadotropin secretions fail. Clinically, fasting, excessive exercise with or without purging and self-induced vomiting cause atrophy or non-development of breasts and amenorrhoea (Figure 23.1).

Hypoestrinism thus induced causes:

- Mortality through cardiac failure, arrhythmia (15%).
- Amenorrhoea, infertility, decreased libido.
- Osteoporosis.
- Hypercortisolism, decreased muscle mass, low IGF-1, hypothyroidism, anaemia granulocytopenia, neutropenia.
- Psychiatric problems.

MANAGEMENT.

- Psychological
- Psychotherapy
- Nutritional
- GnRH to initiate H-P-O axis.
- Hormonal therapy: To initiate or complete H-P-A axis.

Seventy per cent improve with treatment.

Kallmann Disease. This disease occurs in 1:50,000 girls. Low or absent GnRH is due to either autosomal dominant or X-linked autosomal recessive gene. The condition is characterized by anosmia and maldevelopment of neurons in the arcuate nucleus.

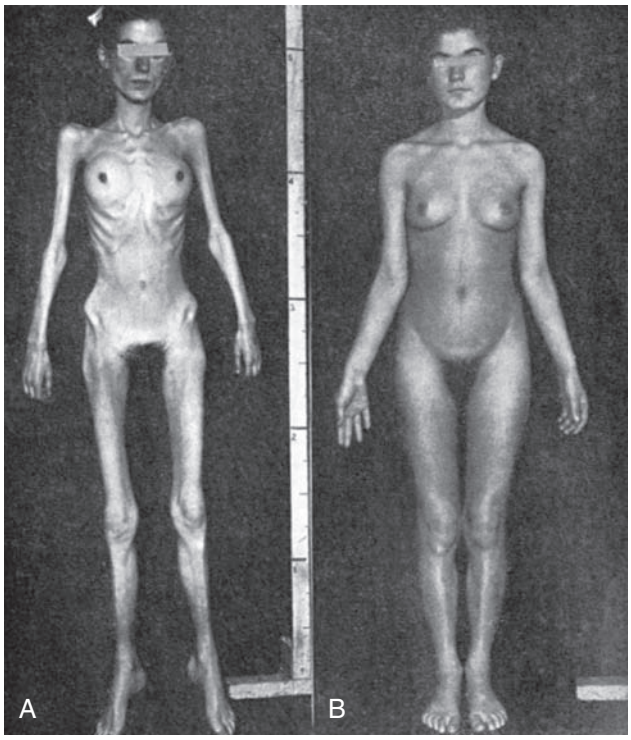

Figure 23.1 **(A)** Anorexia nervosa. **(B)** The same patient after 6 weeks treatment.

MANAGEMENT.

- GnRH and pituitary hormones to induce menstruation, ovulation.
- Oestrogen and progestogen cyclically to induce menstruation.

Clinical Approach

The clinician is required to make an assessment of the cause of primary amenorrhoea on the basis of history, clinical examination and tests that are most likely to provide the answers to the underlying cause. Such information will provide the basis to offer a reasonable prognosis and initiate rational treatment. Table 23.2 offers clinical guidelines for management of primary amenorrhoea.

Some believe in clinical classification based on presence/absence of secondary sex characters, stature and heterosexual development.

Important features to be noted are:

1. History of diabetes, TB, mumps
2. Family history of PCOD, delayed puberty, testicular feminizing syndrome.
3. Height, weight, breast development–certain stigmas.
4. Thyroid enlargement.
5. Abdominal mass
6. Ultrasound.

Management

Hypergonadotropic Primary Amenorrhoea. *Hypergonadotropic primary amenorrhoea patients have gonadal failure.* Various forms of gonadal dysgenesis account for these cases. These women have streak ovaries with absence of ovarian follicles, there is no oestrogen production and they have elevated levels of FSH (>40 mIU/mL) and low oestradiol levels (<25 pg/mL). The sexual development is prepubertal with no endometrial proliferation; *hence, the progesterone challenge test is negative*. Chromosome studies reveal 45 XO chromosomes (Turner's syndrome).

Some patients with mosaicism or minor structural abnormalities of the X chromosome may have a few functional follicles capable of inducing menstruation, stray ovulation and pregnancy. *Chromosome study is relevant*.

Gonadectomy is indicated in patients with testicular feminizing syndrome, as these male gonads are prone to malignancy. Intersex is discussed in Chapter 10.

Women with streak ovaries are infertile, but they can bear children with oocyte donation. All women in this group must be treated with cyclic oestrogen and progestogen to promote feminization and secondary sexual characteristics and prevent osteoporosis. Women with resistant ovarian syndrome have normal ovaries on histology, they show presence of primordial follicles, but there is probably a deficiency of receptors for FSH. They are not amenable to treatment.

Savage syndrome is due to receptor defect to gonadotropic hormones, and resembles autoimmune disease and resistant ovary syndrome. The height is normal, ovaries contain follicles, but FSH is raised.

Eugonadotropic Primary Amenorrhoea. The FSH levels are within normal range, the women have normal breast development, but due to abnormal Müllerian development, the uterus may be rudimentary or absent because of androgen insensitivity (also called testicular feminization), or due to Müllerian agenesis.

TABLE 23.2 Clinical approach to primary amenorrhoea

Clinical Features	Presumptions	Distinguishing Tests
Breasts absent **Uterus present**	Lack of breasts indicates lack of oestrogen production from gonads (causes—HPO failure, lack of ovarian follicles, lack of two active X chromosomes, Turner's syndrome) Presence of uterus indicates that the Y chromosome is absent	**FSH level** identifies cause of oestrogen lack. High FSH (ovarian failure), Low FSH indicates hypothalamic-pituitary failure. GnRH distinguishes hypothalamus (LH ↑) from pituitary cause (no LH response)
Breasts present **Uterus absent**	Presence of breasts indicates presence of gonadal oestrogen. Absent uterus indicates Müllerian agenesis, or presence of Y-chromosome or testicular feminizing syndrome.	S. Testosterone levels high in androgen insensitivity (Y chromosome), but normal in 46 XX with Müllerian agenesis. Karyotyping confirms genetic sex. Gonadectomy advised s.o.s., Müllerian
Breasts absent **Uterus absent**	Absent breast suggests lack of oestrogen. Because of gonadal agenesis, absence of gonads, gonadal enzyme defects. Absent uterus indicates presence of Y-chromosome with testes that suppresses Müllerian development. Presence of normal female external genitals indicates absence of testes, hence no testosterone present when external genitals were developing	Karyotyping - 46 XY, high FSH and testosterone – normal female range suggests gonadal agenesis/absence. Gonadal biopsy to detect enzyme deficiency.
Breasts present **Uterus present**	Presence of breasts indicate oestrogen present. Uterus present indicates Y chromosome is absent	Investigations include: progesterone challenge test, S. prolactin and thyroid profile, tests to exclude genital TB. Urine test for presence of β-hCG and USG are essential to rule out pregnancy.

In women with testicular feminization syndrome, the phenotype is female with a karyotype of 46 XY. The gonads are testes, they are often present in the inguinal canal, the gonads produce testosterone and Müllerian inhibiting factor, but because of androgen insensitivity at target organs (due to deficient androgen receptors or lack of enzymes to convert testosterone to the more active dihydrotestosterone), these patients present with lack of axillary hair and pubic hair, absent uterus and upper vagina. They have a blind pouch of the lower vagina. Breast development appears normal because of peripheral conversion of androgen to oestrogen. These gonads are prone to malignancy; therefore, as soon as full sexual development is achieved by the age of 18–20 years, a prophylactic gonadectomy should be advised, followed by oestrogen therapy to maintain feminization. A vaginoplasty may be contemplated at an appropriate time in the future.

On the other hand, women with simple Müllerian agenesis and a karyotype of 46 XX present with normal secondary sexual characters and functional ovaries (Rokitansky syndrome). They reveal a normal hormone profile. This syndrome is associated with renal and skeletal abnormality in 30% of the cases. These women do ovulate, and appropriate management requires creation of a functional vagina for coital purposes. If they plan to have children, it may be through surrogacy.

In women with cryptomenorrhoea presenting as primary amenorrhoea, the common cause is an intact hymen or vaginal septum. A history of cyclic abdominal colicky pain, retention of urine, presence of a palpable abdominal lump and the visualization of a tense bluish bulging membrane on separation of the labia enables the diagnosis. Ultrasound scan of the pelvis confirms it. A simple cruciate incision of the hymen permits free drainage of the collected menstrual blood and leads to normal reproductive function.

Septate vagina or atresia vagina requires excision and vaginoplasty (see Ch. 9).

The vaginal septum is recognized from the imperforate hymen by a pinkish concave covering in contrast to the bluish convex bulge in the latter. The vaginal septum, i.e. atresia, requires more extensive dissection and vaginoplasty. The atresia in the upper vagina and cervix often restenosis after surgery and eventually requires hysterectomy.

- Polycystic disease is described in the chapter on ovarian tumours.
- 17-hydroxylase deficiency causes deficient cortisol secretion and raised levels of adrenocorticotropic hormone. This causes hypertension, hypernatraemia, hypokalaemia and amenorrhoea.
- Endometrial nonresponsiveness and amenorrhoea is due to absent hormonal receptors. Hormonal profile remains normal.
- Tubercular endometritis requires anti-TB treatment.

Hypogonadotropic Primary Amenorrhoea. These women have FSH level less than 40 mIU/mL. Hypogonadotropinaemia leading to hypogonadism is usually the result of hypothalamic dysfunction, pituitary failure or systemic illnesses. Administration of GnRH helps to differentiate hypothalamic dysfunction from pituitary failure. In the latter, GnRH stimulation will not raise LH level.

Empty sella turcica is characterized by herniation of subarachnoid membrane into the pituitary sella turcica and may exist with pineal gland tumour as prolactin adenoma. Absence of pituitary gland causes absence or low level of FSH and LH. Gonadotropin hormone therapy is required.

Other Hormonal Dysfunctions. Both hypothyroidism (cretinism) and hyperthyroidism can cause amenorrhoea. Congenital adrenal hyperplasia and tumour are also responsible for primary amenorrhoea, so also juvenile diabetes.

Premature ovarian failure seen in 1% of the cases is due to poor germ cell migration from the yolk sac during fetal development or due to accelerated rate of depletion (apoptosis) of unknown reason. In this condition, FSH level is more than 40 mIU/mL, and E_2 level is below 20 pg/mL. Karyotyping is required. The woman presents menopausal symptoms. She needs hormone replacement therapy (HRT).

Nutrition. Excessive weight, anorexia nervosa and malnutrition with loss of weight are also responsible for amenorrhoea in young girls.

The most common cause of hypothalamic dysfunction is related to psychogenic effects, anorexia nervosa, weight loss and inappropriate secretion of neurotransmitters leading to lack of GnRH synthesis (Kallmann syndrome). Women with Kallmann syndrome manifest isolated deficiency of GnRH associated with olfactory dysfunction and anosmia.

Pituitary failure generally follows hypopituitarism, neoplasms or empty sella turcica. Skull radiography or preferably MRI, estimation of prolactin levels and ophthalmic evaluation of the fields of vision help to arrive at a diagnosis. Fröhlich syndrome consists of short stature, lethargy, obesity, genital dystrophy and amenorrhoea. In Laurence–Moon–Biedl syndrome, polydactyly, retinitis pigmentosa and mental deficiency are the additional features.

In all such women, cyclic administration of oestrogen and progestogen to maintain femininity and prevent osteoporosis is essential. In case the woman desires to conceive, induction of ovulation with gonadotropins is warranted. In women with neoplasms, appropriate neurological consultation followed by treatment with bromocriptine for prolactinomas or surgery should be planned.

Secondary Amenorrhoea

Secondary amenorrhoea is defined as amenorrhoea of 6 months or more in a woman with previous normal menstrual patterns in the absence of pregnancy and lactation (2–3% women).

However, in clinical practice, patients seek advice earlier and it is prudent to begin with simpler investigations and reassurance and await the outcome.

Aetiology (*Figure 23.2*)

Many causes are similar to those of primary amenorrhoea. However, the emphasis is somewhat different. Dysfunction of the hypothalamic–pituitary–ovarian–uterine axis accounts for the majority of cases of pathological secondary amenorrhoea.

The causes can be classified as follows:

- **Physiological**
  1. Pregnancy
  2. Lactation
- **Pathological**
  1. Genital tract
     - Acquired obstruction (gynatresia) of cervical canal causing severe stenosis or atresia follows electrocauterization, chemical burns, cervical amputation in Fothergill repair operation, conization for cervical dysplasia or cervical intraepithelial neoplasia (CIN) and genital tuberculosis.
     - Vaginal atresia due to scarring following a traumatic delivery.
     - Asherman syndrome following excessive curettage, uterine infection or endometrial tuberculosis, transcervical resection of endometrium for abnormal uterine bleeding (see Chapter 25) and uterine packing in postpartum haemorrhage.
     - Vesicovaginal fistula—cause unknown.
  2. Ovarian causes
     - Surgical extirpation.
     - Radiotherapy.
     - Autoimmune disease (thyroid, diabetes).
     - Induction of multiple ovulation in infertility—leading to premature menopause.
     - Polycystic ovarian disease (PCOD).
     - Resistant ovarian syndrome—due to absent FSH receptors.
     - Infections—mumps, tuberculosis, and in rare cases, pyogenic infections.
     - Masculinizing ovarian tumours.
     - Premature menopause – premature ovarian failure.
  3. Nutritional causes
     - Anorexia nervosa, bulimia (Figure 23.1).

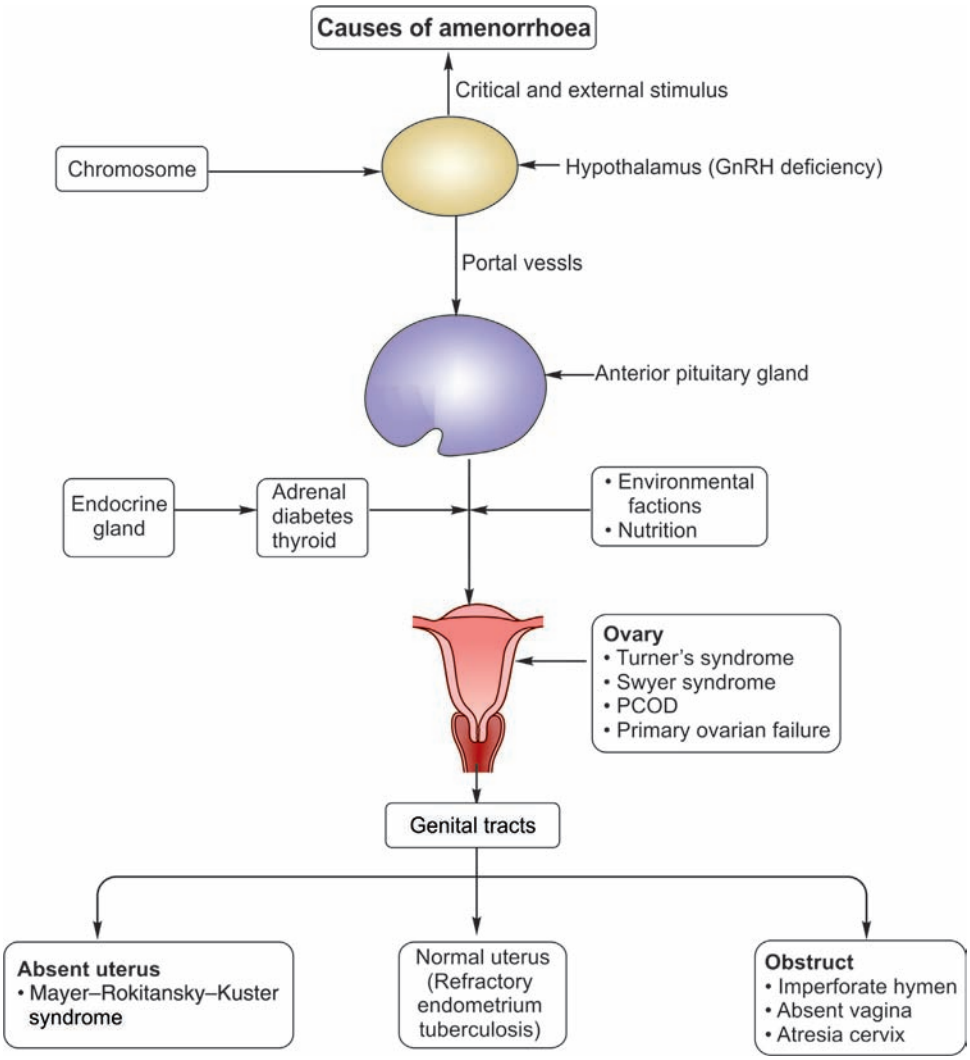

Figure 23.2 Causes of amenorrhoea.

- Extreme obesity.
- Excessive weight loss in athletes and ballet dancers.

4. Pituitary causes (Figures 23.3–23.8)
   - Insufficiency as in Simmond's disease, Sheehan's syndrome.
   - Hyperprolactinaemia.
   - Tumours like prolactinomas and chromophobe adenomas, and Cushing's disease.
   - Empty sella syndrome.
   - Drugs—tranquillizers, oral contraceptive (OC) pills, metoclopramide, dopamine blockers, antihypertensives, antidepressants, cimetidine and phenothiazine.
5. Hypothalamus
   - GnRH deficiency.
   - Vigorous exercise—stress, obesity.
   - Pseudocyesis.
   - Brain tumours.
   - Anorexia nervosa.
6. Suprarenal causes
   - Addison disease.
   - Adrenogenital syndrome.
   - Suprarenal tumour.
7. Thyroid
   - Hypothyroidism, chest wall lesions.
   - Graves' disease.
8. Other causes
   - Diabetes.

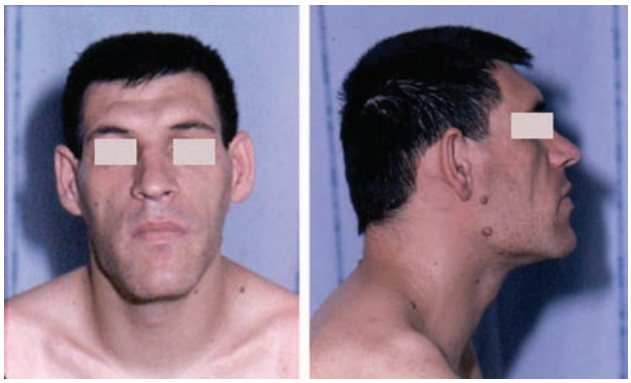

Figure 23.3 Acromegaly. Note the broad enlargement of the nose and coarse facies. (Source: Wikimedia commons.)

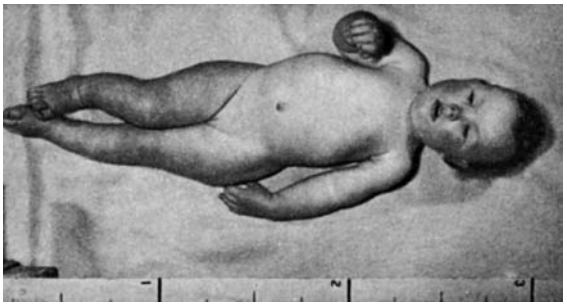

Figure 23.4 Gigantism. Child aged 1 year, measuring over 3 ft in height.

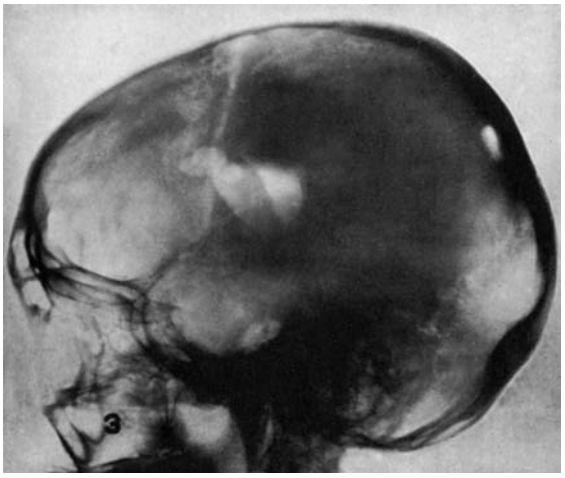

Figure 23.5 X-ray of pituitary fossa showing extreme bone expansion due to pituitary tumour.

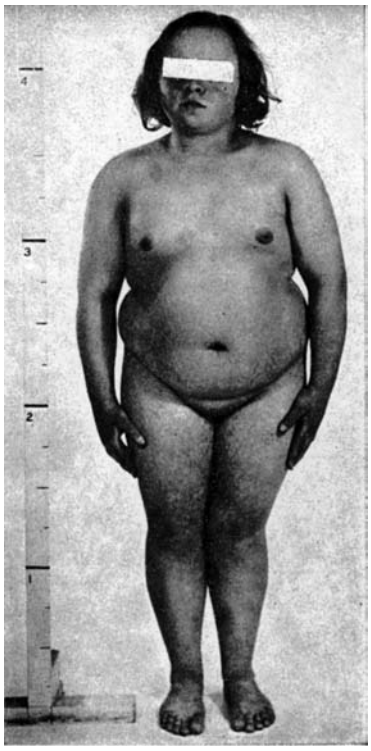

Figure 23.6 Fröhlich's syndrome.

- Tuberculosis—liver disease.
- Renal disease—due to reduced excretion of LH and prolactin.
- Severe anaemia, malnutrition.
- Idiopathic, genetic.

Resistant Ovarian Syndrome. In resistant ovarian syndrome and autoimmune disease, ovaries fail to respond to gonadotropin hormones and cause amenorrhoea. The ovaries show plasma cells and lymphocyte infiltration. Biopsy, however, is not necessary for the diagnosis. FSH level is high. It may be prudent to study antithyroid, rheumatoid factors and antinuclear antibodies to establish autoimmune

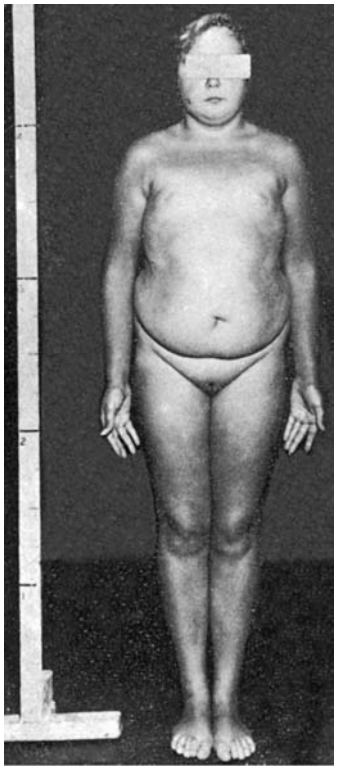

Figure 23.7 Pituitary infantilism, patient aged 17. Note obesity, aplasia of breasts, absence of pubic hair and short stature.

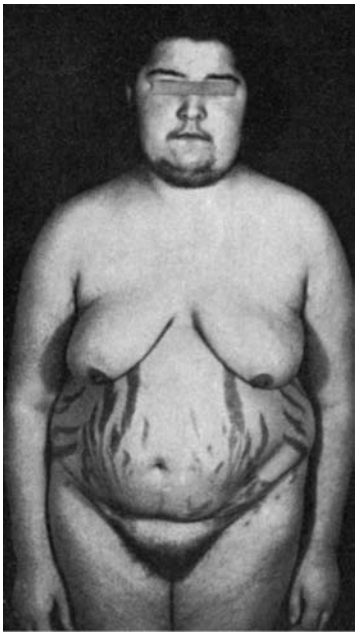

Figure 23.8 Cushing's syndrome. Note hirsutism of face, obesity and striae.

disease. Pregnancy with donor egg in in vitro fertilization (IVF) is possible.

Simmond's Disease. Simmond's disease related to pregnancy and Sheehan's syndrome following severe postpartum haemorrhage cause pituitary necrosis by thrombosis of its vessels, and panhypopituitarism. The woman fails to lactate following delivery, remains lethargic and shows signs of hypothyroidism and cortisol deficiency. She requires appropriate hormonal support. A young woman may require ovulation induction drugs to achieve conception.

In the management of secondary amenorrhoea, the clinician must attempt to answer the following five questions sequentially to arrive at a diagnosis quickly and economically.

- Is the patient pregnant?
- Is her serum prolactin level elevated?
- Is there clinical evidence of oestrogen deficiency?
- Does she have a positive response to the progesterone challenge test?
- Is it premature menopause?
- What are the levels of her serum FSH and LH?

The importance of each of the above questions is analysed in detail below. Detailed history is important.

Investigations (Figure 23.9)

Pregnancy. This is the most common cause of secondary amenorrhoea. Hence, its exclusion must precede all further investigations. Clinical examination, urine pregnancy test and sonographic scan of the pelvis should help to establish the diagnosis beyond doubt.

Elevated Levels of Serum Prolactin. Prolactin secreted by the anterior pituitary gland is normally under the inhibitory effect of hypothalamus by the prolactin-inhibitory factor dopamine. It is stimulated by oestrogen and suckling. It is also present in the decidua and amniotic fluid. Prolactin levels fluctuate episodically; therefore, several measurements may be necessary to confirm hyperprolactinaemia. Hyperprolactinaemia is defined as persistent high level of prolactin in a nonpregnant and nonlactating woman.

CAUSES. Apart from the physiological condition of pregnancy and lactation, it occurs in the following cases:

- During sleep, stress, nipple stimulation and chest wall injury such as herpes zoster.
- Empty sella turcica.
- Hypothalamic tumour, pituitary tumour and head injury (acromegaly, Cushing's disease, Addison disease).
- Twenty per cent cases of PCOD and in some cases of endometriosis.
- Hypothyroidism because of the stimulating effect of raised thyroid-stimulating hormone (TSH).
- Liver and chronic renal disease because of altered metabolism and delay in excretion.
- Drugs like neuroleptics, narcotics, antidepressants, phenothiazine, antihypertensives, calcium channel blockers, OCs, oestrogen (in high doses), cocaine, amphetamine, cimetidine, haloperidol, metoclopramide. Serotonin and opiates reduce the level of dopamine and cause hyperprolactinaemia.

The woman presents with oligomenorrhoea culminating in amenorrhoea due to suppression of FSH and LH. Fifty

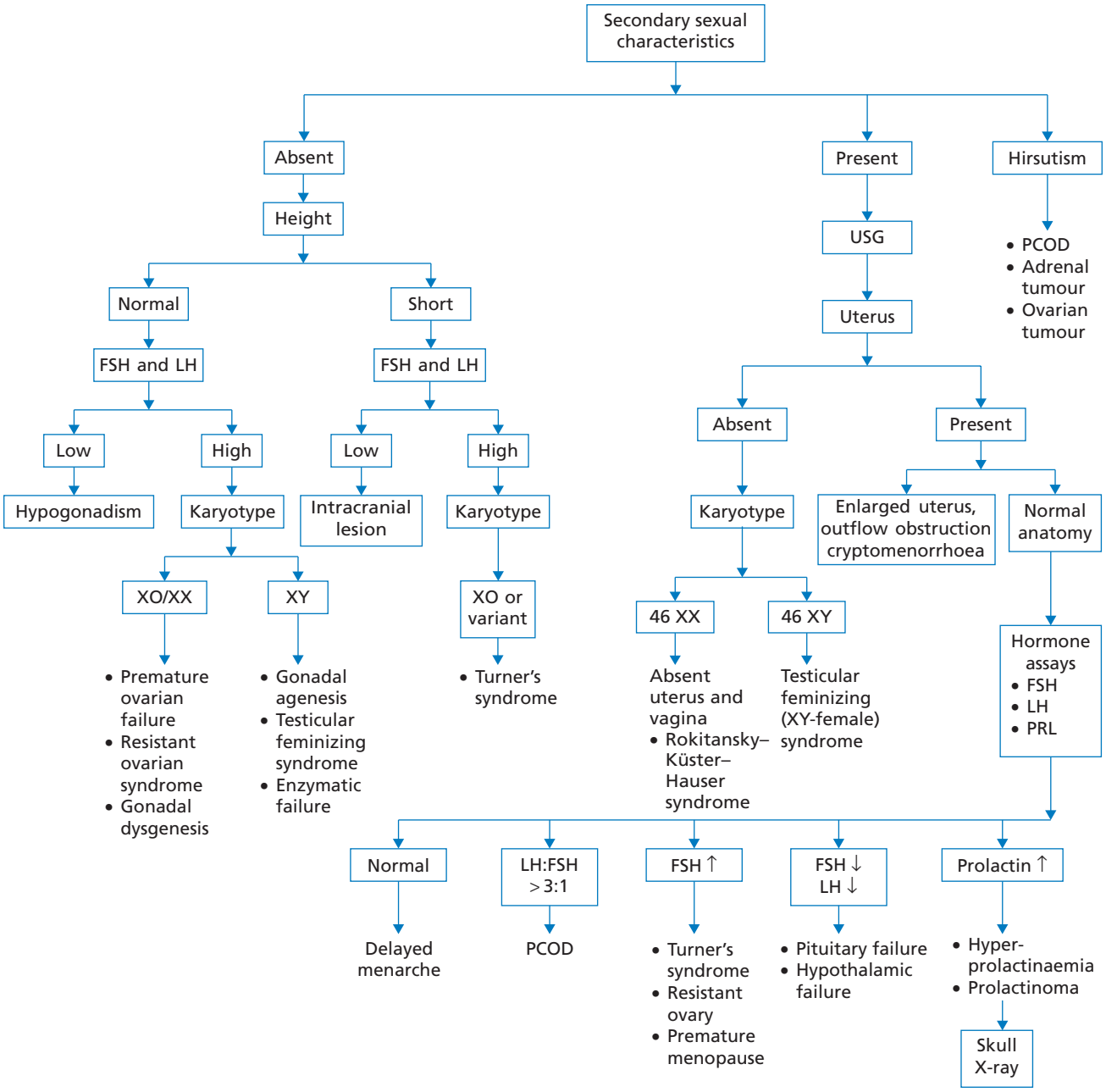

Figure 23.9 Investigations in amenorrhoea.

per cent of the cases develop galactorrhoea. Infertility and abortion through corpus luteal phase defect are other features. Headache and visual disturbances occur when the tumour presses upon the optic nerve. In males, it causes loss of libido, impotency and infertility. The normal level of prolactin is 25 ng/mL. Levels up to 100 ng/mL suggests hyperprolactinaemia and more than 100 ng/mL occurs in the presence of a tumour. CT, MRI and visual check-up are necessary in the diagnosis and follow-up. Thyroid functions need to be checked.

TREATMENT.

- Treat the cause.
- Drug-induced hyperprolactinaemia requires stoppage of drug or alternative therapy.
- Bromocriptine and long-acting derivatives are effective in most cases. Menstrual cycles are restored in 3 months time. Ninety per cent ovulate and 70–80% conceive.
- Quinagolide 25–150 mg daily in divided doses with a maintenance dose of 75 mg daily.
- The drugs are discussed in detail in the chapter on hormonal therapy.
- Macroadenoma (more than 10 mm) and microadenoma not responding to drugs require transsphenoidal adenectomy or radiotherapy 4500 cGY for 25 days. However, 30% recurrence rate is reported within 6 years, and prolonged follow-up is necessary.

Evidence of Oestrogen Deficiency. Hot flushes, loss of breast mass, dyspareunia and dryness of vagina are

suggestive of lack of oestrogen and premature menopause. It requires oestrogen replacement therapy.

Positive Progesterone Challenge Test. This test depends on the presence of oestrogen-primed endometrium in the uterine cavity. The test is considered positive if the patient responds to the administration of oral tablet medroxyprogesterone (Provera/Modus/Deviry) 10 mg daily for 5 days or injection progesterone in oil 100 mg intramuscularly or primolut-N 5 mg three times a day for 3 days. Withdrawal bleeding occurs within 2–7 days. A positive test indicates amenorrhoea secondary to anovulation. The common underlying causes are hypothalamic dysfunction and polycystic ovary syndrome.

Negative test requires giving oestradiol 0.02 mg or conjugated oestrogen 1.25 mg for 25 days and progestogen from 16th to 25th day. Negative test suggests endometrial unresponsiveness in the presence of normal FSH.

Pituitary. In Simmond's disease due to panhypopituitarism, the woman is lethargic, blood sugar and thyroid functions are low. When postpartum haemorrhage causes vascular thrombosis of the pituitary vessels, panhypopituitarism is known as Sheehan's syndrome. CT and MRI detect a tumour. FSH and LH are required.

Hypothalamic dysfunction is the most frequent cause of secondary amenorrhoea. Although in the majority of cases no specific cause can be found, a careful history may reveal a precipitating factor. *Stress and drugs* may contribute to amenorrhoea. Stress situations are often poorly recognized by the patient (examinations, change of jobs, economic problems, breaking up of relationships, etc.). Prolonged use of phenothiazines and tricyclic antidepressant drugs affect dopaminergic systems in the CNS and are associated with raised levels of prolactin hormone. *Post-pill amenorrhoea* (1%) following the use of OC pills is also the result of hypothalamic dysfunction. The diagnosis is made only if spontaneous menses do not resume after 6 months of stopping the pill. In such women, changeover to an OC pill with a higher oestrogen content (ethinyloestradiol 0.05 mg daily for 21 days cyclically, for a few cycles) helps to restore normal cycles. *Weight change and amenorrhoea* are not uncommonly seen in clinical practice. Young adolescent girls and working women are often the subjects of this disorder. A weight loss exceeding 15% of the ideal weight may predispose the woman to menstrual disturbances. Investigations at this stage may reveal normal FSH and LH values and the patient will respond positive to a progesterone challenge test. However, as the weight loss further increases (anorexia nervosa) to 25% or more, low levels of hormones namely gonadotropins and oestrogens are observed, and these are often accompanied by thyroid dysfunction. Proper counselling and advice to regain weight often suffices. However, there is a subgroup of patients who resist advice and may need psychiatric treatment. Excessive weight gain may also be accompanied by menstrual irregularities. Obesity is often a manifestation of a stress situation leading to a compulsive eating disorder. Successful weight reduction often restores regular menstruation. *Polycystic ovary syndrome* is associated with abnormal gonadotropin secretion revealing an increased ratio of LH: FSH exceeding 3:1, which differentiates patients of PCOD from patients with hypothalamic dysfunction. In patients with PCOD, ovarian steroidogenesis is abnormal, leading to an increased production of androstenedione and testosterone, which in turn predisposes the patient to hirsutism, acne and menstrual irregularity. The diagnosis is established on the basis of clinical suspicion, an increased LH: FSH ratio and sonography revealing enlarged ovaries with multiple peripheral cystic follicles. Laparoscopy reveals bilateral enlarged ovaries with thickened tunica albuginea and multiple cystic follicles.

Ultrasound scanning helps in the diagnosis of PCOD, ovarian tumour and uterine lesions such as haematometra and Asherman syndrome.

Specific treatment will depend on the cause and the patient's desire for fertility at the time of consultation. If she desires fertility, the treatment of choice is induction of ovulation with clomiphene citrate or gonadotropins. On the other hand, if the patient does not desire fertility, she may be advised a progestational agent (medroxyprogesterone or dydrogesterone) for 7–10 days every 2 months or so to induce periods. This treatment protects the patient against the ill-effects of endometrial hyperplasia, adenomatous hyperplasia and endometrial carcinoma due to prolonged unopposed oestrogen action on the endometrium. These patients should be advised to use some form of contraception (condoms/diaphragm) to safeguard them against any unwanted pregnancy resulting from a stray ovulation or spontaneous recovery of menstrual function. Premature menopause requires HRT to protect against osteoporosis and avoid menopausal symptoms.

A hysterosalpingogram or preferably a diagnostic hysteroscopy helps to establish the diagnosis of Asherman syndrome, first described in 1948. Operative hysteroscopy to lyse the synechiae, followed by cyclic hormonal therapy with high doses of conjugated oestrogens of 2.5–5.0 mg/day for 3–6 months, results in the restoration of menstruation in about 50% cases. Some surgeons prefer to insert an intrauterine device in the uterine cavity after lysis of adhesions to ensure keeping the cavity patent and prevent recurrence of adhesions. Hypo-oestrogenic subjects of secondary amenorrhoea have serum oestradiol levels of less than 30 pg/mL and benefit with oestrogen and progesterone therapy. Asherman syndrome is caused by dilatation and curettage (D&C), medical termination of pregnancy (MTP), uterine packing in postpartum haemorrhage, uterine infection and tubercular endometritis. It causes amenorrhoea, oligomenorrhoea, dysmenorrhoea, habitual abortion and infertility depending upon the extent of uterine cavity obliteration.

FSH and LH Concentrations. Women with hypoestrogenic amenorrhoea have either ovarian failure or hypothalamic–pituitary dysfunction. Serum concentrations of FSH and LH of more than 40–50 mIU/mL are

diagnostic of ovarian failure. Serial assessments may be necessary because of the pulsatile nature of pituitary gonadotropin secretion. Most women under the age of 40 years belonging to this category have premature ovarian failure, about 10–15% have gonadotropin-resistant ovaries (Savage syndrome) and another 10–15% have autoimmune ovarian failure. The last two entities have their normal complement of primordial follicles, but their granulosa cells do not respond to FSH. There are no other clues to suggest the gonadotropin-resistant ovarian syndrome. However, evidence of any other autoimmune disorder (myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus—SLE) are suggestive of autoimmune ovarian failure with hypergonadotropic amenorrhoea. Hypothalamic–pituitary dysfunction or failure may occur with a weight disorder (<85% or >125% of ideal body weight), a tumour of the hypothalamus or pituitary gland, after head injury, following infiltrating lesions, after surgery or irradiation. Most often the cause is not known. A CT scan or MRI should be asked for if there is evidence suggestive of a central mass lesion. In women with FSH and LH values less than 5 mIU/mL, measurements of thyroid function tests (T_3, T_4 and TSH) and serum cortisol concentrations are important to exclude panhypopituitarism involving other tropic hormones additionally. Such women will require concurrent thyroid and corticosteroid replacement therapy as well. HRT for premature menopause is warranted along with supplementary oral calcium and advice on change of lifestyle. In women with hypothalamic failure, therapy should begin with preliminary priming with GnRH administered in pulsatile fashion with a pump or subcutaneously for several weeks until the circulating levels of serum oestradiol of over 600 pg/mL are achieved, prior to initiating gonadotropin therapy for induction of ovulation in women desiring pregnancy.

See Table 23.3 for aetiology of amenorrhoea according to anatomic sites and recommended diagnostic work-up. The management of secondary amenorrhoea is shown in Figure 23.10.

Sequela of secondary amenorrhoea

1. Menopausal symptoms, osteoporosis
2. Infertility in a young woman
3. Psychological effects, loss of libido

Management

- HRT for menopausal symptoms and prophylaxis
- Induction of ovulation, IVF for infertility
- Induction of menstrual cycles
- Treat the cause

Oligomenorrhoea and Hypomenorrhoea

Oligomenorrhoea

In some women, the pattern of menstruation extends to cycle lengths exceeding 35 days without any impairment of their fertility. Since this is compatible with normal reproductive capacity within the limits of its own infrequent ovulation, it requires no treatment. However, if the cycles are very erratic and infrequent, medical attention is called for. The causes and findings on clinical investigations are similar to those of amenorrhoea. Many of these women are obese, hirsute, with poorly developed secondary sexual characteristics, genital hypoplasia and ovarian subfunction. Amenorrhoea is often the continuum of oligomenorrhoea. This condition is often encountered in women at the extremes of reproductive life and in some lactating women. Other causes are genital tuberculosis and polycystic ovarian disease.

TABLE 23.3 Aetiology of amenorrhoea according to anatomic sites and investigations

Anatomic Level	Anatomic Site	Pathology	Gonadotropin Level	Diagnostic Methods
1.	Hypothalamus	Tumours, Kallmann syndrome, weight loss, exercise	Low	Clinical evaluation MRI/CT scan
2.	Anterior pituitary	Panhypopituitarism, Sheehan's syndrome	Low	History, examination, GnRH stimulation test
3.	Ovary	Gonadal dysgenesis, Turner's syndrome, ovarian failure (premature, radiation, mumps, surgical excision, chemotherapy), steroidogenic defect (adrenal hyperplasia)	High	History, karyotyping, gonadal biopsy
4.	Anovulation	PCOD, hyperprolactinaemia, weight loss, stress, exercise, drugs, chest wall stimulation	Normal	History, progesterone challenge test, USG/MRI/CT scan
5.	Uterus or endometrium	Müllerian agenesis, RKH syndrome, Asherman syndrome, tuberculosis, radio-therapy, androgen insensitivity	Decreased FSH Increased LH Increased prolactin	History, examination, karyotyping, USG, laparoscopy, hysteroscopy
6.	Outflow tract	Imperforate hymen, vaginal agenesis, cervical atresia	Normal	History and pelvic examination/USG

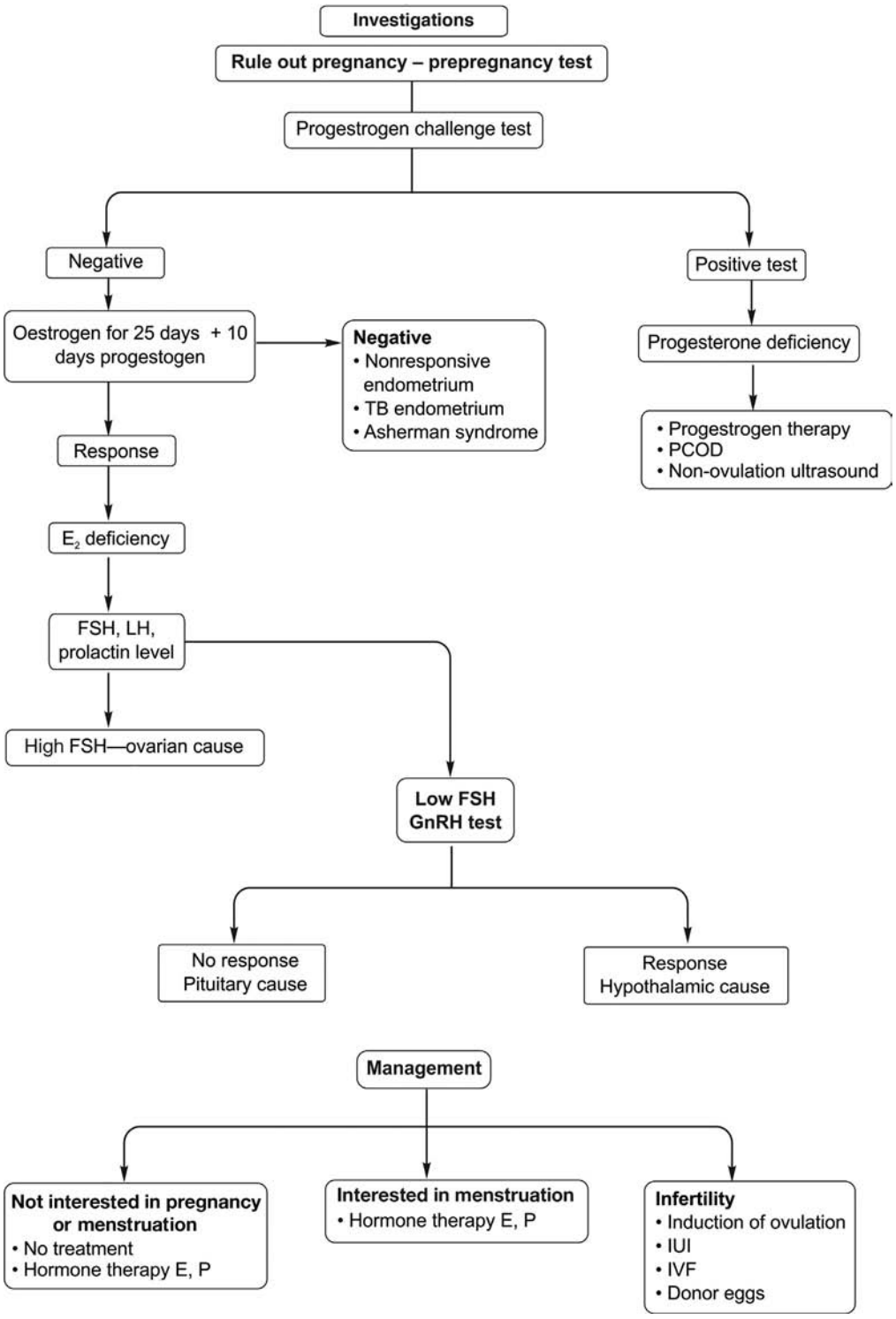

Figure 23.10 Secondary amenorrhoea—management.

Hypomenorrhoea

In some women, menstruation lasts for only 1–2 days, and the blood loss is so scanty that she may need a change of just one to two diapers. Scanty menses, which is otherwise regular, may not be pathological since its regularity presupposes a normal hypothalamic–pituitary–ovarian relationship. In these women, the uterine end organ may be at fault. A small hypoplastic uterus, genital tuberculosis and partial Asherman syndrome also cause hypomenorrhoea and need investigation and treatment. *Oral combined pills also cause hypomenorrhoea*. Scanty periods may precede menopause.

Polymenorrhoea or Epimenorrhoea

Women with polymenorrhoea (epimenorrhoea) suffer from shortened cycles. Menorrhagia often goes hand in hand

with this complaint. It is more frequent in adolescent girls and in perimenopausal women. The exact aetiology of this problem is not known. In most of these women, the follicular phase of the cycle is accelerated resulting in shorter cycles. The ovaries often appear hyperaemic and may contain haemorrhagic follicles. Myohyperplasia of the uterus is a common accompaniment. The lining endometrium is generally of normal thickness; however, in women suffering from polymenorrhagia, the lining endometrium may appear thickened. The cause of the ovarian overactivity seems to be the result of a disturbed endocrine axis.

Polymenorrhagia is frequently observed when women resume menstrual activity after a delivery. It is attributed to the persistence of the activity of the anterior lobe of the pituitary gland, initiated during pregnancy, into the postnatal phase. The excessive stimulation by the gonadotropins causes frequent ovulation and menstruation. In a substantial number of women, associated pelvic pathology such as pelvic inflammatory disease (PID), endometriosis and fibroids is also encountered. Treatment should then be directed to the cause. When no definite cause is identified, treatment with cyclic hormone therapy restores the normal menstrual pattern.

Metrorrhagia

The preferred term 'intermenstrual bleeding' is used to define any acyclic bleeding from the genital tract. In strict terms, the term should be restricted to bleeding arising from the uterus only. The bleeding may be intermittent or continuous. It is superimposed on a normal menstrual cycle.

Intermenstrual bleeding may be physiological, occurring at the time of ovulation when hormonal changes triggering ovulation take place. These women complain of mid-menstrual bleeding (Mittelschmerz) lasting from a few hours to 1 day, a profuse sticky discharge and intermittent cramping pain of short duration. These episodes coincide with ovulation, and this fact can be confirmed by basal body temperature (BBT) charts/sonography. All that is required is to provide an explanation to the patient of the underlying cause and alleviate her anxiety. *A few months of combined oral pills will cure ovulation bleed.*

In elderly women, in particular, postcoital bleeding should not be brushed aside lightly. It may be the earliest symptom of a neoplasm; a meticulous search should be instituted to exclude such a possibility. Besides a thorough clinical examination of the lower genital tract, speculum examination of the cervix in good light for a polyp, vascular erosion, endocervicitis, cancer of the cervix and the presence of an intrauterine contraceptive device (IUCD) should be looked for, so also, lower genital tract ulcers and growths. *A Pap smear examination should be obtained.* A diagnostic hysteroscopy and endometrial curettage for histological study of the endometrial tissue are important. A pelvic sonography to evaluate the pelvic organs is recommended. Refer to Table 23.4 for a brief summary of the types of uterine bleeding.

TABLE 23.4 Types of abnormal uterine bleeding

Terms in Clinical Usage	Menstrual Pattern
Oligomenorrhoea	Cycle length > 35 days
Polymenorrhoea	Cycle length < 24 days
Menorrhagia	Increased menstrual flow/Increased duration at regular cycles
Hypomenorrhoea	Scanty bleeding and shorter days of bleeding
Metrorrhagia	Irregular bleeding in between the cycles
Menometrorrhagia	Increased menstrual flow as well as irregular bleeding between the cycles

Key Points

- Normal menstruation requires the integration of the hypothalamic–pituitary–ovarian axis with a normal functioning uterus, a patent outflow tract and a normal genetic karyotype of XX.
- Menarche occurs between the ages of 10 and 16 years, with a mean age of 12.5 years.
- Amenorrhoea may be due to a hormonal functional disorder or be an early symptom of genital tract abnormalities, hence, the need for thorough investigation.
- Clinical examination, hormone assays, ultrasonography, endoscopic procedures and genetic testing may be required for the diagnosis of amenorrhoea.
- In India, tuberculous endometritis and Asherman syndrome may cause hypomenorrhoea or secondary amenorrhoea.
- Polymenorrhoea may be of functional or organic origin. If conservative measures fail, surgical intervention may be required.
- Treatment of amenorrhoea depends upon the cause. Hormonal therapy on a long-term basis may be required for proper growth and to maintain menstrual functions.

Self-Assessment

1. Define the varieties of menstrual irregularities encountered in clinical practice.
2. Classify the causes of primary amenorrhoea.
3. Describe the management of primary amenorrhoea.
4. What are the causes of secondary amenorrhoea. How would you manage such cases?
5. How would you manage polymenorrhagia in the perimenopausal age group of women?
6. How would you diagnose and manage a case of premature ovarian failure?
7. Describe the menstrual irregularities observed in adolescent girls suffering from polycystic ovaries. How would you diagnose and treat such girls?

Suggested Reading

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Chapter 24 Menorrhagia

CHAPTER OUTLINE

The term 'menorrhagia' is from the Greek word, *men* meaning 'menses' and *rrhagia* meaning 'burst forth'. Menorrhagia denotes cyclic regular bleeding which is excessive in amount or duration. It is generally caused by conditions affecting the uterus or its vascularity, rather than any disturbance of function of the hypothalamic–pituitary–ovarian (H-P-O) axis. Whenever the uterine endometrial surface is enlarged, the bleeding surface is increased, contributing to excessive bleeding. Such conditions prevail in uterine fibroids, adenomyosis, uterine polyps, myohyperplasia and endometrial hyperplasia.

Menorrhagia is also seen in women with increased uterine vascularity such as in chronic pelvic inflammatory disease and pelvic endometriosis. The uterus is often retroverted in position with restricted mobility. Such a uterus tends to be bulky and congested. The presence of an IUCD often leads to heavy and prolonged bleeding. Lastly, menorrhagia may be the result of bleeding disorders like Von Willebrand's disease or an arteriovenous aneurysm.

A normal menstrual blood loss is 50 to 80 mL, and does not exceed 100 mL. In menorrhagia, the menstrual cycle is unaltered, but the duration and quantity of the menstrual loss are increased. Menorrhagia is essentially a symptom and not in itself a disease. It affects 20–30% of women at sometime or other with significant adverse effects on the quality of life in terms of anaemia, cost of sanitary pads and interference with day-to-day activities. Several causes may prevail in a few cases, and attribute to excess bleeding. The underlying cause may be difficult to detect, in a few cases.

Normal Control of Menstrual Bleeding

Once the menstrual bleeding starts, the platelet aggregation forms clots in the opened vessels. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) causes myometrial contractions and constricts the endometrial vessels. The repair and epithelial regeneration begin on the 3rd and 4th day of period, by the growth of epithelial cells from the open endometrial glands aided by the vascular endothelial, epidermal and fibroblast growth factors.

In excessive bleeding with regular menstrual cycles, the H-P-O axis is intact, but endometrial changes get altered. It is observed that, in these cases, PGE_2 (prostacyclin), which is a local vasodilator is increased as compared to $PGF_{2\alpha}$ in the endometrial tissue.

Causes (Table 24.1)

The causes can be divided into: (i) those due to general diseases; (ii) those which are local in the pelvis; (iii) those caused by endocrine disorders; (iv) contraceptives and (v) iatrogenic. The new classification of causes of abnormal uterine bleeding is shown in Figures 24.1–24.4.

General Diseases Causing Menorrhagia

General diseases causing menorrhagia are:

- Blood dyscrasia, i.e. leukaemia, coagulopathy, thrombocytopenic purpura, severe anaemia; coagulation disorders are seen in 20% adolescents; Von Willebrand's disease.

TABLE 24.1 Aetiology of menorrhagia

General Causes	Pelvic Causes	Contraceptive Use	Hormonal/AUB
• Blood dyscrasia	• PID, pelvic adhesions	• IUCD	• Ovulatory—irregular ripening or irregular shedding
• Coagulopathy	• Uterine fibroids, endometrial hyperplasia • Adenomyosis	• Post-tubal sterilization	• Anovulatory—Resting endometrium – 80% • Metropathia haemorrhagica
• Thyroid dysfunction • Genital TB	• Feminizing tumour or the ovary • Endometriosis • Pelvic congestion, varicose veins in the pelvis	• Progestogen-only pills	

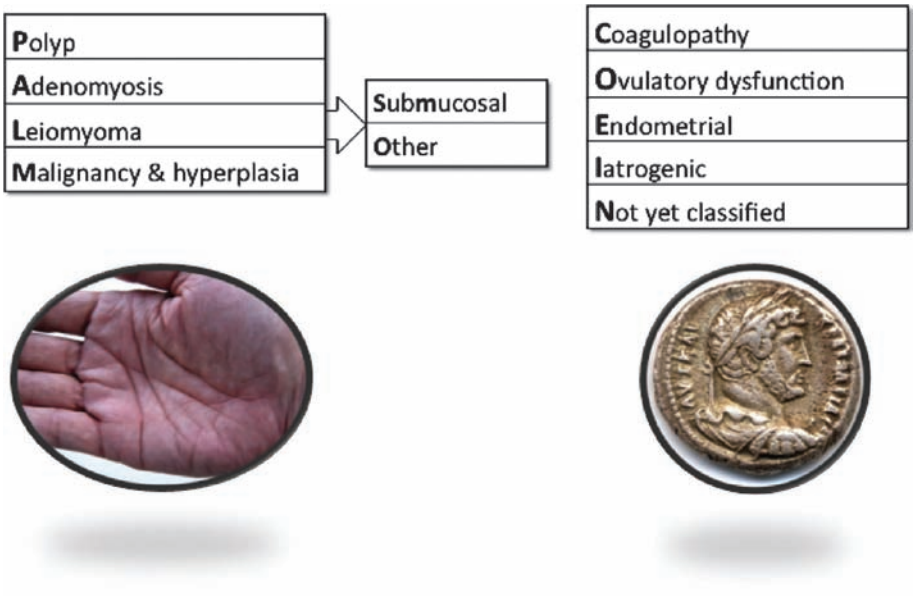


Figure 24.1 Basic FIGO classification system for causes of AUB in the reproductive years. The system includes four categories that are defined by visually objective structural criteria (PALM: polyp, adenomyosis, leiomyoma, malignancy or hyperplasia); four unrelated to structural anomalies (COEI: coagulopathy, ovulatory dysfunction, endometrial, iatrogenic); and one (N) that includes entities not yet classified. (From Figure 1. Malcolm G Munro: Obstetrics and Gynecology Clinics. Vol 38(4): 703–731, 2011.)

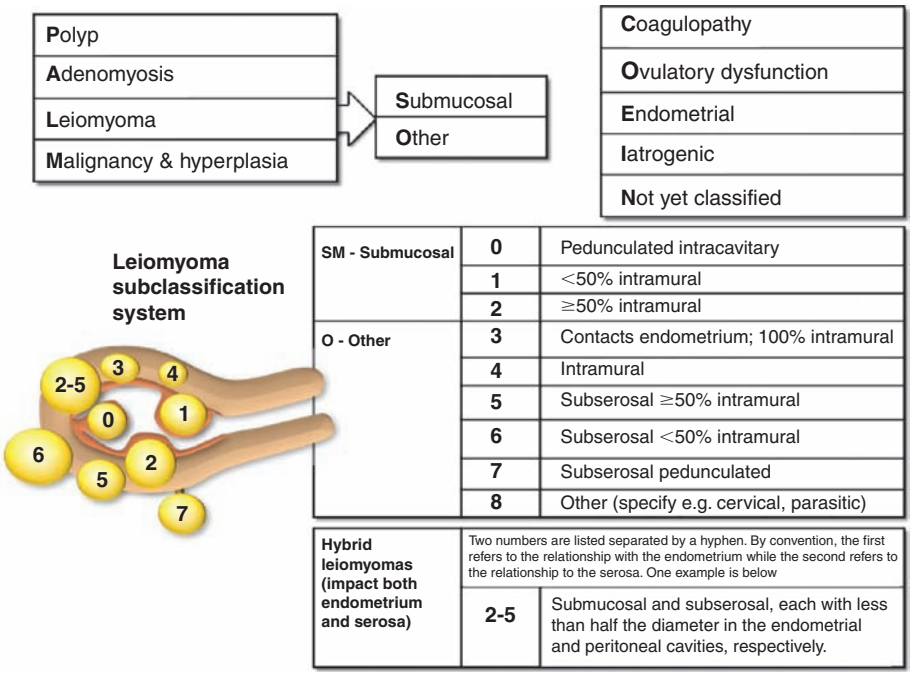


Figure 24.2 FIGO classification system including the leiomyoma subclassification. The classification of leiomyomas categorizes the submucous (sm) group according to the Wamsteker system 12 and adds categorizations for intramural, subserosal, and transmural lesions. Intracavitary lesions are attached to the endometrium by a narrow stalk and are classified as type 0, whereas types 1 and 2 require that a portion of the lesion is intramural, with type 1 being 50% or less and type 2 more than 50%. Type 3 lesions are totally extracavitary but abut the endometrium. Type 4 lesions are intramural leiomyomas that are entirely within the myometrium with no extension to the endometrial surface or to the serosa. Subserosal (types 5–7) myomas include type 5, which are more than 50% intramural; type 6, which are 50% or less intramural, and type 7 being attached to the serosa by a stalk. Lesions that are transmural are categorized by their relationships to both the endometrial and serosal surfaces. The endometrial relationship is noted first whereas the serosal relationship is second (e.g., type 2–5). An additional category, type 8, is reserved for myomas that do not relate to the myometrium at all and include cervical lesions, those that exist in the round or broad ligaments without direct attachment to the uterus, and other so-called parasitic lesions. (From Figure 2. Malcolm G Munro: Obstetrics and Gynecology Clinics. Vol 38(4): 703–731, 2011.)

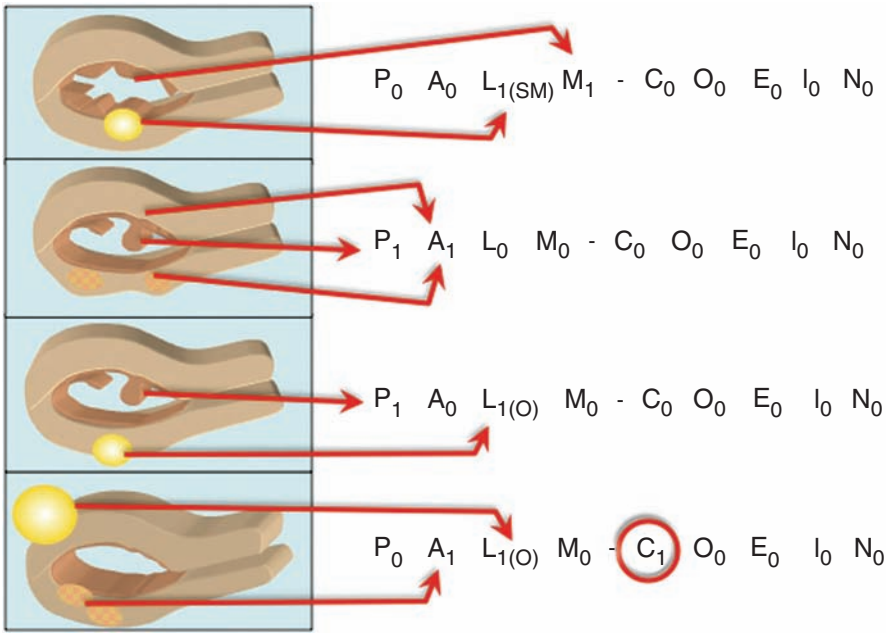


Figure 24.3 FIGO classification system for causes of abnormal uterine bleeding in the reproductive years. FIGO, International Federation of Gynecology and Obstetrics. (From Figure 1. Malcolm G Munro, Hilary OD Critchley and Ian S Fraser: American Journal of Obstetrics and Gynecology, Vol 207(4): 259–265, 2012.)

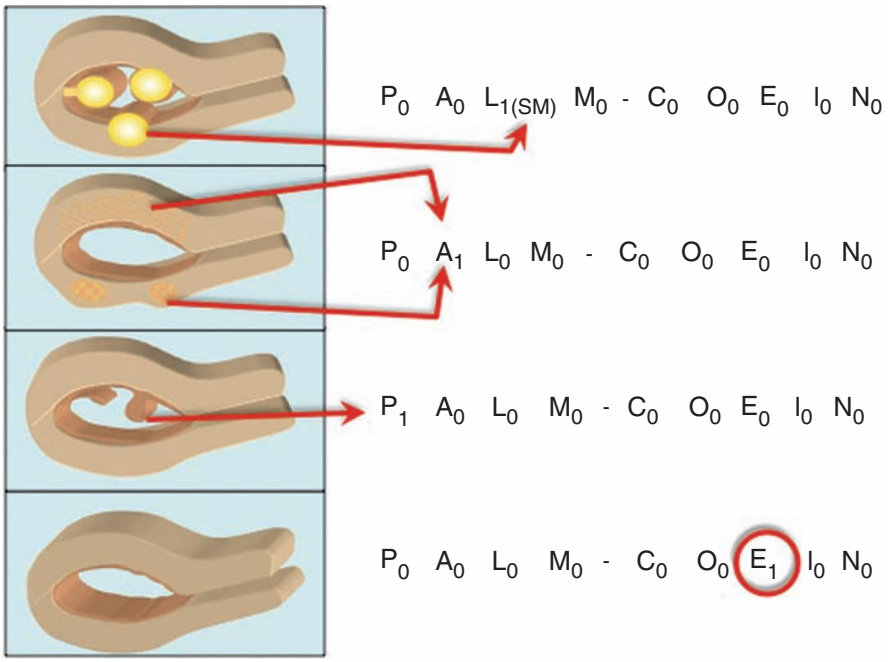


Figure 24.4 Notation for FIGO classification system. FIGO, International Federation of Gynecology and Obstetrics. (From Figure 2. Malcolm G Munro, Hilary OD Critchley and Ian S Fraser: American Journal of Obstetrics and Gynecology Vol 207(4): 259–265, 2012.)

- Thyroid dysfunction—Hypothyroidism and hyperthyroidism in initial stages.
- General tuberculosis may cause menorrhagia initially, but in advanced state, amenorrhoea ensues.

Local Pelvic Causes

These include:

- Uterine causes: Uterine fibroids, fibroid polyp, adenomyosis, endometrial hyperplasia.
- Chocolate cyst, ovarian feminizing tumours, polycystic ovarian disease (PCOD), endometriosis.
- Uterine arteriovenous fistula and varicosity of vessels (rare)—This may be congenital, but quite often it is traumatic following dilatation and curettage (D&C).
- Salpingo-oophoritis, pelvic inflammatory disease (PID), genital TB, varicose veins in the pelvis (Figure 24.5).
- Immediate puerperal and postabortal periods.
- Oestrogen secreting ovarian tumours.
- Endometrial causes increased PGE_2, increased fibrinolysis.

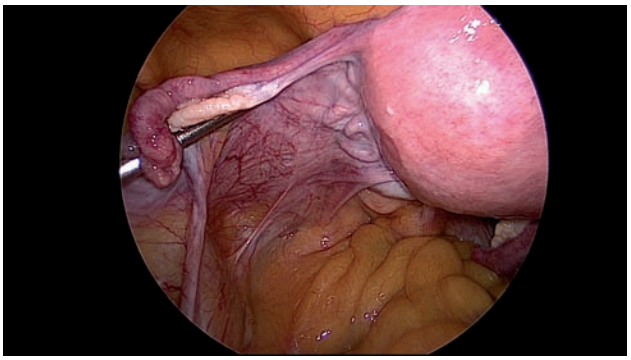


Figure 24.5 Laparoscopic view of varicose uterine vessels. (Courtesy: Dr Vivek Marwah, New Delhi.)

Iatrogenic Causes

Iatrogenic cause of menorrhagia is progesterone administration (mini-pill).

Intrauterine Contraceptive Device

Intrauterine contraceptive device (IUCD) has provided yet another aetiological factor. Five to ten per cent of women wearing the device suffer menorrhagia in the first few months. Poststerilization menorrhagia is reported in 15% cases, but the aetiology is not clear.

No obvious cause is seen in 40–50% of the cases.

Investigations

Menorrhagia patients require to be completely investigated. Besides physical examination, the following tests are advised:

- Complete haemogram.
- Bleeding time and clotting time.
- Thyroid profile as indicated.
- Pelvic sonography—sonosalpingography.
- Diagnostic hysteroscopy.
- Diagnostic laparoscopy.
- Endometrial study by ultrasound and curettage.
- Sonosalpingography can delineate a submucous fibroid clearly.
- Pelvic angiography is required when the cause of menorrhagia is not detected by other means. This shows varicosity and arteriovenous fistula.

Management

Management consists of the following (Figure 24.6):

- General measures to improve the health status of the patient. Advice regarding proper diet, adequate rest during menses, oral administration of haematinics, vitamins and protein supplements and to maintain a menstrual calendar noting duration and extent of blood loss.
- Treat the cause.

In women suffering from menorrhagia, consider the following:

- In ovulatory cycles, oral nonsteroidal anti-inflammatory drugs (NSAIDs) like mefenamic acid 500 mg t.i.d along with antacids. Other drugs in this category include naproxen, ponstan and ibuprofen. Blood loss is reduced by 30–40%. These drugs are effective in ovulatory bleeding and in IUCD users. They are antiprostaglandins and inhibit cyclo-oxygenase activity. They decrease the menstrual bleeding, but have no effect on the duration of menstrual bleeding. These drugs should be taken only during menstruation, which is an advantage, over cyclical hormone therapy.
- Cyclic oral contraceptive pills.
- Progestogens in endometrial hyperplasia.
- Mirena IUCD.
- Minimal invasive surgery includes endometrial thermal ablation, endometrial resection and others (see later).

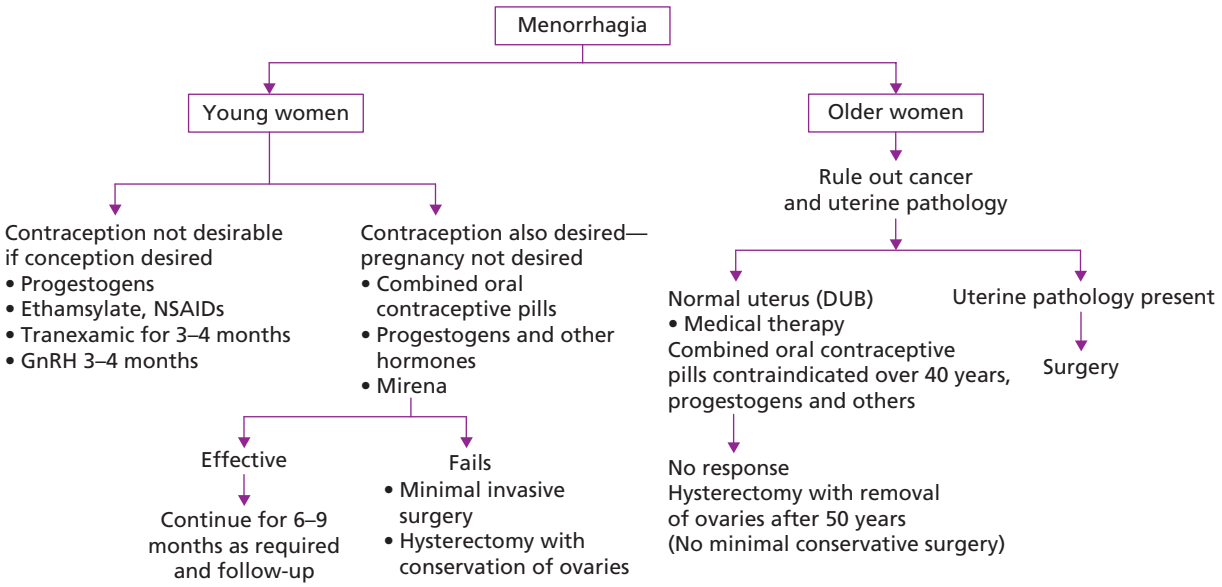


Figure 24.6 Management of menorrhagia.

- Hysterectomy in selected cases.
- GnRH—It is not effective in acute bleeding as it takes 4 weeks to cause effect.

In women manifesting obvious pathology, corrective measures for the same are called for, depending on her age and the desire for retaining menstrual and childbearing functions. Therapeutic measures include:

- Removal of an intrauterine contraceptive device if medical therapy fails.
- Myomectomy/hysterectomy for uterine fibroids.
- Wedge resection/hysterectomy for adenomyosis of the uterus.
- Laparoscopic lysis of adhesions for chronic PID.
- Electrocautery or laser vaporization of endometriosis and drainage of chocolate cysts in pelvic endometriosis.
- Hysterectomy with or without removal of the adnexa according to the age and the individual needs of the patient.
- In patients suffering from bleeding disorders, a haematologist's opinion should be sought.
- Uterine artery embolization in varicose vessels.
- Von Willebrand's disease; intravenous desmopressin.

Abnormal Uterine Bleeding (AUB)

Incidence

About 10–15% of women experience episodes of abnormal uterine bleeding (AUB) at sometime during the reproductive years of their lives. It is common during the extremes of reproductive life, following pregnancy and during lactation. It has been shown that 55.7% of adolescents experience abnormal menstrual bleeding in the first year or so after the onset of menarche because of the immaturity of the hypothalamic–pituitary–ovarian axis leading to anovulatory cycles. It generally takes 18 months to 2 years for regular cycles to be established.

It is not uncommon for a premenopausal woman to develop menorrhagia, and this is often due to anovulatory cycles in 80% cases. However, endometrial malignancy should be ruled out prior to deciding the type of treatment.

The term 'dysfunctional uterine haemorrhage' was specifically used when menorrhagia was not associated with any genital tract abnormalities, general or endocrinological diseases. In this case, hormonal imbalance is considered the root cause of hyperplasia of the endometrium that causes menorrhagia; this often happens in anovulatory cycles with excessive or unopposed influence of oestrogen on the endometrium.

In some cases, abnormal endometrial haemostasis is the cause of abnormal excessive bleeding.

Pathogenesis

Endometrium normally produces prostaglandins from arachidonic acid, which is a fatty acid. Of these, PGE_2 and PGI_2 are vasodilators and antiplatelet aggregates. $PGF_{2\alpha}$ and thromboxane A_2 cause vasoconstriction and platelet aggregates. Progesterone is responsible for secretion of $PGF_{2\alpha}$. In anovulatory cycles, the absence of progesterone and thereby of $PGF_{2\alpha}$ causes menorrhagia. In some cases, tissue plasminogen activator (TPA) which is a fibrinolytic enzyme is increased, thereby causing menorrhagia. Endothelin present in the endothelial wall is also a vasoconstrictor, which may be lacking or low when there is abnormal menstruation.

Classification

Abnormal uterine bleeding is of two types:

1. Anovulatory cycles (80%)
2. Ovulatory cycles (20%)

Puberty Menorrhagia

Aetiology

- The commonest cause lies in the hypothalamic–pituitary–ovarian dysfunction (50%). Immature development of these organs results in anovulation in the earlier years (1–5 years), unopposed oestrogen causing endometrial hyperplasia. As the girl matures, the normal menstrual cycles are established.
- Blood dyscrasia—Coagulation disorders, thrombocytopenia purpura, Von Willebrand's disease, leukaemia account for 20% cases.
- Hypothyroidism—4%.
- PCOD—10–12%.
- Genital tuberculosis (4%).
- Liver disorders.
- Feminizing ovarian tumours—granulosa cell and theca cell tumours.
- Adrenal hyperplasia.

Clinical Features

Menorrhagia may be noticed from the start of menarche, but often the initial cycles may be normal. It takes the form of heavy regular cycles, or normal bleeding lasting for several days, but dysmenorrhoea is invariably absent in anovulatory cycles. Anaemia may supervene. The pelvic findings by ultrasound scanning are normal except in ovarian tumour.

It is important to rule out other causes of menorrhagia before instituting hormonal therapy.

Investigations

- Blood profile—Hb%, bleeding and clotting time, coagulation factors; blood film.
- X-ray chest for tuberculosis.
- Thyroid function tests.
- Pelvic ultrasound PCOD, early fibroid.

- If medical treatment fails, D&C should be done to rule out endometrial tuberculosis by PCR test.

Management

Aim is to:

- Control menorrhagia.
- Prevent or treat anaemia.
- Prevent recurrence.
- Treat the cause.
- **Anovulatory cycles**
  - In an acute episode of bleeding, IV premarin 25 mg 6–8 hourly will control bleeding in 24–48 hours. Thereafter, oestrogen for 21 days with progestogen added for 10 days for 3–6 cycles will regularize the cycles.
  - In chronic menorrhagia, oral combined pills or cyclical progestogen are the first line of treatment. About 70–80% responds well. Medical treatment is detailed below.
- NSAIDs (nonsteroidal anti-inflammatory drugs): Mefenamic acid 250 mg –500 mg t.i.d during periods. Naproxen, ponstan, ibuprofen.
- Androgens (danazol) are not recommended, though effective, because of androgenic effects in young girls.
- GnRH therapy takes 4 weeks to act, so not useful in acute episode. The drug is expensive and prolonged treatment over 4–6 months can cause osteoporosis.
- If progestogens cause side effects, Mirena IUCD for a few months can control menorrhagia.
- Arterial embolization is required in case of varicosity of uterine vessels.
- When the above treatments fail, uterine tamponade using Foley catheter for 24 hours can control bleeding in the acute episode.
- Anti-TB treatment in endometrial tuberculosis.

Blood transfusion may be required to correct anaemia.

Lately, the trend is to give intravenous tranexamic acid 1 gm with 25 mg of oestrogen, and then continue with oestrogen and progesterone as mentioned above. Desmopressin analogue of arginine vasopressin is given intravenously or by nasal spray (1.5 mg/mL – total 150–300 mg in 30 mL diluted) in van Willebrand's syndrome.

Tranexamic acid inhibits tissue plasminogen activator which is a fibrinolytic enzyme, whose level increases in abnormal uterine bleeding.

Outcome: About 70–80% adolescents respond to one or the other above treatments. Puberty menorrhagias does not compromise the reproductive function.

Abnormal Uterine Bleeding (AUB) in the Reproductive Age

'Dysfunctional uterine bleeding' (DUB) was coined to describe abnormal heavy menstrual bleeding when no structural genital tract abnormality or general cause was detected, in a woman of reproductive age in the absence of pregnancy. This condition is due to several causes that make the standard methods of investigations and management inconsistent and difficult. Several causes may be attributed to AUB in an individual whereas none may be detected in some. In some, the lesion detected may not be the real cause of AUB, i.e. an uterine fibroid may be a co-incidental finding, asymptomatic and not the true cause of AUB.

For this reason, FIGO (Federation of International of Gynecologists and Obstetricians) in 2011 came forward with the new nomenclature of AUB instead of dysfunctional uterine bleeding, and a new classification system to define its cause. This classification is named 'PALM–COEIN' system. It stands for polyp, adenomyosis, leiomyoma, malignancy, coagulopathy, ovulatory dysfunction, endometrium, iatrogenic and non classified. The first four are related to visually objective structural uterine abnormalities that can be measured visually with imaging modalities and by histopathological study. The others are non structural and attributed to coagulation disorders and hormonal dysfunction. N stands for no cause detected.

PALM–COEIN classification is further subdivided into secondary and tertiary subclassification according to the findings detected.

Contrary to the PALM group, the COEIN group cannot be detected by imaging and histopathology. This category refers to coagulopathy, ovarian steroid dysfunction, either endogenous or by administration of hormones for various conditions (oral contraceptives, IUCD, drugs).

Abnormal uterine bleeding (AUB) has replaced the term 'dysfunctional uterine bleeding' in a woman of reproductive age in the absence of pregnancy.

AUB may be acute or chronic. Acute bleeding may occur sporadically de novo or may be superimposed on chronic AUB, and requires immediate treatment. Chronic AUB is described as abnormal menstrual bleeding related to volume, timing, regularity and duration of bleeding that lasts for 6 months (minimum 3 months), and requires thorough investigations.

AUB does not include the bleeding caused by lesions in the lower genital tract.

PALM–COEIN Classification

The classification is stratified into 9 basic categories that are arranged according to the acronym PALM–COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia endometrium, coagulopathy, ovulatory disorders, endometrium, iatrogenic and non classified).

Polypus – (AUB-P). It is categorized and defined by ultrasound, saline sonography, hysteroscopy with or without histopathology.

P category is subdivided according to number, size, location and histology.

Adenomyosis (AUB-A). It is diagnosed by ultrasound and MRI. MRI is expensive and not available in many centres. In

such cases, ultrasound alone is used for the diagnostic purpose. The category is subdivided depending upon the depth of endometrial myometrial invasion. It is important to remember that many cases of adenomyosis are asymptomatic and only diagnosed on hysterectomy specimens.

Leiomyoma (AUB-L)

Many leiomyomas are co-incidental findings and are not the cause of AUB. Because of the number, different locations and size, this group is divided into primary, secondary and tertiary group.

The primary classification reflects only the presence or absence of leiomyomas as determined by ultrasound. In the secondary classification, it is necessary to distinguish myomas that involve the uterine cavity, as these are the ones that are likely to cause AUB—the ones away from the endometrium are unlikely to do so.

The tertiary classification involves submucosal growths. It also includes number, size and location of myomas.

Malignancy and premalignant lesions (AUB-M)

This group is rare in the reproductive age, but may occur in a woman with polycystic ovarian disease and chronic anovulation. The diagnosis is by histopathological examination of the endometrium (D/C, biopsy) or by hysteroscopic biopsy.

Coagulopathy (AUB-C)

It consists of a spectrum of systemic disorders of haemostasis that can cause AUB in around 13–20% women of reproductive age. The most common is von Willebrand's disease. However, many of these may be asymptomatic and not related to AUB.

Ovulatory disorders (AUB-O)

Eighty per cent are anovulatory cycles with unpredictable, irregular menstrual cycles, some with heavy bleeding. 20% are ovulatory but may be a consequence of 'luteal-out-of phase' (LOOP) events with deficient progesterone. Some of these are caused by hypothyroidism, hyperprolactinaemia.

Endometrial causes (AUB-E)

The mechanism regulating local endometrial 'haemostasis' secondary to abnormal secretion of prostaglandins is as explained earlier. In rare cases, it is due to tubercular endometritis or infection, particularly chlamydial infection. There are no tests available, except for infections, to estimate the local causes, and the case is placed in this category by exclusion of other causes.

Iatrogenic (AUB-I)

This is caused by steroidal hormones administered as contraceptives, especially in low dose, IUCD, copper T may cause unscheduled 'break-through bleeding' or menorrhagia. The drugs that are responsible are anticoagulants, phenothiazine and tricyclic antidepressants which affect dopamine metabolism.

Not classified (AUB-N)

Rare causes not well defined or diagnosed are arteriovenous malformations, varicose veins of the uterine vessels, myohyperplasia. In others, no cause is discernable by existing investigations. They are all clubbed in this group of unclassified AUB. As and when better investigations become available, they may be allocated to a new category in future.

Abnormal Uterine Bleeding in Childbearing Age and Premenopausal Women

The menstrual cycles are painless as most cases are anovulatory cycles. One point to be emphasized here is that D&C and endometrial study are important in premenopausal women to rule out endometrial carcinoma. In younger women, D&C is done when medical therapy fails. Instead of D&C, uterine aspiration or hysteroscopic biopsy is chosen by some to study the endometrial lining and to detect small polypi that can be missed on ultrasound and to diagnose tubercular endometritis.

Metropathia Haemorrhagica

It is a specialized form of anovulatory AUB, seen in women between 40 and 45 years. It is not related to parity.

The symptoms are typical. The woman develops continuous painless vaginal bleeding, sometimes starting at the onset of menses, or preceded by 6–8 weeks of amenorrhoea (Figure 24.7). Occasionally, the woman reveals a history of menorrhagia prior to this. The uterus is slightly bulky. This condition may simulate abortion and ectopic pregnancy if amenorrhoea precedes bleeding, but pain is conspicuously absent.

Pathology

A mild degree of myohyperplasia with the uterine wall measuring up to 25 mm, and a uniformly enlarged uterus is seen in metropathia haemorrhagica. The endometrium is thick,

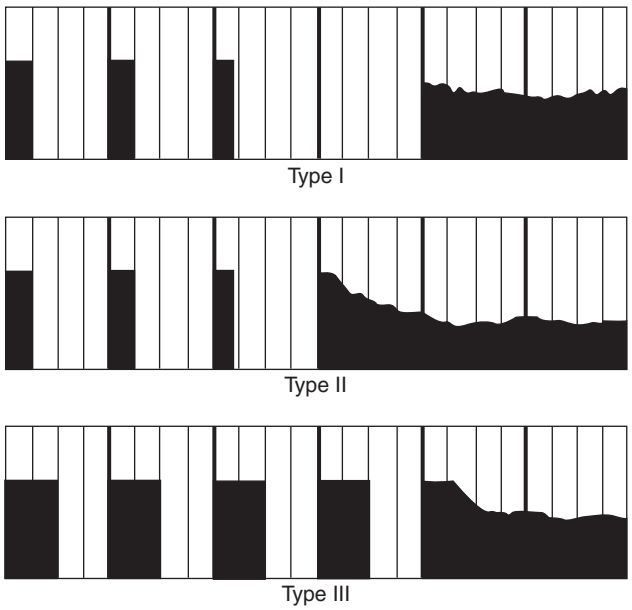


Figure 24.7 Menstrual history in cases of metropathia haemorrhagica. Continuous uterine bleeding is the most constant symptom, and most frequently this is preceded by amenorrhoea of about 8–10 weeks' duration. Sometimes, the bleeding follows upon a normal period, while at other times, the continuous bleeding may be preceded by menorrhagia.

polypoidal, and thin slender polypi project into the uterine cavity (Figure 24.8). The endometrium shows characteristics of cystic glandular hyperplasia (Figures 24.9 and 24.10). The Swiss cheese pattern is another name given to describe this endometrium. The second feature is the absence of secretary endometrium with the absence of cock-screw glands. Areas of necrosis as seen during menstruation can be seen in the superficial surface. One or both ovaries may contain a cyst not larger than 5 cm, but corpus luteum is absent.

Investigations

- A history of the onset, duration and amount of bleeding should be noted. Antecedental causes such as IUCD, pills, pregnancy, abortion, drug therapy are also pertinent in these cases.
- General examination, with special reference to anaemia and thyroid function, blood count, coagulation profile, is carried out. Pelvic examination is done.
- Ultrasound to study pelvic organs and to rule out pelvic organic disease.
- Endometrial study by curettage, uterine aspiration or hysteroscopic biopsy is mandatory in premenopausal women, and necessary in a few younger women suspected to have endometrial tuberculosis.
- Doppler ultrasound to study endometrial vascularity may help in the diagnosis.
- Hysterosalpingography and saline salpingography may be employed if hysteroscopic facilities are not available.

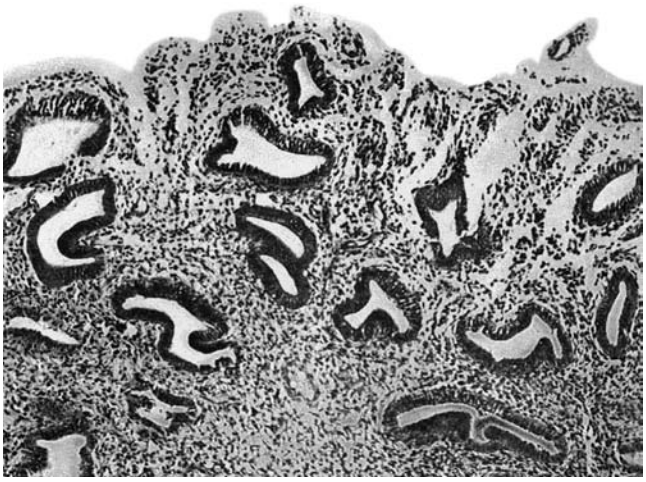


Figure 24.10 Metropathia haemorrhagica. Endometrium showing superficial necrosis.This necrosis resembles that seen on the first day of menstruation. The glands, however, do not show any secretory change (×110).

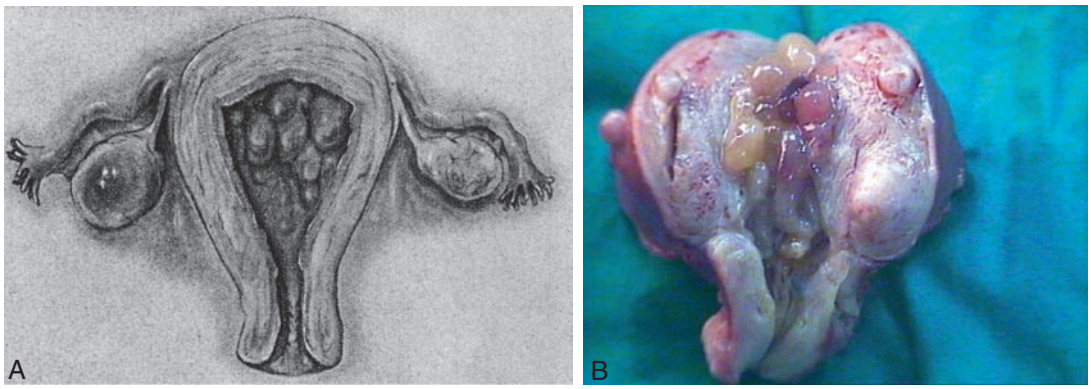


Figure 24.8 **(A)** Metropathia haemorrhagica. Note that the right ovary is cystic and that the endometrium shows diffuse polyp due to hyperplasia. **(B)** Cut section of the uterus showing thickened myometrium (myohyperplasia) and thickened polypoidal endometrium.

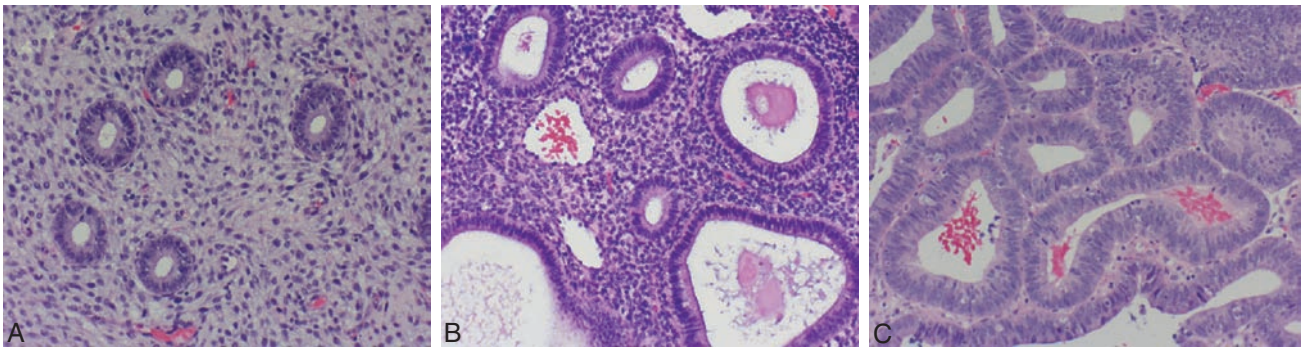
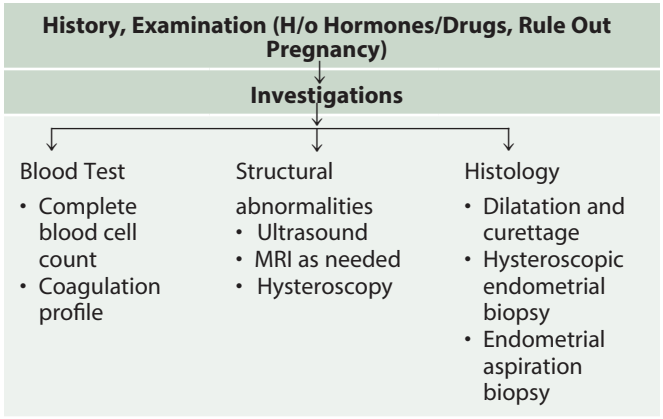


Figure 24.9 Endometrial biopsies of normal proliferative endometrium. **(A)** Simple endometrial hyperplasia without atypia. **(B)** Complex endometrial hyperplasia with **(C)** cellular atypia. (Source: Hacker NF, Gambone JC, Hobel CJ, *Hacker and Moore's Essentials of Obstetrics and Gynecology, 5th ed.* Philadelphia: Elsevier, 2010.)



Treatment of Abnormal Uterine Bleeding (AUB)

- Treat the cause. Menorrhagia without any organic or general disease should be treated as follows:

  A wide variety of treatment modalities are now available. The treatment should be based on the age of the woman, her desire to retain fertility, previous treatment and severity of menorrhagia.
- Anaemia should be treated simultaneously. *First line of treatment is medical therapy*. If that fails, D&C may be helpful mainly for diagnostic purpose, but a few women may benefit from it therapeutically. If hormonal treatment causes side effects, many now prefer to insert a Mirena IUCD. Failing this, decision has to be taken regarding conservative surgery or hysterectomy. Lately, conservative surgeries have reduced the number of hysterectomies for AUB, and are cost effective with quick recovery.

Conservative Treatment

If the menorrhagia is not heavy and the woman is not anaemic, menstrual chart for a few months should be observed. Spontaneous cure is possible and can be awaited. Anaemia can be treated appropriately if it exists.

Hormone Therapy (Table 24.2)

1. Oestrogen therapy alone is not recommended because of the risk of endometrial and breast cancer. Oral combined pills are effective in only select women and not safe after the age of 35 years, in smokers and obese women.
2. Progestogens are the main hormones used in AUB. Progestogen induces oestradiol 17 β-dehydrogenase which converts oestradiol to weak oestrone which in turn suppresses E_2 receptors, DNA synthesis and has anti-mitotic activity. Thus, progestogens cause endometrial atrophy. A high initial dose of 10–30 mg a day should arrest bleeding in 24–48 hours, after which 5 mg daily is given for 20 days. Withdrawal bleeding occurs 2–5 days after stopping the drug, and normal blood loss is expected. A further course of 5 mg daily for 20 days is started on the second or third day of the periods cyclically for 3 to 6 months (given at night to reduce side effects). Duphaston (10 mg) does not suppress ovulation in women who desire pregnancy, and it does not influence lipoproteins. Progestogens used commonly are norethisterone, duphaston, DMPA or newer progestins. *Gestrinone*, a derivative of 19-nortestosterone, is effective in an oral dose of 2.5 mg twice weekly or 5 mg vaginal tablets thrice weekly for 6 months. Instead of a 3 week cyclical therapy, giving progestogen only in the luteal phase is not effective.

TABLE 24.2 Medical therapy

Drugs	Dosage	Side Effects
Combined oral contraceptives	20–30 µg EE_2 + progestogen monthly seasonale–3 monthly (4 cycles in a year)	Nausea, headache, hypertension, hyperglycaemia, thrombosis, liver and gall bladder disease, breast cancer
Progestogens	5–10 mg tablet (10–30 mg daily) for 3 weeks cyclically • Continuous 3 monthly • 3 monthly injections • Implant	Weight gain, depression, headache, acne, abnormal lipid profile, breast tumours
Gestrinone	2.5 mg twice weekly	
Danazol	100–200 mg daily	Acne, hirsutism, weight gain, reduced HDL, cholesterol
GnRH analogues	4 weekly injections	Menopausal symptoms, osteoporosis, loss of libido,
Tranexamic acid	1 g 6 hourly	Nausea, vomiting diarrhoea, headache, visual disturbances, intracranial thrombosis
NSAIDS	Mefenamic acid 500 mg tid	Nausea, vomiting, dyspepsia, gastric ulcer, diarrhoea, thrombocytopenia
Ethamsylate	500 mg four times daily	Nausea, headache, rash
Mirena IUCD	52 mg levonorgestrel	Less than those of oral progestogen—because its action is local resulting in endometrial suppression. However, it takes 2 to 3 months to reduce menorrhagia and the effect lasts for 5 years
Ormeloxifene	60 mg twice weekly	

Three-monthly Depo-Provera is also now recommended to reduce the number of menstruations in a year. Instead of cyclical administration of progestogens, continuous oral progestogens daily for 3 months with a break of 1 week reduces the number of menstrual cycles to 4 in a year which many women welcome.

Fibroplant implant releasing 14 μg daily of levonorgestrel is under trial.

3. Danazol has a limited role when oral contraceptives and progestogens are not suited to a woman. It has androgenic side effects. Danazol 200 mg daily for 3–4 cycles is recommended.
4. Clomiphene is advocated if pregnancy is desired.
5. Ethamsylate reduces capillary fragility, 500 mg four times a day from 5 days prior to anticipated period, up to 10 days reduces menorrhagia by 50% (Table 24.2) in ovulatory cycles.
6. Nonsteroidal anti-inflammatory drugs (NSAIDs) taken during menstruation for 4–5 days control menorrhagia by 70% in ovulatory cycles, post-IUCD and post-sterilization menorrhagia. These drugs inhibit cyclo-oxygenase and prostaglandin productions.
7. Antifibrinolytic agents—Tranexamic acid (epsilon-amino-caproic acid), 1–2 g four times a day for 6–7 days during menstruation is effective in 50% of the cases. Ethamsylate combined with 250 mg tranexamic acid is also advocated. Combined tranexamic acid with mefenamic acid is now available (Trapic-MF).
8. GnRH is employed if the above fail. Depot injection 3.6 mg given monthly for 4–6 months or 6.6 mg implant is nearly 100% successful. Longer duration of treatment with its anti-oestrogenic action causes menopausal symptoms and osteoporosis. This can be counteracted by 'add-back therapy' by giving 5–10 mg norethisterone (not MDPA since it is not bone protective) or tibolone, and this allows longer administration of GnRH (more than 6 months). GnRH takes 4 weeks to act and is therefore not effective in acute episodes of bleeding.
9. **SERM**—A new drug ormeloxifene (selective oestrogen receptor modulator), nonhormonal centchroman 60 mg twice weekly for 12 weeks to 6 months and thereafter weekly, is 50% effective. It does not cause breast or uterine cancer because of its anti-oestrogenic effect. It is also agonist to cardiovascular system and bone protective. It sometimes lengthens the follicular phase and delays menstruation. It can cause functional cyst, dyspepsia and headache at times.
10. When oestrogen is not contraindicated and a woman also needs contraception, a new drug Seasonale (combined oestrogen and progestogen) is used daily for 84 days with a gap of 6 days in a three-monthly treatment. Menstruation occurs during the tablet-free period. It is welcomed by women because of infrequent periods.

Mirena

To avoid side effects of hormonal therapy, Mirena IUCD is now employed to control menorrhagia. It directly suppresses endometrium with minimal side effects. It has no action on the ovaries; therefore, E_2 and progesterone levels remain normal (Figure 24.11). It reduces blood loss by 70–90% in 3 months, and acts as a contraceptive for those who do not desire pregnancy.

Mirena can be retained for 5 years. However it may cause irregular bleeding during the first 3 months, and the woman is advised to persevere retaining Mirena and not get it removed on this account. About 25% of women become amenorrhoeic at the end of 1 year. A quick return of fertility is noted following its removal. 80% conceive by 12 months. Mirena is also useful in women with menorrhagia and dysmenorrhoea associated with uterine fibroid, adenomyosis.

Disadvantages of Mirena

The following are the disadvantages of Mirena:

- Slightly difficult to insert.
- Takes 3 months before it becomes effective.
- Amenorrhoea occurs in 20–25%, which is not desirable in younger women.
- Ectopic pregnancy is reported in 0.2 per 100 women.
- Hysterectomy is required in 25% by the end of 3 years because of recurrence of menorrhagia.

Minimal Invasive Surgery (MIS) (Table 24.3)

- D&C and endometrial study is required if genital tuberculosis or endometrial cancer is suspected or

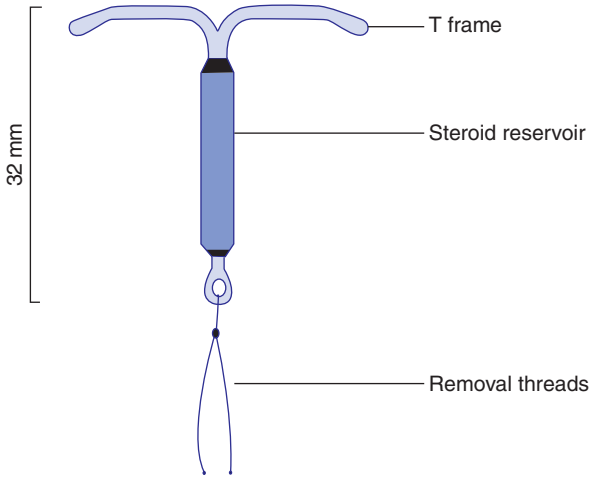


Figure 24.11 Mirena IUCD.

TABLE 24.3 Minimal surgical methods of treating menorrhagia

Ablative technique

1st generation
- Hysteroscopic ablation endometrium resectoscope, roller ball laser (TCRE)

2nd generation
- Radiofrequency-induced thermal ablation, balloon therapy, microwave ablation
- Uterine tamponade in acute bleeding
- Bilateral uterine artery embolization
- Hysterectomy—vaginal, abdominal, laparoscopy

the medical therapy fails. Though mainly performed for diagnostic purpose, 30–40% are relieved of menorrhagia at least for a short period of time.

Ablative Techniques. The idea of endometrial ablation arose from oligomenorrhoea occurring in Asherman syndrome due to synechiae. These procedures are safe, effective with lesser morbidity than hysterectomy, as well as cost-effective with quicker recovery. Hysterectomy is avoided in many cases.

Fertility is not possible following ablative therapy. Therefore, these procedures are mainly suitable for women who wish to preserve the uterus, avoid hysterectomy, but are not interested in pregnancy.

The method should destroy 2–3 mm of myometrium, if recurrence of menorrhagia has to be avoided.

Various procedures have been developed. These are:

- First generation—hysteroscopic endometrial ablation by resectoscope, loop, rollerball coagulation and laser [transcervical endometrial resection (TCRE)].
- Second generation—radiofrequency induced thermal ablation, Cavaterm balloon therapy, microwave endometrial ablation (MEA), laser therapy
- Uterine tamponade
- Bilateral uterine artery embolization.

HYSTEROSCOPIC ENDOMETRIAL ABLATION. These procedures should be performed soon after the menstrual period or the endometrium is thinned out by giving progestogens, danazol or GnRH for 4–6 week prior to the procedure. The patient needs to be selected and contraindications are as noted below:

- Uterine size >12 weeks (12 cm) (volume > 30 mL)
- Uterine fibroid
- Scarred uterus (previous surgery)
- Young woman desirous of pregnancy
- Adenomyosis—TCRE can cause dysmenorrhoea
- Genital infection
- Uterine cancer or preinvasive cancer, atypical hyperplasia

TCRE under general anaesthesia using hysteroscope destroys 4–5 mm endometrium and forms uterine synechiae. The earlier monopolar electrode is replaced by bipolar electrode (VERSAPOINT™).

Complications

- Anaesthetic complications.
- Fluid imbalance with fluid overload (glycine 1.5%), pulmonary oedema, hypertension, hyponatraemia, anaphylactic reaction with dextran, haemolysis and at times death.
- Uterine, bowel and bladder injury with burns and vaginal fistula.
- Embolism, infection and haemorrhage.
- Menorrhagia recurs in 25% cases by the end of 3 years and needs repeat TCRE or hysterectomy.
- Dysmenorrhoea in a few women, and haematometra due to cervical stenosis.

RADIOFREQUENCY-INDUCED THERMAL ABLATION **(RITEA).** It is a blind procedure using radiofrequency electromagnetic thermal energy which destroys the endometrium at 66°C. A 0.6 mm metallic probe is inserted transcervically under general anaesthesia and rotated over 360° for 20 min. About 85% get cured and 30% develop amenorrhoea by the end of 1 year. It is cheaper when compared to TCRE, does not require hysteroscope and complications of distending media are avoided. Contraindications and complications are similar to those of TCRE.

Advantages of RITEA

- Less skill required to perform the procedure. Hysteroscopy not required.
- Less risk with this procedure.

An occasional uterine perforation, vaginal heat leading to vesico-vaginal fistula has been reported.

CAVATERM BALLOON THERAPY (Figure 24.12). First invented by Neuwirth in 1994, this instrument comprises a central computer system, battery and a disposable silicon rubber balloon catheter 5 mm in diameter. Under local anaesthesia, the catheter is inserted transcervically into the uterine cavity,

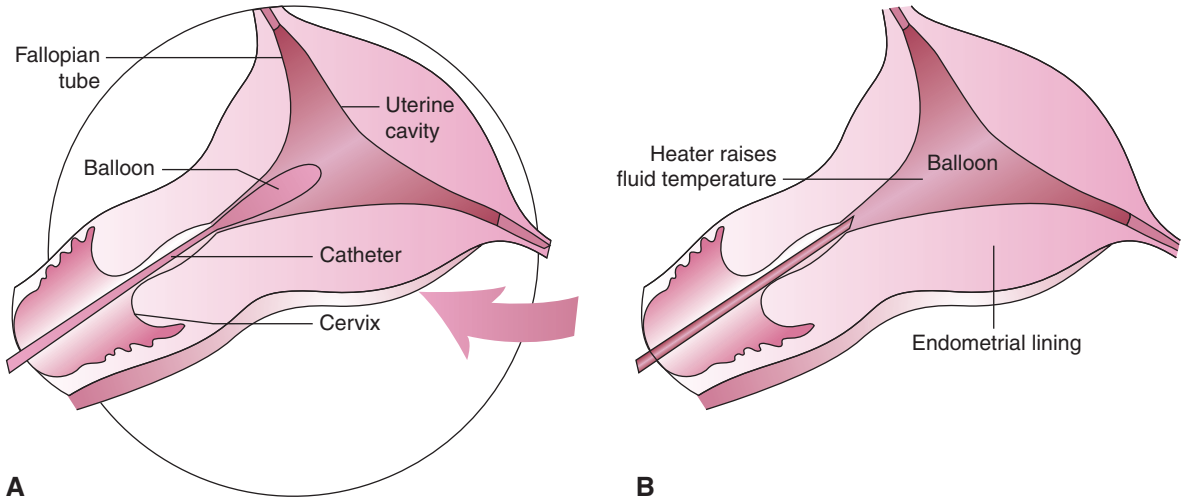


Figure 24.12 Cavaterm balloon. **(A)** Balloon inside the uterus. **(B)** Using the syringe, fluid is injected through the catheter-inflating balloon.

and the balloon is distended with 15–30 mL sterile solution such as 5% glucose or 1.5% glycine. The heating element in the balloon raises the temperature to 87°C (187°F) and this temperature is maintained for 8 min over a pressure of 160–180 mm Hg to exert a tamponade effect. The catheter has an inherent safety design related to time, pressure and temperature, and it gets automatically deactivated to avoid complications. About 6 mm of endometrium gets destroyed, so preoperative endometrium thinning is not required. Approximately, 70–90% resume normal cycles and 15% become amenorrhoeic by the end of 1 year. Hysteroscopy is not required. Failure in retroverted uterus is due to unequal distribution of heat over the endometrium. Cramping felt in the first few hours is treated with NSAIDs and antibiotics are given. Contraindications are endometrium thicker than 11 mm and others similar to TCRE. This technique is easy to learn.

MICROWAVE ENDOMETRIAL ABLATION. It utilizes magnetic energy and works at the frequency of 9.2 GHz. It is an OPD procedure, done under local anaesthesia. It uses an 8 mm applicator with no need of preoperative endometrial thinning. Temperature of 80°C is maintained for 3 min. About 50% become oligomenorrhoeic and 40% amenorrhoeic. Up to 6 mm endometrium gets ablated. No earthing is required unlike in TCRE. Total operating time is 12 min. Hysteroscopy is also not required. The contraindications and complications are similar to other ablative procedures.

VESTA SYSTEM. This system uses a single-use multi-electrode intrauterine balloon to ablate the endometrium. The silicon inflatable electrode carrier has a triangle shape which gets unfold when its insertion sheath is withdrawn. The controller unit is connected to a standard electro surgical generator. It regulates energy to each balloon electrode plate. The temperature is set at 75°C. The balloon is inflated with air following cervical dilatation up to No 9. The procedure takes 5 min under local anaesthesia. Ninety to ninety-four per cent are cured of menorrhagia. The instrument is very expensive and sufficient data is not available to assess its outcome.

UTERINE TAMPONADE. Goldrath advocated uterine tamponade in acute episodes of bleeding by inserting a Foley catheter, distending with 30 mL fluid and leaving the catheter for 24 h.

NovaSure (impedance-controlled endometrial ablation) is the latest and most safe procedure, taking just 90 sec. It uses bipolar radiofrequency and vaporizes endometrium up to myometrium. It takes 90 sec to perform.

Endometrial laser intrauterine thermotherapy (*ELITT*) is a new laser therapy that destroys the entire endometrium as well as 1–3.5 mm of myometrium. It is done as an OPD procedure, and takes 7 min. The machine is known by the name 'GyneLase'.

Second-generation ablative techniques are simpler than TCRE; they are more effective, safe OPD procedures; they are cost effective, and save hysterectomy in several women.

BILATERAL UTERINE ARTERY EMBOLIZATION. Primarily used in uterine fibroids, this technique is extended in intractable AUB in a young woman to preserve her reproductive function. It is also useful in abnormal uterine bleeding complicated by varicose uterine vessels.

Hysterectomy

Hysterectomy for abnormal uterine bleeding is required:

- If medical/MIS fails or menorrhagia recurs.
- In older women more than 40 years not desirous of childbearing, and who opt for hysterectomy as a primary treatment or ablation fails.

Initially performed by abdominal route, it was replaced by laparoscopic hysterectomy or laparoscopic assisted vaginal hysterectomy (LAVH) for its quick recovery, less pain, less abdominal adhesions and avoidance of abdominal scar. Lately, many gynaecologists have shifted to vaginal hysterectomy for undescended uterus which may even be enlarged. This trend is adopted because of lesser morbidity, and lesser postoperative complications of adhesions, scar hernia and pulmonary complications.

Vaginal hysterectomy is contraindicated if:

1. Uterus is grossly enlarged.
2. Previous surgery with possible adhesions, fixity and limitation of uterine mobility.
3. Presence of endometriosis or adnexal mass.
4. Nulliparous women or women with a very narrow vagina. In a woman less than 50 years, ovaries should be conserved unless they are diseased.

Sequele or delayed complications of hysterectomy

Although hysterectomy is a one-time procedure, safe and cures abnormal uterine bleeding, delayed complications are known to occur. These are:

- Ovarian atrophy due to devascularization; the woman develops menopausal symptoms and its complications.
- Adhesions of the ovaries to the vaginal vault causing ovarian residual syndrome, dyspareunia and chronic pelvic pain.
- Vault prolapse.
- Sexual dysfunction—dyspareunia due to a short vagina.
- Chronic abdominal pain due to postoperative pelvic adhesions.
- Urinary and bowel symptoms due to denervation.
- Psychological disturbances.

New Systems

Versapoint bipolar electrosurgical system works in normal saline, is cheap, has excellent haemostasis and causes instantaneous tissue vaporization.

Advantages of Mirena IUCD over ablative techniques:

- Low cost
- OPD procedure—no hospitalization
- Preservation of fertility after its removal

Pregnancy occurs within a year. The only disadvantage is occasional systemic side effects of progestogen.

Summary

1. Medical treatment should be the first line of treatment, unless contraindicated. The drawbacks are the side effects of hormones and the fact that symptoms sometimes return once the hormone therapy is stopped. Prolonged therapy may not be desirable.
2. If medical therapy fails or is contraindicated, consider Mirena IUCD.
3. If Mirena fails or side effects develop, go for ablative techniques. Second generation ablative techniques are safer, quick to perform and are equally effective.
4. When the above methods fail, consider hysterectomy.

Irregular Ripening

It is an ovulatory bleeding due to deficient corpus luteal function. The breakthrough bleeding occurs before the actual menstruation in the form of spotting or brownish discharge. Progestogen given during late luteal phase cures the spotting.

Irregular Shedding (Halban's Disease)

It is rare and self-limited. Irregular shedding is due to persistent corpus luteum. The menstruation comes on time, is prolonged but not heavy. Progestogen can suppress the bleeding, but needs to be taken on tapering dose for 20 days to complete the cycle.

Adenomatous Endometrial Polyp

This form of polypus is really a localized area of endometrial hyperplasia when area or areas of thickened endometrium project into the cavity of the endometrium to look like polypus. The polypus may be single or multiple, small or large enough to protrude through the cervical canal. Mostly, they are sessile and small.

This type of polypus occurs in:

- Endometrial hyperplasia (anovulatory cycles)
- Metropathia haemorrhagica (diffuse polyposis)
- A woman on tamoxifen
- Some cases of fibroid

Pathology

A polypus is covered by cubical epithelium and contains endometrial glands that do not respond to hormones.

Clinical Features

These polypi cause menorrhagia, metrorrhagia or postmenopausal bleeding. The uterus is normal in size or slightly enlarged uniformly. Ultrasound, sonosalpingography and hysterosalpingography detect these polypi, but may miss them if they are very small. Hysteroscopic visualization and ablation is the best treatment, and hysterectomy can be avoided. Histopathology is mandatory to rule out malignant change.

Adenomyomatous polyp resembles adenomatous polyp, but it contains muscle tissue in the stroma. The symptoms and management are similar in both the conditions.

Endometrial Hyperplasia

This occurs in:

- Anovulatory cycles with unopposed oestrogen acting on the endometrium
- Metropathia haemorrhagica
- Obese women
- Polycystic ovarian disease
- A woman on tamoxifen
- A menopausal woman on HRT without progestogen
- Feminizing ovarian tumours

Hyperplasia may be simple hyperplasia, glandular or atypical.

Two per cent women with simple hyperplasia are at a risk of endometrial cancer, and 4–10% women with glandular hyperplasia develop the cancer. Atypical hyperplasia, however, has the tendency to develop into carcinoma in as much as 60–70% cases.

While 80% cases of simple hyperplasia respond to progestogens, response of atypical hyperplasia is only 50%, but with the risk of malignancy. For this reason, atypical endometrial hyperplasia should be treated by hysterectomy and not merely by ablative technique. A small portion of endometrium left behind and undergoing malignancy may not be easily detected following ablative treatment.

Surprisingly, *Mirena is not effective against endometrial hyperplasia caused by tamoxifen.*

Key Points

- Menorrhagia is due to general systemic causes, local pelvic pathology such as fibroid, adenomyosis, endometrial polyp, PID, feminizing ovarian tumours and pelvic endometriosis.
- Abnormal uterine bleeding is due to hormonal imbalance without any coexisting pelvic or systemic cause. It has anovulatory cycles in 80% cases.
- The management of AUB is based on the age of the woman and her parity, and the cause.
- Medical therapy comprising various hormones and drugs should be employed in young women as the first line of treatment. When this fails, Mirena, conservative minimal surgery or hysterectomy should be considered.
- Medical therapy is effective and cheap. Some, however, develop side effects. The prolonged therapy and return symptoms on stoppage requires Mirena IUD, as the next choice.
- Mirena is a non surgical effective method to control menorrhagia, and avoids hysterectomy in many

women. Fertility returns following its removal. It also cures dysmenorrhoea.
- Ablative therapy is effective and retains the uterus, but fertility potential is lost.
- Hysterectomy is the last choice in AUB.
- In a perimenopausal women, D&C is mandatory to rule out malignancy. If benign, either hormonal therapy, ablation technique or hysterectomy will be required.
- Abdominal, vaginal route or laparoscopic hysterectomy remains the decision of the gynaecologist. It also depends upon the safe feasibility of the route.
- Endometrial hyperplasia may be simple or glandular whose malignancy potential is low. It can be treated conservatively with hormones or minimal invasive procedures.
- Atypical hyperplasia has 60–70% risk of malignancy and should be dealt with by hysterectomy. Vaginal hysterectomy is safest; if not feasible, laparoscopic or laparotomy hysterectomy is chosen.

Self-Assessment

1. Enumerate the causes of menorrhagia.
2. How would you investigate and manage a case of menorrhagia.
3. Define abnormal uterine bleeding. How would you manage a case of adolescent abnormal uterine bleeding?
4. Describe the alternatives of minimally invasive surgery in the management of abnormal uterine bleeding.
5. How would you suspect coagulation defects as a cause of abnormal uterine bleeding?. How would you investigate and treat such a case?
6. Discuss the medical management of abnormal uterine bleeding in a woman of 35 years.
7. A woman, 32 years, presents with 3 months amenorrhoea and continuous vaginal bleeding. The uterus is of normal size. Discuss the management.
8. What are the causes of menorrhagia in a 32-year-old woman?
9. Describe puberty menorrhagia and its management.
10. A woman 38–year-old presents with polymenorrhagia. The uterus is 12 weeks size. Discuss the management.
11. Write short notes on:
    - Metropathia haemorrhagia
    - Ovulatory menorrhagica

Suggested Reading

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Chapter 25 Genital Prolapse

CHAPTER OUTLINE

Prolapse is a common complaint of elderly women in gynaecological practice. Normally, when a woman strains there is no descent either of the vaginal walls or of the uterus. In prolapse, straining causes protrusion of the vaginal walls at the vaginal orifice, while in severe cases, the cervix of the uterus may be pushed down to the level of the vulva. In extreme cases, the whole uterus and most of the vaginal walls may extrude from the vagina. This happens mostly in postmenopausal and multiparous women.

Nulliparous prolapse is seen in 2% and vault prolapse in 0.5% cases following hysterectomy.

Supports of the Genital Tract

DeLancey introduced three level system of support.

- Level I—Uterosacral and cardinal ligaments support the uterus and vaginal vault. The cervix remains at or just above the ischial spines, and the vagina lies horizontally.
- Level II—Pelvic fascias and paracolpos which connects the vagina to the white line on the lateral pelvic wall through the arcus tendineus. This includes the pubocervical fascia anteriorly and the rectovaginal fascia and septum posteriorly.
- Level III—Levator ani muscle supports the lower one-third of the vagina. The levator muscle forms a platform against which the pelvic organs (uterus and upper vagina) gets compressed during straining.
- Level I damage causes uterine descent, enterocele, vault descent.
- Level II damage causes cystocele, rectocele.
- Level III damage causes urethrocele, gaping introitus and deficient perineum.

For diagrammatic representations of DeLancey's three levels of support to the genital tract, refer to Figures 25.1 and 25.2.

Clinically unrecognized damages and breaks in these supports can be detected by ultrasound and MRI.

Aetiology of Prolapse (Table 25.1)

The most important aetiological factor in prolapse is atonicity and asthenia that follow *menopause*. Most women who develop prolapse are of menopausal age when the pelvic floor muscles and the ligaments that support the female genital tract become slack and atonic. Many women develop minor degrees of prolapse soon after childbirth, yet if they exercise their pelvic floor muscles and improve their general muscular tone, they can control the prolapse. A major degree of prolapse can be considerably reduced by postnatal pelvic floor exercises because in these young women muscle tone can be regained by exercise. This does not however apply to menopausal women whose support has become atonic due to oestrogen deficiency and decreased collagen content in the fascias.

A *birth injury* is another important aetiological factor. Initial unrecognized injury during childbirth may be considerable. A perineal tear is less harmful than the excessive stretching of the pelvic floor muscles and ligaments that occurs during childbirth because overstretching causes atonicity whereas a torn muscle can be stitched or toned

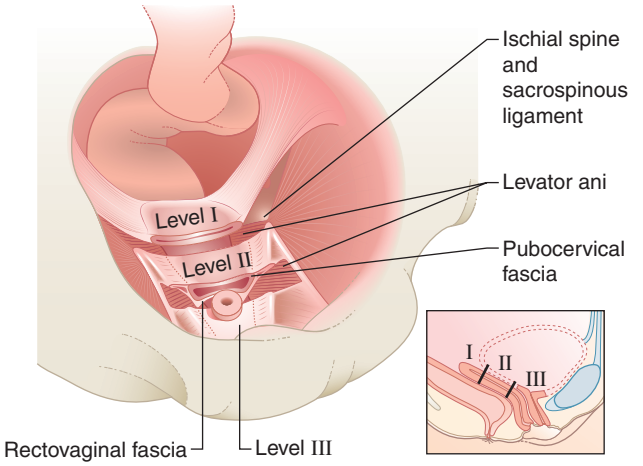


Figure 25.1 Supports of the genital tract (From Figure 21-5. Ian Symonds and Sabaratnam Arulkumaran: Essential Obstetrics and Gynaecology, 5th Ed., Elsevier, 2013.)

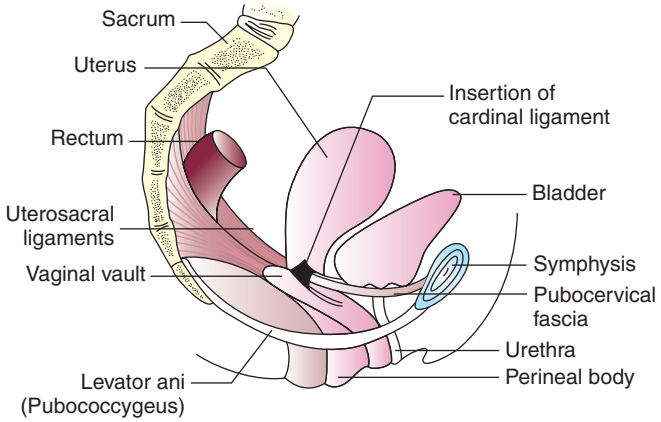


Figure 25.2 Various supports of the uterus.

TABLE 25.1 Aetiology of prolapse

Atonicity	• Menopause • Congenital weakness • Multiparity
Birth injuries	• Prolonged labour • Perineal tear • Pudendal nerve injury • Operative delivery • Multiparity • Big baby • Raised intra-abdominal pressure • Chronic bronchitis

up. For example, a patient with a complete perineal tear probably exercises her levator muscles continuously and to an extreme degree in order to obtain some sphincteric control over the rectum, and in this way, tones up not only the muscles of the pelvic floor but all the ligamentary supports in the pelvis. A complete perineal tear is therefore not followed by prolapse. Squatting position used during delivery may cause excessive stretching of the pelvic floor muscles and ligaments, and lead to genital prolapse a few years later.

In recent years, perineal ultrasound imaging has contributed to our understanding of birth injuries to the pelvic floor muscles and sphincters caused by vaginal delivery.

Peripheral nerve injury such as to the pudendal nerve during childbirth causes prolapse which is reversible in 60%; it may also be responsible for stress incontinence of urine.

In India, a higher incidence and a more severe degree of uterovaginal prolapse occurs in women who are delivered at home by *dais* (untrained midwives). This is because the patients are made to *bear down before full dilatation of the cervix* and when the bladder is not empty. Moreover, the second stage of labour is prolonged with undue stretching of the pelvic floor muscles as episiotomy is not employed by the *dais*. Episiotomy prevents muscle stretching and thereby atonicity. Likewise, the use of forceps in the case of prolonged second stage protects against prolapse. Another reason for a high incidence of prolapse is that circumstances force poor women to *resume their heavy work soon after delivery* without any rest or pelvic floor exercises. Cases delivered by caesarean section hardly ever develop prolapse.

Prolapse seen in unmarried or nulliparous women is attributed to spina bifida occulta and split pelvis which result in inherent weakness of the pelvic floor support. Patients who demonstrate *congenital weakness of the pelvic floor muscles* have an easy or a precipitate labour. Congenital prolapse in the newborn has been reported and though it can be controlled, it is likely that such a prolapse may recur later in life or following childbirth. A family history of prolapse confirms the congenital nature of prolapse.

Ventouse extraction of the fetus *before the cervix is fully dilated* can result in overstretching of both Mackenrodt's ligaments and the uterosacral ligaments, and cause prolapse.

Prolonged bearing down in the second stage and *Credè's method* of downward vigorous push on the uterus to expel the placenta may weaken the ligamentary supports of the genital tract. Lacerations of the perineal body during childbirth, unless sutured immediately, will widen the hiatus urogenitalis.

Delivery of a big baby also stretches the perineal muscles and leads to patulous introitus and prolapse. Precipitate labour and fundal pressure may also be responsible for prolapse.

Rapid succession of pregnancies preclude proper puerperal rehabilitation, and there will be a tendency to develop prolapse.

Raised intra-abdominal pressure due to chronic bronchitis, large abdominal tumours or obesity tends to increase any degree of prolapse which may previously be present. Smoking, chronic cough and constipation are the predisposing factors.

Abdominoperineal excision of the rectum and *radical vulvectomy* are surgical procedures that are known to cause prolapse postoperatively.

Operations for stress incontinence such as Stamey and Pereyra operations leave a hiatus in the vaginal wall causing cystocele and enterocele, while elevating the bladder neck.

Classification of Prolapse (Figures 25.3 and 25.4)

Anterior vaginal wall (Figure 25.5)

Upper two-third—Cystocele
Lower one-third—Urethrocele
} Cystourethrocele

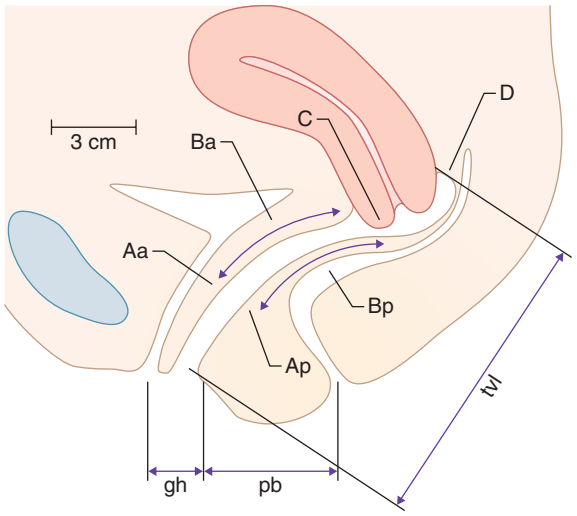


Figure 25.3 Pelvic organ prolapse quantification system (POP-Q). (From Figure 21-9. Ian Symonds and Sabaratnam Arulkumaran: Essential Obstetrics and Gynaecology, 5th Ed., Elsevier, 2013.)

Posterior vaginal wall

Upper one-third—Enterocele (pouch of Douglas hernia) (Figure 25.6)

Lower two-third—Rectocele

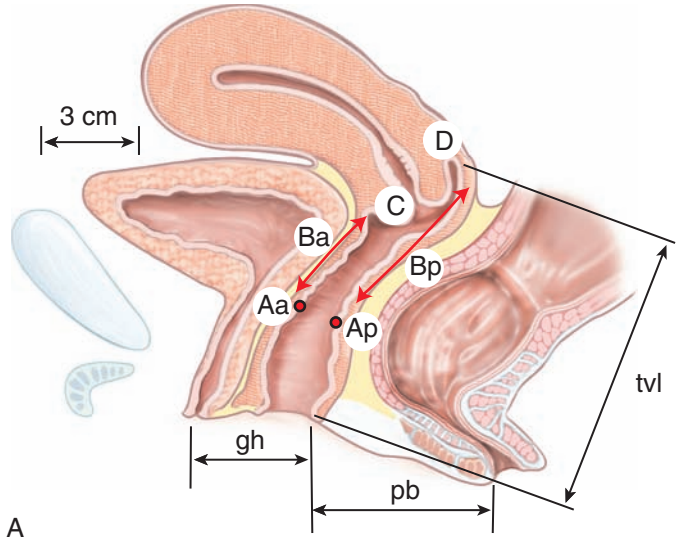
Uterine descent

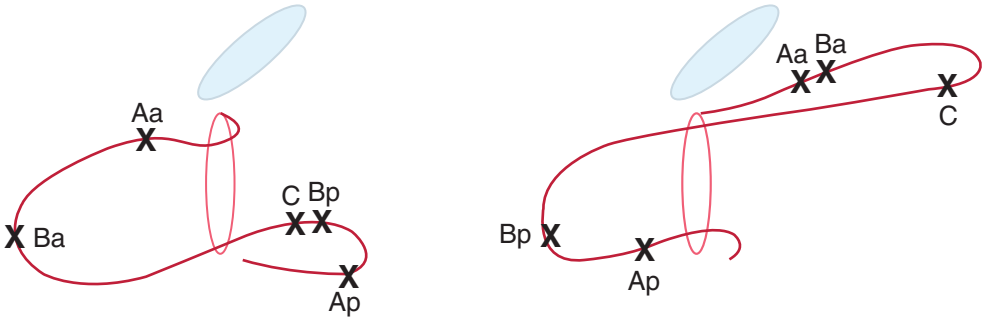
- Descent of the cervix into the vagina
- Descent of the cervix up to the introitus
- Descent of the cervix outside the introitus

Procidentia—All of the uterus outside the introitus (Figures 25.7 – 25.9).

Cystocele

The bladder is supported by pubocervical fascia which extends laterally to the arcus tendineus and fuses with the levator ani muscle below. The urethra is supported by the posterior urethral ligament which is fixed to the pubic bone.





+3 Aa	+6 Ba	+2 C
4.5 gh	1.5 pb	6 tvl
-3 Ap	-2 Bp	–

-3 Aa	-3 Ba	-6 C
4.5 gh	1 pb	8 tvl
+3 Ap	+5 Bp	–

B Profile A Profile B

Figure 25.4 Pelvic organ prolapse quantification (POP-Q) system for staging pelvic organ prolapse. Aa: Point A anterior; Ap: Point A posterior; Ba: Point B anterior; Bp: Point B posterior; C:, Cervix or vaginal cuff; D: Posterior fornix (if cervix is present); gh: Genital hiatus; pb: Perineal body; tvl: Total vaginal length. (From Figure 1.11. Victor Nitti: Vaginal Surgery for the Urologist. Saunders: Elsevier, 2012.)

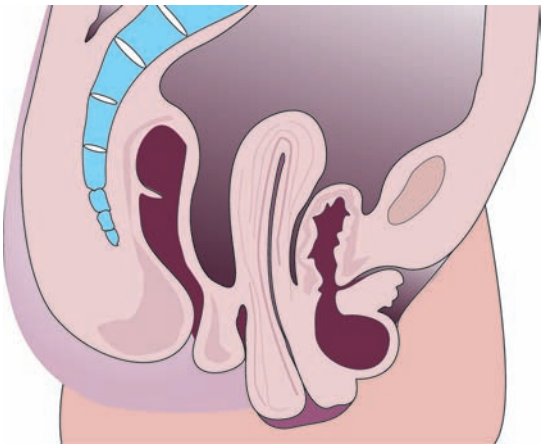


Figure 25.5 Prolapse of the cervix, anterior vaginal wall and bladder. The cervix is elongated and hypertrophied. The anterior vaginal wall and bladder have prolapsed outside the vaginal orifice. The cervix is also prolapsed. In this case, the ligamentary supports hold up the body of the uterus. Note that the almost vertical direction of the uterosacral ligament must follow from the cervix to the junction of the second and third sacral vertebrae. Compare this figure with Figure 25.8.

In prolapse of the anterior vaginal wall, the upper part of the anterior vaginal wall descends and in advanced cases it may protrude outside the vaginal orifice. In these cases, the vesical and vaginal fasciae are thinned out and fail to support the bladder, so that the bladder prolapses with the anterior vaginal wall. This condition is termed as cystocele. In mild cases, the lower portion of the anterior vaginal wall does not prolapse, and the urethra is well supported by the posterior urethral ligament. When the urethra along with the lower one-third of the anterior wall prolapses, it is termed urethrocele, and the patient invariably complains of stress incontinence. When the cystocele protrudes outside the vulva, owing to friction, the vaginal epithelium becomes thickened, hypertrophied and keratinized. Ulceration can occur over the vaginal wall. Senile vaginitis in menopausal women shows a thin reddened vagina. The breaks in the lateral attachment cause the vaginal sulci to disappear and the lateral portion of the bladder prolapses.

Prolapse of the Uterus

If the uterus prolapses, there is always some associated descent of the anterior vaginal wall. It is customary to describe three degrees of prolapse of the uterus. In the first degree, the cervix descends into the vagina; in the second degree, the cervix descends to the level of the vulva; while in the third degree, the cervix protrudes outside the vaginal orifice. In procidentia (Figure 25.9(A)), the whole uterus protrudes outside the vulva, bringing with it both the vaginal walls, and it may be possible to feel the coils of the small intestine in the pouch of Douglas. In most cases, the vaginal portion of the cervix is hypertrophied and in uterine prolapse of the third degree, the epithelium covering the cervix is thickened— keratinization; it is not uncommon for trophic ulcers to form both on the cervix and on the prolapsed anterior wall—these are called decubitus ulcers.

In prolapse of the uterus, the supravaginal portion of the cervix is sometimes elongated. Supravaginal elongation of the cervix must be distinguished from congenital vaginal elongation, in which the fornices are deep and the elongation is restricted only to that portion of the cervix which projects into the vagina (Figures 25.5, 25.8, 25.10 and 25.11).

Prolapse of the Posterior Vaginal Wall

In rectocele, the rectum protrudes with the posterior vaginal wall. The tissues which normally intervene between the posterior vaginal wall and the rectum may have been

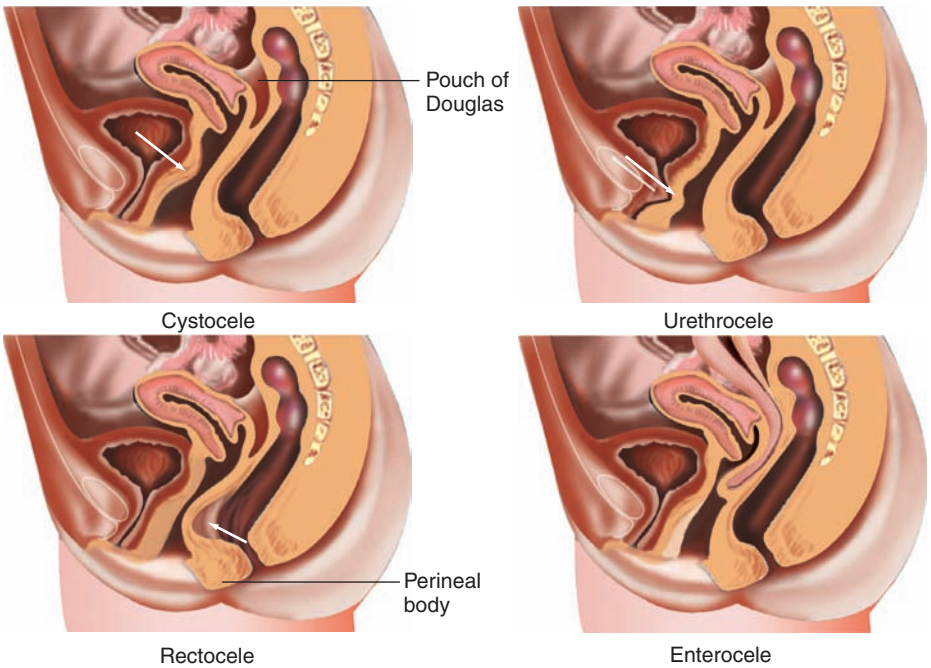


Figure 25.6 The anatomy of prolapse.

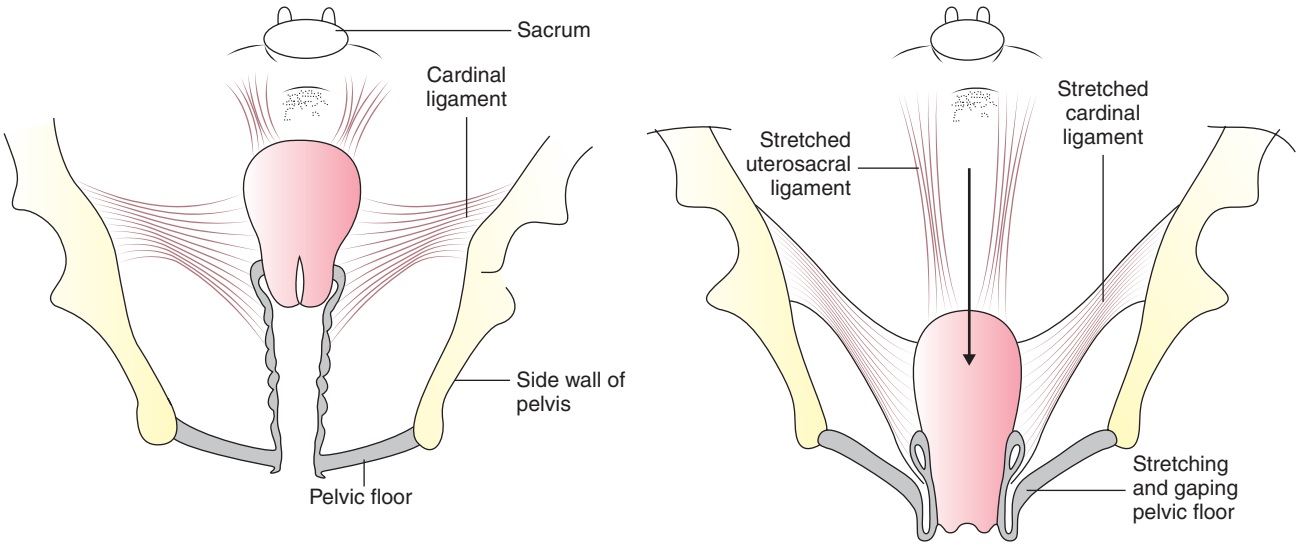


Figure 25.7 Lateral supports of the uterus showing cardinal ligaments.

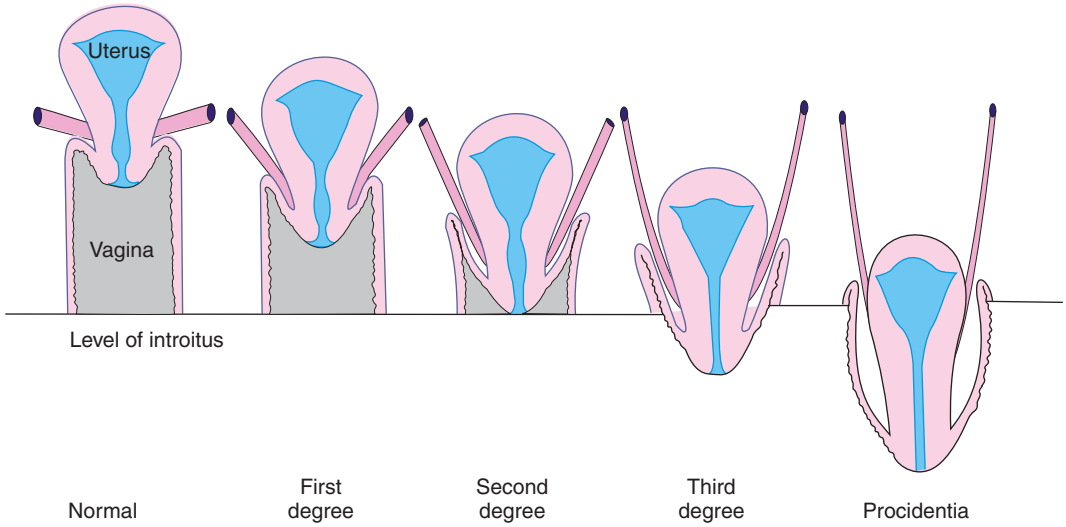


Figure 25.8 Note the descent of the cervix which is accompanied by stretching of the ligaments and by supravaginal elongation of the cervix.

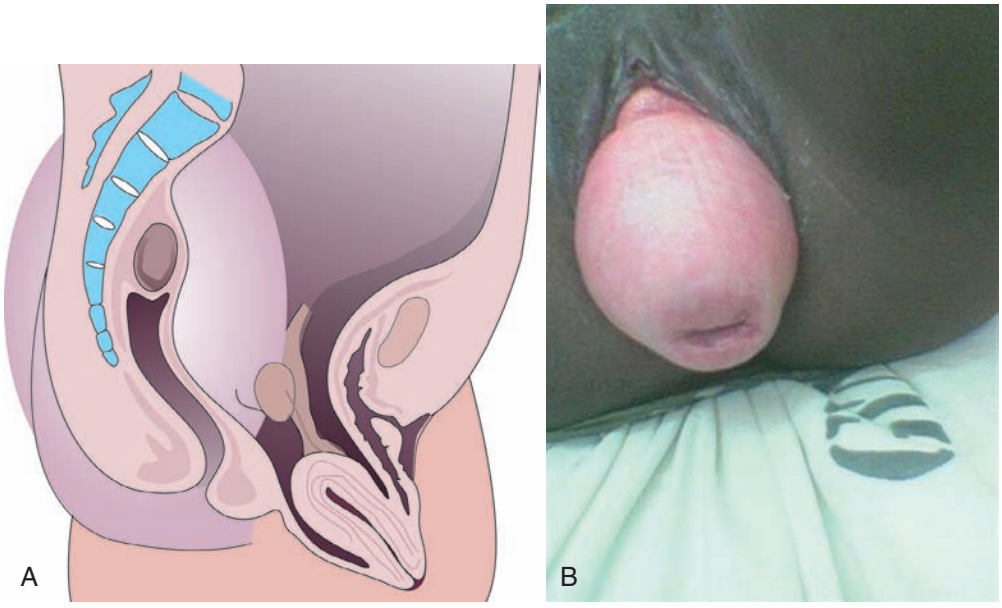


Figure 25.9 **(A)** Complete procidentia. Note that the whole of both vaginal walls lie outside the vaginal orifice. The whole of the uterus also lies below this level. Clearly the ligamentary supports of the uterus must be greatly stretched to allow such a degree of prolapse. Compare this figure with Figure 25.8. **(B)** Procidentia with cystocele, enterocele (From Figure 2. Cyril C Dim, Uchenna A Umeh, Hyginus U Ezegwui, et al. Uterine Procidentia in an African Adolescent: An Uncommon Gynecological Challenge. Journal of Pediatric and Adolescent Gynecology, Vol 2(1): 37–39, 2008.)

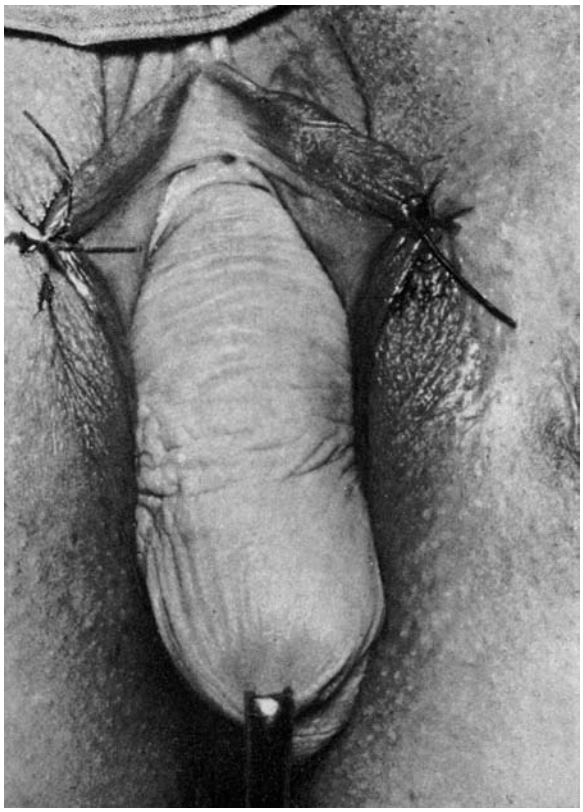


Figure 25.10 Prolapse of the uterus at operation. The cervix has been drawn down, and the whole of the uterus can be pulled outside the vaginal orifice.

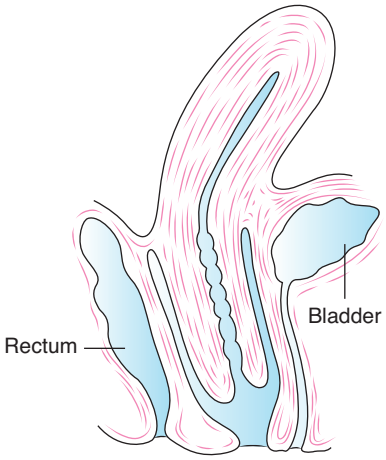


Figure 25.11 Congenital elongation of cervix.

damaged by obstetric injury, and the vagina and rectum may be adherent by scar tissue. In prolapse of the pouch of Douglas, it is not uncommon for the upper part of the posterior vaginal wall to protrude outside the vulva and for coils of the intestine to be palpable in the prolapsed part. The term 'enterocele' is used to describe this type of prolapse (Figure 25.6). Enterocele is herniation of the pouch of Douglas into the rectovaginal septum. It is often associated with uterine prolapse; the greater the uterine prolapse, the bigger is the enterocele.

If a woman with prolapse is examined and asked to strain, the usual sequence of events is for the anterior wall to protrude first, followed by the cervix and then the posterior vaginal wall.

Decubitus Ulcer

Keratinization and pigmentation of the vaginal mucosa as well as ulceration of the prolapsed tissue are caused by friction, congestion and circulatory changes in the dependent part of the prolapse. Reduction of the prolapse into the vagina and daily packing heals the ulcer in a week or two. Decubitus ulcer needs to be differentiated from cancer of the cervix. Apart from cytology and biopsy, the other distinguishing features are that the decubitus ulcer shows a clean edge and heals on reposition and vaginal packing. In rare cases, carcinoma develops over the decubitus ulcer and when a ring pessary is left in situ for a long period.

Elongation of the Cervix

If the supravaginal portion of the cervix is well supported by Mackenrodt ligaments but the vaginal portion of the cervix prolapses with the vagina, the supravaginal portion gets stretched and elongated. This usually happens with second degree and third degree prolapse of the uterus. With procidentia, the entire uterus slides with the vagina and hence the cervix retains its normal length. It is not uncommon for the cervix to elongate to as much as 10 cm in length. The cervix may show hypertrophy and congestion. The uterus is invariably retroverted.

Obstruction in the Urinary Tract

A huge cystocele causes obstructive uropathy and leads to hypertrophy of the bladder wall and trabeculations. The kinking of the distal ureters in procidentia can lead to hydroureter and hydronephrosis if prolapse is not surgically corrected. Urinary tract infection is not uncommon if residual urine remains in the bladder in a huge cystocele.

Incarceration of the prolapse is encountered in rare cases when, due to oedema and congestion, the prolapse becomes irreducible. Head low position, ice-packing or packing with magnesium sulphate reduces the oedema, enabling the prolapse to be reduced.

POP-Q System (Table 25.2, Figure 25.3)

Quantification of prolapse is lately described by the International Continence Society, and is objective and site-specific. The hymen is taken as a fixed point (O). Six reference points are measured, using scaled spatula, and tabulated in a grid (Figure 25.4). The points above the hymen are described as minus and points below as plus.

TABLE 25.2 Staging of POP

Stage 0	No demonstrable prolapse
Stage 1	All points < -1
Stage 2	Lowest point within 1 cm of hymen (between -1 and $+1$)
Stage 3	Lowest point > 1 cm below hymen but not complete prolapse
Stage 4	Complete prolapse with lowest point equal to TVL-2

Symptoms of Prolapse

The patient complains of something descending in the vagina or of *something protruding either at the vulva or externally*. The prolapse is aggravated by straining and coughing, and by heavy work, whereas on rising the physical signs are least obvious. Often the patient states that the prolapse reduces itself when she lies down. If there is a large prolapse, the external swelling may inconvenience her during walking or carrying out her everyday duties. Even in mild degree, patients are conscious of a sense of weakness and of a lack of support around the perineum.

Towards the end of the day, the patient may complain of a vague midsacral discomfort and backache, which are relieved by rest. This symptom is most logically explained as a uterosacral strain. Some women suffer from a 'bearing-down' feeling above the pubes.

In most cases of prolapse, there is some degree of vaginal discharge. The discharge may emanate from a chronically inflamed lacerated cervix, but usually it is caused by the relaxation of the vaginal orifice which allows foreign organisms to invade the vagina and produce a mild degree of vaginitis. A friction or decubitus ulcer is an obvious cause of discharge and bleeding. Menstrual history is usually normal.

One of the important symptoms of prolapse is micturition disturbances. The most frequent is imperfect control of micturition and stress incontinence. This imperfect control of micturition is caused by lack of support to the sphincter mechanism of the urethra. Frequency of micturition is also a common symptom, caused in some, by chronic cystitis and in others, by incomplete emptying of the bladder. In severe degrees of cystocele, patients frequently complain that they have difficulty in micturition, and that the more they strain, the less easily can they pass urine. The explanation of this symptom is that when the intra-abdominal pressure is raised during straining, the urine is pushed down into the cystocele below the level of the internal meatus. Patients usually offer the information that they can only empty the bladder by pressing back the cystocele into the vagina with their fingers. Stress incontinence of urine occurs when the neck of the bladder and internal urinary meatus descend below the level of the pelvic floor muscles.

Rectal symptoms are less remarkable, and constipation is rare (level III damage).

Coital difficulties with third degree uterine prolapse and procidentia are obvious. A major degree of prolapse prevents penetration and orgasm due to a lax outlet.

Urinary symptoms develop when pubocervical fascia is damaged and breaks occur at level III support.

Investigations

The patient with prolapse should be carefully examined, because the treatment is based on the physical signs observed. She is made to cough and strain, and the nature and degree of prolapse noted. The vulva is examined for evidence of any perineal laceration. Inspection will show whether the vaginal orifice is relaxed. The perineal body and levator muscles are palpated to determine the muscle tone and the dimensions of the hiatus urogenitalis. Stress incontinence should be looked for by asking the patient to strain. Speculum examination determines the vaginal prolapse, the degree of uterine descent and the condition of the vagina and cervix. Cervical cytology should be obtained, but it is important to remember that in third degree uterine prolapse and procidentia, the cervix lying outside may be dry and may not yield a satisfactory smear (a high false-negative report). Enterocele should be looked for. If not recognized and corrected surgically, vault prolapse can occur. The vaginal examination should include measuring the length of the cervix, position and mobility of uterus. Any adnexal mass present should be noted. The general condition of the patient should be evaluated to decide on her fitness for surgery. On the whole, there is not much difficulty in arriving at an exact diagnosis.

The laboratory investigations include: (i) haemoglobin, (ii) urine examination, (iii) blood urea, (iv) blood sugar, (v) X-ray chest, (vi) ECG, (vii) urine culture, (viii) high vaginal swab in cases of vaginitis and other investigations mandatory prior to major gynaecological surgery.

IVP will reveal ureteric obstruction in major prolapse. Ultrasound and MRI localize the defects in the supporting structures and help in surgery. Some use proctography in recurrent prolapse to study the anatomical defect.

Transperineal and vaginal ultrasound reveal defect in the levator ani muscles and lateral supports, whereas transrectal ultrasound is useful to confirm enterocele.

Differential Diagnosis

- *Vulval cyst* and Gartner cyst tumour can be easily differentiated from prolapse.
- The *cyst of the anterior vaginal* wall is usually tense with well-defined margins and cannot be reduced on pressure.
- *Urethral diverticula* are rare, always small and are situated low down in the anterior vaginal wall. Urethroscopy helps in the diagnosis.
- *Congenital elongation of the cervix* can be differentiated from prolapse because it is the vaginal portion of the

cervix that is elongated and there is no accompanying vaginal prolapse. The fornices are deep.
- *Cervical fibroid polyps* can be easily identified as the cervix is high up in its normal anatomical position.
- *Chronic inversion* can be recognized because the cervix is further up, and the uterus cannot be defined. The uterine sound will confirm the diagnosis. Ultrasound and laparoscopy will identify the fundal depression and absence of uterine fundus in the pelvis.
- In rare cases, the patient complains of vaginal prolapse, but, in fact, she suffers from *rectal prolapse*.

Complications of Prolapse

1. Kinking of ureter with resulting renal damage can occur in procidentia and enterocele. The ureter can also be included in the sutures at the vaginal vault during surgery.
2. Urinary tract infection (chronic) in a large cystocele with residual urine can lead to upper renal tract infection and renal damage.
3. In rare cases, cancer of the vagina is reported over the decubitus ulcer and if the ring pessary is left in over a long period.

Prophylaxis of Prolapse

Careful attention during childbirth can do much to prevent prolapse.

- Antenatal physiotherapy, relaxation exercises and due attention to weight gain and anaemia are important.
- Proper supervision and management of the second stage of labour is needed.
- A generous episiotomy in most primigravidae and in all complicated labours, for example, breech delivery should be considered. Recently, however, the usefulness and the role of episiotomy in prolapse have been questioned, and complications of episiotomy are listed.
- Low forceps delivery should be readily resorted to if there is delay in the second stage of labour.
- A perineal tear must be immediately and accurately sutured after delivery.
- Postnatal exercises and physiotherapy are beneficial.
- Early postnatal ambulation.
- Provision of adequate rest for the first 6 months after delivery and the availability of home help for heavy domestic duties.
- A reasonable interval between pregnancies so that too many births at too short intervals are avoided. This allows recovery of muscle tone in between pregnancies.
- Avoiding multiparity by using a family planning method so that strain on the ligamentary supports is reduced.
- Prophylactic hormone replacement therapy (HRT) in menopausal women can avoid or delay occurrence of prolapse. HRT has no role in established prolapse.

Treatment (Table 25.3)

One of the most important decisions to consider is the appropriate treatment for prolapse in a young woman following childbirth. It is a great mistake to advise immediate operative treatment in such a case. If the operation is performed within 6 months of delivery, there is always the possibility of recurrence of prolapse. Besides, these women rapidly improve if well-directed conservative measures are adopted. Abdominal exercises, massage and perineal exercises practised early and strenuously, will prevent or reduce prolapse. *Conservative measures should be advised following delivery for 3 to 4 months*.

Surgery is advised in women over 40 unless it is contraindicated or is hazardous on account of some medical disorders. It is also contraindicated during pregnancy.

Pessary Treatment of Prolapse

The ring pessary for prolapse is nearly a thing of the past when majority of elderly women and very young women desirous of childbearing received this treatment. With modern anaesthesia and good preoperative care, advanced age is no longer a contraindication to permanent surgical procedure.

The pessary treatment of prolapse has certain *limitations*:

- It is never curative and can only be palliative.
- It can cause vaginitis.
- Pessary needs to be changed every 3 months.
- The wearing of a pessary is not comfortable to some women and may cause dyspareunia.

TABLE 25.3 Management of genital prolapse

Nulliparous	Abdominal sling operations
Pregnancy Postnatal	Ring pessary up to 16 weeks • Ring pessary and pelvic floor exercises for 3–6 months • Surgery if required thereafter
Young woman <40 years	Conservative vaginal surgery (fertility sparing surgery) • Cystocele, rectocele repair • Manchester repair • Sling operation
Woman beyond 40 years and multipara	Vaginal hysterectomy and pelvic floor repair

- If the vaginal orifice is very patulous, the pessary is often not retained.
- A forgotten pessary can be the cause of ulcer, and in rare cases, carcinoma of the vagina and a vesicovaginal fistula.
- A pessary does not cure urinary stress incontinence.

Current *indications* for use of pessary are:

- A young woman planning a pregnancy.
- During early pregnancy.
- Puerperium.
- Temporary use while clearing infection and decubitus ulcer.
- A woman unfit for surgery.
- In case a woman refuses for surgery.

The ring pessary made of soft plastic polyvinyl chloride material is available in different sizes. In a young woman planning to conceive in the near future, the operation is better postponed till after the childbirth, because a good surgical result could be ruined by vaginal delivery. Similarly, a pregnant woman with prolapse needs a ring pessary in the first trimester of pregnancy. As the uterus grows abdominally, the prolapse gets reduced, and the pessary can then be removed. Pessary treatment may be needed in a puerperal woman with severe degree of prolapse and distressing symptoms, while the conservative measures are being carried out in the first few months after delivery.

Operative Treatment of Prolapse

The type of surgery offered to the patient with prolapse depends on the age of the patient, her desire to retain the uterus either for reproductive or for menstrual function, her menstrual history, general condition as well as the degree of uterine prolapse and uterine pathology.

The aim of surgery is to:

- relieve symptoms
- restore anatomy
- restore sexual function
- prevent recurrence.

Preoperative Treatment

Oestrogen cream applied locally for senile vaginitis should be stopped a few days prior to surgery, as increased bleeding caused by its vascularity during surgery will be undesirable. The patient should receive a course of chemotherapy if urinary infection prevails, and antibiotics for vaginal infection. Decubitus ulcer is healed by vaginal pack soaked in acriflavine or betadine solution for 2 weeks.

Postoperative Care

Postoperative care is important and comprises:

- Parental fluids until bowel sounds return. Early oral fluids are now advocated.
- Antibiotics, sedatives, metronidazole for 24 h IV.
- Indwelling catheter for 48 h.
- Vaginal pack for 28 h.
- Early ambulation.

The commonly performed operations are briefly described here.

Surgery

Anterior Colporrhaphy

Anterior colporrhaphy operation is performed to repair a cystocele and cystourethrocele. Traction is given on the cervix to expose the anterior vaginal wall. An inverted T-shaped incision is made in the anterior vaginal wall, starting with a transverse incision in the bladder sulcus. Through its midpoint, a vertical incision is extended up to the urethral opening (Figure 25.12). The vaginal walls are reflected to either side to expose the bladder and vesicovaginal fascia (Figure 25.13). The overlying vesicovaginal fascia is tightened, and the excess vaginal wall excised to correct the laxity. Then the vaginal is wall sutured. In women suffering from stress incontinence, a Kelly suture to plicate the bladder neck helps to correct stress incontinence (Figure 25.14). The breaks or defects in the lateral supports require further suturing of the pubocervical tissue to the arcus tendineus. This elevates the vaginal wall. In repeat surgery for recurrence or failed surgery, a mesh is supplemented to strengthen the support to the bladder.

Posterior Colporrhaphy and Colpoperineorrhaphy

Posterior colporrhaphy operation is done to correct a rectocele and repair a deficient perineum.

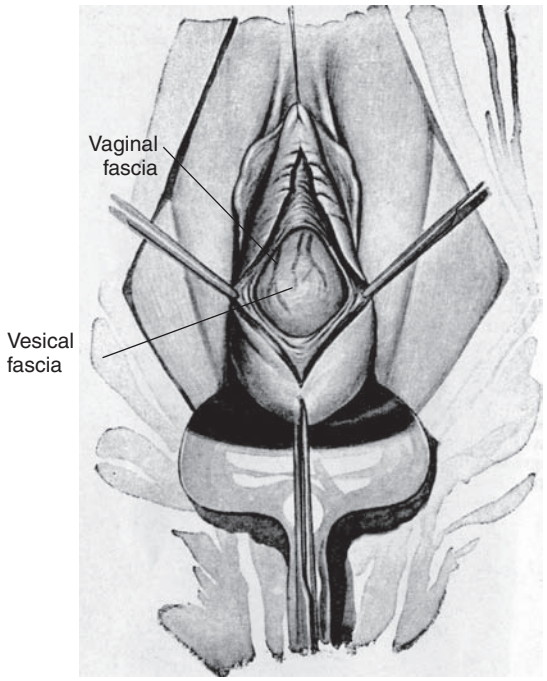


Figure 25.12 Anterior colporrhaphy. A midline incision is made and the vaginal wall and vaginal fascia are cut through. The vesicovaginal space is opened up. The vesical fascia is recognized because of the dilated veins which ramify in its layer.

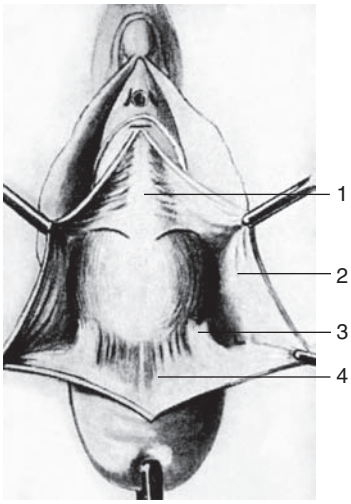


Figure 25.13 The appearance after the dissection of the vaginal flaps: (1) posterior urethral ligament—the well-defined cranial border is emphasized. In the illustration, the vesicovaginal space has been opened up, and the vaginal fascia (2) remains attached to the vaginal wall. (3) Bladder septum. (4) Vesicocervical ligament.

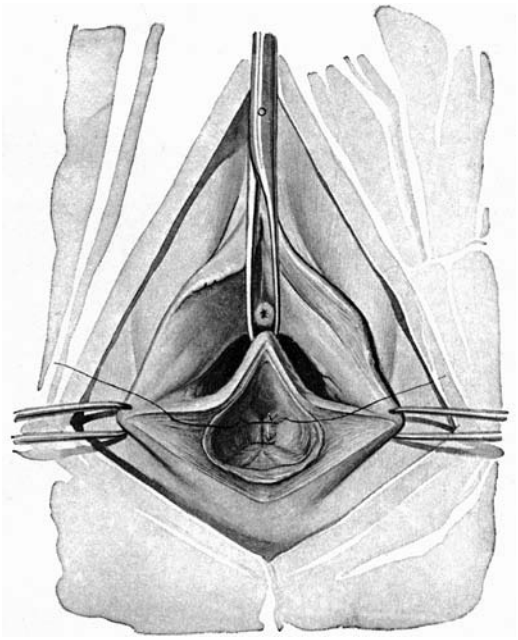


Figure 25.14 Colpoperineorrhaphy. A triangular piece of vagina has been removed and the free edges of the wound are drawn apart. The perineal fascia has been divided and the levator ani muscles have been sutured together in the midline.

The lax vagina over the rectocele is excised, and the rectovaginal fascia repaired after reducing the rectocele. The approximation of the medial fibres of the levator ani helps to restore the calibre of the hiatus urogenitalis, restore the perineal body and provide an adequate perineum separating the hiatus urogenitalis from the anal canal (Figure 25.14).

It is commonly combined with an anterior colporrhaphy, or a vaginal hysterectomy requiring pelvic floor repair, and as part of Fothergill's repair.

To avoid recurrence and to reinforce the weak supportive fascia, some use mesh in the fascial layer. However, dyspareunia, erosion, infection requiring its removal and sinus formation are the disadvantages, apart from the fact that the mesh is expensive.

Fothergill's Repair (Manchester Operation)

In this operation, the surgeon combines an anterior colporrhaphy with amputation of the cervix. The cut ends of the Mackenrodt ligaments are sutured in front of the cervix, and the raw area on the amputated cervix is covered with vaginal mucosa. It is followed up with a colpoperineorrhaphy (Figures 25.15–25.17).

The operation preserves menstrual and childbearing functions. However, fertility is somewhat reduced because of the amputation of the cervix causing loss of cervical mucus. It is suitable for women under 40 years who are desirous of retaining their menstrual and reproductive functions.

Some include dilatation of cervix and endometrial curettage as a preliminary step in Fothergill repair. This is optional, but desirable in a woman complaining of menstrual disorder associated with prolapse.

Cervical amputation may lead to incompetent cervical os, habitual abortions or preterm deliveries. Excessive fibrosis may lead to cervical stenosis and dystocia during labour. In rare cases, it may cause haematometra. Recurrence of prolapse may occur following vaginal delivery in

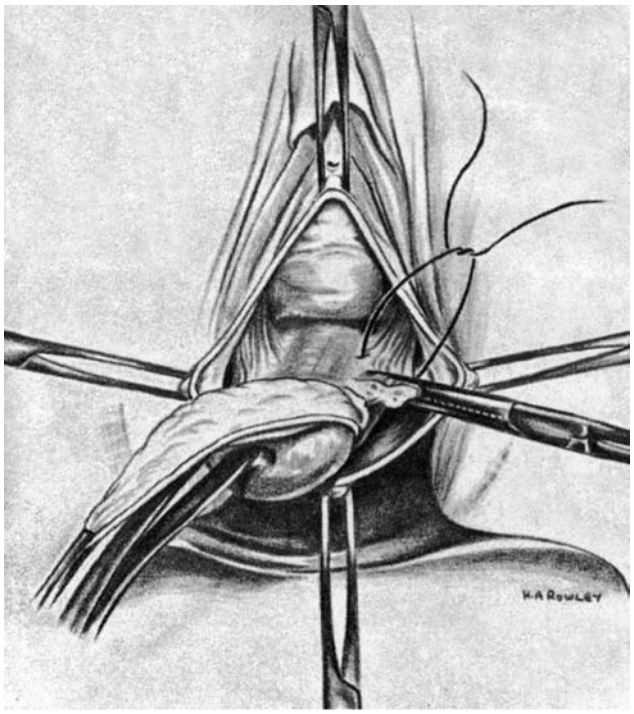


Figure 25.15 The vaginal skin has been excised and pulled down over the cervix. Mackenrodt's ligaments have been clamped and cut, and a suture ligature has been inserted in the left of Mackenrodt's ligament. Note that the bladder has been freely mobilized and pushed well up out of danger.

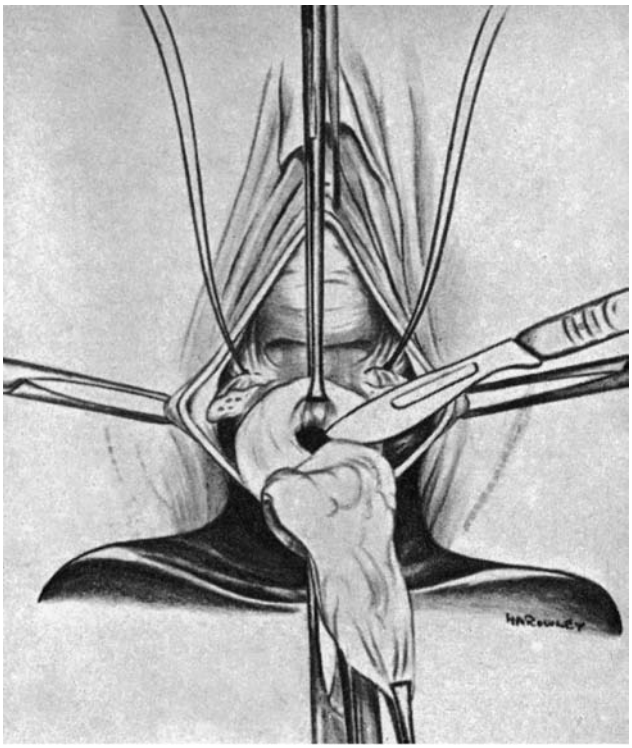


Figure 25.16 Both Mackenrodt's ligaments have now been ligated and the cervix almost completely amputated. A vulsellum is attached to the anterior lip of the cervix above the amputation.

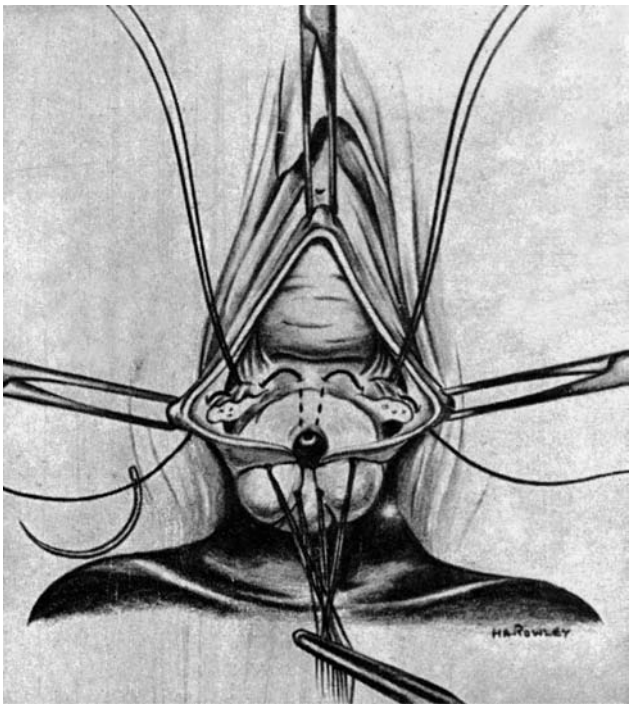


Figure 25.17 A covering for the posterior lip of the cervix has been fashioned from the mobilized vaginal skin of the posterior fornix and this has been secured to the new cervix by deep sutures. Fothergill's stitch is illustrated and it should be noted that it passes through vaginal skin in the region of Fothergill's lateral point, through Mackenrodt's ligament and through the anterior lip of the cervix into the cervical canal, and thence out to the other side and through Mackenrodt's ligament and vaginal skin.

some cases. To avoid the obstetric complications of Fothergill's operation, Shirodkar modified this operation as follows.

Shirodkar's Procedure

Anterior colporrhaphy is performed as usual, and attachment of Mackenrodt ligaments to the cervix on each side is exposed. The vaginal incision is then extended posteriorly round the cervix. The pouch of Douglas is opened, uterosacral ligaments identified and divided close to the cervix. The stumps of these ligaments are crossed and stitched together in front of the cervix. A high closure of the peritoneum of the pouch of Douglas is carried out. The cervix is not amputated and subsequent pregnancy complications avoided. The rest of the operation is similar to Fothergill's operation.

Other conservative surgeries used are:

- Vaginal sacrospinous hysteropexy.
- Abdominal/laparoscopic sacrohysteropexy.

These can be combined with cystocele, rectocele repair. The advantages are:

- Vaginal length is maintained.
- Cervix is preserved for sexual function.

Vaginal Hysterectomy with Pelvic Floor Repair

Vaginal hysterectomy with pelvic floor repair is suitable for women over the age of 40 years, those who have completed their families, and are no longer keen on retaining their childbearing and menstrual functions.

The age limit may be relaxed to 35 years for women who have additional menstrual problems, or the uterus is a seat of fibroids, adenomyosis.

The operation relieves the woman of her prolapse and also of her menstrual problems. A Kelly stitch may be necessary to relieve her of stress incontinence, if this is present.

The Steps of Vaginal Hysterectomy (Figure 25. 18). A circular incision is made over the cervix below the bladder sulcus, and the vaginal mucosa dissected off the cervix all around. The pouch of Douglas is identified posteriorly and peritoneum incised. The bladder is now pushed upwards until the uterovesical peritoneum is visible, and is similarly incised. The uterus is now free in the front and behind. The pedicles containing Mackenrodt's and uterosacral ligaments are clamped on either side close to the cervix, cut on the uterine side and the pedicles transfixed. Next, the uterine vessels are identified, clamped, cut and ligated. The upper portion of the broad ligament holding the uterus contains round and ovarian ligaments and the fallopian tube. These are similarly dealt with on both sides, and the uterus removed. The peritoneal cavity is closed with a purse-string suture, using chromic catgut 0. Anterior colporrhaphy and posterior colpoperineorrhaphy are performed as required.

The vagina is packed with betadine or acriflavine pack for 24 h, a Foley catheter left in the bladder, and urine continuously drained for 48 h.

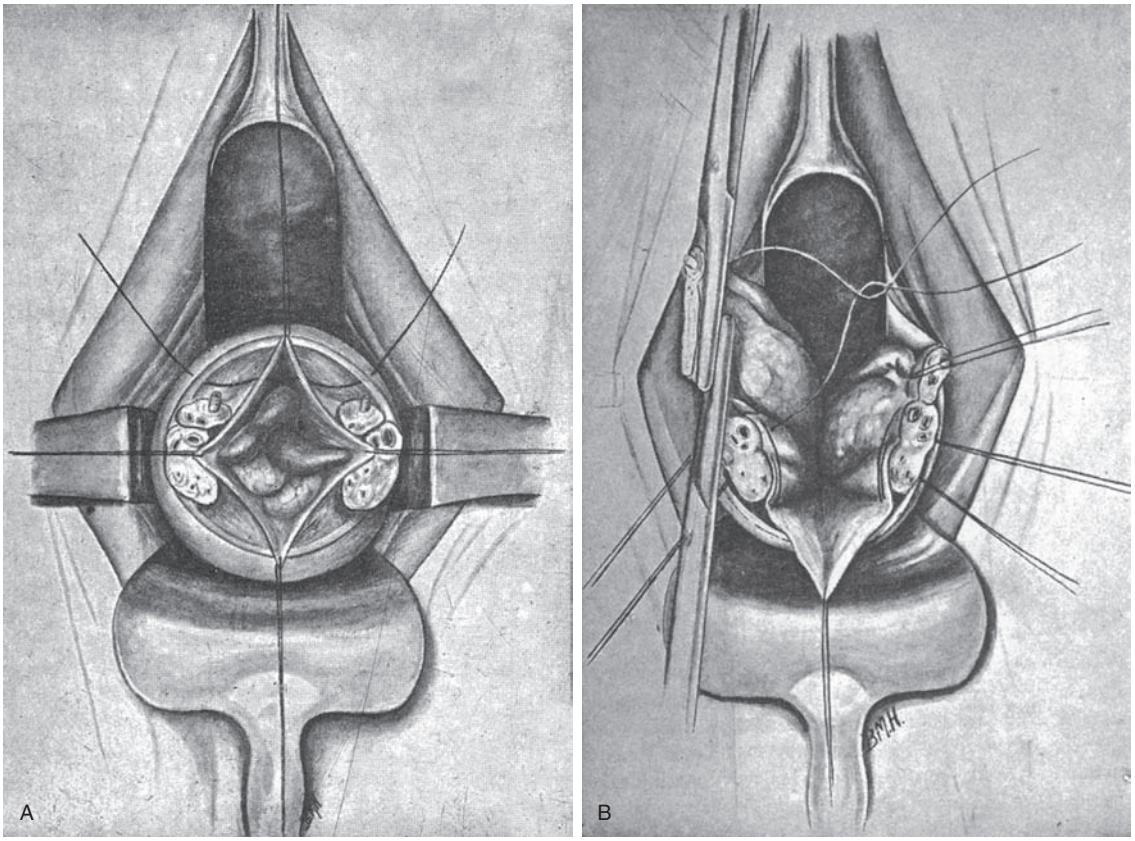


Figure 25.18 **(A)** Peritoneal opening closed in vaginal hysterectomy. **(B)** Pedicles clamped and ligated in vaginal hysterectomy.

Complications are haemorrhage, sepsis, anaesthesia risks, urinary tract infection. In rare cases, trauma to the bladder and rectum may occur. Vault prolapse follows as a late sequela in a few cases. Dyspareunia is caused by a short vagina.

LigaSure. LigaSure vessel sealing system is lately used to secure the pedicles in vaginal hysterectomy. The device consists of a bipolar radiofrequency generator, reusable handpiece and disposable electrodes. The electrodes melt the collagen and elastin in the vessel wall to form a seal zone. Quick surgery with LigaSure is an advantage.

Vaginal hysterectomy is mainly performed for major degree of uterine prolapse in the elderly woman. Lately, however, lower morbidity of the vaginal over abdominal route is well appreciated, and surgeons resort to vaginal hysterectomy in undescended uterus for indications done earlier for abdominal hysterectomy.

While choosing the vaginal route for undescended uterus, the following points should be observed.

Vaginal hysterectomy is contraindicated if the uterus is:

- Very bulky (more than 12–14 weeks).
- The uterus is fixed by abdominal adhesions and inflammatory disease. Abdominal adhesions are likely to be present if the woman had previous abdominal surgery or caesarean section.
- Other pelvic pathology exist such as endometriosis and ovarian tumour. In such cases, proper laparotomy is indicated.

Some experts are also able to remove the ovaries by the vaginal route.

Le Fort's Repair

Le Fort's repair is reserved for the very elderly menopausal patient with an advanced prolapse, or for those women who are poor medical risks and are considered unfit for any major surgical procedure.

Prior to the procedure, a Pap smear and pelvic sonography should be obtained to exclude possible pelvic pathology.

The procedure can be performed under sedation and local anaesthesia, or epidural anaesthesia. The flaps of the vagina from the anterior and posterior vaginal walls are excised, the raw areas apposed with catgut sutures. Thus, a wide area of adhesion is created in the midline which prevents the uterus from prolapsing, the small tunnels on either side permitting drainage of discharge.

This operation limits marital functions; hence, it should not be advised in women who are leading an active sexual life. Some women may develop stress incontinence. Other contraindications are menstruating woman, a woman with a diseased cervix and uterus.

Abdominal Sling Operations

Abdominal sling operations have been designed for young women suffering from second or third degree uterine prolapse, and who are desirous of retaining their childbearing and menstrual functions. The objective of these operations is to buttress the weakened supports (Mackenrodt's and

uterosacral ligaments) of the uterus by providing a substitute in the form of nylon or Dacron tapes used as slings to support the uterus. The advantage of the synthetic tapes is that they are strong and nontissue reactive. Sling operations are best suited to nulliparous prolapse.

The operations in common practice include:

- Abdominal wall cervicopexy.
- Shirodkar's abdominal sling operation.
- Khanna's abdominal sling operation.

Abdominal wall cervicopexy. The operation entails opening of the abdominal wall through a low transverse suprapubic incision deepened down, up to the rectus sheath. By means of transverse incisions made in the rectus sheath, two musculofascial slings are elevated from the midline outwards and laterally up to the lateral border of the rectus abdominis muscles on either side. The peritoneum is opened in the midline, and the uterus brought up into view. The uterovesical fold is incised, and the bladder mobilized from the front of the uterine isthmus. The medial ends of the fascial sling are now directed retroperitoneally between the two leaves of the broad ligaments up to the space created in front of the uterine isthmus; the slings are pulled through and anchored there with stout nonabsorbable ligatures after ensuring adequate correction in the position of the uterus in the pelvis. The uterovesical fold is next sutured, followed by closure of the abdomen in layers. Presently, the surgeon uses a 12 inch long Mersilene/nylon tape to provide the new artificial supports for the uterus. The tape is fixed at its midpoint to the uterine isthmus anteriorly, and its lateral ends brought out retroperitoneally between the two leaves of the broad ligament, so as to emerge at the lateral border of the rectus abdominis muscle on either side. The ends of the tape are now fixed to the aponeurosis of the external oblique muscle of the abdominal wall either by weaving it through the aponeurosis on either side from the medial to the lateral side or by fixing it to the undersurface of the aponeurosis with interrupted nonabsorbable sutures.

Purandare and Mhatre improved on the original operation by attaching the tape posteriorly on the cervix close to the attachments of the uterosacral ligaments. The ends of the tape are then brought forward retroperitoneally as described above, and attached to the external oblique aponeurosis.

This operation can be combined with a Moschcowitz repair to obliterate an enterocele and an anterior colporrhaphy and colpoperineorrhaphy to correct additional genital laxity of the vagina.

Many Indian gynaecologists have contributed significantly to the operative repair of genital prolapse. Amongst the important modifications worth noting are Virkud's sling operation, Mangeshkar's laparoscopic technique, and Neeta Warty's laparoscopic modification of Shirodkar's operation.

Shirodkar's Abdominal Sling Operation for Uterine Prolapse. This operation was designed to meet the special needs of the case of a nulliparous prolapse having inherently weak supports. It is a technically difficult operation to perform but it is based on sound anatomical principles and gives excellent results. Using Mersilene tape, the cervix is fixed to the lumbo-sacral fascia by passing the tape extraperitoneally.

Khanna's Sling Operation. In this operation, the Mersilene tape is fixed to the isthmus posteriorly, and the two free ends brought out retroperitoneally to emerge out at the lateral margin of the rectus abdominis muscle on either side. They are anchored to the anterosuperior iliac spine on either side. The sling supports Mackenrodt's ligaments.

Enterocele

Whenever an enterocele is encountered during prolapse operation, it should be repaired.

During vaginal hysterectomy, the enterocele is repaired after the uterus is removed. The redundant peritoneum of the pouch of Douglas is dissected, the peritoneal sac excised and the neck of the enterocele is ligatured. The enterocele aperture is closed and strengthened by approximating the two uterosacral ligaments and the levator ani muscles. Failure to recognize and *repair the enterocele can* lead to vault prolapse later.

Enterocele can also be repaired during an abdominal operation. The cul-de-sac of the pouch of Douglas is obliterated by several purse-string sutures starting from below. This operation is known as *Moschcowitz repair*. One should take care not to include the ureter in the stitch.

Vault Prolapse

Vault prolapse is a delayed complication of both abdominal and vaginal hysterectomy when the supporting structures at level I become weak and deficient. It also results from failure to identify and repair an enterocele during hysterectomy. Technical error in previous surgery, age, oestrogen deficiency in a menopausal woman, parity, obesity and chronic cough may contribute to its occurrence. Sling operations for urine stress incontinence leave a defect in the posterior fornix, leading to enterocele in 15% cases. It follows soon after the technical error in surgery, but within 2 years in 50% if due to weakness in the supporting structures. Vault prolapse occurs in 10% following hysterectomy for prolapse and 1% following abdominal hysterectomy, for benign lesions.

The current incidence of 3–6 per 1000 is increasing on account of longer survival, and desire for sexual life beyond menopause that brings the woman to the gynaecologist.

The woman complains of coital difficulty and difficulty in walking. Backache, urinary and rectal symptoms may exist.

Degrees of Vault Prolapse

First degree—The vaginal apex is visible at the introitus.
Second degree—The vault protrudes through the introitus.
Third degree—The entire vagina is outside the introitus.
Vault prolapse is often associated with cystocele and enterocele.

Prevention

- Enterocele should be recognized and repaired during the primary first surgery.
- Attachment of the uterosacral and cardinal ligaments to the vaginal vault during hysterectomy reduces the incidence of vault prolapse.

Treatment (Table 25.4)

- *Right transvaginal sacrospinous colpopexy* in obese and elderly women not fit for abdominal surgery was first described by Ritcher in 1968. Bilateral fixation is rarely required. It is now the preferred surgery of choice in most cases.

The vaginal vault is fixed to the sacrospinous ligament, so that in the upright position, the vagina lies in the horizontal position and gets compressed against the levator ani muscles. McCall culdoplasty comprises fixing the uterosacral and Mackenrodt's ligaments to the vaginal vault and the peritoneum of the pouch of Douglas. Ureteric obstruction and kinking are reported in 10% (Figure 25.19). Vaginal route is safer for elderly women. Abdominal surgery in young women avoids dyspareunia.

Complications of surgical procedures:

- Haemorrhage – primary, reactionary, secondary haemorrhage.
- Sepsis
- Trauma to the bladder, urethra rectum mainly in repeat surgery.
- Urinary infection.
- Thrombo-embolism
- Late sequelae
- Narrow scarred vagina and dyspareunia.
- Granulation tissue.
- Recurrence of vault prolapse
- Fistula

TABLE 25.4 Vault prolapse

Vault prolapse	
Young woman	Old woman
Abdominal sling surgery Sacropexy Colpopexy Laparoscopy Colpopexy	Vaginal sling surgery
	• Right transvaginal sacrospinous colpopexy • Transabdominal (laparoscopy) sacropexy • Colpocleisis • Le Forte's operation • Abdominoperineal surgery • Ring pessary • Posterior intravaginal slingoplasty

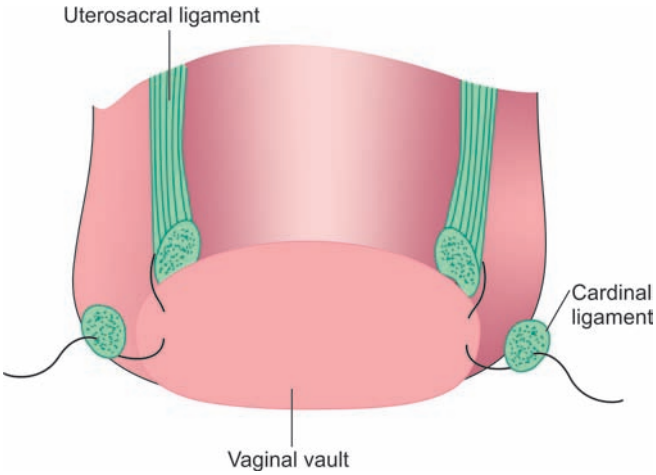


Figure 25.19 McCall's culdoplasty.

Right Transverse Vaginal Sacrospinous Colpopexy

Following opening of the posterior vaginal wall vertically, a window space is created between the vagina and the rectum towards the right sacrospinous ligament. A synthetic sling such as the Mersilene mesh fixes the vault to the sacrospinous ligament with a Miya hook 4 cm away from the ischial spine using nonabsorbable suture. During surgery, care is taken not to injure the rectum, pudendal vessels, and nerves at the ischial spine, sciatic nerve and sacral plexus which lie above the ligament. Ninety per cent success has been claimed. Previous rectal surgery and drainage of pelvic abscess contraindicate this surgery. Buttock pain (15%) following this operation resolves gradually. It is caused by nerve injury. Cystocele may develop at a later date. Recurrence of vault prolapse (20–30%) and detrusor overactivity are reported (Figure 25.20). Enterocele should be repaired before closing the vagina.

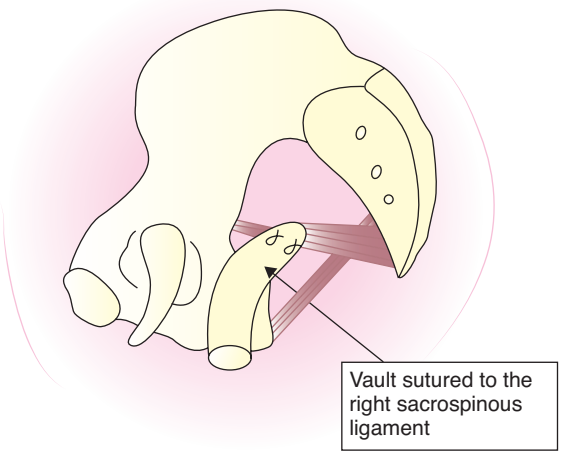


Figure 25.20 Sacrospinous fixation.

- *Transabdominal sacral colpopexy* comprises suspending the vault to the sacral promontory extraperitoneally using Gore-Tex or Mersilene tape. Injury to the ureter, bladder, sigmoid colon and middle sacral artery should be avoided.

It is best suited for younger women, since coital difficulty following vaginal surgery is avoided (Figure 25.21)

Haemorrhage, infection and stress incontinence are the other complications. Mesh erosion requiring its removal is reported in 3%. Recurrence is reported in 10% cases. Lumbar plexus neuropathy is reported in a few.

- *Colpocleisis* is permissible if sexual activity is not desired. In this, vaginal mucosa is denuded all around and the cavity is obliterated with a series of purse-string sutures starting from the apex downwards. Stress incontinence of urine may follow this operation.
- *Le forte's* operation is another alternative. A small rectangular portion of the anterior and posterior vaginal wall are denuded and sutured to each other with several Vicryl sutures, thus obliterating the vagina in the middle. It is suited for old women not interested in sexual function.
- Lately, *laparoscopic colpopexy* has been attempted.
- *Abdominoperineal surgery* described by Zacharin is a difficult surgery required in complicated cases, and if rectal prolapse is also present.
- Ring pessary is recommended in a woman not fit for surgery.
- Anterior and posterior colporrhaphy may be required for cystocele and rectocele in addition.
- Posterior intravaginal slingoplasty.

Petros described this operation in 1997. Posterior intravaginal sling plasty using monofilament polypropylene tape (8 mm wide, 40 cm long) is used to support uterosacral ligaments by creating neo-uterosacral ligaments and the vault is relocated. Although associated with less morbidity, this surgery can cause ureteric and rectal injury, and postoperative coital difficulties and pain. Recurrence of prolapse in 10% is also a disadvantage. Mesh erosion can also occur.

Abdominal surgery is elected in young women to avoid coital difficulties, so also in women who develop recurrence following vaginal repair.

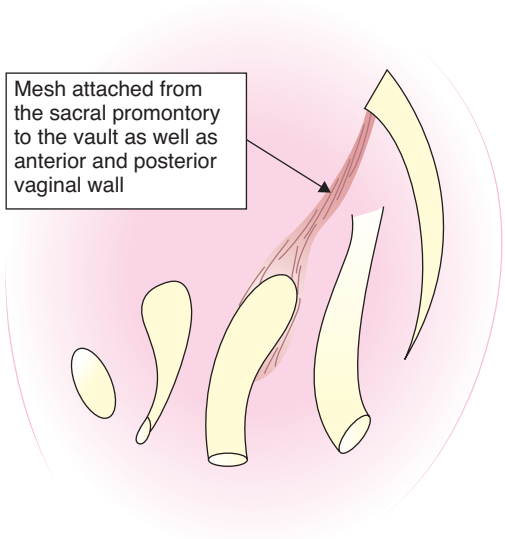


Figure 25.21 Sacrocolpopexy.

Recurrent Prolapse and Prosthetics

About 30% of women who have undergone previous surgery for genital prolapse suffer from recurrence. They often need repeat surgical interventions. The high failure rate of primary surgery is attributed to poor collagen health of the patient's damaged tissues. Further stress and menopausal changes predispose recurrence.

The introduction of synthetic and biological prosthesis has been utilized extensively to reduce recurrence in high-risk cases, but is mainly used during repeat surgery.

Classification

1. Synthetic materials
   A. Macro porous, nonabsorbable (Marlex, prolene): The pore size is more than 75 nm to allow infiltration by macrophages, fibroblasts, new vessels and collagen fibres. The long-term problem is mesh erosion, infection and dyspareunia caused by hard mesh; it may require its removal surgically.
   B. Absorbable polyglactin (Vicryl): It is free of mesh complications, but long-term results need further evaluation.
2. Biological materials
   A. Autologous material (rectus fascia, fascia lata): This requires two sites of operation, vaginal and in facia lata, prolongation of surgery. Poor quality of tissues can also cause recurrence of prolapse and wound infection.
   B. Xenografts of porcine.
3. New system
   A. Polypropylene tape is used in posterior intravaginal sling plasty.
   B. Apogee and perigee, used in sling operation. The mesh is secured to the arcus tendineus pelvic fascia through transobturator approach.

Complications of surgical procedures:

- Haemorrhage – primary, reactionary, secondary haemorrhage.
- Sepsis
- Trauma to the bladder, urethra and rectum mainly in repeat surgery.
- Urinary infection.
- Thrombo-embolism.

Late sequelae:

- Narrow scarred vagina and dyspareunia.
- Granulation tissue.
- Recurrence of vault prolapse
- Fistula

Key Points

- Prolapse is a common problem encountered in clinical practice.
- Genital organ descent results from congenital weakness of the pelvic connective tissues, acquired tissue damage following prolonged, difficult or vaginal instrumental delivery, conditions causing rise in intra-abdominal pressure, and menopause leading to tissue atrophy.
- Cystocele, urethrocele, rectocele and uterine descent are manifestations of the same pathology.
- These women suffer from symptoms of genital organs protruding out of the vulva, urinary symptoms of high frequency, incomplete voiding, stress incontinence, repeated urinary infections and in rare cases, retention of urine. Difficulty during defaecation, infertility, coital problems, backache and difficulty in locomotion are also encountered.
- In younger women desirous of retaining childbearing functions, conservative surgical repair operations are indicated, whereas in perimenopausal and menopausal women, vaginal hysterectomy with repair of the pelvic floor is the operation of choice.
- In a younger woman, abdominal surgery avoids dyspareunia, and is a preferred route of repair.
- Vault prolapse is a sequela of abdominal as well as vaginal hysterectomy which requires surgical repair. Ring pessary is applicable in a woman unfit for surgery.
- Recent introduction of prosthetic materials to supplement weakened tissues has resulted in long-term benefits in the management of recurrent prolapse, but the cost and complications should be borne in mind.
- A patient with vault prolapse also has other vaginal defects. These need correction along with repair for vault prolapse.
- By fixing the uterosacral and cardinal ligaments to the vaginal vault at the time of hysterectomy, vault prolapse can be prevented.
- Sacrocolpopexy is considered the gold standard surgical procedure for vault prolapse and can be combined with vaginal wall repair if required.

Self-Assessment

1. Describe the normal supports of the uterus.
2. How would you classify genital prolapse?
3. Describe the symptomatology of genital prolapse.
4. Discuss the prophylaxis of genital prolapse.
5. Describe the surgical procedures for repair of genital prolapse.
6. What are the causes of genital prolapse?
7. A woman, 50-year old, presents with 3rd degree uterine prolapse. How will you manage this case?
8. A 30-year-old woman, para 2, complains of something coming out per vagina. Discuss the investigations and management of this case.
9. Discuss the management of nulliparous prolapse.
10. A 60-year-old woman presents with something coming out per vagina following abdominal hysterectomy 2 years ago. How will you manage the case?

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Chapter 26

Displacements

CHAPTER OUTLINE

Introduction

The uterus is kept in place by a cross formation of four ligaments (pubocervical ligaments, uterosacral ligaments, and a pair of cardinal (Mackenrodt's or transverse cervical ligaments), by the pelvic floor muscles and the sheet of connective tissue enveloping the hollow pelvic viscera providing them with support. For different reasons, uterine displacement may occur; the disorder may happen sideways but more commonly backwards, or downwards.

Pelvic inflammatory disease and endometriosis may leave behind adhesions that may bind the uterus to other structures, thus leading to uterine displacements—commonly presenting as a fixed retroversion or a lateral tilting following adhesions with adnexal structures. Uterine tumours may push or drag the uterus into various abnormal positions. Similarly, tumours in surrounding structures may move the uterus out of its normal position. Faulty development of the structures supporting the uterus may also cause uterine displacement.

There are two common types of uterine displacements that are often the cause of physical distress—retroversion and prolapse.

In retroversion, the uterus tips backwards and also possibly sags downward. In prolapse, the uterus settles downward; sometimes, the displacement is so extreme that the cervix protrudes out from the vulva, and may even drag down with it part of the rectum and bladder. In other cases, the entire uterus and vagina prolapse out of the introitus causing procidentia. Prolapse is more common after menopause Prolapse has been discussed in the previous chapter.

A uterine displacement may prevent a woman from conceiving; if she does become pregnant under such a condition, it may end in abortion. With the backward position of the uterus, as what happens in retroversion, the ligaments that support the organ may be stretched which can result in kinking of the fallopian tubes, and congestion of the ovaries and the uterus itself. The same condition can likewise cause backache, dyspareunia, dysmenorrhoea, infertility, abortion, menstrual irregularities, leucorrhoea and constipation. Many patients with mobile retroversion, however, are symptomless.

Retroversion

The usual position of the uterus is one of anteversion and anteflexion, in which the uterine body is bent forwards at its junction with the cervix. Version refers to the direction of the cervical canal, whereas flexion refers to the inclination of the body of the uterus at the cervix. The normal uterus is not a static organ; its position is altered by the state of the bladder which, when full, displaces the uterus backwards. In most cases of retroversion, the uterus is also retroflexed, so that the body of the uterus is flexed backwards (Figure 26.1).

Aetiology

It is difficult to explain why the uterus is normally anteverted and anteflexed. The round ligaments do not maintain this position on their own, although they are used to correct the retroversion during surgery. It appears that the position of the uterus in relation to the cervix is largely inherent in the uterine myometrium.

Mobile Retroversion

The uterus is retroverted in 20% of patients, with no gynaecological symptoms.

This condition is normally found in case of prolapse, but it is difficult to say if it precedes prolapse or that prolapse causes retroversion. Sometimes, the displacement of the uterus is caused by tumours such as anterior myomas and ovarian cysts in the pelvis, which push the uterus backwards.

A large number of retroversions are seen in women after childbirth. Such displacements often correct themselves spontaneously once the patient's muscle tone improves.

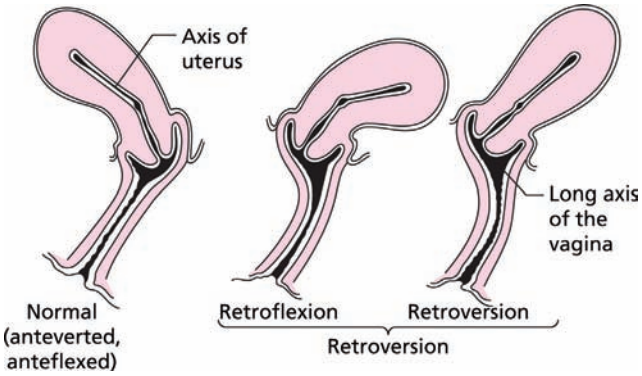

Figure 26.1 Normal and retroverted uterus.

Fixed Retroversion

Fixed retroversion means that the uterus is bound by adhesions or tumours in the retroverted position. Most fixed retroversions result from pelvic inflammatory diseases (PID) such as salpingo-oophoritis and pelvic tumours. In salpingo-oophoritis, the oedematous, distended fallopian tubes prolapse behind the uterus and, partly by their weight and partly through forming adhesions to the posterior surface of the uterus, pull back the uterus. In the process of healing, adhesions form which bind the uterus firmly in its retroverted position. Fixed retroversion is also caused by chocolate cysts of the ovary and pelvic endometriosis.

Symptoms

The significance of retroversion per se in clinical practice has receded during the last several years. This is due to the appreciation of the fact that the symptoms earlier attributed to this displacement are either not related to it or they are related to the aetiological factors causing retroversion. Therefore, asymptomatic retroversion does not need treatment, and treatment of symptomatic fixed retroversion is directed towards the disease that causes it.

Dysmenorrhoea

Both congestive and spasmodic dysmenorrhoea have been wrongly attributed to mobile retroversion. The incidence of dysmenorrhoea is the same as it is in women with an anteverted uterus. Fixed retroverted uterus can cause dysmenorrhoea.

Menorrhagia

Menorrhagia associated with mobile retroversion is either due to myohyperplasia or abnormal uterine bleeding (AUB). Manual or surgical correction of retroversion will not relieve the menstrual symptoms. In fixed retroversion, menorrhagia is due to pelvic congestion caused by pelvic pathology.

Pressure

A normal-sized retroverted uterus does not cause pressure on the rectum or on the bladder neck.

Backache

More likely, the backache is due to an orthopaedic cause and not due to the retroverted uterus.

Dyspareunia

Of all the symptoms of retroversion, dyspareunia may be one which is genuine and attributable to retroversion. During vaginal examination, the body of the retroverted uterus is tender and the patient may wince when it is touched. Besides, the ovary may prolapse in the pouch of Douglas and cause dyspareunia during coitus. Following coitus, she may complain of ache in the pelvis that persists for 12–24 h. This may lead to frigidity and marital disharmony.

Infertility

To implicate retroversion as a cause of infertility, it is necessary to perform a Sims–Huhner test (postcoital test). Abundant motile sperms are seen in the vaginal pool but their failure to show up in the cervical canal indicates that the cervical canal is away from the seminal pool and is not accessible to the motile sperms. In such a case, retroversion is the cause of infertility. Surgical correction of the retroversion should result in conception. Fixed retroversion due to salpingo-oophoritis cause infertility through tubal blockage.

Abortion

Retroversion as a cause of abortion has been greatly exaggerated. Fixed retroversion would more often lead to infertility rather than abortion, because of the tubal block.

Diagnosis

There should be no problem in the diagnosis of the retroverted uterus on bimanual vaginal examination. In rare cases, the uterus felt in the pouch of Douglas may be mistaken for an ovarian tumour or a fibroid. The fact that the mass in the pouch of Douglas moves with the cervix confirms that this is the uterine body.

Treatment

If the retroversion is mobile and the patient free of symptoms, no treatment is required.

Pessary Treatment

If the patient complains of dyspareunia, or backache and the uterus is found to be retroverted, the uterus is bimanually replaced (Figure 26.2) and kept in the anteverted position by inserting a Hodge pessary into the vagina (Figure 26.3). The pessary is made of plastic.

The pessary is retained in position for 3 months and then removed. If the symptoms persist in spite of the uterus being in anteversion, operative treatment for the retroversion is unjustifiable, as the symptoms are not due to retroversion. This is known as the pessary test. Recurrence of symptoms as soon as the pessary is removed strongly suggests retroversion as the cause.

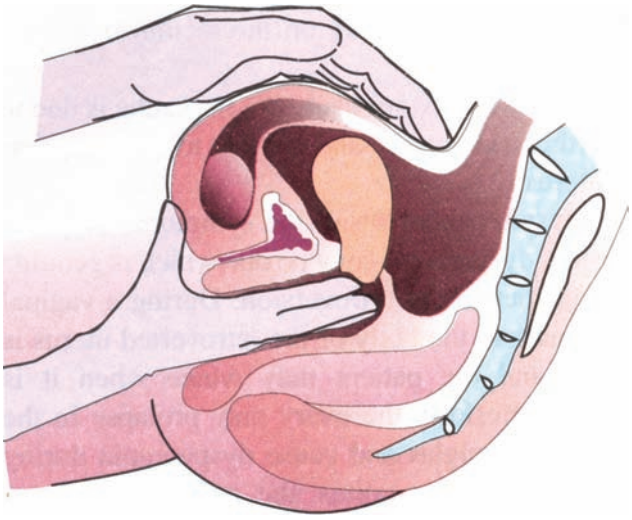

Figure 26.2 Digital replacement of a retroverted uterus. The fingers placed on the abdomen, by pressing the body of the uterus downwards, together with help from the internal fingers which push the cervix upwards, correct the displacement.

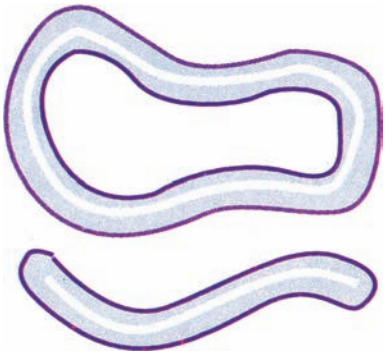

Figure 26.3 A Hodge pessary.

Surgery

Indications

1. Fixed retroversion requires surgery for the primary organic lesion such as the pelvic inflammatory mass and tumour. At the end of the surgery, the uterus is brought forward by shortening the round ligaments, as mentioned below, and maintained in an anteverted position.
2. In patients for whom the pessary test proves that the symptoms and infertility are caused by retroversion.
3. Following tuboplasty and myomectomy operation, uterus is ventrosuspended to prevent or minimize the formation of tubal and pelvic adhesions.

Ventrosuspension

One of the most popular surgical procedures to correct the retroversion is the modified Gilliam's operation in which the round ligament is first held by nonabsorbable suture, close (1 cm) to the uterine cornu. The ends of this suture are left long. A long curved forceps is now passed between the anterior rectus sheath and the muscle at the level of the anterior superior iliac spine. It is now directed close to the internal abdominal ring into the space between the two layers of the broad ligament towards the uterine cornu. The forceps point is then pushed through the peritoneum of the broad ligament and the ends of the ligature around the round ligament withdrawn along the tract of the forceps. These ends are now anchored to the anterior rectus sheath. The round ligament is thus drawn up against the anterior abdominal wall.

Plication of Round Ligaments

Shortening of round ligaments by plication using a nonabsorbable suture is a simple form of ventrosuspension operation for fixed retroversion associated with organic pelvic disease and fibroids.

Baldy–Webster Operation

The round ligaments are passed through the anterior and posterior leaves of the broad ligament and are sutured to the posterior surface of the uterus, thus shortening the round ligaments and ventrosuspending the uterus.

Inversion of the Uterus

In inversion, the uterus is turned inside out. At first the fundus is pushed down into the cavity of the uterus leaving a cup-shaped depression on the peritoneal surface. As a result of contractions of the uterus, the invagination becomes pushed further and further down, until finally the whole uterus is turned inside out and hangs into the vagina. If the peritoneal surface of the uterus is inspected, the fallopian tubes, the ovarian and the round ligaments can be seen to pass down into a deep hollow in the position where the body of the uterus should be. Inversion of the uterus is described as complete or partial according to the degree to which the uterus is turned inside out (Figures 26.4 and 26.5).

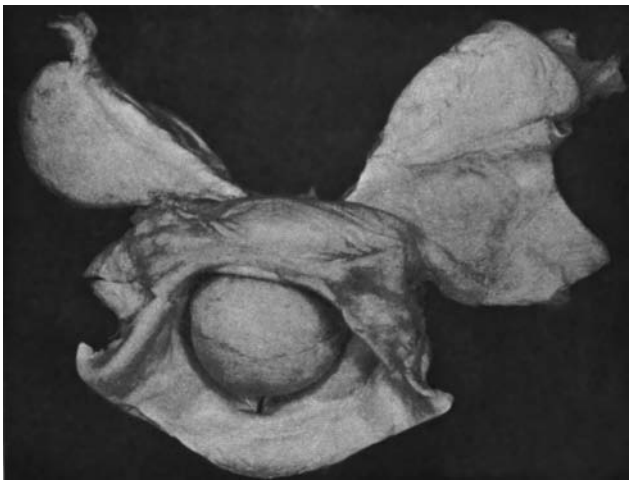

Figure 26.4 Inversion of the uterus. The vagina has been cut through below and the rounded projection into the vagina is the inverted fundus of the uterus. The two ovaries lie above.

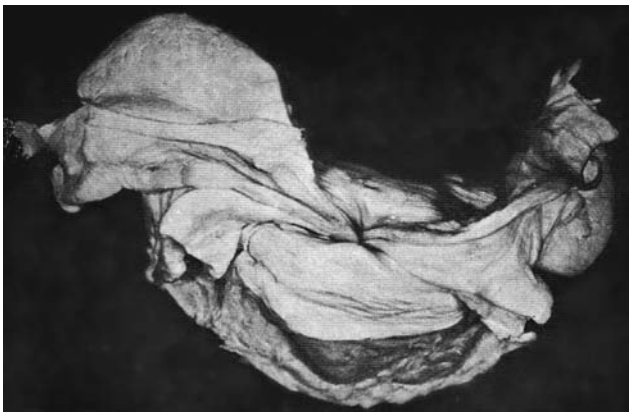

Figure 26.5 The same specimen as in Figure 26.4 seen from above. The fallopian tubes, broad ligaments and ovarian ligaments pass into a cup-shaped depression at the fundus of the uterus.

Acute Inversion

Most acute inversions of the uterus are puerperal. Some are due to traction being applied to the umbilical cord when the placenta is morbidly adherent, while others are produced by squeezing a relaxed uterus immediately after delivery. Nevertheless, most puerperal inversions are probably spontaneous, although the exact aetiology is unknown. It has been suggested that the puerperal contractions of the body tend to invaginate the fundus into the uterine cavity. The presence of muscle defects in the region of the uterine fundus may also allow a dimple to occur and progressive invagination to follow. Puerperal inversion of the uterus is complete when the whole uterus lies outside the vagina. The condition is associated with severe degree of shock, and the inverted uterus bleeds profusely.

Prevention

Proper management of the third stage of labour can prevent acute inversion.

Treatment

The treatment of acute puerperal inversion depends mainly upon the circumstances. The ideal treatment is immediate replacement. If the inversion occurs in the presence of a doctor or nurse, it should be promptly reposited by exerting firm and constant pressure on the inverted uterine fundus. If the placenta is attached to the uterus, it must not be removed until after the replacement has been effected. In all instances, the shock should be treated simultaneously by transfusion with blood or plasma substitute. In domiciliary midwifery, resuscitation must be continued until facilities for replacement of the uterus become available. The best method of performing this has been described by O'Sullivan. The patient is anaesthetized with the least possible delay. One gallon of warm sterile water is prepared for irrigation into the vagina, using an irrigating can raised 3 to 4 feet above the level of the patient. After gently pushing the inverted uterine fundus back into the vagina, the nozzle of the irrigating cannula is inserted into the vagina, and the vaginal orifice is closed by the hands of the operator and an assistant. As much as 3 L of fluid may be needed, the inversion being slowly corrected by the hydrostatic pressure. If this method fails, manual reposition may be attempted under deep anaesthesia. As a last resort, the abdomen should be opened and, if the inverted fundus cannot easily and without damage be pulled back into position with simultaneous pressure from the vagina, the tight cervical ring may be divided to restore the uterus and then its cut edges repaired. In some cases, total abdominal hysterectomy *will be desirable if the patient is in the older age group* and has completed her family. Antibiotic cover should be provided.

Chronic Inversion

Chronic inversion of the uterus consists of late puerperal cases in whom the initial stages of the inversion, occurring in the immediate postpartum period, have been overlooked and those associated with extrusion of a submucous myoma of the fundus. Clinically, chronic inversion associated with fundal myoma is suspected if the woman complains of intermittent lower abdominal pain and irregular vaginal bleeding. Over the period, the myoma becomes infected and causes offensive blood-stained discharge. In fibroma associated with inversion, often fibrosarcoma exists, which by softening the uterine wall is responsible for inversion. Diagnosis of chronic inversion is often difficult. A cup-shaped depression must be identified in the situation of the fundus. In complete inversion, the cervix is drawn up and the vaginal portion of the cervix will not be palpable. In partial inversion, the uterine sound can be passed only a short distance along the uterine cavity, and this will help to distinguish the partial inversion from a myomatous polypus of the body of the uterus. When the tumour which protrudes through the cervix is pulled down with a vulsellum forceps, if the cervix moves upwards, then it is most suggestive of an inverted uterus. If the tumour is a polypus, traction brings down the cervix or the tumour may be pulled further through the external os without the cervix being drawn up. In chronic inversion, the inverted fundus is likely to be ulcerated and infected, and resembles an infected fibroid polypus.

Ultrasound and laparoscopic examination of the uterine fundus will confirm inversion.

Degree of Inversion (Figure 26.6)

- In first-degree inversion, the fundus of the uterus inverts into the uterine cavity.
- In second-degree inversion, the uterine fundus protrudes through the cervix and lies in the vagina.
- In third-degree inversion, the whole of the uterus is inverted and protrudes through the introitus.

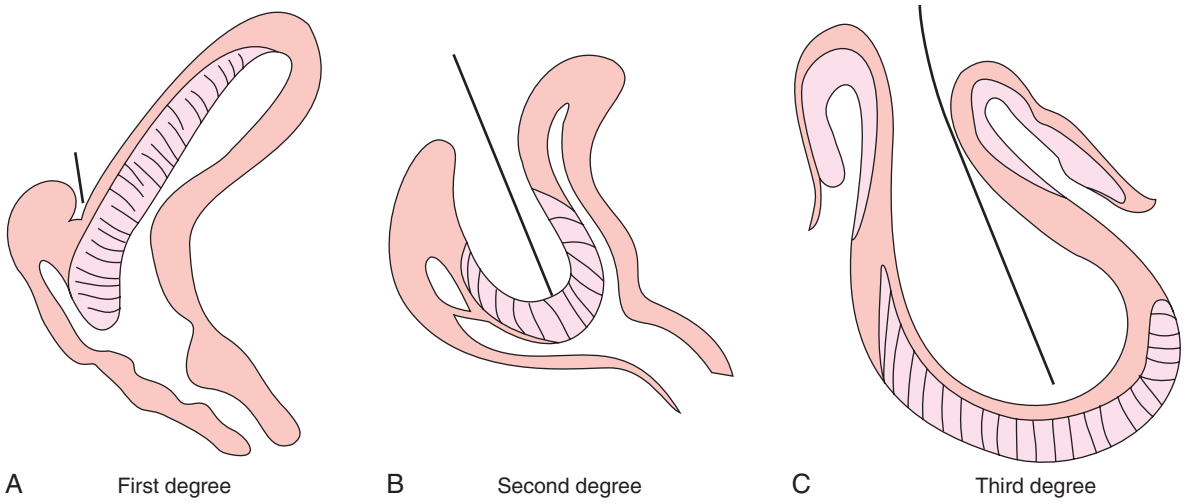

Figure 26.6 Inversion of the uterus: **(A)** First degree. **(B)** Second degree. **(C)** Third degree.

Treatment

Before attempting any surgical correction of a chronic inversion, the patient should be treated with antibiotics and local antiseptic packing.

- If it is desirable to conserve the uterus in young patients, the inversion can be corrected either by vaginal or by an abdominal approach. In either instance, the important step in the operation is the section of the constricting ring of the cervix after which it is easy to restore the fundus to its correct position. The transected cervix is then repaired by suture. In vaginal Spinelli's operation, the anterior cervical ring is cut, the inversion corrected and the cut edge sutured.
- If it is not desired to conserve the uterus in a multiparous woman, vaginal or abdominal hysterectomy is performed.
- Inversion caused by extrusion of fundal myoma will mandate radical hysterectomy followed by radiotherapy.

In a young woman, vaginal myomectomy under laparoscopic guidance will safeguard against uterine perforation.

Key Points

- The uterus is not a static organ; however, its usual position is that of anteversion and anteflexion.
- The uterus is retroverted in about 20% of women; mobile retroversion is often asymptomatic and requires no treatment.
- Fixed retroversion is often the aftermath of pelvic inflammatory disease or a result of endometriosis; these women may complain of chronic backache and deep dyspareunia which may contribute to infrequent coitus and infertility.
- Pessaries to correct retroversion were in vogue some years ago. Surgical correction is indicated in women with symptomatic retroversion. The operation of choice is ventrosuspension. This procedure is carried out concomitantly at laparotomy performed for other gynaecological causes like myomectomy or tuboplasty.
- Acute inversion is always obstetrical, caused during the third stage of labour.
- Chronic inversion of the uterus is a rare clinical entity. It is likely to be mistaken for a submucous polyp or cervical cancer. Pelvic ultrasound examination and laparoscopy help to establish the diagnosis. Treatment of the condition is surgical.

Self-Assessment

1. Describe the varieties of displacement in the pelvis observed in clinical practice
2. Describe uterine retroversion. When would it require surgical correction?
3. Describe the role of pessary in the treatment of retroverted uterus.
4. Describe the clinical features of acute inversion of the uterus. How would you manage such a case?
5. Describe the clinical features of chronic inversion of the uterus and its management.
6. Enumerate the various causes of uterine displacement.
7. Describe the clinical symptoms associated with uterine displacement in modern day practice.
8. Discuss diagnosis and management of uterine inversion.
9. What is the place of the operation of ventrosuspension? Describe the various surgical operations for the same.

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Chapter

27 Diseases of the Vulva

CHAPTER OUTLINE

Introduction

A variety of developmental, trophic, inflammatory, allergic and neoplastic disorders can occur in the vulvar skin and its appendages. The common vulvar disorders affecting its various constituents are:

1. *Epidermis and dermis*. Common dermatological disorders, allergies, infections, naevi, dystrophies, ulcers and new growths.
2. *Skin appendages*. Folliculitis, sebaceous cysts, hidradenomas, Bartholin's cyst or abscess and Paget's disease.
3. *Adjacent structures*. Lipomas, fibromas, haemangiomas, varicosities, carcinomas, sarcomas and endometriosis.
4. *Developmental.* Vulvovaginal cysts, intact hymen, vulval anus and intersex problems.
5. *Hormonal*. Vulval atrophy in menopausal women.

Despite the fact that vulvar diseases are not uncommon, and the vulva is easily accessible to clinical examination, there is often a delay in arriving at an early diagnosis due to a false sense of modesty which prevails and prevents the patient from seeking early advice.

The symptoms most commonly produced by vulvar lesions are itching, swelling, ulceration or altered pigmentation which may be accompanied by itching, pain or bleeding. An accurate diagnosis can usually be made by inspection, palpation, smear and culture examination and biopsy.

Congenital anomalies are described in Chapter 4.

Benign Conditions of the Vulva

Benign conditions of the vulva may be classified as:

- *Inflammatory lesions*. (a) Skin diseases, (b) sexually transmitted diseases, (c) contact vulvitis and (d) vulvar infections associated with vaginitis.
- *Ulcers*. (a) Simple acute ulcers, (b) tuberculosis, (c) traumatic ulcers and (d) malignant ulcers.
- Atrophy.
- Dystrophies.
- Cysts and neoplasms.

The above classification is obviously incomplete, but takes note of the commonly encountered disorders. Most of these can be diagnosed by simple clinical examination and tests.

Inflammatory Lesions

Skin Infections

Intertrigo and Folliculitis

Intertrigo and folliculitis are commonly seen in obese women, using tight garments which prevent evaporation of the moisture from these parts leading to chaffing followed by bacterial and fungal infection. Pyogenic bacteria can cause folliculitis. The treatment involves weight reduction, use of loose undergarments, advice regarding personal hygiene, use of bland soap and unmedicated protective dusting powder. Antimicrobial ointments may be useful initially to control secondary bacterial infection. Local application of 0.5% hydrocortisone ointment three to four times daily helps to relieve itching.

Tinea Cruris

Tinea cruris or ringworm of the thigh, vulva and groin is not infrequently encountered in the tropics. The causative organism is *Trichophyton rubrum.* It tends to be chronic and frequently relapses after treatment. The characteristic erythematous circumscribed areas are found in the skin flexures of the thighs and outer aspect of the labia. A fine papular rash is usually seen sharply demarcated from the adjacent healthy skin. Patients experience intense itching; scratching

leads to superimposed infection. Treatment consists of meticulous hygiene, the use of frequently changed light underclothes, dusting with fungicidal powder or application of fungicidal ointment containing benzoic and salicylic acids. Oral administration of griseofulvin is also highly effective.

Threadworms

Enterobius vermicularis may secondarily infect the vulva from the anorectal area, particularly in children. The diagnosis is easily established on stool examination. The treatment is with anthelmintic drugs like piperazine or mebendazole.

Vulvovaginitis

Vulvovaginitis in children may be nonspecific due to a foreign body accidentally introduced in the vagina or threadworm infection. Gonococcal and fungal infection may rarely be due to contamination. Bartholinitis is mostly gonococcal but other cocci may also be responsible, and present with a painful and tender swelling over the labia majora (Figure 27.1). Recurrent bartholinitis is not uncommon. Bartholinitis needs antibiotics.

Bartholin's Abscess

Bartholin's gland is mainly infected by gonococci, though other nonspecific organisms may be involved. The woman presents with a painful vulval swelling and purulent discharge. The swelling is inflamed and painful. It requires drainage under anaesthesia. The pus should be cultured and appropriate antibiotics instituted. After drainage, the area heals by granulation.

Psoriasis

Psoriasis (Figure 27.2) affects the vulva causing plaques of scaly well-defined patches. The silvery scale can be easily scraped off to reveal a red papular underlying surface. The aetiology is not known but the condition responds satisfactorily to treatment with local steroids. Psoriasis is also seen characteristically on the elbows and knees. A search for lesions at these sites helps in establishing the diagnosis.

Filariasis

This is caused by the worm *Wuchereria bancrofti* which is spread by mosquitoes. The parasite reproduces in the lymphatics and causes lymphatic oedema of the legs and elephantiasis of the legs and vulva. It is prevalent in tropical countries.

Contact Vulvitis

Contact vulvitis often represents a local reaction to undergarments made from synthetic materials, to soaps and detergents, to chemicals (deodorants) and occasionally to medicaments and industrial pollutants. Examination reveals oedema and reddening of the vulvar skin and vestibule without accompanying vaginitis. The acute symptoms can be controlled by administering oral antihistamines, application of local steroidal ointments or creams, using cotton underwear, advocating the use of bland soaps and scrupulously avoiding offending drugs.

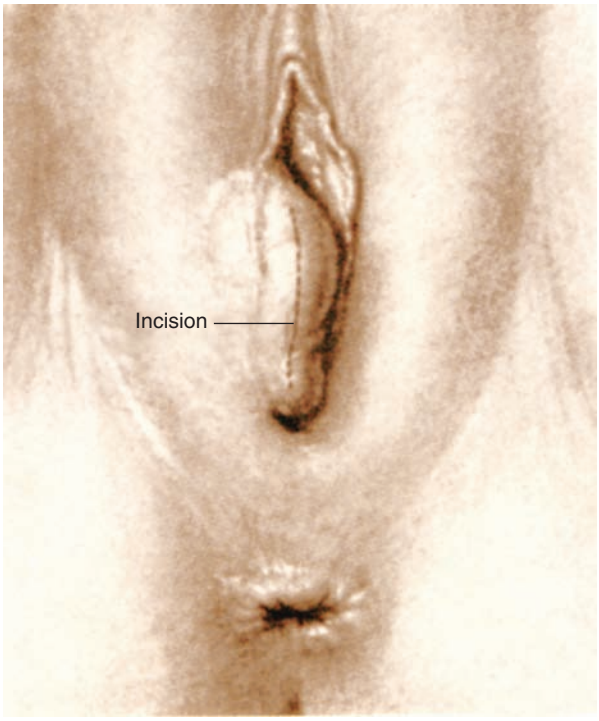

Figure 27.1 Bartholin's gland cyst. (Source: Wharton, LR. *Gynaecology with a Section on Female Urology*, 2nd ed. Philadelphia: WB *Saunders*, 1947.)

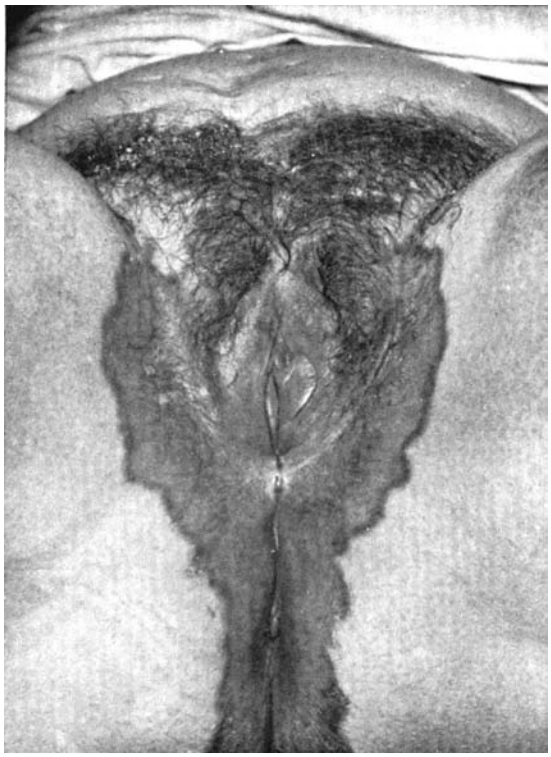

Figure 27.2 Psoriasis of the vulva. Note the extent of the lesion extending laterally to the inner thighs and posteriorly to involve the perianal skin and cleft.

Pruritus Vulva

Pruritus vulva is an itching sensation with a desire to scratch the vulva. Vulvar irritation is not the same as pruritus, but it is a painful condition associated with burning. Prolonged or severe pruritus can eventually lead to vulval irritation through scratching and abrasions.

Aetiology. There are several causes, though often it may be difficult to elucidate the cause, and the treatment becomes empirical. Well-known aetiological factors in pruritus vulva are:

- *General disease.* For example, diabetes, jaundice, uraemia, cirrhosis, haemochromatosis.
- *Nutritional*. Iron deficiency anaemia, vitamin A and B_{12} deficiency, achlorhydria.
- *Generalized or localized* dermatitis, like psoriasis, eczema.
- *Allergy* to drugs, contact dermatitis, allergy to soap, detergents, antiseptics, phenol, Dettol, dusting powder, deodorants, wearing tight synthetic undergarments, imperfectly rinsed underclothes.
- *Cervical* causes like cervicitis; erosion produces excessive mucoid secretion which causes vulval itching.
- *Vaginal discharge* due to *Trichomonas vaginalis* or fungal monilial infection accounts for 80% of all cases of pruritus vulva. The vaginal discharge may be slight but causes extensive pruritus within the introitus as well as on the vulva. Purulent discharge on the other hand, produces irritation rather than pruritus.
- *Vulval parasitic infections* like pediculosis, scabies.
- *Vulval diseases* like condyloma acuminata, granulomas, Behcet syndrome, Paget's disease and vulval cancer.
- *Anal.* Threadworm infestation.
- *Urinary.* Bacilluria, acidic urine, incontinence and glycosuria, bladder fistula.
- *Allergy* to condoms or diaphragms, spermicidal agents.
- *Psychological*. Psychoneurosis due to stress. The scratching habit may develop following sexual frustration, feeling of guilt, overmasturbation or other sexual practices.
- *Chronic vulval dystrophies* of vulval skin like leucoplakia, lichen sclerosis, kraurosis vulva of menopause and Paget's disease.
- Radiation vulvitis.

Clinically, the woman develops an itching sensation and begins to scratch the vulva. Persistent and prolonged scratching can lead to abrasions, inflammation and irritation with soreness. The patient may lose sleep because of itching and become irritable.

Treatment. The cause of pruritus should be investigated systematically and treated. Antihistamines and sedation may allay the symptoms. Hydrocortisone ointment locally or Eurax ointment often helps. Oestrogen cream is useful in kraurosis vulva due to menopausal changes. Fungal infection is treated with nystatin cream or one of the imidazole group of antifungal drugs like miconazole, econazole, clotrimazole, terconazole or oral antifungal drugs like fluconazole/ketoconazole. Oral metronidazole is specific for *Trichomonas* infection. Oral nystatin is used for perianal pruritus. If the skin is hard and tends to crack, a cream made of zinc oxide (40 parts) and olive oil (60 parts) or cod-liver oil helps to soften the skin. Injection of absolute alcohol subcutaneously 0.5–1 mL breaks the scratch habit, but if given very superficially or in deep tissues or in excessive amount, it may cause sloughing of the tissues. Ball's operation, now rarely performed, comprises division of cutaneous nerves by a circular incision around the vulva. The effect lasts for 3–6 months. Lately, interferon is used as an ointment (human leucocyte interferon) with 90% regression (Ikic et al.); 4000 units/g ointment applied four times a day for 5 weeks is recommended. Systemic intramuscular interferon 2,000,000 units daily for 10 days has yielded 90% cure rate (Schonfeld); fever, myalgia, headache are the side effects of the systemic use of interferon.

Ulcers

Traumatic ulcers are easily recognized by their appearance, contused edges and history of hurt. Treatment includes local applications of antibiotic ointment to prevent infection and administration of oral analgesics to relieve pain.

Tuberculous ulcers appear like thin serpiginous ulcers with undermined edges and a thin yellowish discharge at the base. Biopsy from the edge reveals the typical, tuberculous granulomatous lesions showing the giant type of Langhans' cells.

Venereal diseases like syphilis, chancroid and granuloma inguinale present with ulcers on the vulva.

Vulval cancers present as nonhealing ulcers with raised everted edges or as growths which breakdown and ulcerate.

Ulcers are classified as:

Primary disease

- Fungal infection, streptococcal infection, syphilis, TB.

Presenting as ulcer

- Chancroid, Behcet disease, traumatic ulcer, amoebiasis, lymphogranuloma venereum, granuloma inguinale.

Dermatitis

- Lichen sclerosus, lichen planus, Crohn's disease, allergy to drugs. Viral infection
- Herpes simplex, immunological.
- Vulvar intraepithelial neoplasia (VIN), Paget's disease, malignant ulcer.

Clinical Features

Most ulcers are painful except malignant ulcers. Pruritus if present suggests infective condition. General and systemic examination will reveal general or primary skin lesion. Serological tests, culture and biopsy confirm the nature of the ulcer.

Behcet Disease

Behcet disease is associated with oral and ocular ulcers. Since it is a chronic inflammatory multisystem disorder of unknown aetiology, the treatment is nonspecific. Corticosteroid cream helps.

Atrophy

Atrophy occurs as a normal consequence of decreased oestrogen secretion after menopause. The labia become flatter and the skin hangs loosely due to loss of subcutaneous fat. The epithelium is pale, smooth and thin. The introitus narrows down. Atrophic changes can be prevented from settling in by timely administration of oestrogens and progestogens. However, once the tissues undergo atrophy, these changes cannot be reversed by hormones. Women who undergo menopause after radiation therapy or following surgical castration appear to be more prone to this change. The disease is akin to lichen sclerosus.

Vulval Pain Syndrome

Lynch introduced this term in 1991 to describe women with unprovoked 'chronic vulval discomfort of burning, stinging and irritation' in the absence of any visible abnormalities on the vulva, or rawness around the vulva.

Several causes have been implicated and it is at times difficult to elucidate and treat the cause. Urinary oxalate excretion and deficient immune system are also probable causes. The treatment then remains empirical. Some of the known causes are:

- Skin infection—Human papilloma virus and fungal infection, herpes.
- Organic disease
- Autoimmune disease
- Iatrogenic—Topical agents, deodorants
- Irritants and allergy
- Tense levator ani muscles
- Psychological
- Urinary oxalate causing vulval burning
- Hormonal—Low oestrogen and oral contraceptives
- Pelvic floor muscle tension
- Vulval vestibulitis.

The woman is usually 20–40 years.

Vestibulitis

Vestibulitis causes pain on touch, local tenderness on pressure and erythema in the vestibular region. A woman of childbearing period may complain of superficial dyspareunia. Intensity of pain varies from mild to severe discomfort.

Dysaesthetic Vulvodynia

Dysaesthetic vulvodynia is a cutaneous dysaesthesia which causes nonlocalized vulval pain, unprovoked constant neurologic pain in the vulva and perianal region. A burning ache similar to postherpetic pain occurs usually in perimenopausal and postmenopausal woman; therefore, history of dyspareunia is rarely reported. A woman is often psychologically disturbed and anxious. This affects normal activity, walking, social life and sexual function.

Management

- Remove and treat the cause.
- Thirty per cent have spontaneous remission in a year's time.
- Medical—Topical lignocaine 1–2% may help, so also steroid creams.

Interferon gel cures only 20% of the cases. Amitriptyline, tricyclic for neuralgic pain in a dose of 10 mg daily is given, gradually increasing to 60 mg daily as required. The drug causes dry mouth, weight gain and has a sedative effect. The woman should not conceive or breast feed while on these drugs. Other drugs are Tegretol (carbamazepine) in severe cases, gabapentin 300 mg orally. Tricyclic antidepressant in chronic pain may help. Amitryptyline 10 mg daily increasing to 60 mg daily is also applicable.

Biofeedback therapy with electromyelography for pelvic floor muscles and Kegel exercise cures 80% cases.

In a severe case, a woman may need vestibulectomy. It consists of excision of the horseshoe-shaped vestibule and inner labial fold and covering the raw area with vaginal mucosa dissected from the posterior vaginal wall.

Dystrophies

Now known as non-neoplastic epithelial disorders, vulvar dystrophies represent a spectrum of atrophic and hypertrophic lesions caused by a variety of stimuli resulting in circumscribed or diffuse 'white lesions'. These lesions also often show differing microscopic patterns varying from mild dysplasia to frank malignancy in different parts of the same lesion. Multiple biopsies are therefore necessary, and the toluidine blue test helps in identifying areas of maximum epithelial hyperactivity that are most suitable for biopsy. A variety of causes are implicated in the development of vulval dystrophies, such as trauma of scratching, allergy, folic acid and B_{12} deficiency, chronic infection, metabolic disorders of diabetes and thyroid, immunosuppression and autoimmune diseases such as systemic lupus erythematosus (SLE).

The present-day histological classification of vulvar dystrophy (Table 27.1) is based on the recommendations of the International Society for the Study of Vulvar Diseases. The histological classification is more meaningful in the management than relying on the gross morphology which may not be helpful in the diagnosis.

Hyperplastic Dystrophy (Squamous Cell Hyperplasia), Previously Known as Leukoplakia

Chronic irritation or chronic vulvovaginal infection often leads to benign epithelial thickening and hyperkeratosis. Some of these women suffer from autoimmune diseases such as diabetes, thyroiditis, achlorhydria. During the acute phase, the lesions may appear red and moist due to secondary infection. As epithelial thickening develops, the

TABLE 27.1 Vulvar dystrophies

Type of Dystrophy	Hyperplastic Lesions	Lichen Sclerosis	Mixed Dystrophy
Gross appearance	White/greyish white, focal or diffuse	Small bluish-white papules that coalesce into white papules	Combination of both
Symptoms	Pruritus	Pruritus, dyspareunia, dysuria	Combination of both
Feel on palpation	Firm, cartilage like	Thin, parchment-like	Combination of both
Histology	Thickened keratin with proliferative epithelium—Acanthar	Moderate hyperkeratosis with epithelial thinning. Loss of rete hyalinization in dermis	
Pathophysiology	Reactive phenomenon from irritation	Unknown	
Method of diagnosis	Biopsy	Biopsy	
Treatment	Fluorinated corticosteroids	Testosterone cream	

environment of the vulva causes maceration and a raised white lesion which may be circumscribed or diffuse; it looks rubbery. It may involve any part of the vulva, perianal area, perineum or skin of the adjacent thighs. These lesions have also been designated lichen simplex chronicus or neurodermatitis. Patients suffer from pruritis, soreness, discharge and dyspareunia (Figure 27.3). The woman is often premenopausal. The lesion begins as white polygonal papules which coalesce to form plaques giving the appearance of being 'splashed with white wash'—fissures may develop due to scratching.

Microscopic examination reveals irregular down growth of the rete pegs deep into the dermis. The cells of the basal layers show active mitosis, the prickle cell layer is increased in thickness, and there is a heavy accumulation of keratin on the surface. The dermis reveals infiltration with inflammatory cells (Figure 27.4). Ten to thirty per cent of these cases develop malignant change. Initial treatment with oestrogens is worthwhile. Oral administration of 0.625 mg of conjugated equine oestrogen (Premarin) helps to control vulval pruritus. Bland local medicaments like Calamine lotion, crotamine or zinc oxide paste are soothing. In case of suspected superadded inflammation, steroid ointment containing 1% hydrocortisone, betamethasone, fluocinolone with or without antimicrobial agents like neomycin, Soframycin (antibiotic), miconazole or chiniofon (antifungal) are very useful. A prescription for a mild sedative at bedtime to ensure adequate rest helps recovery and prevents patients from scratching. Two per cent lignocaine ointment also relieves pain. Clobetasol 0.05% cream is also used.

In case malignancy is suspected, multiple-site biopsies are mandatory. Lesser degrees of dysplasia require extended observation, but in more advanced lesions surgical excision is indicated to relieve pruritus as well as to remove the potential site of malignancy. Colposcopic inspection using acetic acid and toluidine blue is desirable. One per cent aqueous toluidine blue is applied and washed off after 1 min with 1% acetic acid. Blue areas are biopsied.

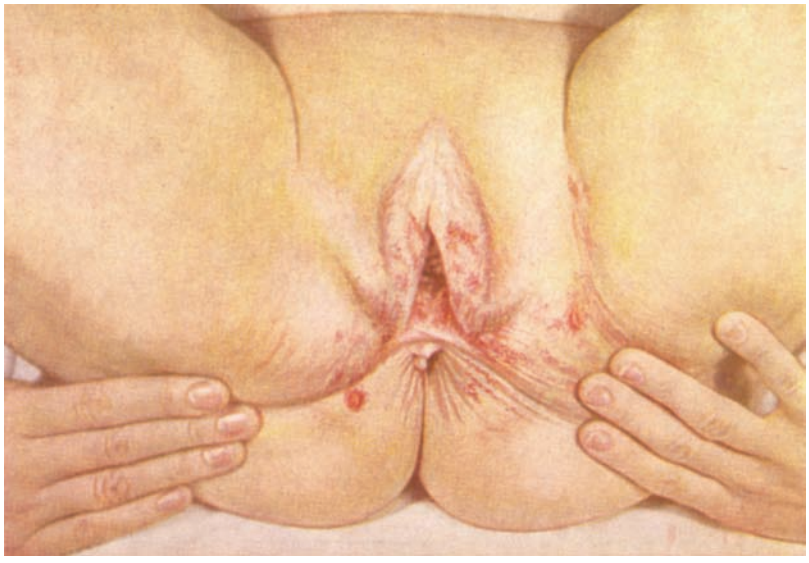

Figure 27.3 Leucoplakia of the vulva showing scratch marks and ulcerations. (Source: Novak Emil and Novak Edmund, *Gynaecologic and Obstetric Pathology*, 4th ed., Philadelphia and London: WB Saunders, 1958.)

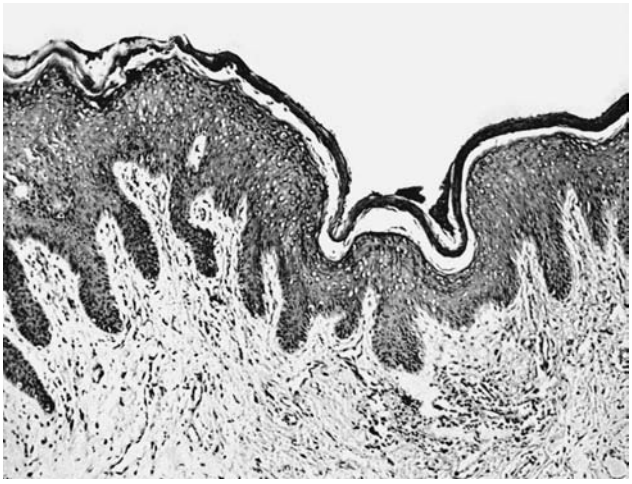

Figure 27.4 Hypertrophic leucoplakia of vulva showing irregular down growth of papillae, abnormal basal cells and superficial keratinization.

Lichen Sclerosus (Atrophic Dystrophy)

With aging, endogenous oestrogen decreases and atrophic changes in the vulvar skin and subdermal tissues appear some years after advanced atrophy of the vaginal mucous membrane. There is contracture of the vaginal introitus, and the vaginal mucous membrane becomes thin and is easily traumatized (Figures 27.5 and 27.6).

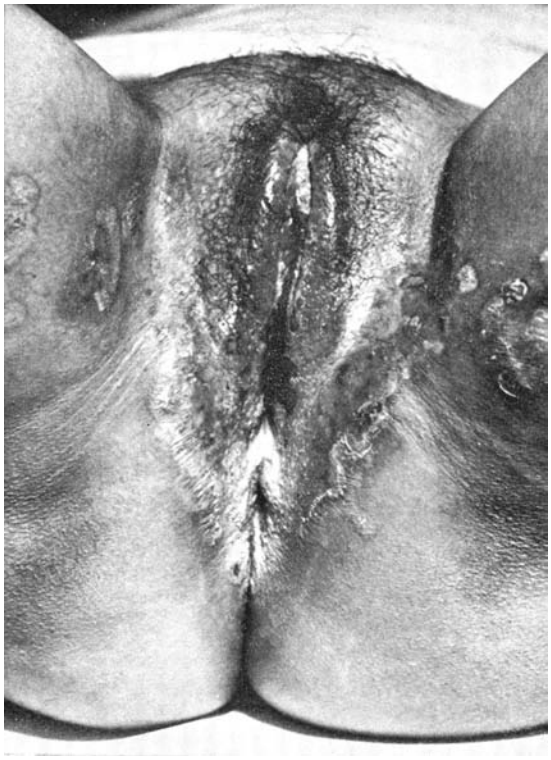

Figure 27.5 Lichen sclerosus et atrophicus of the vulva.

Goolamal et al. showed that this lesion is linked to autoimmune diseases in 40% cases and is seen in diabetes, thyroid disorders, SLE syndrome and pernicious anaemia. Antithyroid antibodies are often detected.

It is usually a disease of elderly women over the age of 65 years; genetic and familial tendency is also noted. During the acute phase, the lesion may appear dusky involving the vulva, perineum and perianal area in an hour-glass pattern (figure-of-eight). The skin is papery thin and wrinkled. As the disease progresses, the labia minora blend into the labia majora and cause a narrow introitus. Although the lesion is essentially atrophic, areas of dysplasia and malignancy may occur in 1–5% cases. All suspicious areas must be biopsied. The chief symptoms are intense pruritus, dysuria, dyspareunia and local discomfort. Biopsy reveals hyperkeratosis, thinning of the epidermal epithelium, flattening of the rete pegs and hyalinization of the tissue beneath the epidermis. Treatment with bland creams is recommended. The condition responds well to local application of steroids, such as oestrogen cream and testosterone propionate.

Two per cent testosterone ointment in white petroleum resolves pruritus in 6–8 weeks. Andractim gel (5 g) dose can be gradually reduced because of the risk of virilization and acne. Eighty per cent response is reported. Testosterone by converting to dihydrotestosterone brings about favourable skin changes.

Excision of the areas to relieve pruritus is often followed by recurrence of the lesion around the excised margins. Hypertrophic changes may follow, for which biopsy is advisable. Lichen sclerosus is now treated with 0.05% clobetasol (Dermovate) ointment for 8–12 weeks followed by Trimovate (clobetasone plus nystatin and oxytetracycline) to maintain symptomatic relief.

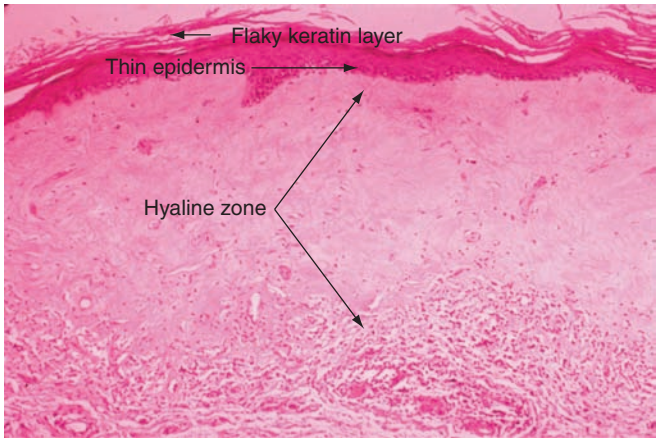

Figure 27.6 Lichen sclerosis. Histology shows hyperkeratosis, but the epidermis is thinner than normal. The most striking feature of lichen sclerosis is the presence of a hyaline zone in the superficial dermis. This is the result of oedema and degeneration of the collagen and elastic fibres of the dermis. (Source: Hacker NF, Gambone JC, Hobel CJ, *Hacker and Moore's Essentials of Obstetrics and Gynecology*, 5th ed. Philadelphia: Elsevier, 2010.)

Oestrogen and testosterone creams are useful in older women. In young women, topical progesterone is preferred to avoid side effects of oestrogen and testosterone. Vitamin A is useful, and retinoid analogues have been administered. Twenty to thirty milligrams acitretin given for 4 months is effective in 60–70% cases. It can cause dryness of skin, eye irritation, hair loss and myalgia. Its teratogenic effect prevents its use during pregnancy, and young women should use contraceptives to prevent pregnancy. Intralesional interferon is successful in some cases.

It must be emphasized that prior to medical treatment, multiple or selective biopsy is mandatory to rule out malignancy or preinvasive lesion, as 5–10% of these lesions show concomitant malignancy or develop these changes in due course of time. Pap smear is also desirable to check on the cervical histology.

Surgery is rarely employed and not curable. Fresh lesion may appear in the vicinity of the excised area. Skinning vulvectomy, cryo- and laser ablation and vulvectomy in older women have been employed.

The treatment therefore is directed towards symptomatic relief, preventing cancer by regular follow-up and improving the appearance of the vulval skin. This indicates the need for prolonged and continuous follow-up.

Mixed variety shows histological changes of hypertrophied as well as atropic dystrophy at different sites in the same lesion. The treatment is also based on predominance of type of lesion seen.

Denervation of vulva by 'Mering' procedure with a curved incision around the vulva up to the subcutaneous tissue is sometimes recommended.

Cysts and Neoplasms

Vulval Cysts

Sebaceous Cyst

Sebaceous cyst results from blockage of the duct of the sebaceous gland and contains cheesy material. It is commonly seen between the labia majora and minora and can get infected.

Bartholin's Cyst

Bartholin's cyst is formed when its duct is blocked either by inflammation or by inspissated secretion. It appears as a swelling on the inner side of the junction of the anterior two-thirds with the posterior one-third of the labium majus. A small cyst remains asymptomatic, but a larger one bulges across the vaginal introitus and causes dyspareunia, discomfort—it may get infected, thus needing excision or marsupialization. The latter is easy to perform, causes less bleeding and retains the function of the gland. The incision runs along the long axis of the labia majora away from the introitus to avoid a painful scar and dyspareunia. The cavity is scraped, haemostasis secured and the edge sutured to the skin. The cavity shrinks and heals by granulation tissue.

Cyst of the Canal of Nuck

Cyst of the canal of Nuck is a remnant of the processus vaginalis beneath the anterior part of the labia minora.

Vulval Neoplasms

Fibroma and Lipoma

Fibroma and lipoma are rare pedunculated benign growths that need excision.

Hidradenoma

Hidradenoma arises in the apocrine glands, rarely exceeding 1 cm in size. Histologically, it shows cystic spaces enclosing a papillary adenomatous mass. In rare cases, it may undergo malignant change, therefore requiring excision.

Pigmented Mole or Naevi

Pigmented mole or naevi are not uncommon over the vulva and may develop into melanoma. A growing mole should be excised and subjected to histology.

Endometriosis

Endometriosis is a purplish swelling seen over the labia majora or episiotomy scar over the perineum. It grows during menstruation and becomes painful but recedes in between menstruation. It requires excision.

Elephantiasis Vulva

Elephantiasis vulva is a filarial disease of the tropics and is caused by *Wuchereria bancrofti*. It causes elephantiasis vulva and inguinal lymphadenitis. By the time chronic lymphatic obstruction occurs, filariae are not detected. If diethylcarbamazine fails to cure the condition, surgical excision is needed. Tuberculosis is a rare cause of elephantiasis vulva.

Key Points

- Vulva is a common site of sexually transmitted diseases such as syphilis, herpes, condyloma acuminata.
- Pruritus vulva has several aetiological factors which need evaluation. Some are idiopathic and respond to empirical treatment.
- Vulval dystrophies represent a spectrum of atropic and hypertropic lesions which may be localized or diffuse. Ten to thirty per cent develop malignancy, and malignancy may exist in the same lesion. It is therefore important to rule out cancer by toluidine blue test, colposcopy and biopsy.
- Vulvodynia is a painful vulval condition without an obvious clinical lesion. It is difficult to elucidate the cause. Symptomatic relief with drugs is the first line of treatment.

Self-Assessment

1. Enumerate the components comprising the vulva.
2. Describe the benign lesions of the vulva encountered in practice.
3. How would you manage a case of vulval pruritus?
4. How would you manage a complaint of vulvodynia?
5. What are the types of vulval dystrophies? Discuss their management.

Suggested Reading

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Chapter

28

Diseases of the Vagina

CHAPTER OUTLINE

Biology of the Vagina

In a healthy adult woman of childbearing age, the vaginal contents consist of white coagulated material comprising squamous cells, Döderlein's bacilli and coagulated secretion. Döderlein's bacilli are large gram-positive organisms which are sugar fermenting. This ability to convert glycogen into lactic acid is responsible for the high acidity (pH) of the normal healthy adult vagina. The vaginal contents are mostly derived from the squamous cells of the vaginal mucosa. Some contribution comes from endometrial and cervical secretion. In healthy women, cervical secretion is small in amount and there is little secretion from the endometrium of the body of the uterus even during the secretory phase of the menstrual cycle. Pathological conditions such as erosions and ectropion of the cervix cause increased mucous secretion and the patient complains of a mucous discharge at the vaginal orifice.

The superficial cornified cells of the vaginal mucosa produce glycogen under oestrogen stimulation and are continuously desquamated. Subsequently, as a result of the breaking down of the cells, glycogen is liberated and ultimately converted into lactic acid. In the newborn, before the appearance of the Döderlein's bacilli, glycogen is broken down into lactic acid and there is some evidence that the process is brought about by enzyme action. After the appearance of Döderlein's bacilli, the production of the lactic acid is augmented by the action of bacilli on simple sugar.

The amount of normal vaginal secretion varies with age, in health and in disease. Pregnancy increases it and it is maximal in the early days of the puerperium and in women following an abortion. It varies at different times in the menstrual cycle increasing at ovulation and just before menstruation. In health, it is dependent upon the vascular state of the genitalia, and this itself is largely oestrogen-dependent. Congestive conditions of the genitalia and adjacent pelvic organs increase vaginal transudation such as prolapse with hypertrophied cervix and cervicitis and retroversion with a congested and myohyperplastic uterus. The pelvic congestion of chronic constipation also aggravates vaginal discharge.

1. The normal moistness of the vagina is sufficient to lubricate the vagina and labia minora without staining or moistening the underclothes except at ovulation, the immediate premenstrual phase, during pregnancy and under the stimulus of sexual excitation.
2. In a moderate increase in vaginal secretion, the underclothes are undeniably soiled and require changing and washing frequently.

3. An excessive degree of vaginal secretion requires the wearing of some extra absorbent pad, diaper or internal tampon and is genuinely pathological. It is to be stressed, however, that this excessive discharge is not necessarily pathologically infected, but could be hormonal.

The components of vaginal secretion are from the following:

- The sweat and sebaceous glands of the vulva and the specialized racemose glands of Bartholin's. The characteristic odour of vaginal secretion is provided by the apocrine glands of the vulva.
- The transudate of the vaginal epithelium and the desquamated cells of the cornified layer. This is strongly acidic.
- The mucous secretion of the endocervical glands which is alkaline.
- The endometrial glandular secretion.

All these play a varying part at different times of the menstrual cycle, the last two being most active just before menstruation.

Structure of Vaginal Epithelium

The squamous cells are divided into three layers: superficial, middle and deep. The deep layer consists of two types of cells, basal and parabasal. The basal cell is the less mature, smaller and more basophilic cell. It is a small round cell with a basophilic cytoplasm and a relatively large central nucleus which is uniform in shape and size. Vaginal smears where this cell predominates are typical of low oestrogen content, for example, menopausal, lactating or postpartum smears (Figure 28.1). The parabasal cell is similar to the basal cell but slightly more mature. The middle cell type is represented by a cell intermediate between the basal and the superficial or fully cornified cell. It is three times larger than the basal cell and ellipsoid or quadrilateral in shape. The cytoplasm stains blue more faintly and the nucleus is smaller and less deep staining than in the basal cell. The nucleus is vesicular. The presence of parabasal cells in a vaginal smear indicates a low but not absent oestrogenic influence as seen in normal menopause. Its presence in large numbers is also characteristic of rapid desquamation of the vaginal epithelium which may result from vaginal infection or basal cell hyperplasia. The superficial cells are of two types: precornified and cornified. The precornified cell is larger than the intermediate cell, being a hexagonal or octagonal flat wafer. Its main point of distinction from the fully cornified cell is that its cytoplasm is still fairly basophilic. Its nucleus is small and pyknotic. The cornified or fully mature cell represents the final phase of complete oestrogenic maturity. It has a pink eosinophilic cytoplasm, the largest cytoplasm of any vaginal cell (Figure 28.2). The nucleus is pyknotic. The maximum level of cornification is usually seen in the late proliferative phase of a normally menstruating woman whose oestrogen production is optimal near ovulation.

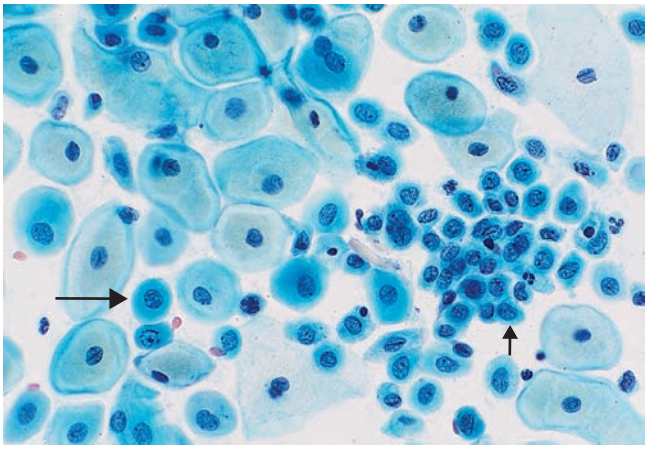

Figure 28.1 Parabasal and basal cells (postpartum smear). Parabasal cells (large arrow) are oval and typically have dense cytoplasm. Basal cells (small arrow) are similar but have less cytoplasm. Many cells have abundant pale-yellow staining glycogen, a characteristic but nonspecific feature of squamous cells of pregnancy and the postpartum period. (From Figure 1-5. Edmund S Cibas and Barbara S Ducatman. Cytology: Diagnostic Principles and Clinical Correlates, 4th ed. Saunders: Elsevier, 2014.)

Physiological Changes in the Vaginal Epithelium

It is possible to demonstrate cyclical variations in the vaginal epithelium during the menstrual cycle by cytological

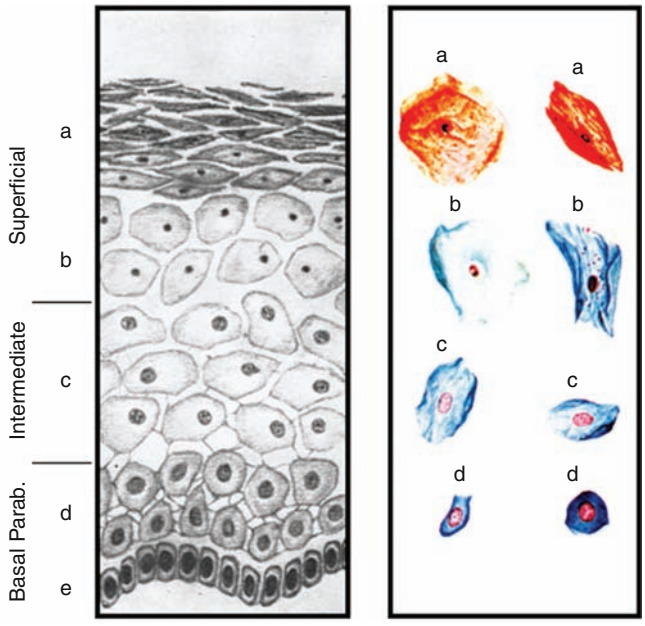

Figure 28.2 The layers of vaginal epithelium of the well-estrogenized adult. The superficial layer contains surface cells that are cornified (squamous) with eosinophilic cytoplasm and pyknotic nuclei (a) as well as large intraepithelial cells that are also karyopyknotic but basophilic (b). The intermediate zone contains basophilic cells that have less cytoplasm and intermediate-size nuclei (c). Parabasal and basal cells have successively smaller amounts of basophilic cytoplasm and more vesicular nuclei (d, e). (From Figure 15-29. Mark A Sperling: Pediatric Endocrinology, 4th Ed. Saunders: Elsevier, 2014.)

examination. This technique has become so well authenticated that a competent cytologist can diagnose the date of the menstrual calendar from an examination of the vaginal smear with nearly the same accuracy as can be accessed from the study of the endometrium. The cornification index (the percentage of the cornified cells) is one simple method of assessing oestrogen activity. The vaginal cytology during the different phases of the menstrual cycle is as follows:

1. **Menstruation**. Endometrial debris, red and white blood corpuscles and histocytes are present. The vaginal squames are immature in that they have basophilic cytoplasm; they are adherent or conglomerate and their nuclei are larger than those of mature cells.
2. **Early proliferative phase**. Polymorphs are few and the squames tend to be discrete and more mature, their cytoplasm more acidophilic and their nuclei more pyknotic and smaller; the cornification index rises.
3. **Late proliferative phase**. As the oestrogen activity reaches its maximum, the squames become uniform and mature, and the nuclei are small and pyknotic. The cells are separate, and the cornification index is the highest.
4. **Early secretory phase**. The squames become clumped together in clusters. They are less mature, the cytoplasm is now largely basophilic, and the nuclei are bigger, less dark-staining and vesicular. The cells are no longer flat but appear to be folded with a crinkled or crumpled appearance. Some are pointed and characteristically spear shaped. The cornification index falls.
5. **Late secretory phase**. Intermediate precornified cells predominate. There is lack of cornification. Cytoplasm is basophilic—the cells are crumpled and folded. The nuclei are large, pale staining and vesicular. Pyknosis and concentration of nuclear substance are absent. Polymorphs are on the increase. The background is mucky.

The cyclical changes in the vaginal epithelium show that the activity is at its maximum during the week before the onset of menstruation. Brown staining of the vagina, when the walls are painted with Lugol's iodine, gives a rough indication of the glycogen content of the cells lining the vaginal epithelium, and thereby the oestrogenic titre of the patient's blood. The maximum glycogen content in the vaginal epithelium is found in the vaginal fornices, where it is present to the extent of 2.5–3.0 mg%, and it is at its lowest in the lower third, where its value is 0.6–0.9 mg%.

Cytology of the Vagina

Cornification of the vagina is well marked in the vagina of the newborn because of the high oestrogen level which has been transmitted from the mother. After about 10 days, the vaginal epithelium becomes thinner and remains in this state until the approach of puberty. At puberty, the functional layer increases in thickness. In the first half of a normal pregnancy, the cornification index is low and should not exceed 10%. A progesterone deficiency is shown by a rise in the cornification index, and if the index rises over 25%, the patient is liable to abort. In late pregnancy, the cornification index falls even lower and at term, it may fall below 10%. After menopause, although the ovaries have ceased to function, some degree of cornification is usually present, the oestrogens probably being derived from the adrenal cortex and from conversion of androstenedione (from ovary) into oestrone in the peripheral fat.

In the postmenopausal phase, the vaginal epithelium atrophies with withdrawal of the oestrogen support. The epithelium becomes thin and parchment like and is prone to infection (senile vaginitis). The vaginal smear shows mainly the basal basophilic rounded cells with large nuclei. The background shows leucocytic infiltration. The superficial squames are absent and the intermediate cells are few and far between.

Vaginal Acidity

The vaginal acidity is due to lactic acid, which may be present as much as 0.6%. The pH value is 5.7 in the newborn and reaches 6–8 in children, and falls to 4 at puberty. During pregnancy, the pH value is usually 4. After menopause, the pH rises to 7. The normal pH in healthy women during the childbearing period is about 4.5.

It is important to understand that Döderlein's bacillus is almost the only organism which will grow at a pH of 4–4.5. As the acidity of the vagina falls and the pH rises, nonresident pathogens are able to thrive.

Natural Defence Mechanism of the Vagina Against Infection

The skin of the vagina is a tough stratified squamous epithelium devoid of glands. It presents a smooth unbroken surface to the attack of pathogenic organisms. There are no crypts where organisms can comfortably multiply as in the endocervix. The pH is low and the high acidity mitigates against bacterial growth. The thickness of the armour, the epithelium and the hostile pH depend upon oestrogen, and therefore, it is only in extreme youth, before puberty, and in senescence, i.e. after menopause, that bacterial inroads are likely. There are certain times when the pH is raised:

- During menstruation, when the cervical and the endometrial discharge, which is alkaline, tends to neutralize the vaginal acidity.
- After abortion and labour, when the alkaline lochia has a similar effect.
- An excessive cervical discharge, such as occurs in endocervicitis, has the same effect.

Apart from these exceptions, the vagina is naturally self-sterilizing.

- Döderlein's bacilli maintain the normal ecosystem in the vagina.

Flora of the Female Genital Tract

In healthy women, the fallopian tubes, the cavity of the uterus and the upper third of the cervical canal are free of micro-organisms. The lower third of the cervical canal always contains micro-organisms, as does the vagina.

a. **Lactobacilli (Döderlein's bacilli) –** mainly responsible for the production of hydrogen peroxide which is toxic to anaerobes. They also protect against bacteria and candida.
b. **Facultative organisms** (low, non-pathogenic numbers)
   (1) Diphtheroids
   (2) Coagulase negative staphylococci
   (3) Streptococci (groups B and D)
   (4) *E. coli*
   (5) Ureaplasma urealyticum
   (6) Mycoplasma hominis
c. **Anaerobic organisms** (poor concentration)
   (1) Peptostreptococci
   (2) Bacteroides
   (3) Fusobacterium species

In healthy women, Döderlein's bacillus is the only organism found in the upper two-third of the vagina; but in the neighbourhood of the vulva, both saprophytic and parasitic organisms can be demonstrated. Döderlein's bacilli have been found in the vagina of the newborn within 9 h after delivery, although the usual time for them to appear is 15 h. The vagina of the newborn is probably inoculated during parturition.

During the puerperium, acidity of the vagina is reduced and foreign organisms such as coliform bacilli and other pathogens can grow.

Vaginal discharge increases around ovulation, during pregnancy and intercourse. Antibiotics and barrier contraceptives also make vaginal secretion more alkaline and conduce to increased secretion.

During the climacteric and after menopause, the number of Döderlein's bacillus is reduced and sometimes, this organism cannot be demonstrated in the vagina. The importance of Döderlein's bacillus is that its presence is associated with the production of lactic acid contained in the vagina and this acidity inhibits the growth of other organisms. In multiparous women, when the vaginal orifice is patulous as a result of lacerations during childbirth, foreign organisms may be found in the lower part of the vagina which by producing a low-grade vaginitis give rise to discharge.

Leucorrhoea

The term *leucorrhoea* should be restricted to those conditions when the normal vaginal secretion is increased in amount. In such patients, there will be no excess of leucocytes present when the discharge is examined under the microscope, and the discharge is macroscopically and microscopically nonpurulent. Purulent discharges due to specific infections such as gonorrhoea, trichomoniasis and moniliasis, ulcerated growths of the cervix and the vagina and discharges caused by urinary fistulae are of a different type and should be excluded from the term 'leucorrhoea'. Some clinicians use the term to describe any white or yellowish-white discharge from the vagina. An increase in the normal vaginal secretion develops physiologically at puberty, during pregnancy, at ovulation and, in some women, during the premenstrual phase of the menstrual cycle. During pregnancy, the normal discharge is increased in amount because of the vascularity of the female genital tract. During the latter part of the menstrual cycle, the hypertrophied premenstrual glands of the endometrium secrete mucus which is discharged through the cervix into the vagina. The leucorrhoea of puberty is probably caused by the increased vascularity of the uterus, cervix and vagina at that time. It is of temporary duration and needs no treatment. This secretion contains proteins, polysaccharides, amino acids, enzymes and immunoglobulins.

Nonpathogenic leucorrhoea, therefore, can be classified into: (i) cervical and (ii) vaginal.

Excessive Cervical Secretion (Cervical Leucorrhoea)

Mucous discharge from the endocervical glands increases in such conditions as chronic cervicitis, cervical erosion, mucous polypi and ectropion. When the mucous secretion of the cervix is produced in excess, it undergoes little change in the vagina and appears as mucoid discharge at the vulva.

Excessive Vaginal Secretion (Nonpathogenic Vaginal Leucorrhoea)

This form of leucorrhoea is seen when the discharge originates in the vagina itself as a transudation through the vaginal walls. Almost all the lactic acid of the healthy vagina is formed from the glycogen contained in the keratinized cells of the vaginal mucosa and the vaginal portion of the cervix. These cells are constantly being desquamated when their glycogen liberated is fermented by Döderlein's bacilli, which produces lactic acid. This process is under the control of oestrogen, the level of which determines the pH of the vagina.

Local congestive states of the pelvic organs such as pregnancy, acquired retroversion and prolapsed congested ovaries, chronic pelvic inflammatory disease (PID) and even chronic constipation associated with a sedentary occupation are all reasonable causes of an increased vaginal secretion.

Leucorrhoea must be distinguished from specific vaginitis by bacteriological examination and care must be taken to differentiate between the cervical discharge of chronic cervicitis and excessive vaginal secretion. It is useless to treat the cervix for chronic cervicitis if the discharge is caused by an increased transudation from the vaginal walls. A speculum examination of the vagina will usually decide the source of leucorrhoea. If cervical, an excessive mucoid discharge will be obvious at the external os.

Specific Vaginal Infections

- Gonococcal
- Trichomonad 15–20%

- Monilial 20–25%
- Chlamydial
- Bacterial vaginosis 50%

Except bacterial vaginosis, the other infections are mostly sexually transmitted and therefore described in Chapter 11.

Vaginitis

Vaginitis causes significant inflammatory response seen in the vaginal wall. There is evidence of increase in WBCs in the vaginal fluid. This is commonly seen in infections caused by trichomoniasis, candidiasis and herpes, STDs including HIV infections.

Vaginosis

Vaginosis (also known earlier as nonspecific vaginitis/Gardnerella vaginalis/Corynebacterium vaginitis and anaerobic vaginitis) is associated with minimal inflammatory response, the vaginal fluid reveals few leucocytes. The concentration of bacteria is increased manifold (100–1000 fold) as compared to normal women.

General Features

1. **Symptoms**—Pruritus, burning
   a. Malodourous discharge and dyspareunia.
2. **Physical findings:**
   a. Congestion of vaginal walls, microhaemorrhages, presence of abnormal vaginal discharge—It may be copious in amount and frequently foul smelling.
   b. Increase in vaginal pH (alkacid papers).
   c. Tenderness/discomfort during examination.
3. **Investigations**
   a. **Hanging drop examination**—Reveals presence of motile trichomonas organisms.
   b. **KOH treated preparation of vaginal discharge—** This reveals presence of pseudomycelia and spores of candidal organisms.
   c. **Whiff test**—The fishy odour is suggestive of the presence of bacterial vaginosis.
   d. **Gram's stain**—This may reveal presence of gram negative intracellular and extracellular diplococci suggestive of gonococci, *Clue cells* suggestive of bacterial vaginosis.
   e. **Culture:**
      - *Chocolate Agar*—Gonococci
      - *Sabouraud's medium* or *Nickerson's medium*—Candida
      - *Special enriched medium*—Trichomonas
      - Trichomonas infection.
4. ***Diagnosis:*** This is based on clinical suspicion followed by confirmatory tests to establish the diagnosis.
   (1) **Clinical Findings:** These include
      - Vulvar erythema and oedema
      - Copious frothy yellowish-green foul smelling discharge
      - Punctate lesions of cervix (strawberry cervix)
      - Vaginal pH >4.5

   (2) **Hanging drop test:** Reveals presence of motile pear shaped flagellate organisms.
   (3) **Culture:** Requires use of special media, these are not easily available.
5. ***Treatment:***
   - **Prevention—**Use of barrier contraceptives.
   - **Medication—**Treatment should include both partners.
   - **Oral Metronidazole—**500 mg orally twice daily after meals for 7 days. Or 2 g stat.
   - Advisable to defer treatment during first trimester of pregnancy.
   - *Side effects:* nausea, metallic taste, antabuse – like reaction to alcohol.

Candidal Vaginitis

(a) ***Epidemiology:*** *Candida albicans* is the next common cause of vaginitis.
   1. **Risk factors altering the immune response include**
      a. Pregnancy
      b. Medications—Oral contraceptives, antibiotics, corticosteroids, cancer chemotherapy
      c. HIV and other STDs
      d. Diabetes mellitus
   2. **Poor personal hygiene**
   3. **Run down condition of health in general.**

(b) ***Diagnosis:***
   (1) **Clinical data**
      - Complaints of pruritus, burning, dysuria
      - Evidence of vulvar erythema, oedema, scratch marks
      - Discharge: whitish, flaky or curd-like
      - Vaginal pH , 4.5

   (2) **Investigations:**
      - ***A KOH treated wet mount*** of the vaginal discharge helps to dissolve all cellular debris, leaving behind the resistant hyphae and spores of candida.
      - ***Culture:*** Vaginal discharge can be cultured on *Sabouraud's agar*—Presence of discrete creamy rounded colonies appear in 48–72 h, giving a typical yeast-like odour.
      - *Nickerson's Medium* is a special medium, on which candida colonies appear in 48–72 h as brown-black discrete round colonies.

   (3) **Management**
      - ***Preventive measures—***These include the following:
        a. Improve personal hygiene
        b. Discontinue offending medications
        c. Control diabetes
      - ***Antifungal creams or pessaries*** for 7–14 days.
        a. Clotrimazole, Miconazole, Terconazole, Butoconazole
      - ***Oral antifungal agents—***Flucanazole – single oral dose of 150 mg.

Miscellaneous

(a) **Excessive discharge:**
  (1) **Common causes**
    - Sexual excitement
    - Erosion cervix
    - Ovulation time
    - Psychological factors
  (2) **Management**
    - Thorough clinical evaluation to exclude pathology
    - Counselling and education
    - Electrocautery of erosion cervix

(b) **Other micro-organisms implicated.**
  (1) **Common micro-organisms suspected include**
    - Chlamydia trachomatis
    - Gonorrhoea
    - Herpes
    - Foreign body
    - Chemical irritation
    - Senile vaginitis

(c) **Management options**
  - Advice about personal hygiene.
  - Avoid irritant exposure to douches, vaginal contraceptives (chemical creams, foam tablets).
  - Remove foreign body—retained condom, tampon).
  - Chlamydia—treat with tetracycline/doxycycline/erythromycin.
  - Gonorrhoea—treat with penicillin/ceftriaxone/ciprofloxacine.
  - Herpes—treat with Acyclovir and allied derivatives.

Gardnerella (Bacterial) Vaginosis

Bacterial vaginosis is termed *vaginosis* rather than *vaginitis*, because it is associated with alteration in the normal vaginal flora rather than due to any specific infection. There is a considerable decrease in the number of lactobacilli in the vaginal discharge with 100-fold increase in growth of other anaerobic bacteria. Since lactobacilli reduce pH and release hydrogen peroxide toxic to other bacteria, reduction in their number allows other bacteria, i.e. aerobic and anaerobic bacteria, to grow. These are *Haemophilus vaginalis, Gardnerella, Mobiluncus* and *Mycoplasma hominis*. *Mobiluncus* is a gram-positive rod-shaped bacteria with a characteristic corkscrew spinning anaerobe. Bacterial vaginosis is therefore a polymicrobial condition (Figure 28.3).

It is not sexually transmitted and has a variable incubation period. About 50% women are asymptomatic carriers of infection, but majority complain of vaginal discharge without itching.

The characteristics of vaginal discharge are as follows according to Amsel's criteria:

- White, milky, nonviscous discharge adherent to the vaginal wall.
- pH of the discharge is more than 4.5. (5–7 pH).
- Fishy odour when mixed with 10% KOH is due to amino-metabolites from various organisms (amine or whiff rest).
- Presence of *clue cells*—the epithelial cells have a fuzzy border due to adherence of bacteria (Figure 28.4(A) and (B)).
- Increased number of *Gardnerella vaginalis* and other organisms and reduced number of lactobacilli and leucocytes.
- Gram-negative stain and culture are additional investigations.

The woman has minimal vulval irritation. The diagnosis is based on wet smear and culture. The smear reveals clean background with few inflammatory cells and other organisms, but scanty lactobacilli. Many epithelial cells present a granular cytoplasm caused by small gram-negative bacilli adhering on their surface, the so-called *clue cells*. Free floating clumps of *Gardnerella* are seen. Gram stain is 90%

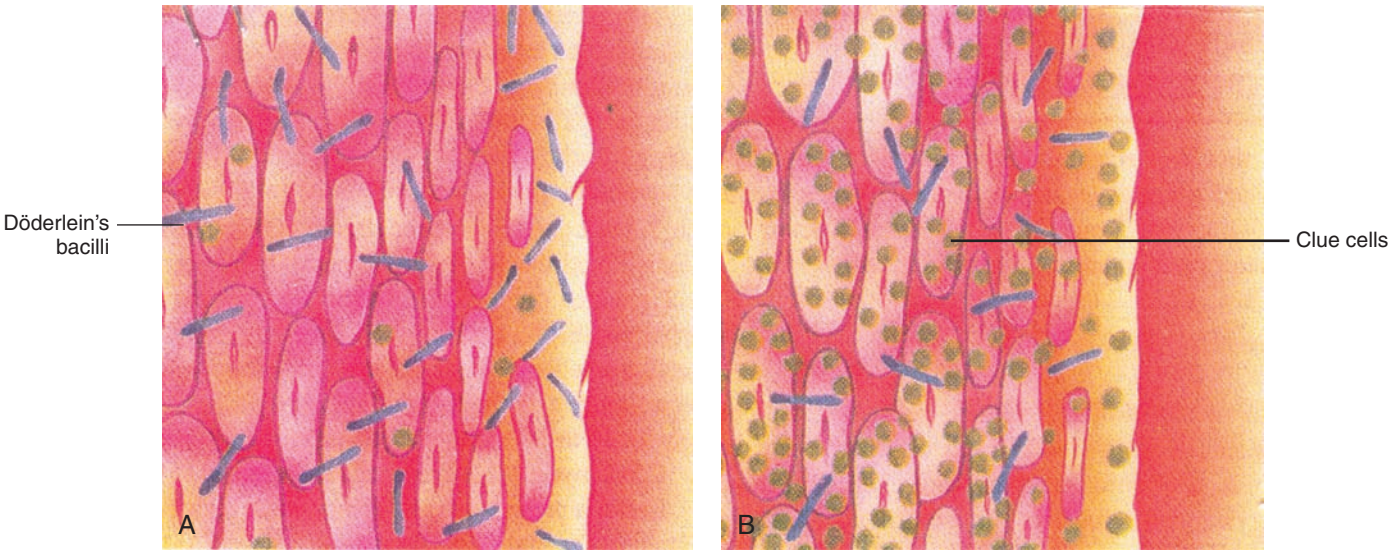

Figure 28.3 **(A)** Normal mature vaginal cells with Döderlein's lactobacilli. **(B)** Clue cells with very few Döderlein's bacilli.

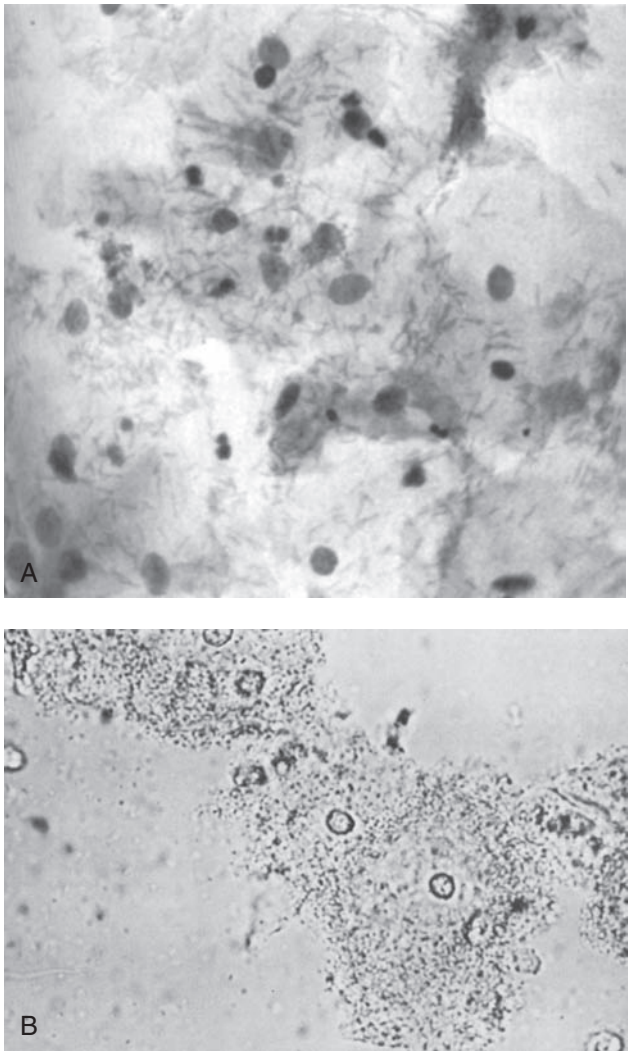

Figure 28.4 Bacterial vaginosis. **(A)** Vaginal smear showing Döderlein's bacilli. **(B)** Clue cells suggestive of bacterial vaginosis.

sensitive; a 83% specific DNA probe for *G. vaginalis* is now available. Gas liquid chromatography is useful.

Gardnerella vaginosis can cause PID, chorioamnionitis, premature rupture of membrane (PROM) and preterm labour.

Treatment

The 7-day course of metronidazole 500 mg twice daily is effective in 85% cases, whereas a single dose of 2 g cures only 45%. Ampicillin 500 mg or cephalosporin 500 mg bid for 7 days is also effective. Tetracycline 500 mg four times a day, doxycycline 100 mg twice a day and sulphafurazole 1 g four times daily for 10–14 days are the alternative antibiotics.

Clindamycin 2% cream locally is effective in 85%. Oral clindamycin 300 mg daily for 7 days is effective. Ornidazole 500 mg vaginal tablet daily for 7 days is also effective. Vaginal tablets avoid first-pass effect in liver seen with oral route.

Lacteal is a protein-free acidifying lactate gel which neutralizes the vaginal pH (lactic acid 5% W/V, 0.1% glycogen)—5 mL is applied daily for 7 days.

Recurrence rate is 30%.

Metronidazole does not reduce the number of lactobacilli unlike clindamycin and may be considered superior to the latter. The vaginal cream is also effective.

Ecoflora

Ecoflora capsule contains *Lactobacillus rhamnosus GR-I* and *Lactobacillus reuteri Rc-14*. These are probiotic agents, effective against gram-negative pathogens and resistant to spermicides. They also have anti-inflammatory activity. They secrete collagen-binding proteins that prevent pathogen adhesions. The ecoflora adhere to the epithelial cells, prevent adhesion of other pathogens and produce H_2O_2, thus maintaining pH in the vagina. One to two capsules daily for 30 days are followed by one capsule daily for another 30 days. The drug is, however, contraindicated during pregnancy.

Inflammations of the Vagina

In this important group of disorders, a variety of mixed pathogens are recoverable on smear and culture, i.e. *Staphylococcus, Streptococcus*, both haemolytic and anaerobic, and *Escherichia coli*.

Aetiology

Chemicals, drugs, douches, pessaries, tampons, trauma, foreign bodies such as rubber ring pessaries, contraceptives and even vaginal and cervical operations are all causative. Alteration in the pH towards alkalinity always favours nonspecific infection; hence, its common incidence is in the puerperium. The association of coccal secondary infection with trichomoniasis is important, since the isolation of the secondary organism may mask the presence of the *Trichomonas*, which is really responsible for the discharge. Hence, it is important to use selective culture media in all cases where response to treatment is disappointing.

Symptoms and Signs

A red, swollen, tender vagina with irritation, burning and often dysuria with frequency of micturition are present. The vaginitis is mild or severe and acute or chronic, and the colour, consistency and amount of discharge are variable. The infection is more common during menstruation or following intercourse.

Diagnosis

Diagnosis is done by smear and culture.

Treatment

Treatment varies according to the infecting organisms and is general and local.

General

All measures are designed to improve the general health of the patient.

Local

- The correction of the vaginal pH to 4.5 by a water-dispersible, buffered vaginal jelly which can be inserted in graduated amounts with a special disposable applicator (Figure 28.5).
- A locally applied bactericidal cream such as triple sulpha (sulphathiazole 3.42%, *N*-acetyl sulphanilamide 2.86% and *N*-benzoyl sulphanilamide 3.70%, excipient to 100%) (Figure 28.6) or antibiotic pessaries when the organism and sensitivity are known.
- The elimination of infection in the genital tract such as chronic endocervicitis by diathermy cauterization and conization. A woman with nonspecific vaginitis can be conveniently treated without extensive laboratory investigations with 1-day therapy using the FAS-3 kit. This contains fluconazole 150 mg, azithromycin 1 g, for gonorrhoea and chlamydia, and 1 g of secnidazole with 45% cure rate. This is repeated a week later if required.

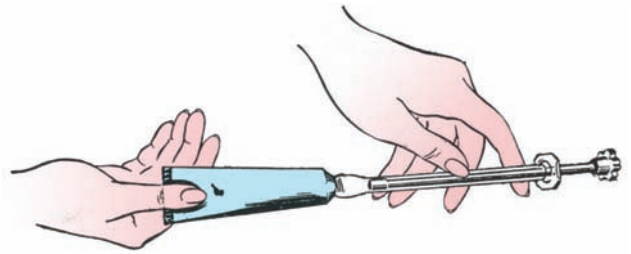

Figure 28.5 pH corrected using a special disposable applicator.

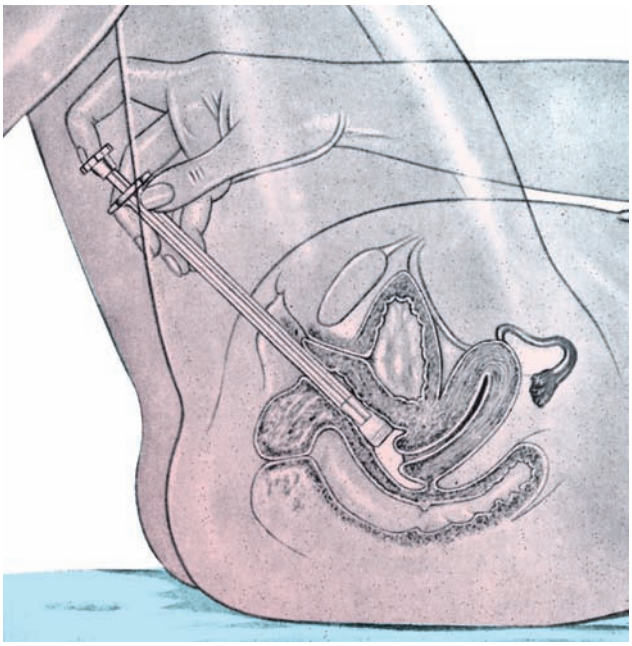

Figure 28.6 Applicator inserted in the vagina and the cream injected (local application).

Oestrogen Deficiency Vaginitis

Oestrogen deficiency vaginitis is seen as vulvovaginitis in children and as senile vaginitis in postmenopausal women. In both these age groups, the vaginal epithelium is thin and ill-protected against infection; glycogen content is low. Döderlein's bacillus is thinly populated and the vaginal pH is higher than normal, approaching or exceeding 7.4. Cytology reveals basal and parabasal cells.

Vulvovaginitis in Children

The common age group is in the first 5 years of life, but any prepubertal girl can be affected. The infecting organism is the gonococcus; any pyogenic coccus or *E. coli, Trichomonas vaginalis* and *Monilia* may be present but are rare. Infection is transmitted from adults or another child by hands, toilet, utensils or clothes. Threadworms which encourage scratching are a fairly common causative factor. The possibility of a foreign body inserted in the vagina, the variety of which baffles enumeration, must not be forgotten. This primitive Freudian urge accounts for many otherwise inexplicable vaginal discharge in young children.

Symptoms and Signs

A reddened, oedematous vulva bathed in a profuse purulent discharge, with soreness and irritation. The child is fidgety and constantly handling or scratching the external genitalia. Labial adhesions may sometimes form.

Diagnosis

Examination under anaesthesia is probably the most effective method of excluding a foreign body, obtaining an adequate smear and inspecting the upper vagina.

Treatment

Ethinyl oestradiol 0.01 mg increases the vaginal epithelial resistance and improves the vaginal acidity and is often all that is needed to affect a cure.

- Specific chemotherapy to which the infecting organism is sensitive. This is best given systemically and not locally.
- No local treatment is desirable in young girls.
- Isolation from other children to prevent cross-infection.

If not adequately treated and speedily eradicated, the infection can become chronic and resistant.

Senile Vaginitis

In many respects, senile vaginitis is comparable to vulvovaginitis in children. As a result of oestrogen deficiency, the vaginal epithelium becomes thin and atrophic, the glycogen content and acidity of the vagina are lowered and the ever present mixed pathogens obtain a footing.

Aetiology

Apart from women with natural menopause, prolonged lactation or premature menopause, women who have undergone oophorectomy are prone to develop senile vaginitis.

Symptoms and Signs

Dry vagina, dyspareunia and a purulent, often slightly blood tinged, discharge are evident. The vagina is inflamed and tender and the mucosa is excoriated. Urinary symptoms of more frequency and dysuria are common. On examination, the urethral meatus is pouting and shows a low-grade chronic urethritis often misdiagnosed as a urethral caruncle. There is a patchy granular vaginitis, the spots of which are red and bleed easily when swabbed. These raw and inflamed areas may become adherent and cause an obliteration of the canal in the region of the vault. The infection may spread upwards to involve the endometrium and produce a senile endometritis, and later a pyometra.

Diagnosis

The clinical features outlined above are easy to interpret, but certain reservations are of great importance.

- Senile vaginitis does produce a blood-stained discharge, but this does not exclude the coincident cancer of the endometrium or endocervix.
- Senile vaginitis and senile endometritis may coexist.

It is therefore obligatory to examine women with postmenopausal bleeding under anaesthesia and perform a diagnostic curettage to exclude cancer of the endometrium, endocervix and a pyometra.

Treatment

- Oestrogen is given to improve the resistance of the vaginal epithelium, raise the glycogen content and lower the vaginal pH. Ethinyl oestradiol 0.01 mg daily for 3 weeks should suffice.
- Local treatment by pessary containing oestrogen can be employed.
- As an alternative to pessaries which may be difficult for the patient to insert, a vaginal cream containing the same ingredients may be injected by special applicator illustrated in Figures 28.5 and 28.6.

This treatment should be effective and can be repeated if the symptoms recur.

Secondary Vaginitis

All varieties of vaginitis in which the primary cause is not vaginal are included in this section.

- **Foreign body**. The presence of a vaginal pessary to control prolapse or retroversion invariably causes vaginitis. Contraceptives and vaginal tampons operate in a similar way, if forgotten and left inside for a long period.
- **Infective conditions of the cervix**. Vaginitis is frequently secondary to chronic infection of the cervix, usually an endocervicitis, the effective eradication of which is sufficient to clear up the vaginal infection. Childbirth injuries of the genital tract, such as cervical tear, provide another example.
- **Vesicovaginal, ureterovaginal urinary fistulae and rectovaginal fistulae**. These are causes of vaginal infection, though surprisingly, the vagina is often resistant to such obvious portals of infection.

Malignant Disease of the Genital Tract

The growth is always infected and may involve the vagina.

Vaginitis Medicamentosa

It is caused by chemicals, douches, arsenic pessaries and occasionally contraceptives.

Rare forms of Vaginitis

Emphysematous Vaginitis

In this extremely rare condition, the vaginal walls are distended with gas-containing vesicles. The sub-epithelial tissues are indurated and oedematous, and the clinical picture suggests a malignant infiltration. There is, however, no ulceration. The main symptom apart from a swollen vagina is profuse vaginal discharge. The aetiology is unknown except that the patients are usually pregnant and the treatment is expectant as the condition resolves spontaneously. Less severe varieties of this emphysema have been described in which the gas-containing vesicles are found on a routine inspection of the vagina, and these cause minimal symptoms.

Treatment

In case of vaginal discharge in which there is some local cause, such as a retained pessary, the cause must be removed. In vaginitis due to prolapse and secondary vaginitis caused by the fistulae, it is useless to treat vaginitis without dealing with the primary cause. Specific infections of the vagina are treated by appropriate antibiotics as soon as the causative organism has been identified. There are various methods of treating vaginal discharge.

Vaginal Irrigations. Vaginal irrigation is rarely employed nowadays. In cases of prolapse, Betadine is the best antiseptic cleansing agent, but occasionally acriflavine pack has been used.

Introduction of Pessaries. The pessaries may contain the following:

- Oestrogen to promote keratinization of the epithelium and to increase glycogen content and vaginal acidity. The pessaries contain 0.1 mg (1000 international units) or 1 mg (10,000 international units) oestrone.
- Antibiotics.
- Cortisone or bacteriostatic drugs, Betadine.

- Specific fungicidal drugs, nystatin (100,000 units), imidazole derivatives, ketoconazole or the more recent terconazole; antiprotozoal and other bactericidal drugs.

Bactericidal Creams. *Bactericidal creams* such as triple sulpha cream, Betadine. Swabs should be taken for culture from the cervix, vagina and the urethra and the appropriate antibiotic given systemically or locally as soon as the organisms and their sensitivities are known.

Toxic Shock Syndrome

Toxic shock syndrome, reported first by Todd in 1978 follows the use of vaginal tampons during menstruation, and at times during the puerperium.

It is caused by *Staphylococcus aureus* and rarely by β-haemolytic streptococci, both the organisms releasing the toxin which causes sudden pyrexia over 39.9°C, myalgia, diffuse skin rash and oedematous erythema. The patient may suffer from vomiting, diarrhoea and hypotension. Leucocytosis, thrombocytopenia, and increased serum bilirubin and liver enzymes are obtained. The blood culture, however, is sterile. Toxin and release of bradykinin account for the syndrome.

Treatment. The treatment comprises correction of hypovolaemia with intravenous fluid, β-lactamase-resistant penicillin, cephalosporin and gentamicin.

The mortality is around 15%.

Precaution. Vaginal tampons or contraceptive sponge (Today Sponge) should never be left in the vagina for more than 24 h at a time.

Ulcerations of the Vagina

Ulcerations of the vagina are rare. Foreign bodies like a retained pessary usually cause ulceration high up in the posterior vaginal fornix, and the presence of granulation tissue and unhealthy offensive vaginal discharge are other manifestations. Following long-standing irritation, an ulcer may undergo malignant transformation; hence, a biopsy is mandatory in suspicious cases. Removal of the ring pessary, local douche and oral antibiotics can heal the ulcer.

Venereal Ulcers

These are commonly seen on the vulva, but occasionally the vagina may also be involved.

Tuberculous Ulcers

Tuberculous ulcers are rare and if they do occur, concomitant lesions are commonly present on the cervix or the vulva.

Chemical Ulcers

Introduction of potassium permanganate pessaries to induce abortion has been a practice in some communities. The chemical irritation can cause ulceration, occasionally followed by widespread cicatrization and stenosis of the vagina.

Radiation Ulcers

Ulceration of the vagina may develop following radiotherapy particularly in cancer of the cervix. Ulcers of this kind do not heal readily; they may cause adhesion and distortion of the vaginal vault.

Trophic Ulcers

These are observed in women suffering from procidentia.

Vaginal Granulation

These are seen in scars following surgical procedures like vaginal hysterectomy. The most common site is the vaginal vault. Patients complain of an offensive, occasionally blood-stained discharge which may persist for a few weeks to months after surgery. Cauterization of the granulation tissue gives relief.

Scars, Stenosis and Atresia of the Vagina

Exclusive scarring of the vaginal and the paravaginal tissues are not uncommon. The possible causes are injuries during childbirth, extensive repair operations for genital prolapse, radiotherapy for genital malignancy or chemical burns. Severe fulminant vulvovaginal infections in young girls and puerperal or menopausal women may also lead to such sequelae.

Amoebiasis

Amoebiasis of vagina appears as a fungating subcutaneous ulcer causing foul smelling discharge and postmenopausal bleeding. The biopsy confirms the diagnosis. Metrogyl 400 mg twice daily for 7 days cures the ulcer.

Cysts and Neoplasms of the Vagina

Vaginal Cysts

The vaginal cyst is rare, and most commonly located in the anterior vaginal wall. They are usually small, but may attain a size of 7.5 cm in diameter.

Gartner's duct cyst arises from the remnants of the mesonephric duct and lies in the anterolateral aspect of the vaginal wall. A small cyst remains asymptomatic. A large cyst if causing dyspareunia requires excision.

Inclusion cyst is mainly seen at the lower end of the vagina on its posterior surface and is caused by tags of mucosa embedding inside the scar that later forms a cyst.

Bartholin cyst at times extends into the vagina and causes dyspareunia.

Endometriotic cyst appears as a bluish bulge in the posterior fornix. It behaves similar to endometriotic cyst of the vulva. It is treated with either danazol or surgical excision.

Vaginal Neoplasms

Tumours of the vagina are rare. In rare cases, a benign tumour like a fibromyoma occurs.

Malignant tumours are described in Chapter 29.

Key Points

- Leucorrhoea is a common complaint in a woman of childbearing age. Apart from cervical lesions and nonspecific causes, specific vaginitis is caused by gonococci *Trichomonas, Chlamydia* and *Monilia* bacteria and bacterial vaginosis.
- Vulvovaginitis in children is rare; senile vaginitis due to oestrogen deficiency in menopausal women causes dry vagina, dyspareunia and urinary symptoms, and is cured with vaginal oestrogen.
- Bacterial vaginosis is the most common vaginal infection caused by reduction in the number of lactobacilli. This allows *Gardnerella*, aerobic and anaerobic organisms to grow and produce typical discharge with fishy odour. The clue cells in the smear are pathognomic of this infection. During pregnancy, it is the cause of chorioamnionitis, premature rupture of membrane and preterm labour.

Self-Assessment

1. Describe the ecosystem of the vagina
2. What are the common causes of leucorrhoea? Discuss its management
3. Enumerate and briefly describe the causes of ulcers in the vagina.
4. Describe the microscopic appearance of the normal vaginal epithelium in an adult woman. Describe the cytological changes observed during the normal menstrual cycle. What alterations in structure occur after onset of menopause?
5. Describe the management of senile vaginitis.
6. What are the causes of bacterial vaginosis? How will you treat it?
7. Write a short note on vulvovaginitis in a child.

Suggested Reading

Hamill HA. In: Normal vaginal flora in relation to vaginitis. Obstet Gynecol Clin N Am 16: 329–336, 1989.

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O'Connor MI, Sobel JD. Epidemiology of recurrent vulvo vaginal Candidiasis: Identification and strain differentiation of *Candida albicans*. J Infect Dis 154: 358–363, 1986.

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Chapter 29

Benign Diseases of the Uterus

CHAPTER OUTLINE

Fibromyomas of the Uterus and Uterine Polyps

Uterine Polyps

Uterine polyps are usually benign comprising endometrial, fibroid, adenomyomatous and placental polyps. Cervical polyps are mucous and fibroadenomatous polyps arise from the endocervix.

Endometrial Polyp

Endometrial polyps mostly arise from hyperplasia of the endometrium, some of the endometrial lining protruding into the uterine cavity as polyps. They may be single or multiple; they appear as pink swellings, 1–2 cm in diameter, with a pedicle. The polyp is composed of endometrial glands and stroma covered with a single layer of columnar epithelium. Secondary malignant change may occur in a benign polyp and it is mandatory to study its histology.

In a malignant polyp arising ab initio, the entire polyp shows malignancy including its base, whereas secondary malignancy is seen at the apex of the polyp—the base or the pedicle shows no such change. Adenomyomatous polyp has smooth muscle as well as endometrial elements. Tamoxifen can cause endometrial hyperplasia and polyps.

A *fibroid polyp* is a submucous fibroid developing a pedicle and protruding into the uterine cavity or projecting through the os with a long pedicle. It is pale looking, firm with infection and necrosis at the base if it protrudes through the cervix. It can also be a pedunculated cervical fibroid.

Placental Polyp

Placental polyp formed from retained placental tissue causes secondary postpartum haemorrhage (PPH) or intermittent vaginal bleeding following an abortion or a normal delivery.

Clinical Features

Uterine polyps cause menorrhagia, metrorrhagia or postmenopausal bleeding. If it protrudes through the os, it may cause postcoital bleeding or continuous bleeding in a young woman.

Clinically, the uterine polyp may not be evident, and the uterus may or may not be enlarged; it is easy to diagnose when the polypus protrudes through the cervical canal. Ultrasound can detect the uterine polyp, so also saline sonosalpingogram or hysterosalpingogram.

Hysteroscopy is both diagnostic and therapeutic.

Management

D&C can scrape the polyp. Hysteroscopic removal of multiple polyps may be desirable to ensure their complete removal.

Endocervical polyps have been dealt with in the chapter on inflammation of the uterus and the cervix.

Fibromyomas

Fibromyomas (leiomyomas, fibroids or simply myomas) are generally benign uterine neoplasms, commonly encountered in gynaecological practice (5–20% of women in the reproductive age group). They are slow growing tumours and take 3–5 years to be clinically palpable, unlike ovarian tumours.

Aetiology

Each myoma is derived from smooth muscle cell rests, either from vessel walls or uterine musculature.

Although oestrogen, progesterone growth hormone and possibly human placental lactogen have been implicated in the growth of myomas, the evidence in support of

oestrogen and progesterone dependence for their growth is impressive:

- Myomas are rarely found before puberty, and they generally cease to grow after menopause.
- New myomas rarely appear after menopause.
- The association of fibroids in women with hyperoestrogenism is evidenced by endometrial hyperplasia, abnormal uterine bleeding and endometrial carcinoma.
- Myomas are known to increase in size during pregnancy and with oral contraceptives and shrink after delivery.
- Treatment with mifepristone to shrink the fibroid proves that progesterone, like oestrogen is responsible for the growth of the fibroid. GnRh also shrinks the fibroma.
- Less common in smokers, because of associated hypoestrinism.

Unusual forms of leiomyomas include intravenous leiomyomatosis, which is characterized by polypoid projections of smooth muscle tumours into the veins of the parametrium and broad ligaments. These appear as worm-like cords of benign fibrous tissue when pulled out of the veins. Fragments of tumour emboli can cause obstruction of blood flow from the atrium and sudden death. Similarly, a rare form of disseminated intraperitoneal leiomyomatosis involving large areas of subperitoneal surfaces is seen during pregnancy and while on oral contraceptives. The fibroids are often associated with adenomyosis, pelvic endometriosis and pelvic inflammatory disease.

Anatomy

A typical myoma is a well-circumscribed tumour with a pseudocapsule. It is firm in consistency. The cut surface is pinkish white and has a whorled appearance. The capsule consists of connective tissue which fixes the tumour to the myometrium. The vessels that supply blood to the tumour lie in the capsule and send radial branches into the tumour. Because of this arrangement of blood supply, the central portion of the tumour receives the least blood supply, and degeneration is noticeable early and most often in this part of the tumour. On the other hand, calcification begins at the periphery and spreads inwards along the vessels. The vessels are best seen over the subserous myoma, while in the case of large intramural growth, they can be seen beneath the peritoneal covering of the uterus—this serves to distinguish the enlargement of the uterus due to a myoma from a normal intrauterine pregnancy.

Microscopically, the tumour consists of bundles of plain muscle cells, separated by varying amount of fibrous strands. Areas of embryonic muscle tissue may be present in a myoma.

The tumour may grow symmetrically, remaining within the myometrial wall, when it is called 'intramural' or 'interstitial'. If the tumour grows outwards towards the peritoneal surface, it shows itself as a bossy growth and is termed 'subserous'. Further extrusion outwards with the development of a pedicle makes it a pedunculated fibroid. In rare cases, such a tumour gets attached to a vascular organ and is cut off from its uterine origin (parasitic fibroid). Uterine contractions may force the myoma towards the cavity where it is covered only by a thin endometrium, it is then called 'submucous' myoma. This myoma may force itself downwards towards the vagina by a pedicle, and become a 'submucous myomatous polyp'. In only 1–4% cases, the myoma grows primarily in the cervix.

The distribution of myoma in the body of the uterus is broadly classified as follows (Figure 29.1A):

- Intramural (interstitial) 75%
- Submucous 15%
- Subserous 10%

The majority of myomas arise in the uterus but they may also arise from the round ligament, the utero-ovarian and uterosacral ligaments, the vagina and the vulva. Tumours can therefore be classified as uterine and extrauterine—the uterine growth is further divided into those that arise from the body and those that arise from the cervix (Figures 29.2–29.7). Subserous and cervical myomas

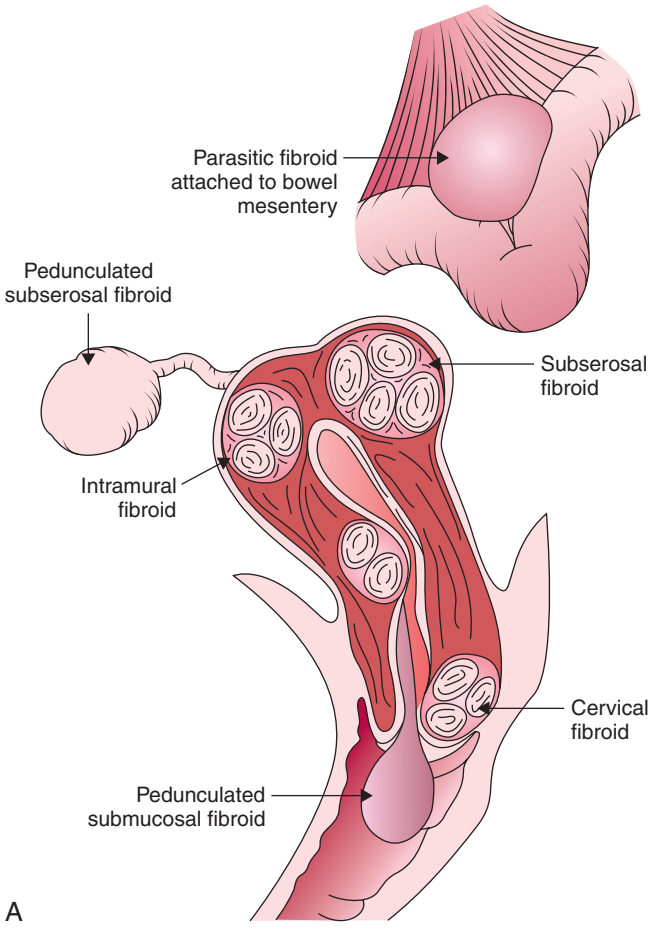


Figure 29.1 **(A)** Varieties of submucous fibroid. Various anatomical sites of fibromyomas. (Source: *Hacker and Moore's Essentials of Obstetrics and Gynaecology*, 4th ed. Saunders, 2004.)

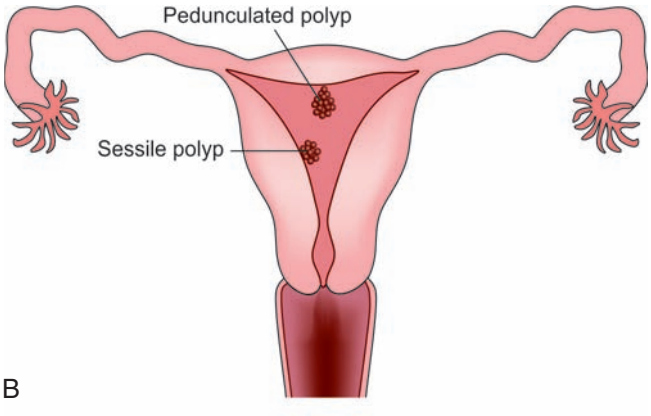


Figure 29.1, cont'd **(B)** Endometrial polyps.

Figure 29.2 Calcified intramural fibroid and subserous fibroid on the right of the picture.

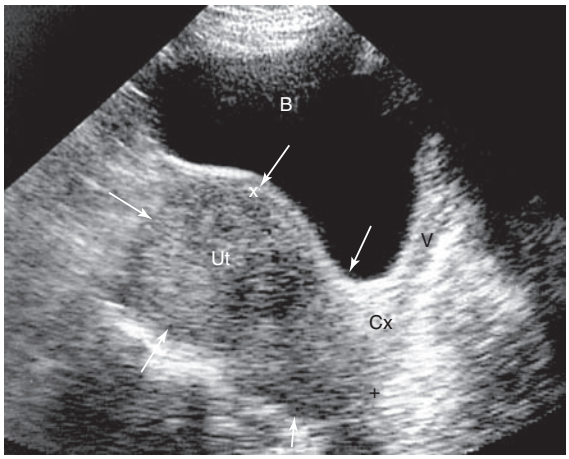


Figure 29.3 Ultrasound image of a uterus (Ut) enlarged and irregularly distorted by multiple leiomyomas (*arrows*). Such studies are useful to exclude ovarian enlargement. B: bladder, Cx: cervix, V: vagina. (Source: Hacker NF, Gambone JC, Hobel CJ, *Hacker and Moore's Essentials of Obstetrics and Gynecology, 5th ed. Philadelphia: Elsevier, 2010.*)

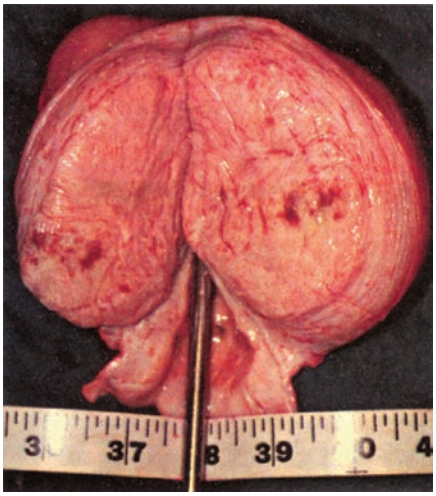


Figure 29.4 Interstitial fibroid uterus.

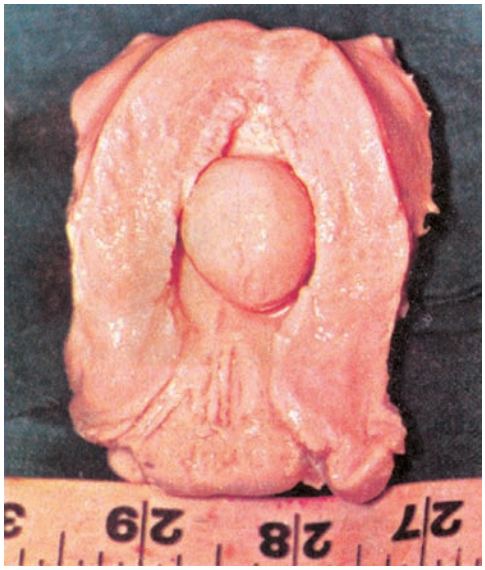


Figure 29.5 A submucous myoma.

contain more fibrous tissue and less of muscle as compared to other varieties of uterine myomas.

The presence of myoma causes hyperplasia of the myometrial wall. The cavity of the uterus is often distorted and enlarged. The endometrium tends to be thicker due to endometrial hyperplasia. The ovaries at times are enlarged, cystic and hyperaemic with evidence of salpingo-oophoritis in about 15% cases.

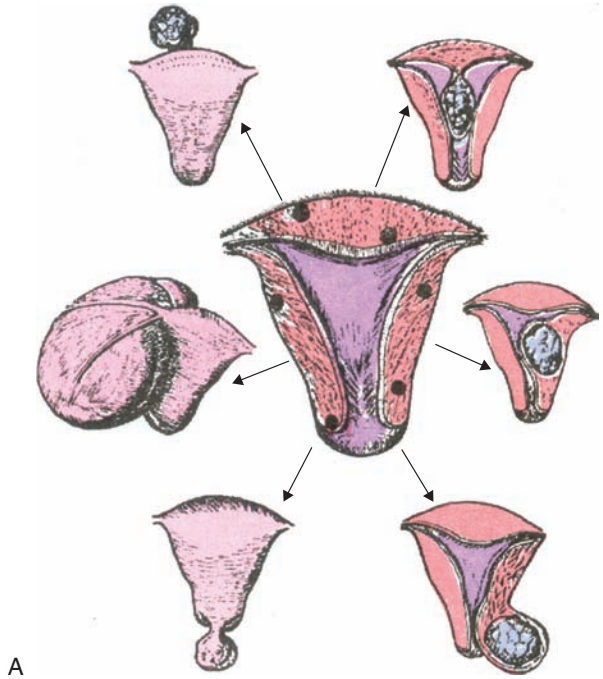
Cervical, submucous and broad ligament fibroids are usually single. Interstitial and subserous fibroids may be single or multiple, varying in size from a seedling fibroid to a huge neoplasm.

Cervical Fibroid

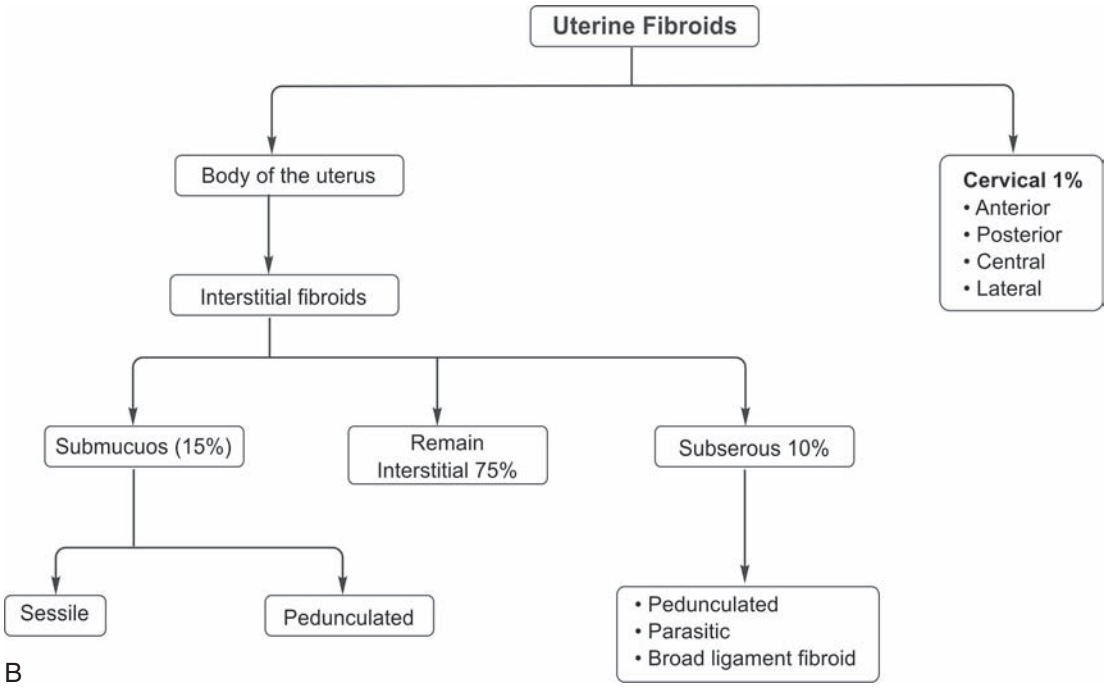
Cervical fibroid is a single fibroid encountered in 1% of all fibroids. It may develop as a central, anterior, posterior fibroid or grow laterally in the broad ligament.

Symptoms

A cervical fibroid exerts pressure on the bladder, ureter and in rare cases on the rectum. A woman may feel a lump in the lower abdomen. During pregnancy, it can cause retention of urine. Obstructed labour occurs if the cervical



A



B

Figure 29.6 **(A)** The development of different types of uterine myomas. **(B)** Types of fibroids.

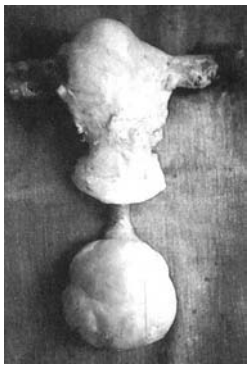


Figure 29.7 Submucous fibroid polyp protruding through the cervix. (Courtesy: Dr Narayan M Patel, Ahmedabad.)

fibroid lies below the presenting part. The other clinical features are those of uterine fibroids.

Secondary Changes: (*Table 29.1*)

Atrophy. As a result of diminished vascularity after menopause, there is a shrinkage in the size of the tumour, which becomes firmer and more fibrotic. A similar change occurs in myomas after delivery, when a tumour easily palpable during pregnancy may be difficult to define. Temporary shrinkage by 50% occurs following GnRH therapy, but regrows after stoppage of therapy.

Hyaline, cystic and fatty degenerations that occur in the central areas are of no clinical significance and are caused by

TABLE 29.1 Secondary changes and complications in fibromyomas

- Hyaline change, cystic degeneration and atrophy
- Calcareous degeneration, osseous degeneration
- Red degeneration
- Sarcomatous change
- Torsion, haemorrhage
- Infection/ulceration, particularly in the dependent part of a submucous polyp
- Inversion of the uterus
- Endometrial carcinoma associated with fibromyoma
- Endometrial and myohyperplasia
- Accompanying adenomyosis
- Parasitic fibroid

diminished vascularity in large fibromyomas (Figures 29.8 and 29.9).

Calcareous Degeneration. In calcareous degeneration, phosphates and carbonates of lime are deposited in the periphery along the course of the vessels. The best examples of calcareous myomas are those in old patients with long-standing myomas. They are like 'womb-stones' in graveyards. Calcareous tumours are easily identified by radiography (Figures 29.10 and 29.11).

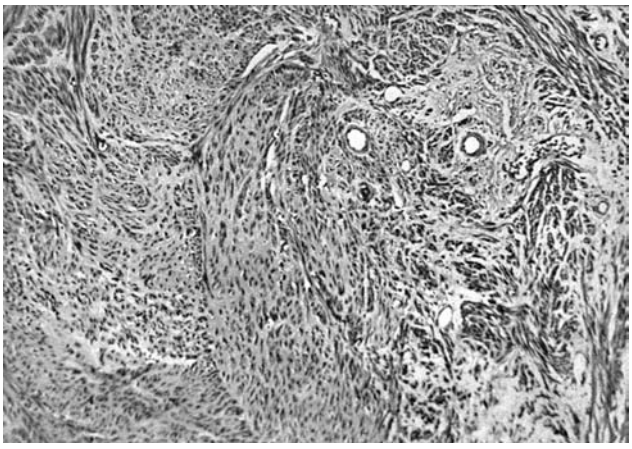


Figure 29.8 Early hyaline degeneration. Note the diffuse intercellular hyaline material (×100).

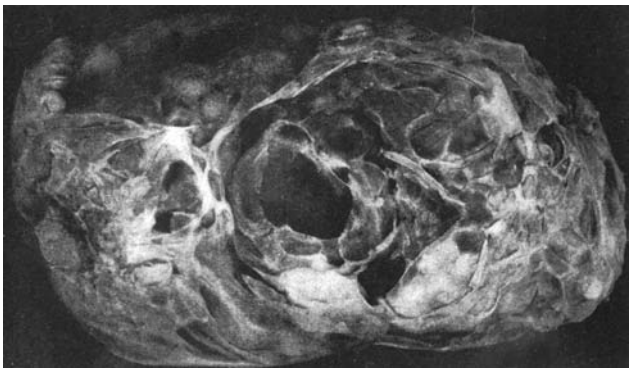


Figure 29.9 Cystic degeneration in a fibroid.

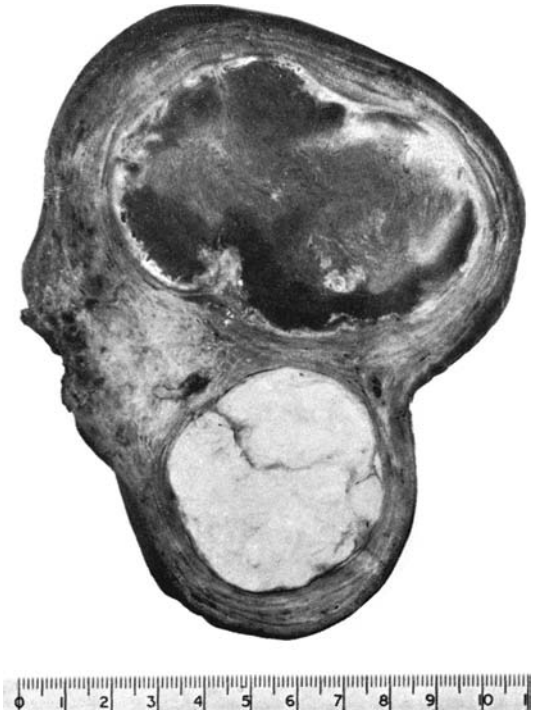


Figure 29.10 Myomas, the upper one showing peripheral calcification and haemorrhage into the tumour.

Red Degeneration. This complication of uterine myomas develops most frequently during pregnancy, although it is not rare in cases of painful myomas in women over the age of 40. The myoma becomes tense and tender and causes severe abdominal pain with constitutional upset and fever. The tumour itself assumes a peculiar purple red colour and develops a fishy odour. If the tumour is carefully examined, some of the large veins in the capsule and the small vessels in the substance of the tumour will be found thrombosed.

The discolouration is possibly caused by diffusion of blood pigments from the thrombosed vessels. Histologically, apart from thrombosis, no specific appearances have been identified. Little is known of the exact aetiology and particularly, of why only the myoma should be involved and not the myometrium. Although the patient is febrile with moderate leucocytosis and raised ESR, the condition is an aseptic one (Figure 29.12). It needs to be differentiated from appendicitis, twisted ovarian cyst, pyelitis and accidental haemorrhage. Ultrasound is useful in the diagnosis.

Sarcomatous Change. Sarcomatous change in a myoma is extremely rare, and the incidence is not more than 0.5% of all myomas. Intramural and submucous tumours have a higher potential for sarcomatous change than subserous tumours. It is rare for malignant change to develop in a woman under the age of 40. It is more commonly seen in a postmenopausal woman when it is observed that the tumour grows suddenly, causing pain and postmenopausal bleeding. To the naked eye, a sarcomatous myoma is yellowish grey in colour and haemorrhagic. The consistency is soft

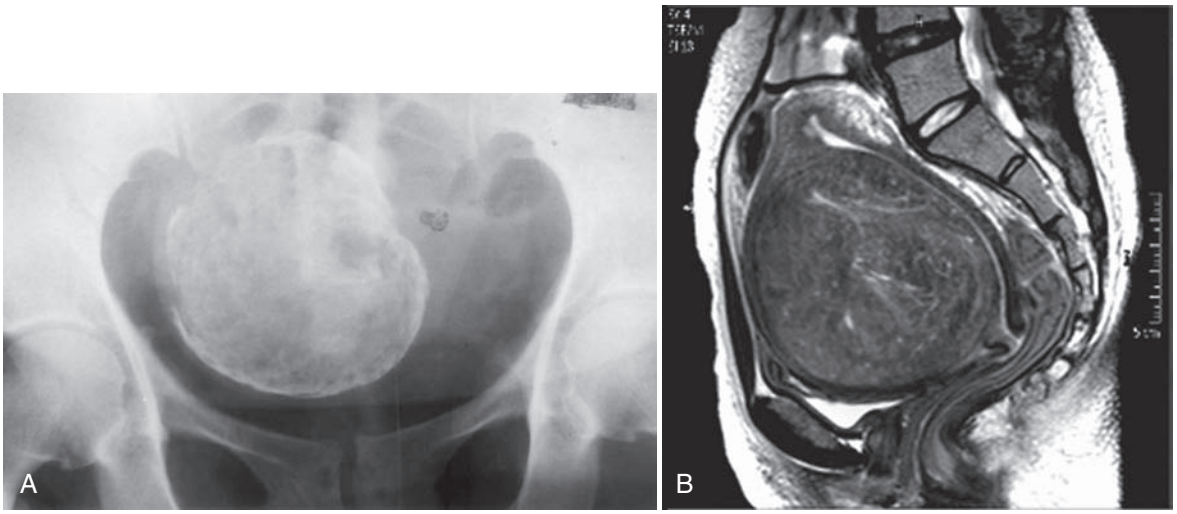


Figure 29.11 **(A)** Radiograph showing large calcified myoma. **(B)** MRI showing degenerative fibroid. (Courtesy: Dr Parveen Gulati, New Delhi.)

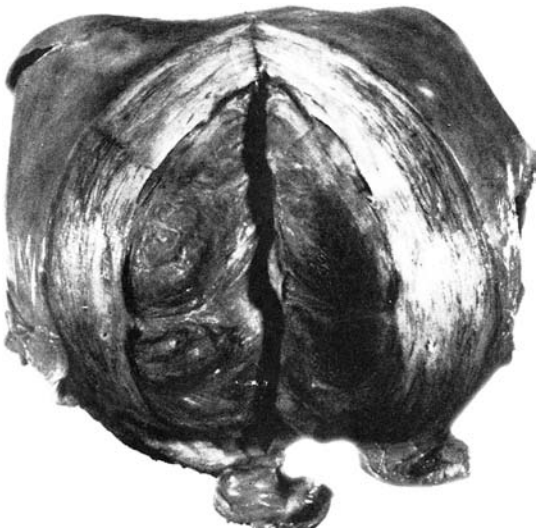


Figure 29.12 Red degeneration of a myoma. Note that the encapsulated tumour shows uniform dark discolouration.

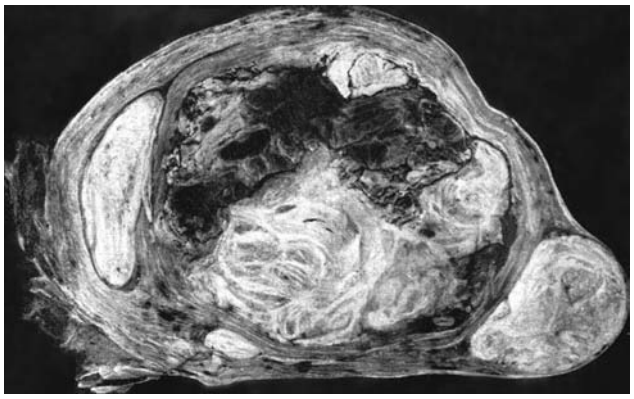


Figure 29.13 Sarcomatous change in a uterine myoma. The dark irregular areas in the substance of the myoma which lie in the middle of the specimen represent areas of sarcomatous change.

and friable, and not firm like a simple myoma (Figure 29.13). Another important sign is the nonencapsulation of the tumour. Sarcoma is highly malignant and spreads via the blood stream.

Other Complications of Myomas

Torsion. A subserous pedunculated myoma may undergo rotation at the site of its attachment to the uterus. As a result, the veins are occluded and the tumour becomes engorged with blood. Very severe abdominal pain is experienced. In very rare cases, the rotated tumour may adhere to an adjacent viscera, obtain a fresh blood supply from these adhesions and finally be detached completely from the uterus—the so-called 'wandering fibroid' or parasitic fibroid. Axial torsion of a subserous myoma is a rare phenomenon.

Axial rotation of the whole myomatous uterus itself is a very rare occurrence. In such cases, a large subserous myoma is attached near the fundus, the uterus itself being only slightly enlarged, and the site of rotation is in the neighbourhood of the internal os, at about the level of Mackenrodt's ligaments; the symptoms are comparable with those developing with torsion of a subserous myoma.

Inversion. Inversion of the uterus caused by a submucous fundal myoma has been described in the chapter on displacements of the uterus.

Capsular Haemorrhage. If one of the large veins on the surface of a subserous myoma ruptures, profuse intraperitoneal haemorrhage can cause acute haemorrhagic shock.

Infection. Infection is common in submucous and myomatous polyps if they project into the cervical canal or into the vagina.

An infected polyp causes blood-stained purulent discharge. Infection is also common in the puerperium and causes puerperal sepsis. If the tumour causes delayed PPH or sepsis, it should be removed vaginally.

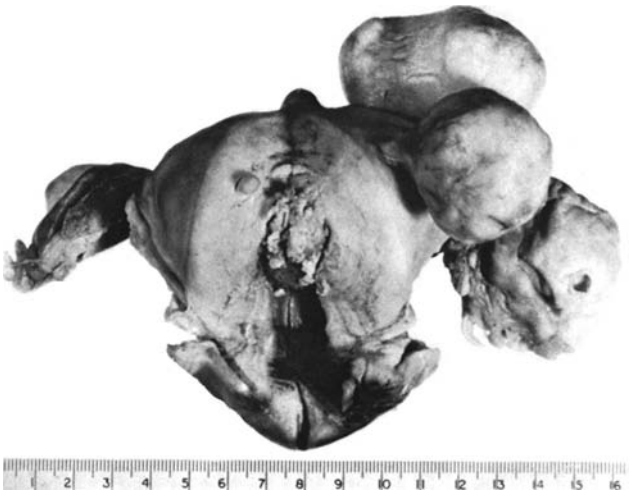


Figure 29.14 Myomas with concomitant carcinoma of the endometrium.

Associated Endometrial Carcinoma. Endometrial carcinoma is associated with fibromyoma in women over 40 years of age in 3% cases. Hyperestrogenism explains the coexistence of these two conditions (Figure 29.14 and Table 29.1).

Symptoms (Table 29.2)

- Menorrhagia, polymenorrhoea, metrorrhagia, continuous or postmenopausal bleeding
- Infertility, recurrent abortions
- Pain
- Pressure symptoms
- Abdominal lump
- Vaginal discharge

Not all fibroids cause symptoms.

As many as 50% women are asymptomatic. These fibroids are detected during gynaecological check-up or ultrasound done for unrelated symptoms. The woman may have a single symptom or present with several complaints depending upon the number, size and location of the tumours. The fibroid is seen in women of childbearing age group, 30–40 years (rarely before 20 years), nulliparous or of low parity (only 20–30% women are multiparous). Delayed menopause is observed in a postmenopausal woman complaining of postmenopausal bleeding.

TABLE 29.2 Clinical symptomatology and complications associated with uterine fibromyomas

- Menstrual disturbances—menorrhagia, polymenorrhagia, intermenstrual bleeding, continuous bleeding, postmenopausal bleeding
- Infertility
- Pain—spasmodic dysmenorrhoea, backache, abdominal pain
- Lump in the abdomen or mass protruding at the introitus
- Pressure symptoms on adjacent viscera—bladder, ureters, rectum
- Pregnancy losses, postpartum haemorrhage, uterine inversion
- Vaginal discharge

Menstrual Disorders

Progressive menorrhagia seen in intramural and submucous myoma is due to increased vascularity, endometrial hyperplasia and enlarged uterine cavity. Further away from the cavity, lesser is the possibility of menorrhagia. For this reason, subserous and pedunculated fibroids do not cause menorrhagia.

Polymenorrhoea occurs when cystic ovaries and pelvic inflammatory disease (PID) coexist with fibromyomas.

Metrorrhagia is common with submucous fibroids. An infected polyp will also cause purulent discharge. Metrorrhagia in a woman over 40 requires D&C to rule out endometrial cancer, which is associated with fibroids in 3% cases.

Infertility

Fibroids do not necessarily cause infertility. Infertility is either due to associated PID, endometriosis or anovulatory cycles, or due to distortion of the uterine cavity causing obstruction to sperm ascent, poor nidation or cornual tubal block. A fibroid bigger than 4 cm in size can cause infertility.

Submucous myoma is responsible for infertility and recurrent pregnancy loss in 20% cases.

Pain

Most women complain of heaviness in the lower abdomen. Congestive and spasmodic dysmenorrhoea are often symptoms of fibroid or associated pelvic diseases. A submucous fibroid often causes spasmodic dysmenorrhoea.

Acute pain is seen when a fibroid is complicated by torsion, haemorrhage and red degeneration. Pain in a rapidly growing fibroid in an elderly woman may be due to sarcoma.

Pressure Symptoms

Anterior and posterior fibroids lodged in the pouch of Douglas cause increase in frequency and retention of urine, more often premenstrually because of premenstrual congestion and enlargement of the tumour. Broad ligament fibroids can cause hydroureter and hydronephrosis which is reversible following surgery.

Constipation is rare, and intestinal obstruction, if it occurs, may be due to a loop of intestine round the pedunculated fibroid.

Abdominal Lump

A large fibroid may be observed as an abdominal tumour which grows slowly or not at all over a long period. A rapid growth only occurs during pregnancy, due to oral contraceptive hormones and malignancy. A pedunculated fibroid feels separate from the uterus and gives the impression of an ovarian tumour.

Other symptoms due to anaemia are dyspnoea and palpitation. A rare condition of pseudo-Meigs syndrome is associated with a pedunculated fibroid causing ascites. Haemorrhagic shock due to intraperitoneal haemorrhage is rare.

Vaginal Discharge

Vaginal discharge is a rare symptom and often is blood stained in a pedunculated submucous fibroid.

The acute clinical conditions associated with uterine fibroids are:

- Acute retention of urine and acute abdominal pain with red degenerative fibroids during pregnancy.
- Retention of urine, torsion of a pedunculated fibroid, haemorrhage infection, sarcomatous change cause severe abdominal pain.
- Rare case of thrombo-embolism.

Physical Signs

Anaemia may be noted. An abdominal lump may be felt arising from the pelvis, with well-defined margins, firm in consistency, smooth or bossy surface. The tumour is mobile from side to side unless fixed by its own large size or adhesions, or by broad ligament fibroid. Ascites is rare.

Bimanual examination will reveal an enlarged uterus, regular or bossy depending upon the number and size of the tumours. The cervix moves with the swelling which is not felt separate from the uterus unless it is pedunculated. In a cervical fibroid, the normal uterus is perched on top of the tumour. A broad ligament fibroid displaces the uterus to the opposite side.

In a myomatous polyp, the cervical os is open and its lower pole felt. The uterine fundus cannot be palpated if inversion is associated with fundal submucous fibroid polyp. The uterus is uniformly enlarged in submucous fibroids. Intravascular and disseminated peripheral fibroids rarely exist, but are often diagnosed only at laparotomy.

Differential Diagnosis (Table 29.3)

TABLE 29.3 Differential diagnosis in a patient with suspected uterine fibromyomas

• Haematometra/Pyometra	• Amenorrhoea, ultrasound
• Pregnancy	• Amenorrhoea, ultrasound
• Adenomyosis	• Ultrasound, doppler
• Bicornuate uterus	• Ultrasound
• Endometriosis	• Ultrasound
• Ectopic pregnancy	• Amenorrhoea, pain, bleeding, pregnancy test, ultrasound laparoscopy
• Chronic PD	
• Ovarian tumour	• Ultrasound
• Chronic inversion	• History, ultrasound
• Full bladder	• Endometrial study
• Bilateral tubo-ovarian masses	• Ultrasound
• Pelvic endometriosis	
• Endometrial carcinoma	
• Uterine sarcoma	
• Ovarian neoplasms	
• Fibroid polyp/uterine inversion	
• Paraovarian cysts	
• Pelvic kidney	

Pregnancy

A cystic degenerated fibroid causing a soft enlarged uterus can be mistaken for pregnancy, especially in an unmarried girl denying a proper history. The breast sign, soft cervix, pregnancy test and ultrasound resolve the doubt.

Haematometra

Haematometra, caused by cervical stenosis, causes enlarged uterus and secondary amenorrhoea. Ultrasound and pregnancy test are useful.

Adenomyosis

Adenomyosis shares the same clinical features as uterine fibroma. The uterus of more than 12 weeks size or an irregular enlarged uterus favours the diagnosis of fibroma. Besides, adenomyomatous uterus is often tender. Ultrasound confirms the diagnosis. Doppler ultrasound shows peripheral vessels in a fibromyoma, but for adenomyosis, the vessels are diffused inside.

Bicornuate Uterus

Bicornuate uterus can be diagnosed by hysterogram, hysteroscopy and ultrasound.

Endometriosis, Chocolate Cyst

The clinical features are similar, but the uterus is normal in size and adherent to the pelvic mass.

Ectopic Pregnancy

Chronic ectopic pregnancy with pelvic haematocele can give the clinical impression of a fibroid. However, the history is different—ultrasound will clear the doubt.

Chronic PID

The history and clinical findings may be identical, but inflammatory masses are slightly tender and the uterus normal sized and fixed.

Benign Ovarian Tumour

A subserous or pedunculated fibroid may resemble an ovarian tumour. Menorrhagia may not be present in all cases of fibroids. Ultrasound will show the nature of the tumour, but at times the true nature of the tumour is revealed only at laparotomy.

Malignant Ovarian Tumour

One of the grave errors is to mistake a malignant ovarian tumour for the uterine fibroid. Laparotomy should be performed in case of doubt.

Endometrial Cancer

Endometrial cancer and myoma coexist in elderly women. Abnormal bleeding requires curettage to rule out malignancy.

Myomatous Polyp

Myomatous polyp protruding through the os may be mistaken for products of conception and cervical cancer. The history and tissue biopsy establish the diagnosis.

Chronic Inversion of Uterus

Chronic inversion of uterus is often associated with fibroid polyp. The sounding of uterine cavity and laparoscopy are mandatory prior to surgical excision, if uterine perforation is to be avoided.

Pelvic Kidney. The history is unlike uterine fibroids. The tumour is fixed, behind the normal-sized uterus. Ultrasound will reveal absence of the abdominal kidney and IVP will locate the pelvic kidney.

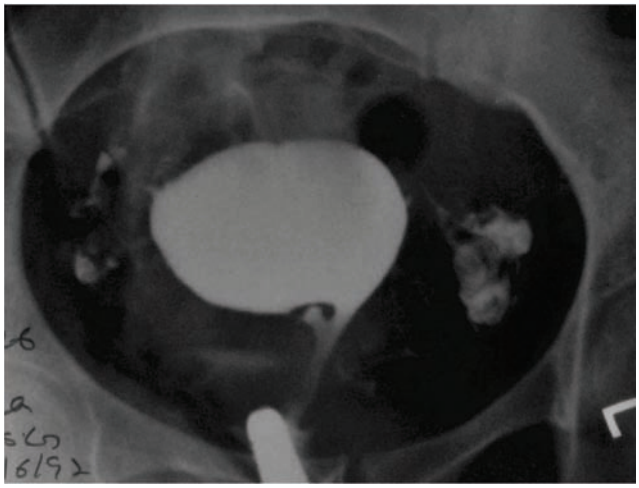


Figure 29.15 HSG showing uterine cavity is enlarged in size with a diverticulum in the uterocervical junction in the right wall. Cavity was enlarged due to large interstitial fibroid. (Courtesy: Dr K K Saxena, New Delhi.)

Investigations

In a majority of cases, the clinical features are clear cut, and elaborate investigations are not required. The following investigations may be carried out:

- Haemoglobin, blood group.
- Ultrasound (see Figure 29.3). A fibroma shows specific features of a well-defined rounded tumour, hypoechoic with cystic spaces if degeneration has occurred. Ultrasound can also identify adenomyosis as a diffuse growth with intramural cystic spaces, ovarian tumour, ectopic and adnexal mass. Preoperative ultrasound checks the number, location and size of the fibroids, and helps to reduce overlooking small fibroids during surgery, which might lead to persistence or recurrence of symptoms. Ultrasound is useful in the follow-up of fibroids after menopause and while following GnRH therapy. However, it does not recognize sarcomatous change in a fibroid—MRI does. Three-dimensional ultrasound is very useful in deciding management. Doppler ultrasound shows vascularity of the uterus and fibroids. Besides, it can differentiate between fibroids and localized adenomyosis. *The blood flow surrounds a fibroid, but diffuses through adenomyosis*. The 3D ultrasound is precise in locating the site and type of fibroids.
- Hysterosalpingography and sonosalpingography identifies a submucous myoma and checks the patency of fallopian tubes in infertility (Figure 29.15).
- Hysteroscopy not only recognizes a submucous polyp but also allows its excision under direct vision.
- D&C is required to rule out endometrial cancer. It is necessary in a woman complaining of menstrual disorder and postmenopausal bleeding. Histopathology of the endometrium gives clue to its aetiology and rules out endometrial cancer.
- Laparoscopy is required in inversion of uterus while excising a myomatous polyp and to detect associated PID and endometriosis.
- Radiography has been superseded by ultrasound. Calcification seen as a peripheral calcified area is also seen in certain ovarian tumours, TB mass, calcified mucocele of appendix and bony tumour. MRI is very useful in virgins and old women when pelvic examination clinically is not desirable in the former and hysteroscopy may be difficult due to narrow cervix.
- CT scan is not very useful, but MRI is accurate in identifying adenomyosis and sarcoma (Figure 29.16(A) and (B)).
- Intravenous pyelography is required for broad ligament fibroids to check the anatomy and pathology of ureter and to identify a pelvic kidney.
- With the development of minimal invasive surgery, it is very important to know the exact location of a fibroid. The 3D is important in this connection, although MR provides more valuable information than 3D to the interventional radiologist.

Treatment

Small and asymptomatic uterine fibroids do not require removal or medical treatment. They can be observed every 6 months. It is needless to emphasize that malignant lesion should be ruled out, and diagnosis of fibromyoma should be certain. A young woman should be informed about the presence of this tumour, so that she understands the possibility of growth and red degeneration during pregnancy. Similarly, a perimenopausal woman should realize the importance of regular follow-up. *Also it should be noted that tumour can grow if a menopausal woman is on HRT*.

During pregnancy, surgery is contraindicated, except in the case of a pedunculated fibroid if it undergoes torsion. Acute retention of urine is treated by continuous catheterization for 48–72 h, when the growing uterus rises above the pelvic brim. Red degeneration merits conservative treatment.

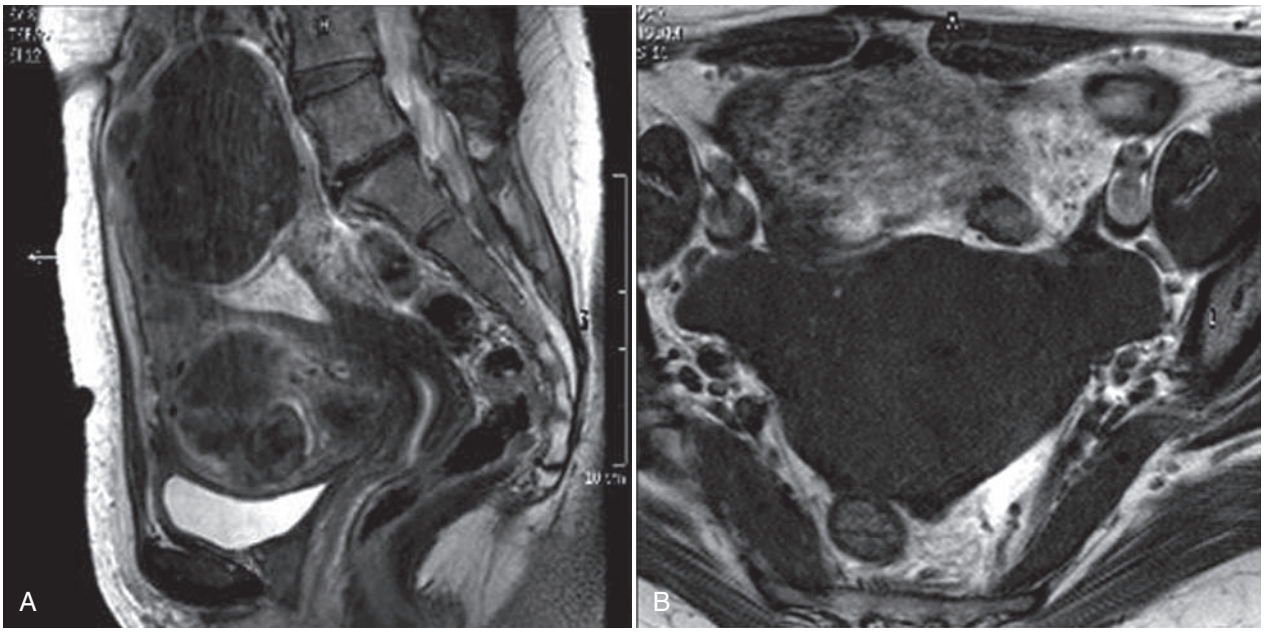


Figure 29.16 **(A)** MRI shows multiple uterine fibroids (Courtesy: Dr Parveen Gulati, New Delhi). **(B)** MRI showing submucous fibroid (Courtesy: Dr Parveen Gulati, New Delhi.)

Similarly, myomectomy is not advisable during caesarean section, because of the uncontrolled bleeding that may ensue, except for a pedunculated fibroid.

Indications for treatment in an asymptomatic fibroid are as follows:

- Infertility caused by a cornual fibroid blocking the tube and habitual abortions due to a submucous fibroid. Other causes of infertility and abortions should be ruled out before myomectomy is undertaken.
- A fibroid more than 12 weeks size and a pedunculated fibroid which can cause torsion.
- An asymptomatic fibroid causing pressure on the ureter, that is broad ligament fibroid and pressure on the bladder, leaving residual urine and causing urinary infection.
- Rapidly growing fibromyoma in a menopausal woman implying impending malignancy and requiring surgery.
- When the nature of the tumour cannot be ascertained clinically (laparotomy is needed in this occasion).
- All symptomatic fibroids.

Faced with a woman having symptoms, it is important to determine if the fibroids are really responsible for these symptoms, or they are mere 'innocent bystanders'. If so, they can be followed up and the cause of symptoms managed appropriately. Performing surgery for fibroids in such a woman may not relieve her symptoms.

Treatment may be (see Table 29.4):

- Medical
- Minimal invasive surgery
- Surgery

Medical Treatment (Table 29.5)

- Iron therapy for anaemia. Blood is rarely used preoperatively.
- The drugs used to control menorrhagia have been described in Chapter 24. Mirena controls menorrhagia provided the uterus is not enlarged beyond 12 weeks.
- The purpose of medical therapy is to control menorrhagia and improve haemoglobin before surgery or to shrink the fibroid, prior to surgery.
- In older women, successful medical therapy will allow women to reach menopause when the fibroid will shrink and cease to be a problem.

RU 486 (Mifepristone) 10–25 mg daily for 3 months causes amenorrhoea and shrinkage of the tumour by 50%. Danazol 400–800 mg daily for 3–6 months reduces the size of the tumour by 60%. However development of hirsutism and other side effects, as well as the cost, preclude its routine use. Recurrence of fibroid is reported following stoppage of the drug.

Low dose oral contraceptives, gestrinone 2.5 mg thrice a week are also effective. Asoprisnil, selective progesterone receptor modulator is better than mifepristone.

GnRH Therapy

GnRH analogues used for 6 months, reduce the tumour size by 50–80%. This treatment in premenopausal women, young women with infertility caused by cornual fibroids eliminates the need for surgery. It is also useful in reducing vascularity besides size, preoperatively, and by causing amenorrhoea or reducing menorrhagia, restores the haemoglobin level. Shrinkage of the fibroid allows Pfannenstiel incision in abdominal operation, minimal invasive surgery or a vaginal hysterectomy instead of an abdominal hysterectomy and also reduces bleeding. Monthly depot injection of 3.6 mg should not be extended beyond 6 months to avoid menopausal symptoms and osteoporosis. *One should remember that the tumour can regrow after stoppage of the drug.*

TABLE 29.4 Advantages and disadvantages of medical and surgical treatment

Advantages	Disadvantages
Medical	
• Avoids anaesthesia and surgical risks • Cures menorrhagia and controls anaemia, cures pressure symptoms • Reduces the size of the tumour and blood supply. Therefore, less operative bleeding and allows Pfannenstiel incision • Allows laparoscopic myomectomy, by reducing vascularity and size	• Side effects of the drugs do not allow treatment over indefinite period (see GnRH therapy) • Failure of treatment • Recurrence of symptoms and regrowth after stoppage of treatment • Surgery may still be required
Surgery	
• Removes fibroids and cures symptoms in one sitting • Improves fertility in 40% cases • Risk of malignancy eliminated	• Risks of anaesthesia and surgery (bleeding, trauma) • Risk of postoperative adhesions • Recurrence of fibroids due to growth of seedling fibroids (5–10%) • Persistence of menorrhagia in 5–10% due to congestion, enlarged uterine cavity

TABLE 29.5 Management of uterine fibromyoma

Asymptomatic
- Observation with regular follow up
  - Size <12 weeks
  - Uncomplicated pregnancy with fibroid
- Surgery
  - Size >12 weeks
  - Cornual fibroid causing infertility
  - Pedunculated cornual fibroid
  - Pregnancy with torsion of pedunculated fibroid

Symptomatic
- Medical
  - Hormones to shrink the fibroid–Surgery
  - Uterine artery embolization
  - Myomectomy
  - Lap myomectomy
  - Lap myolysis
- MRI guided ablation
  - Total/Subtotal abdominal hysterectomy
  - Vaginal hysterectomy
  - Total laparoscopic hysterectomy
  - Lap hysterectomy
  - Laparoscopic-assisted vaginal hysterectomy

Cervical 1%
- Vaginal polypectomy or myomectomy
- Myomectomy
- Lap myomectomy
- MRI guided myolysis
  - Vaginal hysterectomy
  - Total abdominal hysterectomy

Instead of monthly injection, three monthly leuprolide acetate 11.23 mg may be convenient to administer. Pure anti-oestrogen (faslodex) may be effective for the same purpose. These hormones however do not relieve dysmenorrhoea. Other anti-E_2s like raloxifene and aromatase inhibitor fadrozole are under trial.

The disadvantages of GnRH therapy preoperatively are that the fibroid capsule may thin out making enucleation rather difficult. Small fibroids become invisible at surgery, but recur later. *Mirena IUCD can be used to control menorrhagia and dysmenorrhoea due to fibroids.* GnRH analogues are expensive and need to be injected subcutaneously.

Add-back therapy with oral combined pills, tibolone or progesterone with GnRH, can reduce the side effects and allow longer use of GnRH. GnRH antagonists are better than agonists, as they avoid initial 'flare up' effect and act faster.

Isoprisinol (selective progesterone receptor modulator) is under trial. *HRT should not be offered to a menopausal woman with fibroids.*

Aromatase inhibitors like letrozole have been employed. They inhibit conversion of androgens to oestrogen in the ovaries and in peripheral fat, and shrink the fibroid by 50%.

Surgery

The techniques used are conventional myomectomy and hysterectomy, by laparotomy or laparoscopically.

Newer minimal invasive procedures successfully introduced in recent years are:

- Uterine artery embolization
- MRI guided laser ablation
- Laparoscopic myolysis

Myomectomy. *Myomectomy* refers to the removal of fibroids, leaving the uterus behind. It is indicated in an infertile woman or a woman desirous of childbearing and wishing to retain the uterus.

PREOPERATIVE REQUISITES

- Haemoglobin should be restored.
- Autotransfusion arranged a few days before surgery is preferred to donor transfusion at surgery to avoid transmission risk of HIV, malaria and hepatitis B.
- In infertility, other causes of infertility should be excluded.
- Signature for hysterectomy is required in difficult unforeseen circumstances.
- Myomectomy should be performed in the preovulatory menstrual cycle to reduce blood loss during surgery.

- Endometrial cancer to be ruled out by D&C.
- Bowel preparation avoids bowel injury.

TECHNIQUE OF MYOMECTOMY (Figure 29.17)

- Opening the abdominal cavity by Pfannenstiel incision is possible if the uterus is less than 16–20 weeks size and is mobile. If difficulty is anticipated as with a large uterus, fixed uterus with adhesions, associated PID and endometriosis, a vertical paramedian incision is safer.
- Care should be taken not to injure the bladder while incising the parietal peritoneum, as the bladder may be elevated in cervical and low-lying anterior wall fibroids.
- The pelvic organs should be carefully inspected and the feasibility of myomectomy confirmed.
- An incision over the anterior uterine wall is preferred whenever possible and as many fibroids removed through minimal tunnelling incisions.
- Haemorrhage should be controlled with the myomectomy clamp. The clamp should be applied from the pubic end of the abdominal wound and the round ligaments which will include the uterine vessels should be gripped. The ovarian vessels may be temporarily occluded with a sponge forceps. If the myomectomy clamp cannot be applied as in cervical fibroids, a rubber tourniquet will serve the purpose.
- The capsule should be incised and the fibroid enucleated. This will minimize bleeding as well as avoid trauma to the bladder and ureter. Myomectomy screws help during enucleation (Figures 29.18 and 29.19).

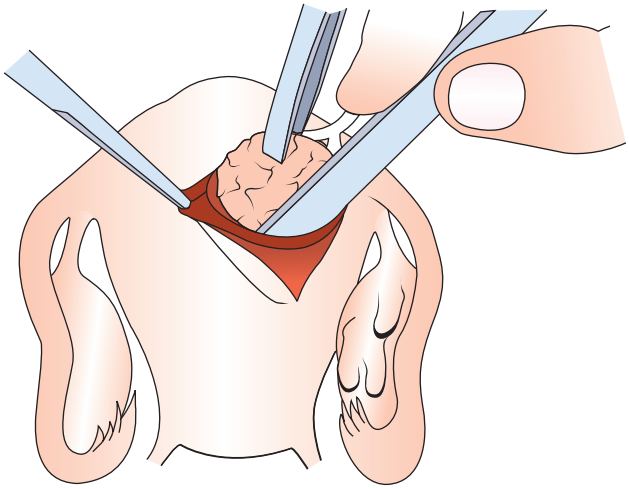


Figure 29.17 Myomectomy operation.

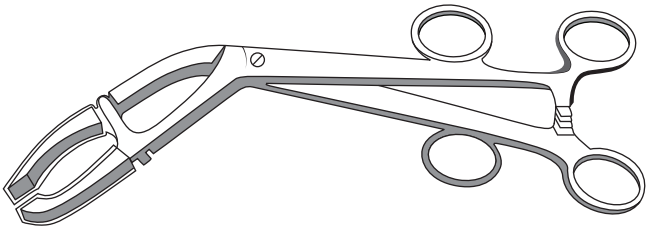


Figure 29.18 Bonney's myomectomy clamp.

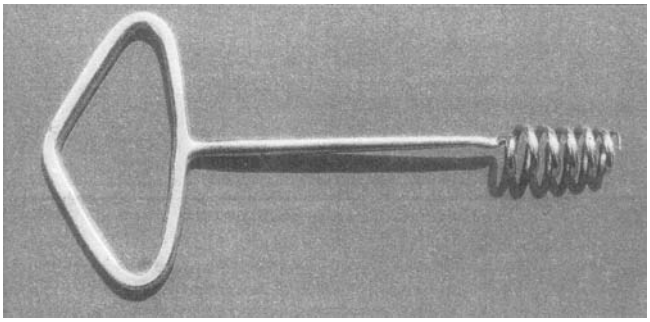


Figure 29.19 Myoma screw.

- Following enucleation, the haemostasis is secured and the cavity obliterated with several catgut sutures. This will avoid scar rupture during subsequent pregnancy and labour.
- The clamp should be released and haemostasis confirmed.
- The raw visceral area should be well-peritonized to prevent postoperative adhesions. Hydrofloation also reduces adhesions (see Chapter 42). The uterus remains bulky following myomectomy and requires to be anteverted by plicating the round ligaments with non-absorbable sutures.

RESULTS. Pregnancy rate of 40–50% has been reported following myomectomy and pregnancy loss reduced. However, 10–15% continue to suffer from menorrhagia. Recurrence of fibroids in 5–10% cases is due to overlooking seedling fibroids at the time of surgery.

COMPLICATIONS. The complications that may result from myomectomy are:

- Primary, reactionary and secondary haemorrhage
- Trauma to the bladder, ureter and bowel during surgery
- Infection
- Adhesions and intestinal obstruction
- Recurrence of fibroids and persistence of menorrhagia

Vaginal myomectomy (Figure 29.20). It is indicated in submucous fibroid polyps. Vaginal myomectomy is possible in cervical fibroids and pedunculated fibroid polypus and if more than 50% submucous fibroids project into the cavity.

Hysteroscopic myomectomy. Hysteroscopic myomectomy has become possible for submucous fibroids not removable by the simple vaginal route. The fibroid is excised either by cautery, laser or resectoscope. It is best done under laparoscopic guidance to avoid uterine perforation. Complications of hysteroscopic myomectomy are:

- Cervical trauma, uterine perforation
- Thermal injury
- Bleeding—Foley catheter can be used as tamponade to stop bleeding
- Infection
- Failure
- Uterine adhesions
- Complications of distending media

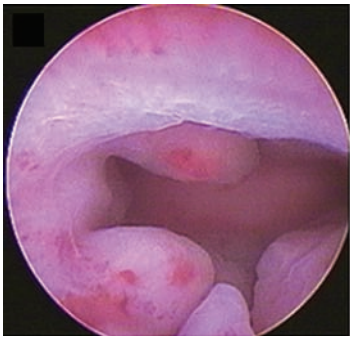


Figure 29.20 Hysteroscopy reveals multiple endometrial polyps. (From Figure 2A. Chunxia Cheng, Ting Zhao, Min Xue, et al.: In: Use of Suction Curettage in Operative Hysteroscopy. Journal of Minimally Invasive Gynecology, Volume 16(6): 739 -742, 2009.)

Laparoscopic view of various fibroids is shown in Figures 29.21 and 29.22.

Laparoscopic myomectomy (Figure 29.23A–I) is feasible in:

- A pedunculated fibroid.
- Subserous fibroid not exceeding 10 cm in size and not more than four in number. Multiple fibroids of any size should be approached by laparotomy. Unipolar, bipolar cautery and laser have been employed to remove the fibroma and obtain haemostasis. The fibroma is retrieved through posterior colpotomy, minilaparotomy or by morcellation. Myolysis, a technique of destruction of myoma tissue by laser or cautery, is a sophisticated technology practised by endoscopists.
- Laparoscopic-assisted vaginal hysterectomy (LAVH) enables vaginal hysterectomy to be completed from below in the presence of pelvic pathology.

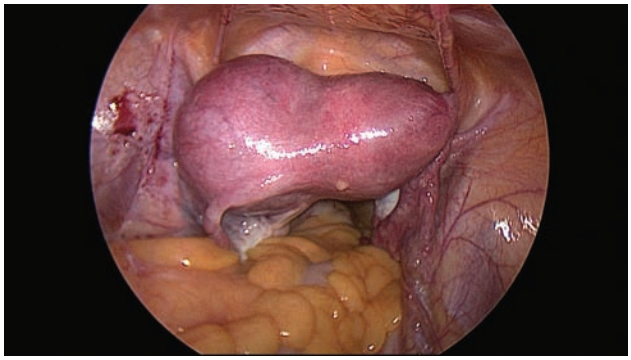


Figure 29.21 Subserous fibroid seen on laparoscopy. (Courtesy: Dr Vivek Marwah, New Delhi.)

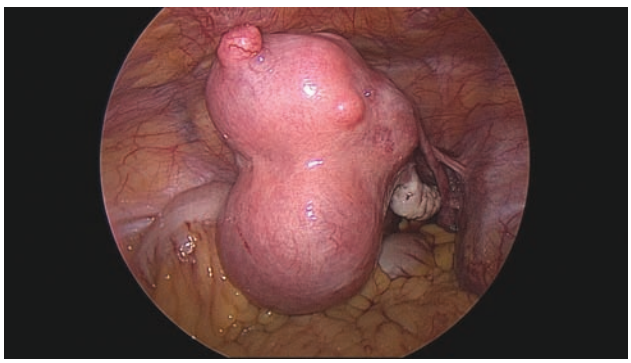


Figure 29.22 Multiple uterine fibroids. (Courtesy: Dr Vivek Marwah, New Delhi.)

Laparoscopic myomectomy is made easier and faster by newer instruments, morcellator, newer energy sources and newer suture materials. The bleeding is controlled by infiltration of myoma with vasoconstrictors and bilateral uterine artery ligation prior to myomectomy.

A single portal laparoscopic surgery is a new innovative technique developed recently.

Disadvantages of laparoscopic myomectomy. Although a minimal invasive surgery, and without an abdominal scar, laparoscopic myomectomy can cause more bleeding because of nonapplicability of a haemostatic clamp and being an adhesiogenic procedure, takes longer to perform. Postoperative adhesions can increase the infertility rate. Scar rupture is also reported in late pregnancy and during labour. Some use intercede (oxidized regenerated cellulose) to prevent or reduce adhesions. The major complication is rupture of the myomectomy scar during pregnancy or labour due to imperfect or inadequate suturing of the myomectomy wound. *Laparoscopic myomectomy may therefore not be safe in an infertile woman*. A small fibroid unrecognized at laparoscopy may grow and show up as recurrence. The recurrence rate is reported as higher than that in laparotomy.

Uterine Artery Embolization. In 1991, Jacques Ravina, a French gynaecologist, first performed uterine artery embolization (UAE) preoperatively to reduce vascularity and the size of the fibroid. Improvement of symptoms cancelled definitive surgery is some cases. Menorrhagia was relieved in 80–90%, pressure symptoms in 40–70%, the volume decreased by 50% at the end of 3 months by 60% at 6 months and 75% at the end of 1 year. Thus, this technique is now employed successfully in selective cases.

CONTRAINDICATIONS

- Subserous and pedunculated fibroids. Necrosis and fall of the tumour into the peritoneal cavity can occur. Big fibroids are not suited for UAE.
- Submucous fibroid is not cured.
- Infertility rate may increase following this technique because of postembolization pelvic adhesions.
- Calcified fibroid cannot shrink with this technique.
- Associated inflammatory disease may also preclude the employment of this technique.

TECHNIQUE. Under local sedation, bilateral UAE is approached through percutaneous femoral catheterization. It is done using polyvinyl alcohol (PVA), gel foam particles or metal coils. Embolization reduces vascularity and the size of the fibroid in 3–4 months (Figure 29.24) (40% at 6 weeks and 75% at 1 year).

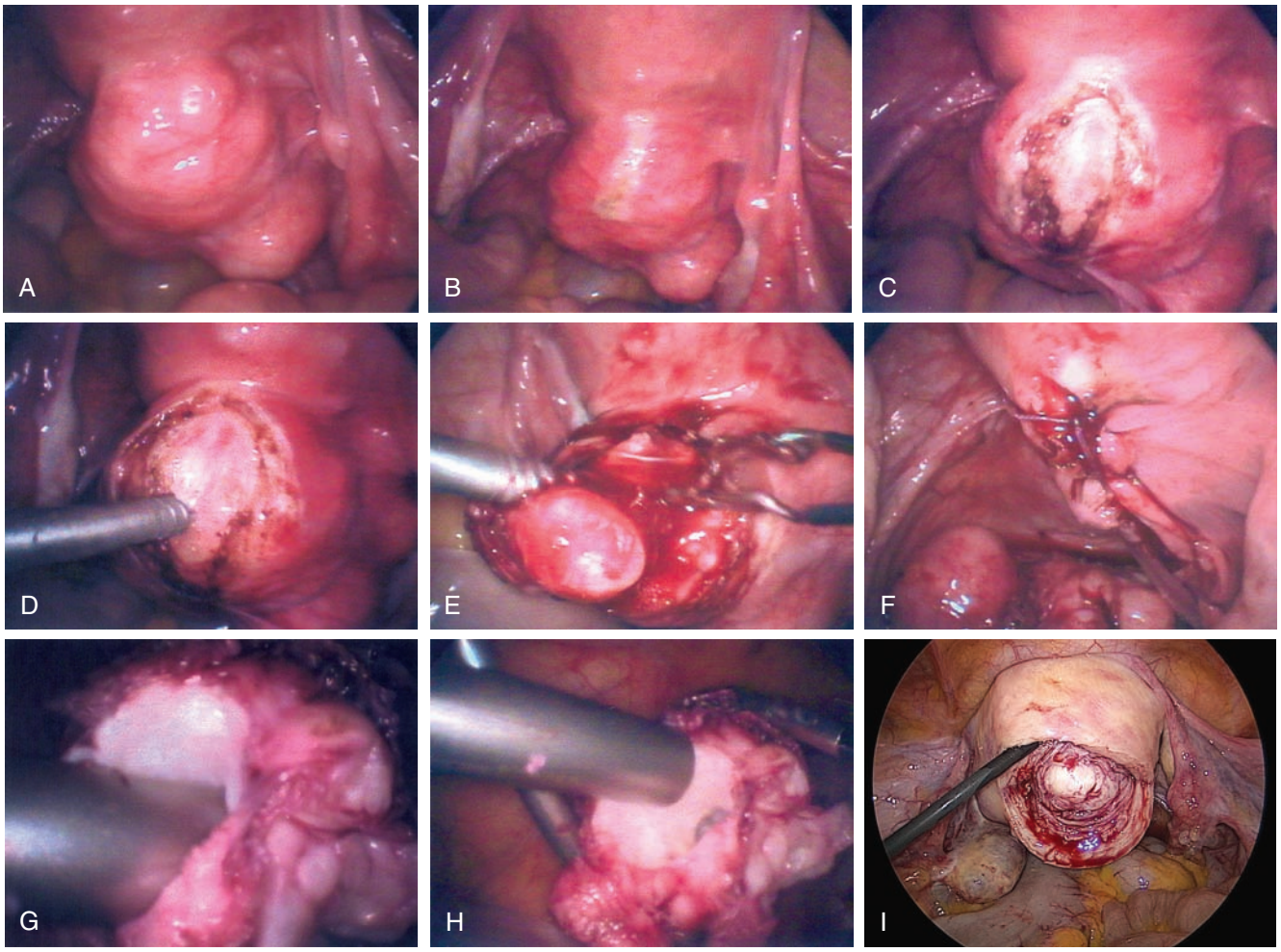


Figure 29.23 Laparoscopic myomectomy—steps of operation: **(A)** Fibromyoma uterus. **(B)** Incision taken on the fibromyoma. **(C)** Fibromyoma exposed. **(D)** Myoma screw inserted to steady the myoma. **(E)** Myoma dissected from its bed. **(F)** Edges of myoma bed approximated with interrupted Vicryl sutures. Removed myoma seen in POD. **(G)** Myoma being morcellated. **(H)** Tunnel in myoma after removal of cylindrical mass. **(I)** Laparoscopic myomectomy. (Courtesy: Dr Vivek Marwah, New Delhi.)

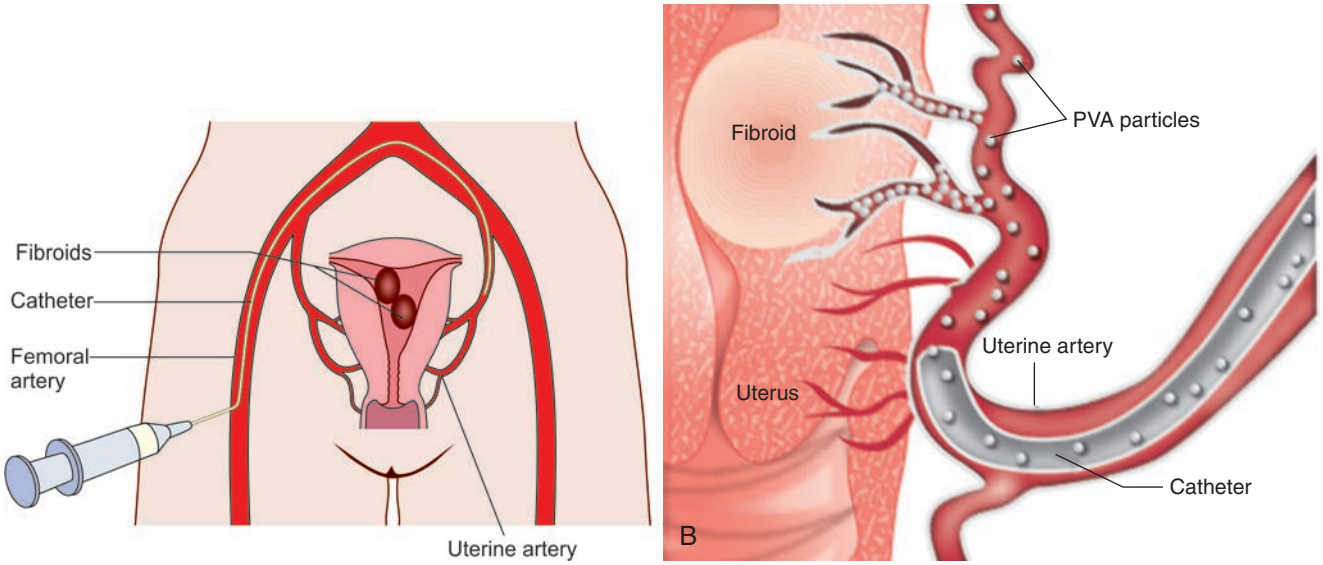


Figure 29.24 **(A)** Transfemoral catheterization of the uterine arteries. **(B)** Injection of polyvinyl alcohol particles. (Source: Rao, K.A. *Textbook of Gynaecology,* India: Elsevier, 2008.)

The symptoms are relieved in 70–80% women. The following are the postoperative complications:

- Fever and infection.
- Vaginal discharge and bleeding (5%).
- Ischaemic pain suggests successful therapy, but can be unbearable and requires analgesia.
- Pulmonary embolism.
- Ovarian failure following accidental ovarian vessel blockage and premature menopause (up to 30%).
- Fertility rate is reduced due to adhesions.
- Failure due to inadequate embolization caused by arterial spasm or tortuosity of the vessels.
- Expulsion of a fibroid into the peritoneal cavity (10%).
- Allergic reaction and contrast induced renal failure.
- Radiation exposure.
- Haematoma at the femoral site.
- Extrusion of a subserous fibroid into the peritoneal cavity which requires retrieval.
- Intraperitoneal adhesions.

The proper selection of patients is key to clinical success and avoiding complications. The follow-up with ultrasound 6 months later is also necessary to observe the shrinkage of the fibroid and register success or failure of this treatment.

Other indications for UAE besides fibroids are:

- Arteriovenous aneurysm or increased uterine vascularity causing menorrhagia.
- Postpartum haemorrhage.
- Placenta accreta to reduce bleeding prior to placental removal, or caesarean delivery.

Laparoscopic localized uterine artery occlusion using clips or electrodessication is being tried. This avoids ovarian devascularization.

UAE is most suited for menorrhagia in a multiparous woman.

The following are the advantages of UAE:

- No major surgery.
- No intraoperative bleeding.
- Short hospital stay.
- Less abdominal adhesions.
- 75–80% women are satisfied.

MRI-guided percutaneous laser ablation using high-intensity focused ultrasound (HIFU) has been recently attempted with success. This generates heat, 55°C at the focused point on the fibroid for few seconds. It ablates the vessels as well as the tumour. The woman is able to return to work in 2 days time. This technique may also find a place in the treatment of adenomyosis.

MRI Guided Focused Ultrasound. This is a noninvasive technique and uses high-intensity focused ultrasound beam that heats and destroys the fibrous tissue. MRI guides in targeting the beam path towards the fibroid.

A large fibromyoma can be treated in two sessions or the fibroid reduced in size with monthly GnRH injections for 3–4 months prior to treatment.

Side effects are:

- Skin burn
- Pain
- Nerve damage (rare)

Advantages

1. Noninvasive technique
2. Local anaesthesia—takes 1 to 2 h to do
3. No hospitalization
4. No scar
5. Quick recovery
6. Fertility preservation technique

Contraindications

1. Calcified fibroid.
2. Degenerated fibroid.
   - Interstitial laser ablation is done laparoscopically by inserting laser fibres into the myoma.

Laparoscopic Myolysis. This is an optional surgery using Nd:YAG laser, cryoprobe or diathermy to coagulate a subserous fibroid. It is used in a multiparous woman. The contraindications and complications are similar to those of UAE.

Hysterectomy (Table 29.6). Hysterectomy, the removal of the uterus, is indicated in a woman over 40 years of age, multiparous woman or when associated with malignancy. Uncontrolled haemorrhage and unforeseen surgical difficulties during myomectomy may also necessitate hysterectomy. Hysterectomy guarantees removal of all fibroids and relief of symptoms. Normally, the aim is total hysterectomy. However, subtotal hysterectomy may be performed in the presence of

TABLE 29.6 Indications for hysterectomy

Abdominal	Vaginal
Benign	Prolapse
Menorrhagia	Carcinoma in situ
Uterine fibromyoma	Cancer cervix + lymphadenectomy
Adenomyosis	Menorrhagia uterine fibroid
Tubo-ovarian mass	Genital prolapse
carcinoma in situ	
atypical endometrial hyperplasia	
Endometriosis	
Malignant	
Ca cervix	
Ca endometrium	
Ca ovary	
Uterine sarcoma mixed mesodermal tumour	
Choriocarcinoma (rare)	
Obstetric	
Rupture uterus	
PPH, molar pregnancy	
Ca cervix	

PID, endometriosis and any technical problem, when the cervix is left behind. Prior cervical cytology is desirable.

TYPES OF HYSTERECTOMY

- Abdominal hysterectomy
- Vaginal hysterectomy
- Laparoscopic hysterectomy

ABDOMINAL HYSTERECTOMY. Abdominal hysterectomy include:

- Total hysterectomy
- Subtotal hysterectomy when the cervix is retained
- Pan-hysterectomy when ovaries are also removed
- Extended and Wertheim hysterectomy in cancer of the cervix and uterine cancer

Most perform total hysterectomy, and prevent chronic cervicitis and cancer occurring at a later stage. However, occasionally, subtotal hysterectomy may have to be resorted. Advantages of subtotal hysterectomy are:

- Cervix retained for sexual function. The normal cervical discharge is beneficial.
- Vault prolapse is less common. Less bleeding and less risk of bladder, ureter trauma.
- In a difficult surgery, total hysterectomy may increase the surgical morbidity due to trauma to the bladder and denervation, causing difficult micturition and incontinence.

Pap smear prior to surgery ensures that the cervix is normal.

What about the ovaries?

In benign conditions, the ovaries should be retained to avoid menopausal symptoms in a premenopausal woman provided they look normal.

Disadvantage of conserving the ovaries:

- Benign or malignant ovarian tumour develops in 1% cases.
- Residual ovarian syndrome is known to occur in some cases and cause dyspareunia.
- Atrophy of the ovaries has been reported due to kinking of the ovarian vessels, within 3–4 years of hysterectomy; they become nonfunctional and cause early menopause.

Total abdominal hysterectomy

Hysterectomy is straightforward in most cases of fibroids. However, in case of a cervical low anterior and posterior fibroid, and one encroaching into the broad ligament, the bladder, ureter and rectum are displaced from their normal anatomical position and are at risk of injury. In a cervical and huge anterior wall fibroid when the tumour overhangs the vaginal vault and is close to the bladder, it is prudent to perform myomectomy first. This allows a clear view of the vaginal vault and safeguards against bladder injury. Thereafter, hysterectomy can be performed. Similarly, in a low posterior fibroid, the upper portion of the broad ligament may not be accessible until the fibroid is first enucleated.

In a central cervical fibroid, and a huge posterior fibroid, hemi-section of the uterus and enucleation of the fibroid will allow safe hysterectomy.

VAGINAL HYSTERECTOMY. Vaginal hysterectomy is possible if the uterus is mobile, uterine size is less than 14 weeks, no previous surgery or there is no other pelvic pathology; in all other cases, abdominal hysterectomy is performed. The ovaries may be conserved in a woman less than 50 years provided they are healthy. Vaginal hysterectomy is not suited in nulliparous women with narrow vagina.

Lately, **vaginal hysterectomy** is extended to uterine size more than 12-week size, provided the uterus is not fixed by adhesions, adnexal inflammatory mass or endometriosis by performing

- previous laparoscopy to confirm the absence of pelvic adhesions, size of the uterus and rule out pelvic pathology.
- bisection of uterus, and removing each half separately.
- myomectomy and enucleation of fibroid first.
- morcellation.

LAPAROSCOPIC-ASSISTED VAGINAL HYSTERECTOMY (LAVH). This avoids an abdominal scar, minimizes pain, and shortens the recovery period and hospital stay.

Contraindications to LAVH are:

- Uterus more than 14–16 weeks in size
- The fibroid is located in the broad ligament, cervical fibroids and extensive pelvic adhesions, endometriosis

COMPLICATIONS OF HYSTERECTOMY

- Primary, reactionary and secondary haemorrhage.
- Trauma to the bladder, ureter and bowel may occur in cervical and broad ligament fibroma; associated PID and endometriosis expose the ureter to injury.
- Sepsis.
- Anaesthetic complications.
- Paralytic ileus, intestinal obstruction due to postoperative adhesions.
- Thrombosis, pulmonary embolism, chest infection.
- Burst abdomen, scar, hernia.
- Postoperative infection such as wound infection, peritonitis, pelvic infection and embolism—chronic pelvic pain.
- Abdominal adhesions cause chronic abdominal pain.
- Dyspareunia due to short vagina, and ovarian adhesions to the vaginal vault.
- Vault prolapse.
- Residual ovarian syndrome and atrophy of the ovaries due to decreased vascularity causing premature menopause in 2–3 years.
- Ovarian cancer in 1% if ovaries are left behind during hysterectomy.
- Urinary dysfunction due to denervation.
- Granulation tissue at the vault requires treatment.
- Prolapse of the fallopian tubes.

Management of uterine fibromyoma is summarized in Table 29.5

Family Planning

A young woman with uterine fibroids may seek contraceptive advice. Oral hormonal contraceptives should not be offered to her because the fibroid may grow in size under the hormonal influence. Intrauterine contraceptive device (IUCD) can cause menorrhagia and dysmenorrhoea and is

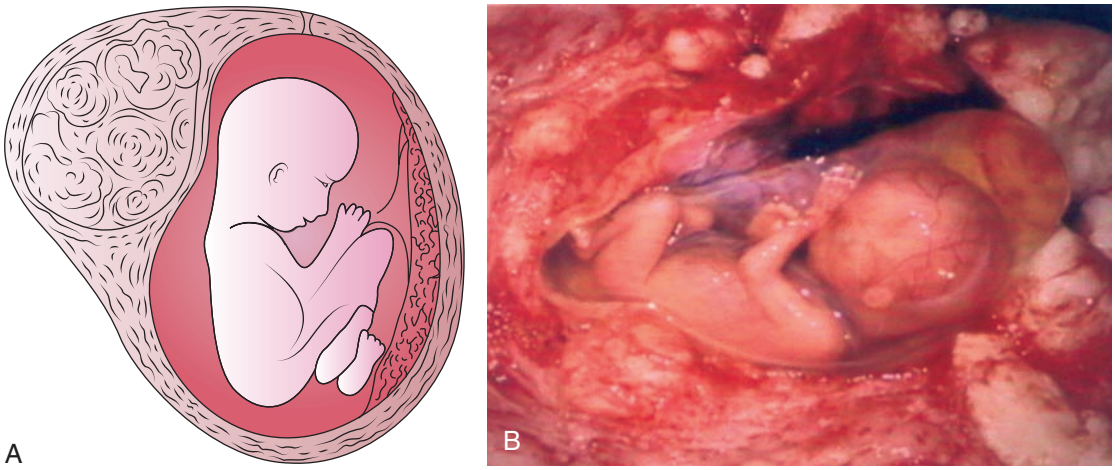


Figure 29.25 **(A)** Subserous fibroid associated with uterine pregnancy. **(B)** Uterus studded with multiple fibroids and pregnancy.

therefore not suitable in this woman. She can choose between a barrier method and centchroman.

Emergency laparotomy is required in torsion of a fibroid and subcapsular haemorrhage.

Cervical Fibroid

This requires myomectomy or hysterectomy, usually, by bisecting the uterus, enucleating the fibroid and then following up with hysterectomy as required. This safeguards against ureteric injury. GnRH can shrink the fibroid preoperatively.

Fibroids Complicating Pregnancy

Some women with uterine fibroids are infertile. In case conception takes place, the chances of complications are significant. Pregnancy generally causes an increase in the size of the fibroids (Figure 29.25); there is an increase in their vascularity and a high tendency to undergo degenerative changes like hyaline change and cystic degeneration. Red degeneration is a result of softening of the surrounding supportive connective tissue. The capillaries tend to rupture and blood effuses out into the myoma causing a diffuse reddish discolouration of the same. There is an opinion stating that release of a biochemical haemolysin-like substance is responsible for the diffuse blood staining of the fibromyomatous tissues. Such a patient complains of severe pain in the abdomen and may present as an emergency admission for acute abdomen pain; examination reveals the pain to be restricted to the uterus at the site of the fibroid, and all other parameters remain stable. Such a patient is treated conservatively with bed rest and analgesics until the pain subsides. On rare occasions, when laparotomy is carried out, the myoma is seen to be dusky in appearance; its cut section has an appearance of cooked meat and is known to emit a fishy odour. Fibroids by their sheer size may cause respiratory embarrassment, retention of urine or obstructed labour. They are sometimes known to adversely affect the outcome of pregnancy and there is an increased risk of abortion or miscarriage, preterm labour, abnormal presentation, accidental haemorrhage, dystocic labour, postpartum haemorrhage (PPH), puerperal sepsis and uterine inversion.

Mesodermal Mixed Tumour (Including Botryoid and Grape-Like Sarcoma)

Uterine sarcoma arises typically in the body of the uterus, while sarcoma of the cervix is very rare. Eight per cent follow pelvic radiotherapy. Pathologically, the tumours should be regarded as mesodermal mixed tumours as they often contain cartilage, striated muscle fibres, glands and fat. The stroma is embryonic in type, similar to the embryonal mesenchyme. Grape-like sarcoma of the cervix arises typically in adult women, metastases develop rapidly, and local recurrence follows their removal.

Somewhat similar tumours are known to develop in the vagina in children at a very early age, and such tumours contain striated muscle fibres and an embryonic stroma. Rather similar tumours sometimes develop in the body of the uterus in old women, and in this way, three types of mixed tumours, namely the vaginal tumours of children, the grape-like sarcoma of the cervix, and the mixed tumours of the body of the uterus of old women can be distinguished. In all cases, the prognosis is bad and rapid recurrence follows their removal.

Key Points

- Fibromyomas are mostly benign neoplasms of the uterus affecting 5–20% of women in the reproductive age group.
- Fibromyomas may be present without symptoms. However, depending on their size and location, they may contribute to menstrual irregularities, dysmenorrhoea, infertility, pain in the abdomen, abdominal fullness, pressure symptoms and complications during pregnancy.
- Ultrasonography, laparoscopy and hysteroscopy help in establishing the diagnosis of uterine fibromyomas. They are also useful to determine the number, location and size of the tumours. This helps in planning treatment.
- Asymptomatic tumours often do not require treatment but follow-up is recommended.

- Symptomatic fibroids require treatment. Myomectomy is indicated in younger women desirous of retaining the childbearing function, whereas in elderly women, hysterectomy is the procedure of choice.
- Medical treatment does not cure fibroids except to relieve menorrhagia. They are adjuvants to surgery when a huge fibroid or multiple fibroids are encountered. They shrink the fibroids and reduce the blood loss during surgery.
- Endoscopic procedures enable the removal of moderate-sized myomas.
- Hysterectomy is advised in elderly and multiparous women.
- Laparoscopy, hysteroscopy and arterial embolization provide minimal invasive surgery and have reduced the number of abdominal surgery in women with uterine fibroids. MRI-guided high frequency ultrasound is now possible.
- Laparoscopic myomectomy and uterine artery embolization are not recommended in women with infertility, because of pelvic adhesions and risk of scar rupture during pregnancy or in labour.
- Location, size and number of fibroids decide the route of operation.

Self-Assessment

1. Discuss the clinical features of uterine fibroids.
2. How will you manage a case of uterine fibroids in a 32-year-old, para 1 woman?
3. Discuss the management of uterine myoma in a nulliparous woman.
4. A woman, 38-year-old, presents with menorrhagia. She shows three fibroids on ultrasound. How will you manage the case?
5. A postmenopausal woman presents with postmenopausal bleeding. Ultrasound shows two interstitial fibroids. Discuss the management.

Suggested Reading

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Chapter

30

Endometriosis and Adenomyosis

CHAPTER OUTLINE

Endometriosis

The condition was first described by Carl von Rokitansky in 1860.

Endometriosis is one of the most mysterious and fascinating benign gynaecological disorders. By definition, endometriosis is the occurrence of ectopic benign endometrial tissues outside the cavity of the uterus. These islands of endometriosis are composed of endometrial glands surrounded by endometrial stroma, and are capable of responding to a varying degree to cyclical hormonal stimulation. The disease owns a unique pathology of a benign proliferative growth process yet having the propensity to invade the normal surrounding tissues.

The incidence is about 10%, but awareness of more cases is increasing on account of diagnostic laparoscopy. Amongst infertile women, incidence is 20% and is 15% in women with chronic pelvic pain (CPP). The incidence is very high amongst Japanese women.

Characteristics of endometriosis

- The ectopic endometrial tissue responds to ovarian hormones.
- While proliferative endometrium is always seen, secretory endometrium depends upon the presence of progesterone receptors in the tissues.
- Blood oozing during menstruation in ectopic endometrium causes local adhesions in the pelvis.
- Malignancy is extremely rare, though endometrial tissue is highly proliferative.

Aetiology

Endometriosis is a proliferative hormonal dependent disease of the childbearing period. It is extremely rare before menarche and disappears after menopause. Its incidence appears to be on the increase, partly due to improvement in diagnostic techniques and partly due to changing social patterns like late marriage and limitation of family size. It tends to occur more amongst the affluent class, and is frequently associated with infertility. Genetic susceptibility and familial tendency is seen in 15% cases.

Several theories have been propounded to explain endometriosis; chief among these are the following.

Implantation Theory

Sampson's pioneering work in 1922 attributed endometriosis to reflux of menstrual endometrium through the fallopian tubes and its subsequent implantation and growth on the pelvic peritoneum and the surrounding structures. Sampson observed that in cases of uncomplicated endometriosis, the fallopian tubes were usually patent. Several workers then questioned the viability of desquamated endometrium and its capacity to implant and grow. Convincing support to Sampson's theory of retrograde menstruation, implantation and spread has been provided by the experimental work of Scott, Te Linde and Wharton. The occurrence of scar endometriosis following classical caesarean section, hysterotomy, myomectomy and episiotomy further supports this view.

Lately, it has been suggested that hypotonia of the uterotubal junction influences the quantity of retrograde spill and occurrence of pelvic endometriosis. The occurrence of endometriosis in young girls with cryptomenorrhoea, and retrograde collection of menstrual fluid is also a proof of Sampson's implantation theory.

Coelomic Metaplasia Theory

Meyer and Ivanoff (1919) propounded that endometriosis arises as a result of metaplastic changes in embryonic cell rests of embryonic mesothelium, which are capable of responding to hormonal stimulation. Embryologically, Müllerian ducts arise from these same tissues, hence such a transformation in later life seems plausible.

Metastatic Theory

While the above theories can explain the occurrence of endometriosis at the usual sites, they found it difficult to explain its occurrence at less accessible sites like the umbilicus, pelvic lymph nodes, ureter, rectovaginal septum, bowel wall, and remote sites like the lung, pleura, endocardium and the extremities. Hence it was suggested by Halban et al. (1924) that embolization of menstrual fragments through vascular or lymphatic channels occur, and this leads to the launching of endometriosis at distal sites. Endometrial tissue has been retrieved in pelvic lymphatics in 20% women with endometriosis.

Hormonal Influence

Whatever the initial genesis of endometriosis, its further development depends on the presence of hormones, mainly oestrogen. Pregnancy causes atrophy of endometriosis chiefly through high progesterone levels. Regression also follows oophorectomy and irradiation. Endometriosis is rarely seen before puberty and it regresses after menopause. Hormones with anti-oestrogenic activity also suppress endometriosis and are used therapeutically.

Cyclical hormones stimulate its growth, but continuous hormone secretion or therapy suppresses it. Smoking reduces oestrogen level, and thereby the incidence of endometriosis proliferation.

Immunological Factor

The peritoneal fluid in endometriosis contains macrophages cytokines and natural killer (NK) cells which clear blood spilled into the peritoneal cavity. Impaired T cell and NK cell activity and altered immunology in a woman may increase the susceptibility to proliferation and growth.

Other Factors

Other factors implicated in the occurrence of endometriosis are genetic, multifactorial, vaginal or cervical atresia encouraging retrograde spill. The more frequent the cycles, and the more the bleeding, greater is the risk of endometriosis. Prostaglandins secreted by endometriotic tissue may exacerbate chronic pain and dysmenorrhoea.

Risk factors are polymenorrhagia, retroverted uterus which increases the risk of retrograde spill. A woman who has undergone tubectomy operation rarely develops endometriosis. History of familial tendency is reported in 15%.

Genetic basis accounts for 10% of endometriosis; incidence in first-degree relative is sevenfold. It may be that several factors are involved in the aetiology of endometriosis at different sites and none of the above theories fits into the development of endometriosis in a particular category.

Sites of Endometriosis (Table 30.1)

Endometriosis is found widely dispersed throughout the lower pelvis, and below the level of the umbilicus. The common sites are the ovaries, the pouch of Douglas including the uterosacral ligaments, peritoneum overlying the bladder, sigmoid colon, back of the uterus, ovarian fossa, intestinal coils and appendix. Endometriosis is seen in the umbilicus following an operation, in laparotomy scars, in tubal stumps following sterilization operation, in the amputated stump of the cervix, and in the scars of the vulva and perineum (Figure 30.1). Scar endometriosis following lower segment caesarean section is seen in only 0.2%, but is high following classical caesarean section.

Rectovaginal septal endometriosis has a different origin and is described later in this chapter.

TABLE 30.1 Varieties and sites of endometriosis

- Pelvic endometriosis
  - Pelvic peritoneum, pouch of Douglas, uterosacral ligament
- Rectovaginal endometriosis
- Ovarian endometriosis
- Chocolate cyst of ovary
- Other sites—appendix, pelvic lymph nodes. Metastatic—lungs, umbilicus, scar endometriosis

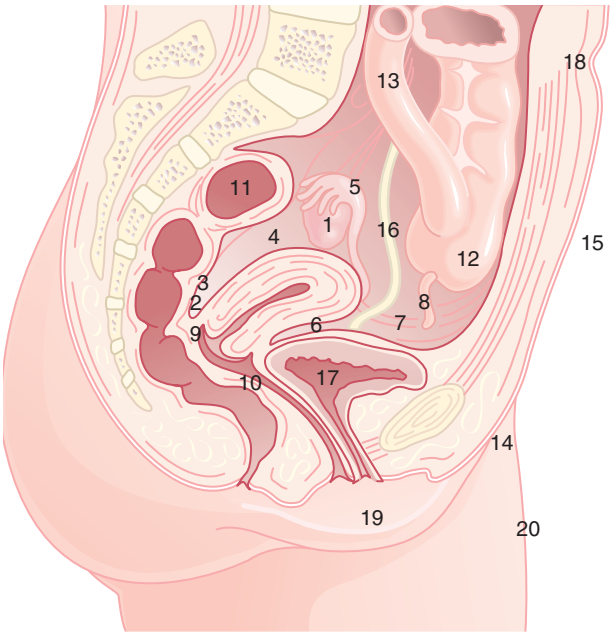


Figure 30.1 Common sites of endometriosis in decreasing order of frequency: (1) ovary, (2) cul-de-sac, (3) uterosacral ligaments, (4) broad ligaments, (5) fallopian tubes, (6) uterovesical fold, (7) round ligaments, (8) vermiform appendix, (9) vagina, (10) rectovaginal septum, (11) rectosigmoid colon, (12) cecum, (13) ileum, (14) inguinal canals, (15) abdominal scars, (16) ureters, (17) urinary bladder, (18) umbilicus, (19) vulva and (20) peripheral sites. (Source: Hacker NF, Gambone JC, Hobel CJ, *Hacker and Moore's Essentials of Obstetrics and Gynecology, 5th ed.* Philadelphia: Elsevier, 2010.)

Pathology

There are three categories of endometriosis.

- **Pelvic endometriosis** may be localized or diffused and scattered over the pelvic peritoneum, pouch of Douglas and utero-sacral ligaments.
- Ovarian endometriosis or chocolate cyst.
- Rectovaginal endometriosis.

Each category has a different mode of development.

Pelvic Endometriosis

Early lesions appear papular and red vesicles are filled with haemorrhagic fluid with surrounding flame-like lesions. With age, these vesicles change colour and *endometriotic areas* appear as dark red, bluish or black cystic areas adherent to the site where they are lodged. Scarring around the endometriosis gives it a puckered look. Lately, atypical lesions such as nonpigmented areas or yellowish-white thick plaques have been noticed, which are healed lesions. Peritoneal cavity contains yellowish-brown fluid in the cul-de-sac, and this contains prostaglandin responsible for pain. Powder burnt areas are the inactive and old lesions seen scattered over the pelvic peritoneum.

Sometimes, healed areas of endometriosis appear as small peritoneal defects (windows) or white patches.

Chocolate Cysts

Chocolate cysts of the ovaries represent the most important manifestation of endometriosis. To the naked eye, the chocolate cyst shows obvious thickening of the tunica albuginea, and vascular red adhesions are well marked on the undersurface of the ovary. The inner surface of the cyst wall is vascular and contains areas of dark brown tissue. The chocolate cyst lies between the ovary and the lateral pelvic wall (Figures 30.2–30.4).

Histology fails to reveal endometrial tissue in most chocolate cysts. The lining epithelium is usually columnar with a tendency to form papillae. Beneath the epithelium, a zone of tissue containing large cells with brown cytoplasm, polyhedral in shape and resembling lutein cells is nearly always seen. These pseudoxanthoma cells are probably large macrophages or scavenger cells, and their brown colouration is due to ingested blood pigments such as haemosiderin. The chocolate cyst develops as an invagination into the ovarian cortex. Circular peritoneal defects over the broad ligament and uterosacral ligaments reveal endometriotic tissue by biopsy in 50% cases, and they are healed areas of endometriosis. The levels of tumour necrosis factor and matrix metalloproteinase inhibitors are raised in pelvic endometriosis.

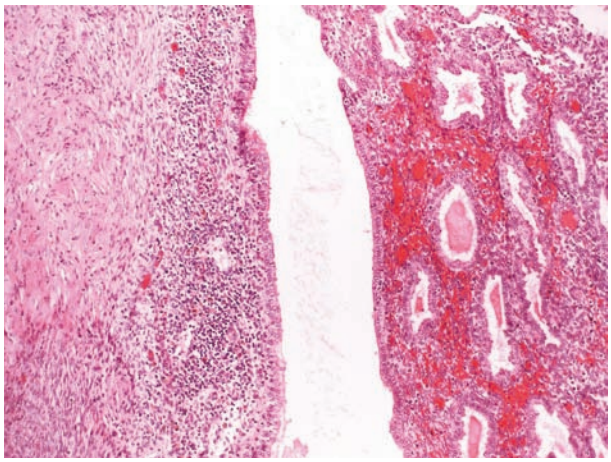


Figure 30.2 Typical endometriotic cyst lining containing endometrial glands (right) or a more attenuated lining with sparse stroma (left). (From Figure 22-48. Christopher P Crum, Marisa R Nucci and Kenneth R Lee: Diagnostic Gynecologic and Obstetric Pathology. Elsevier: Saunders, 2011.

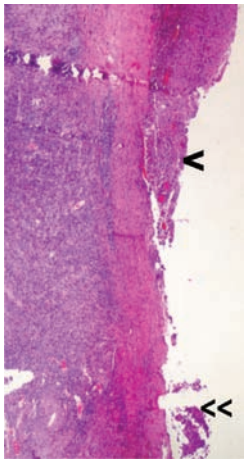


Figure 30.3 Lining of the primary squamous cell carcinoma of the ovary showing endometriosis at the top (<) and carcinoma at the bottom (<<) (magnification×4). (From Figure 1. International Journal of Gynecology and Obstetrics. In: Primary squamous cell carcinoma of the ovary associated with endometriosis. Pages 16–20, 2009.)

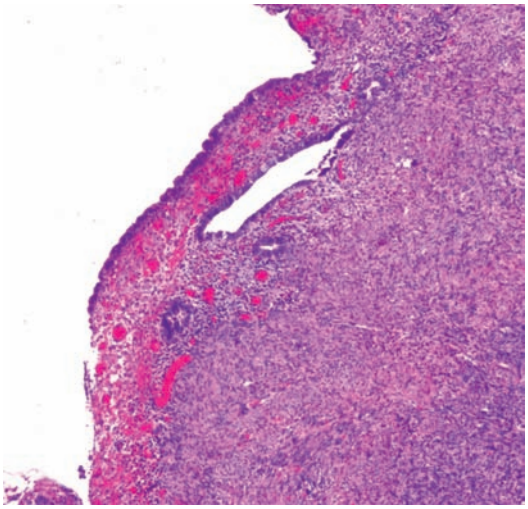


Figure 30.4 Focus of ovarian endometriosis adjacent to carcinoma (magnification×10). (From Figure 1. International Journal of Gynecology and Obstetrics. In: Primary squamous cell carcinoma of the ovary associated with endometriosis. Pages 16–20, 2009.)

Classification

The current classification (Table 30.2) is based on the appearance, size, depth of peritoneal and ovarian implants,

TABLE 30.2 Revised American fertility society classification of endometriosis (1985)

Patient's Name	**Age Date**		
Stage I	(Minimal)	Score 1–5	Laparoscopy/Laparotomy/ photography
Stage II	(Mild)	Score 6–15	Recommended treatment
Stage III	(Moderate)	Score 16–40	
Stage IV	(Severe)	Score > 40	
Total	*Prognosis*		
Peritoneal endometriosis	**<1 cm**	**1–3 cm**	**>3 cm**
Superficial	1	2	4
Deep	2	4	6
Ovarian endometriosis	**<1 cm**	**1–3 cm**	**>3 cm**
Right side—Superficial	1	2	4
Deep	4	16	20
Left side—Superficial	1	2	4
Deep	4	16	20
Posterior cul-de-sac obliteration	**Partial**		**Complete**
	4		40
Ovarian adhesions	**<1/3 Enclosure**	**1/3 to 2/3 Enclosure**	**>2/3 Enclosure**
Right side—Flimsy	1	2	4
Dense	4	8	16
Left side—Flimsy	1	2	4
Dense	4	8	16
Tubal adhesions*	**<1/3 Enclosure**	**1/3 to 2/3 Enclosure**	**>2/3 Enclosure**
Right side—Flimsy	1	2	4
Dense	4	8	16
Left side—Flimsy	1	2	4
Dense	4	8	16

*If the fimbriated end of the fallopian tube is completely closed, change the assignment to 16.
Note additional endometriosis. Note presence of any associated pathology.
Reproduced from *Fertility and Sterility* 1985; 43: 351–52.

presence and extent of adnexal adhesions, and the degree of obliteration of the pouch of Douglas. It does not take into account complaints like infertility or pain; however, it forms the acceptable basis for comparison of therapeutic outcomes, in relieving symptoms and improving fertility.

Availability of laparoscopic procedures has made it possible to diagnose with confidence small and early lesions, which are often asymptomatic, assess the extent and severity of the disease, and allow an accurate classification prior to initiating therapy. The classification described by the American Fertility Society (1985) is based on the size and location of the endometriotic lesion and is classified as minimal, mild, moderate and severe (Figure 30.5). This classification is correlated with fertility outcome rather than pain symptoms.

Minimal. Small spots of endometriosis seen at laparoscopy, but no clinical symptoms.

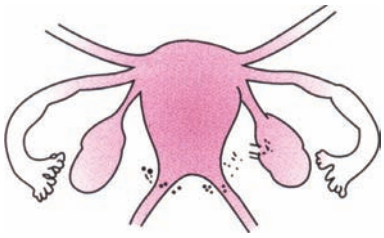
Mild. Scattered fresh superficial lesions. No scarring or retraction. No adnexal adhesions.

Moderate. Ovaries are involved, with some scarring and retraction. They contain endometriomas not more than 2 cm in size. There is minimal peritubal and periovarian adhesions. Endometriotic lesions in the anterior and posterior peritoneal pouch with some scarring and retraction may be seen.

Severe. Ovaries are involved, with the size of the endometriomas exceeding 2 cm. Dense peritubal and periovarian adhesions severely restrict mobility. The uterosacral ligaments are thickened and involved and lastly, there may be evidence of involvement of the bowel and urinary tract.

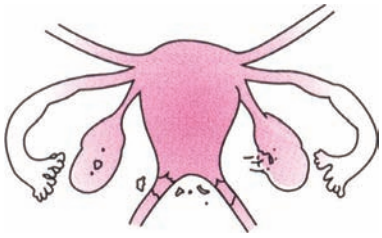
Laparoscopic findings vary with the duration of the lesion, size and location. 'Powder-burn'—puckered black spots, red vascular, bluish, blackish cysts, chocolate cysts and dense adhesions in the pelvis as well as yellow-brown peritoneal fluid are the findings. Biopsy of the lesion may be necessary to confirm the diagnosis in doubtful cases. Early and fresh lesions appear red flame-like raised areas, whereas older and healed lesions present yellow brown patches and white plaques over the peritoneum. The lesions are more marked on the left side, because the sigmoid colon forms a conduit for the tissue to grow. It is not surprising for

Stage I (Minimal)



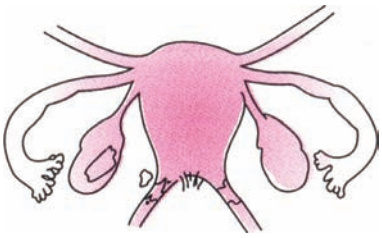
Peritoneum			
Superficial endo	–	1–3 cm	2
R. ovary			
Superficial endo	–	<1 cm	1
Filmy adhesions	–	<1/3	1
Total points			4

Stage II (Mild)



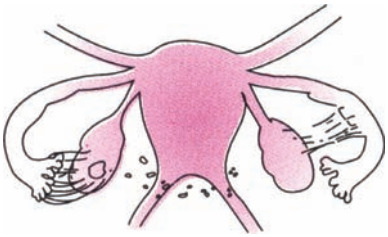
Peritoneum			
Deep endo	–	>3 cm	6
R. ovary			
Superficial endo	–	<1 cm	1
Filmy adhesions	–	<1/3	1
L. ovary			
Superficial endo	–	<1 cm	1
Total points			9

Stage III (Moderate)



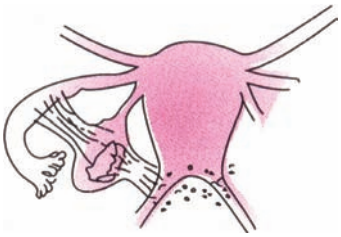
Peritoneum			
Deep endo	–	>3 cm	6
Cul-de-sac			
Partial obliteration	–	<1 cm	4
L. ovary			
Deep endo	–	<1–3 cm	16
Total points			26

Stage III (Moderate)



Peritoneum			
Superficial endo	–	>3 cm	3
R. tube			
Filmy adhesions	–	<1/3	1
R. ovary			
Filmy adhesions	–	<1/3	1
L. tube			
Dense adhesions	–	<1/3	16•
L. ovary			
Deep endo	–	<1 cm	4
Dense adhesions	–	<1/3	4
Total points			29

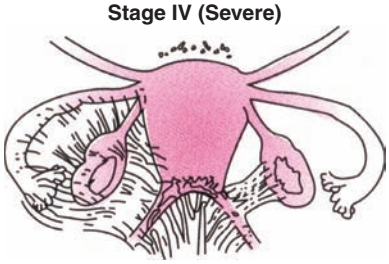
Stage IV (Severe)



Peritoneum			
Superficial endo	–	>3 cm	3
L. ovary			
Deep endo	v	<1–3 cm	32••
Dense adhesions	–	<1/3	8••
L. tube			
Dense adhesions	–	<1/3	8••
Total points			51

•Point assignment changed to 16
••Point assignment doubled

Stage IV (Severe)



Peritoneum			
Deep endo	–	>3 cm	6
Cul-de-sac			
Complete obliteration		40	
R. ovary			
Deep endo	–	<1–3 cm	16
Dense adhesions	–	<1/3	4
L. tube			
Dense adhesions	–	>2/3	16
L. ovary			
Deep endo	–	1–3 cm	16
Dense adhesions	–	>2/3	16
Total points			114

Figure 30.5 Endometriosis: American Fertility Society Classification (endo: endometriosis).

laparoscopy to reveal pelvic endometriosis in an asymptomatic woman.

Poor correlation between the naked eye appearance and histology is well documented. Therefore, biopsy of the suspicious areas becomes necessary to prove the presence of endometriosis.

Clinical Features

Endometriosis affects women in the reproductive age, around 30 years. It may occur in an adolescent if obstruction in the lower genital tract causes cryptomenorrhoea and retrograde spill of menstrual fluid. A rare case of endometriosis has been reported in a postmenopausal woman on hormone replacement therapy (HRT).

Symptoms

The symptoms vary according to the site, depth of lesion and do not always correlate well with the extent of disease. The classic symptom complex includes dysmenorrhoea, dyspareunia, menorrhagia and infertility. About 30% of the patients are asymptomatic. Overlapping of symptoms are common. The following are the common symptoms.

Dysmenorrhoea

This is the most common symptom. Seventy per cent pain begins before the onset of menstruation, builds up continuously until the flow begins, and thereafter, it gradually declines. The character of pain can be very variable, from a dull ache to grinding or crushing pain, colicky pain or a bearing-down pain. Backache is a common accompaniment. Sometimes, there may be radiating pain along the sciatic nerve. With passage of time, the intensity and duration of pain increases and dysmenorrhoea may persist for a few days after menstruation. Pain of endometriosis is chiefly related to the location and not the extent of the lesion. Deeper lesions cause more pain than superficial ones. The peritoneal fluid contains prostaglandin which is supposed to cause dysmenorrhoea and abdominal pain.

Abdominal Pain

Lower abdominal pain of varying intensity may appear at any time, but is usually common around menstruation. It is a dull ache culminating in dysmenorrhoea. Occasionally, the pain suddenly becomes very severe, presenting as an acute abdomen necessitating immediate surgery. At laparotomy, a ruptured chocolate cyst is observed.

Dyspareunia

Endometriotic involvement of the cul-de-sac and the uterosacral ligaments may produce adhesions and fixation of the uterus and nodular thickening of the uterosacral ligaments. Movements of the cervix elicit tenderness. Dyspareunia and backache may be the result of this pathology. These patients are often reluctant to attempt intercourse, and this adds to the magnitude of infertility (25–50%).

Infertility

Endometriosis affects fertility at all stages of the disease but in asymptomatic women with mild disease, infertility is difficult to explain. While about one-fifth of all women who are infertile tend to suffer from endometriosis, the incidence of infertility amongst women suffering from endometriosis ranges between 30% and 40%. Endometriosis possibly interferes with tubal motility and function. It may inhibit ovulation, ovum pick-up by the fimbria and because of dyspareunia there is reduced frequency of sexual intercourse. Other causes of infertility are luteinized unruptured follicular (LUF) syndrome, increased prolactin and corpus luteal phase defect, nonovulation and tubal blockage. Prostaglandin affects the tubal motility and also causes corpus luteolysis. The activated macrophages in the peritoneal fluid engulf the sperms or immobilize them.

Menstrual Symptoms

Menorrhagia (20%) is common with adenomyosis and irregular bleeding may occur with cervical and vaginal lesions. Polymenorrhoea is noted with ovarian involvement (10–30%).

Chronic Pelvic Pain (CPP)

Endometriosis is one of the important causes of CPP. Brownish-yellow peritoneal fluid containing prostaglandin E_2 is responsible for this pain. Nerve entrapment in endometriosis tissue may also be responsible for pain.

Other Symptoms

Urological symptoms like increase in frequency, dysuria and in rare cases, haematuria during menstruation may result from bladder or ureteral involvement. Obstruction of the ureter directly or as a result of kinking by adhesions leads to hydronephrosis and renal infection. Bowel symptoms are often the result of direct involvement of the sigmoid colon and rectum causing painful defaecation, diarrhoea and melaena around menstruation. Occasionally, pelvic endometriotic adnexal masses can cause obstructive symptoms of constipation and present with a painful abdominal mass or as an acute abdomen simulating peritonitis, appendicitis or an ectopic pregnancy. Scar endometriosis causes cyclical pain and enlargement, and pulmonary lesion causes cyclical haemoptysis.

Physical Findings

Abdominal examination may reveal a cystic swelling which simulates an ovarian tumour in a chocolate cyst of the ovary. The swelling is often fixed and may be slightly tender. Speculum examination may reveal bluish or blackish puckered spots in the posterior fornix, and these spots may be tender to touch. The presence of these puckered spots is pathognomonic of endometriosis. Vaginal examination reveals a tender fixed retroverted uterus. A fixed tender cystic mass or bilateral masses may be felt in the pelvis. If the uterosacral ligaments and the pouch of Douglas feel thickened and shotty with multiple small nodules palpable through the posterior fornix, the diagnosis becomes reasonably certain. These are described as cobblestone feel of uterosacral ligaments. During vaginal examination, tenderness in the lateral fornices indicate the possible existence of endometriosis even in absence of any adnexal mass.

Endocrinologic Abnormalities

Endometriosis is often associated with anovulation, abnormal follicular development, luteal insufficiency and premenstrual spotting. Luteinization of the unruptured follicle is known to occur, and hyperprolactinaemia with associated galactorrhoea are noted findings. However, no definite correlation between these endocrine events and the degree of endometriosis has been established. Cortisol and prolactin may be slightly raised.

Differential Diagnosis

Because of varied clinical features, endometriosis poses a diagnostic challenge at times.

- Chronic pelvic inflammatory disease (PID) closely mimics endometriosis in its symptoms and signs. Both the conditions produce pelvic pain, congestive dysmenorrhoea, menorrhagia and sterility. Endometriosis may, if there is leakage of blood contents, produce leucocytosis, raised erythrocyte sedimentation rate (ESR) and moderate fever. Both also have similar physical signs. Laparoscopic visualization of the pelvis will reveal the true pathology.
- Uterine myomas, unless degenerate, are painless and the uterus is not fixed. Ultrasound and laparoscopic visualization will differentiate one condition from the other.
- Ovarian malignant tumour with metastatic deposits in the pouch of Douglas can be mistaken for endometriosis. The history, pain, the age of the patient and other symptoms suggestive of endometriosis are against the diagnosis of cancer, but the physical signs, apart from tenderness, are very similar to those of an ovarian neoplasm.

- Rectosigmoid involvement will cause rectal symptoms which resemble the symptoms of rectal carcinoma. It may be impossible to make an accurate diagnosis until sigmoidoscopy and biopsy are performed.
- If the chocolate cyst ruptures, all possibilities of an acute abdominal catastrophe must be considered, including a ruptured tubal gestation, though the most frequent error is to operate for acute appendicitis.
- Chronic pelvic congestion syndrome due to other causes must be excluded by ultrasound, CT, MRI and laparoscopy.

TABLE 30.3 Investigations

Laparoscopy—diagnostic and therapeutic. Gold standard.
CA 125 > 35 U/mL
Ultrasound—mass, echogenic areas
MRI:
Colour Doppler—increased blood flow
Cystoscopy—Urinary cause
Sigmoidoscopy – rectal cause
Antiendometrial antibodies

Investigations (Table 30.3)

Laparoscopic Findings

These have already been described earlier. Laparoscopy should be employed not merely for diagnostic purposes; the endoscopist should be able to proceed with minimal invasive surgery (see below) in the presence of this pathology. *Laparoscopy is the gold standard in the diagnosis of endometriosis*. The diagnosis should be validated by peritoneal and tissue biopsy (Figure 30.6), because corpus luteal haematoma can resemble a chocolate cyst.

Role of laparoscopy

- To detect and diagnose pelvic endometriosis.
- Locate the site of endometriosis and staging.
- To take biopsy.
- To surgically treat endometriosis by ablation, removal.

CA-125, glycoprotein and cell surface antigen, is raised to more than 35 U/mL in 80% cases of endometriosis and the level is directly proportional to the extent of the disease. The level is not specific, because it is also raised in abdominal tuberculosis, PID, malignant epithelial ovarian tumour, chronic liver disease and in 2% normal women, especially during menstruation. While CA-125 estimation may not be helpful in the initial diagnosis, once the diagnosis is established, raised level of CA-125 indicates either persistence or recurrence of the disease in the follow-up.

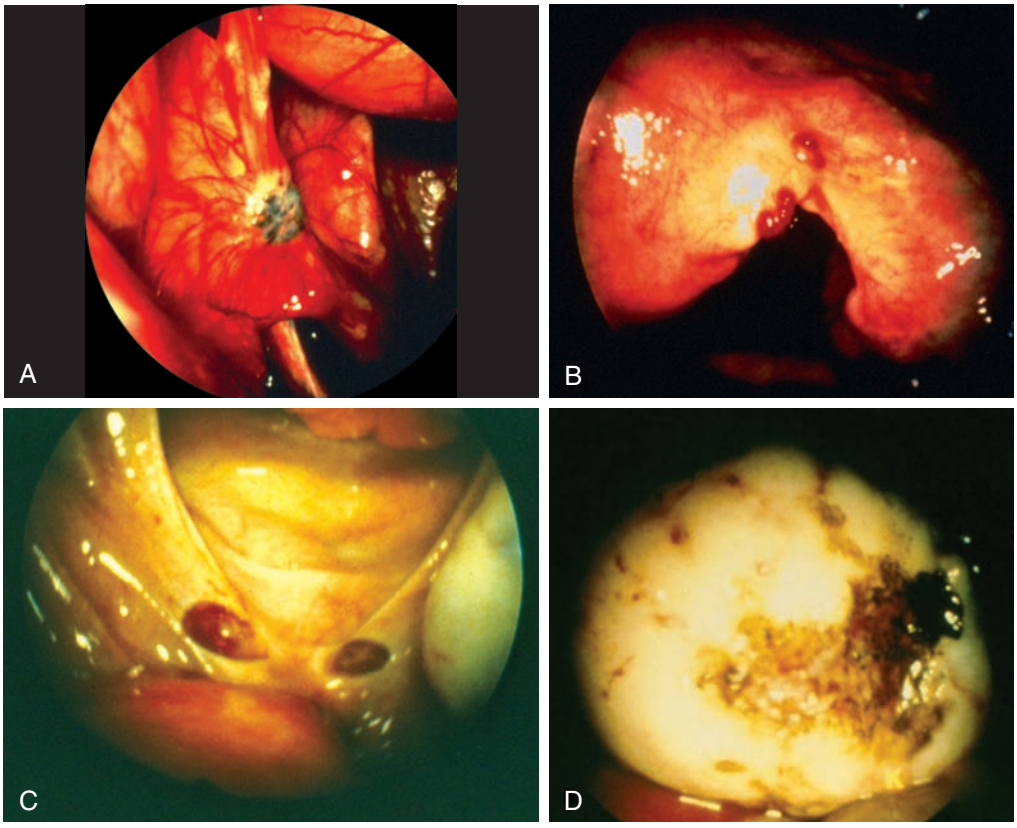


Figure 30.6 (A)–(D) Appearance of old endometriosis with 'tattooing' (blue-grey lesions), and red, brown, and black raised lesions of active endometriosis at the time of laparoscopy. (Source: Hacker NF, Gambone JC, Hobel CJ, *Hacker and Moore's Essentials of Obstetrics and Gynecology*, 5th ed. Philadelphia: Elsevier, 2010.)

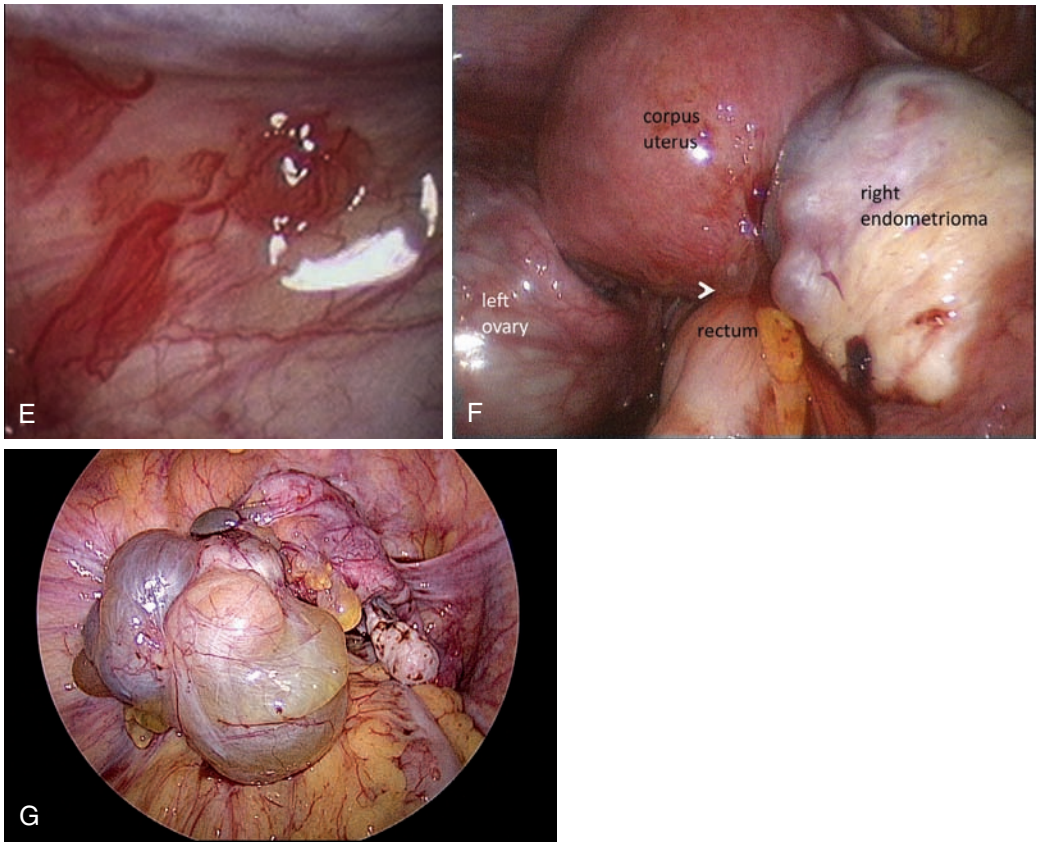


Figure 30.6 **(E)** Pelvic endometriosis showing red lesions on laparoscopy. **(F)** Complete obliteration of the pouch of Douglas (white arrowhead) was noted during diagnostic laparoscopy. **(G)** Laparoscopic view of bilateral endometriosis. (Courtesy: Dr Vivek Marwah, New Delhi.)

Ultrasound and MRI

Transvaginal ultrasound reveals an echo-free cyst, low-level echoes or clumps of high-density level echoes representing clots. The cyst wall is thick and irregular, and multiple cysts in different phases of evolution may be observed. Ultrasound is 83% sensitive and 98% specific as small nodules may not be picked up by ultrasound.

CT and magnetic resonance imaging give identical picture as in ultrasound and are not more useful in the diagnosis of endometriosis.

- Colour Doppler flow shows increased vascularity but does not confirm the diagnosis—vascularity is diffuse; in a fibroid, blood vessels are seen in the periphery.
- Cystoscopy will identify involvement of the bladder.
- Sigmoidoscopy is required if the woman develops bowel symptoms. A biopsy is required if malignancy is suspected.
- Antiendometrial antibodies are identified in the serum, peritoneal fluid and endometriotic fluid as well as in normal endometrial tissue. However, as yet these are not measured to be of screening value and used as a tissue marker. They may also not be sensitive and specific.
- Tumour necrosis factor is raised proportionate to the severity of the disease.

Prophylaxis

- Low-dose oral contraceptive pills reduce the menstrual flow and protect against endometriosis. Three monthly oral pills are convenient to take and effective.
- Tubal patency tests should be avoided in the immediate premenstrual phase to avoid spill.
- Operations on the genital tract should be scheduled in the postmenstrual period.
- Classical caesarean section and hysterotomy operation which cause scar endometriosis are now rarely performed.

Management

Minimal asymptomatic cases should be observed over 6–8 months. Infertility should be investigated and treated as necessary (Figure 30.5).

All symptomatic women need treatment. The treatment (Figure 30.7) depends upon the age of the patient, need for preserving reproductive functions, severity of the symptoms, extent of the disease, response to medical treatment, relief obtained with any previous conservative surgery and the attitude of the patient towards her problem. The objective of the treatment should be to eradicate the lesion and avoid recurrence of the disease process, alleviate symptoms, facilitate childbearing and enable the patient to lead

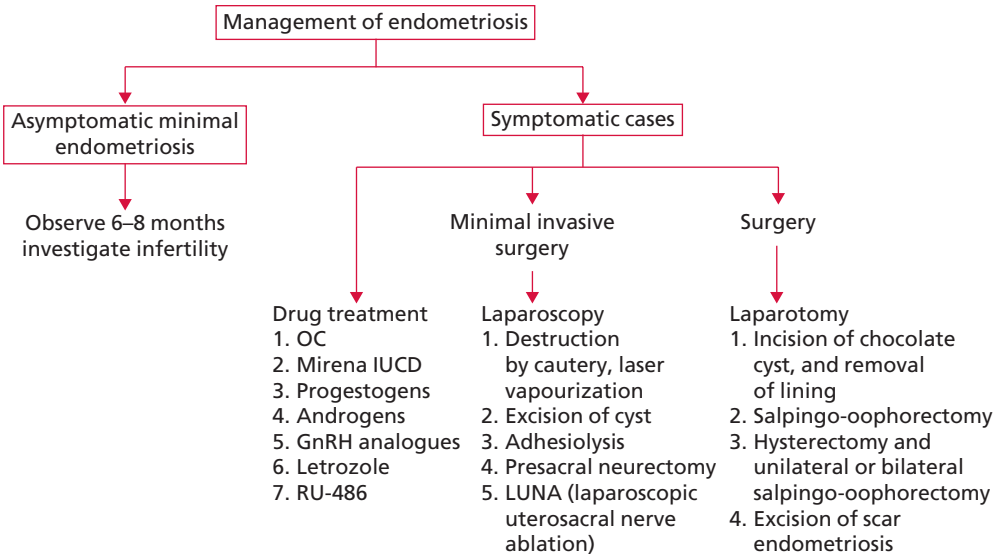


Figure 30.7 Management of endometriosis.

a comfortable life. Therefore, the treatment should be individualized. The treatment comprises medical surgical and a combination of both.

Drug Treatment

Drug treatment should aim at causing atrophy of the ectopic endometrium with minimal side effects.

Endometriosis is oestrogen dependent. Hormones act on the receptors in the endometriotic tissue and cause their atrophy and shrinkage. The purpose of administration of various hormones is to act as anti-oestrogens; the drugs produce a hypo-oestrogenic effect. Superficial lesions respond better than the deeper ones. One, however, must note that hormonal therapy suppresses endometriosis for the duration of therapy; it does not prevent recurrence once the therapy is stopped. Moreover, the hormones delay pregnancy by their contraceptive effect and cause side effects on prolonged therapy, besides the drugs being expensive. *The drugs are best suited for multiparous women.*

1. **Combined oral contraceptives (OC).** Administered intermittently or continuously, oral contraceptives may alleviate the disease. However, high incidence of side effects and risk of thrombo-embolism limit their prolonged use. Thirty per cent pregnancy rate is reported following this treatment. OCs delay pregnancy. *Seasonale OC for 84 days, with 6 days tablet free, reduce the menstrual periods to just four cycles in a year and may be suited in endometriosis.*
2. **Oral progestogens.** These drugs exert an anti-oestrogenic effect and their continuous administration causes decidualization and endometrial atrophy. The treatment over a period of 6–9 months produces a state of pseudopregnancy which ultimately causes regression of the disease. The drugs in common use are norethisterone 5.0–20.0 mg daily, or dydrogesterone 10–30 mg daily. Dydrogesterone 40–60 mg daily in the luteal phase relieves symptoms. *This hormone does not prevent ovulation and is suitable for a woman trying to conceive.* It also has less toxic side effects. Instead of restricted luteal phase administration, it can be given 10 mg BD from day 5–25 days for three cycles. Tibolone is also useful in endometriosis. Medroxyprogesterone acetate may be administered as a long-acting depot preparation, 50 mg intramuscularly weekly, 100 mg intramuscularly every 2 weeks for 3 months, followed by 200 mg monthly for 3–6 months or oral 30 mg daily. About 50–70% symptomatic relief and pregnancy rate of 40–50% have been reported. Weight gain and irregular bleeding are the side effects of progestogens. Other side effects include reduced libido, mental depression, breast tenderness and decreased high-density lipoprotein (HDL). Moreover, fertility is impaired for 2 years after prolonged hormone therapy. The side effects are dose and duration related. *Mirena IUCD reduces dysmenorrhoea and menorrhagia in endometriosis*. It is a one-time treatment lasting 5 years with minimal systemic side effects. Danacrine, an anabolic drug does not cause menopausal symptoms, as E_2 level does not drop below 50 pg/mL. The progesterone levels rises in 15 min, peaks in a few hours and stabilizes thereafter. It causes endometrial gland atrophy, and decidualization of stromal cells. It is ideal to relieve pain and menorrhagia in premenopausal women who have completed their families.
3. **Danazol**, a synthetic derivative of ethinyl testosterone, inhibits pituitary gonadotropins. It is mildly anabolic, anti-oestrogenic and anti-progestational. It reduces sex hormone binding globulin (SHBC) and releases free testosterone. It is a very effective though an expensive drug

and is administered in doses of 200–800 mg daily for 3–6 months starting on the first day of menses. It causes symptoms simulating menopause if used in higher doses over 6–8 months. The lesions regress remarkably, but many patients suffer from side effects like weight gain, hirsutism, excessive sweating, muscle cramps, depression, atrophy of breasts and vaginal epithelium, lowering of HDL, and liver and renal damage. The resulting amenorrhoea promptly corrects itself on withdrawal of the drug. The chances of successful pregnancy following this therapy range from 30 to 50%. It is reported that 80% endometrial implants resolve with danazol. Recurrence however is likely after stoppage of the drug (30%). It is contraindicated in liver dysfunction and pregnancy should be avoided as it is teratogenic. Recently, danazol is implicated in the development of ovarian cancer, and many gynaecologists are now reluctant to use this drug.

Gestrinone is a 19-nortestosterone derivative similar in action to danazol, but it has fewer side effects and is long-acting. It reduces the LH surge and SHBG. Dose is 2.5–5 mg twice weekly. Eighty-five to ninety per cent patients experience amenorrhoea. Anti-inflammatory drugs like mefenamic acid, 500 mg three times a day during menstruation, relieve dysmenorrhoea in 70–80% patients. Other antiprostaglandin and anti-inflammatory (nonsteroidal) drugs like naproxen are also useful.

4. **Gonadotropin releasing hormone (GnRH).** GnRH is administered continuously to down regulate and suppress pituitary gonadotropins; it causes atrophy of the endometriotic tissue in 90% cases. The synthetic analogue of GnRH is given in doses of 10–20 mg intravenously twice daily, or 200–400 mg intranasally daily for 6 months. Monthly depot injection (Zoladex) of 3.6 mg is also available. Discontinuation of GnRH and danazol causes recurrence of endometriosis within a year in 50% cases. GnRH is better tolerated than danazol. However, prolonged GnRH therapy over 6 months causes hypo-oestrogenism and menopausal symptoms such as hot flushes, dry vagina, urethral syndrome and osteoporosis. To avoid this, add-back therapy with progestogens and tibolone or etidronate is recommended. This also allows prolonged therapy with GnRH for 2 years.

   Other drugs available are:

   - Buserelin and leuprolide (nonapeptides).
   - Nafarelin and goserelin (decapeptide). The superficial lesions respond better than the deep-seated lesions.
   - Cetrorelix (GnRH antagonist)—3 mg weekly × 8 weeks.
   - Goserelin 3.6 mg monthly subcutaneously.
   - Leuprolide 3.75 mg IM monthly or 11.25 mg 3 monthly.

5. **Aromatase inhibitors.** Aromatase inhibitors available are letrozole (2.5 mg), anastrozole (1–2 mg) and rofecoxib (12.5 mg) daily for 6 months. They are anti-oestrogen and should be given with vitamin D (400 g IU) and calcium (1 g) to prevent osteoporosis. Nausea, vomiting and diarrhoea are the other side effects. Anastrozole is less osteoporotic than others. They block aromatase activity by preventing conversion of androgen to oestrogen. They may be combined with 2.5 mg norethisterone.
6. **RU-486** (antiprogestogen) is also tried at a dose of 50 mg daily for 3 months. It reduces pain and delays recurrence.

The failure and recurrence following medical therapy is due to the following:

- The drug cannot penetrate the fibrotic capsule.
- Ectopic endometrium responds less to hormones as compared to normal endometrium.
- Side effects—Hormones prevent conception, besides other consequences.

Minimal Invasive Surgery

Since hormones delay pregnancy, primary surgery is preferred in infertile women. Recent advances in gynaecology have introduced laparoscopy in the management of pelvic endometriosis in young women. This offers the advantages of conserving the ovaries and the fallopian tubes, and improving fertility.

The methods employed are:

- Aspiration of peritoneal fluid in cul-de-sac: It removes PGE_2 and relieves dysmenorrhoea, pelvic pain and improves pregnancy rate.
- Destruction of endometriotic implants less than 3 cm by diathermy cauterization, or vaporization by CO_2 or Nd:YAG laser. Superficial lesions are easier to destroy and yield better fertility results than the deep implants. Laser has the advantage of controlling the depth of destruction by adjusting the power density. It does not cause adhesions and fibrosis. It can be applied to the bowel and bladder.
- Larger lesions and chocolate cyst can be excised. The residual lesion can be dealt with by hormonal therapy. Cauterization of the cyst wall is preferred in young women. It avoids ovarian destruction with peeling off of the cyst wall, but recurrence is slightly high.
- Role of surgery
  - Failed medical therapy
  - Infertility
  - Recurrence
  - Chocolate cyst ovary
- The consensus of opinion is that cystectomy is more beneficial in extent of pain relief, longer recurrence time and longer pain-free intervals. However, the excision of the cyst wall deprives the patient of potential ova and thereby reduces her fertility potential. In older women, excision of cyst wall is recommended.
- Laparoscopic breaking of adhesions in the pelvis relieves dysmenorrhoea and pelvic pain. It also restores patency of the fallopian tubes and ovulation. Presacral neurectomy can be simultaneously performed. Bleeding and haematoma is its complication. Pregnancy rate following minimal surgery is around 30–50%.

- LUNA (Laser uterosacral nerve ablation) for midline pain in endometriosis is effective in some cases.
- Pregnancy rate following conservative surgery is 40%, 50% and 70% in severe, moderate and mild endometriosis, respectively.
- Prolapse of genital tract and bladder dysfunction is noted with LUNA. It is advisable to postpone laparoscopic technique for 3 months if hormone therapy has already been given, to avoid under diagnosis.

Other Modalities in an Infertile Woman Associated with Pelvic Endometriosis (Figure 30.8)

Ultrasonic guided chocolate cyst aspiration followed by mifepristone for 6 months is also tried.

- **Mild endometriosis.** Surgery followed by superovulation and IUI/IVF (aspiration of endometriosis cyst).
- Advanced endometriosis involving the fallopian tube. The choice is between tuboplasty and IVF. Alternatively, 3 months of medical therapy followed by IVF.
- Postoperative medical therapy to deal with the residual tissue and prevent recurrence.
- Dydrogesterone 40 mg in the luteal phase relieves pain without compromising infertility as it does not prevent ovulation.
- Pre- and postoperative hormonal therapy may alleviate symptoms, but delay pregnancy.

Surgery

Recurrence following conservative surgery is 10% at the end of 1 year and 25% at the end of 3 years. Adhesions form in 10%, more with cauterization than laser. These women may require second surgery which may be technically difficult. Therefore, some prefer laparotomy over laparoscopy when repeat surgery is required. Indications for surgery:

- Advanced stage of disease detected
- Large lesion—can be dealt with
- Medical therapy fails or is intolerable
- Recurrence occurs
- In elderly parous women

Laparotomy

Laparotomy is also required in advanced stages and in larger lesions if medical therapy fails or hormones cannot be tolerated and for recurrence.

- Dissection and excision of a chocolate cyst.
- Salpingo-oophorectomy.
- Abdominal hysterectomy and bilateral salpingo-oophorectomy. Surgery can be difficult due to adhesions.

Mirena IUCD is an alternative to a repeat surgery.

A premenopausal woman may need HRT after the radical surgery; tibolone is safer than E_2 P therapy. Scar endometriosis requires excision or danazol.

Hormone replacement therapy following bilateral ovarian removal in young women may be prescribed under strict monitoring, as the risk of recurrence remains. Calcium and vitamin D is added to HRT.

As mentioned before, tibolone 2.5 mg daily is better than E_2 and progestogen.

Metastatic endometriosis is dealt with using hormone therapy.

Combined Therapy

Combined therapy is indicated in the following conditions.

- Preoperative GnRH monthly for 3 months reduces the size and extent of the lesions, softens the adhesions and makes the subsequent surgery easier and more complete.
- Postoperative hormonal therapy may be required if the surgery has been incomplete, and some residual lesion is left behind due to technical difficulty. It also reduces the recurrence rate.

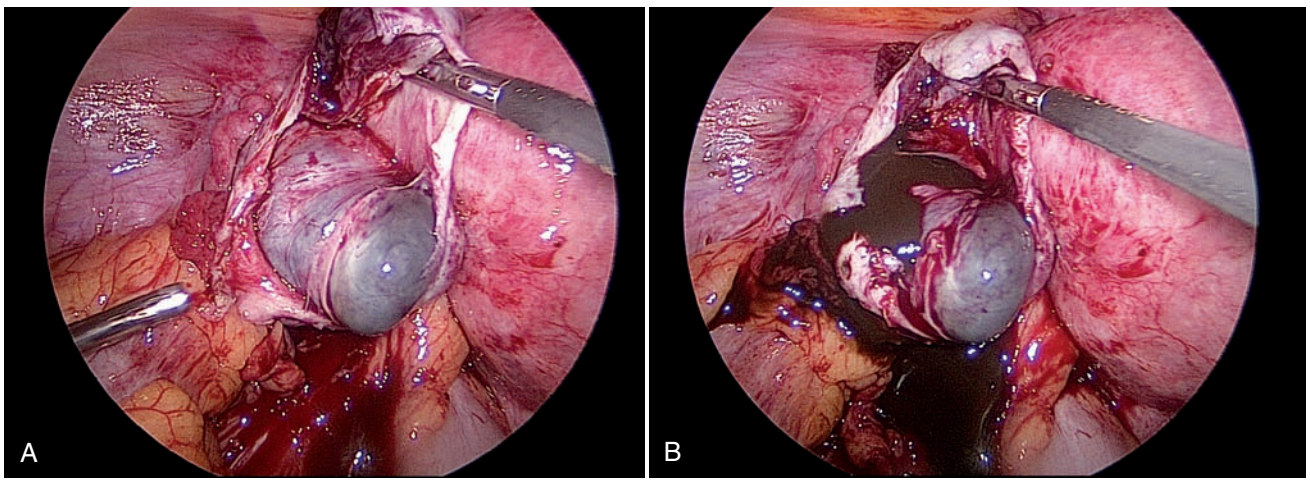


Figure 30.8 **(A)** Endometriotic cyst (chocolate cyst). (Courtesy: Dr Vivek Marwah, New Delhi.) **(B)** Same as Figure 30.8A) except that the cyst has burst (Courtesy: Dr Vivek Marwah, New Delhi.)

Endometriosis of the Rectovaginal Septum

Rectovaginal endometriosis with obliteration of the pouch of Douglas involves the uterosacral ligaments, posterior fornix and anterior wall of the rectum and sigmoid colon. The aetiology of this condition differs from that of pelvic endometriosis. It is not caused by deep infiltration of pelvic endometriosis and retrograde menstruation but according to Nicolle et al., it is derived from embryologically derived Müllerian tissue and the theory of Müllerian metaplasia applies here. Rectovaginal endometriosis contains more fibrous tissue than glandular tissue with flame-like appearance. Laparoscopically, it is seen as a yellowish-white appearance with small haemorrhagic areas and dense fibrotic adhesions.

Clinical Features

The woman is often of reproductive age. She complains of dysmenorrhoea, dyspareunia abdominal pain, backache and menorrhagia. If the rectum is involved, rectal pain, constipation and occasional diarrhoea may occur. Cyclical rectal bleeding is also reported. Ureteric compression with uterosacral ligament involvement causes renal damage.

Speculum examination is painful. Red spots are seen in the posterior fornix. Bimanual examination reveals thickening of the posterior fornix and uterosacral ligaments. Rectal examination should be performed to assess the rectal involvement.

Differential Diagnosis

The clinical features mimic PID, diverticulitis, colonic cancer and inflammatory bowel syndrome.

Investigations

They include ultrasound using rectal probe, CA-125 (may be raised), MRI, but they are nonspecific and unrewarding. Proctoscopy and sigmoidoscopy rule out malignancy. IVP needs to be done if ureter appears involved. Laparoscopy is both diagnostic and therapeutic, and biopsy should confirm the diagnosis.

Management

Poor hormonal response makes laparoscopic surgery, the treatment of choice. Bowel preparation preoperatively is necessary in case bowel is involved and needs resection. Ablative and excisional techniques are employed depending upon the degree of involvement. Normally, bowel mucosa is spared, but in case stricture has formed, resection of bowel mandates the involvement of anorectal surgeon. Mirena IUCD is very effective in relieving symptoms.

Prognosis

Morbidity and quality of life are influenced by CPP, dysmenorrhoea, dyspareunia and renal damage.

Malignant change is rare (1:150) and manifests as endometrioid cancer.

Adenomyosis

Adenomyosis, also labelled uterine endometriosis, is a relatively common condition in which islands of endometrium are found in the wall of the uterus. It is observed frequently in elderly women. More than one-third of the hysterectomy specimens from women aged 40 years and above reveal the presence of adenomyosis, irrespective of the indications for hysterectomy. The disease often coexists with uterine fibromyomas, pelvic endometriosis (15%) and endometrial carcinoma.

Grossly, the uterus appears symmetrically enlarged to not more than 14 weeks size. The cut section may show only a localized nodular enlargement. Most of the time, the affected area reveals a peculiar, diffuse, striated and noncapsulated involvement of the myometrium, mostly the posterior wall, with tiny dark haemorrhagic areas interspersed in between (Figure 30.9).

Laparoscopy reveals a uniformly enlarged uterus (Figures 30.10 and 30.11).

Histological examination reveals islands of endometrial glands surrounded by stroma, in the midst of myometrial tissue at least two low-power fields beyond the endomyometrial junction (Figure 30.12), more than 2.5 mm beneath the basal endometrium.

These women are usually parous, around the age of 40 years. Some are asymptomatic, others present with

Figure 30.9 Adenomyosis of the uterus. The uterus is enlarged asymmetrically, and the rounded dark areas consist of spaces full of blood. The enlargement is caused by hyperplasia of muscle cells surrounding areas of endometrium which have bled during menstruation.

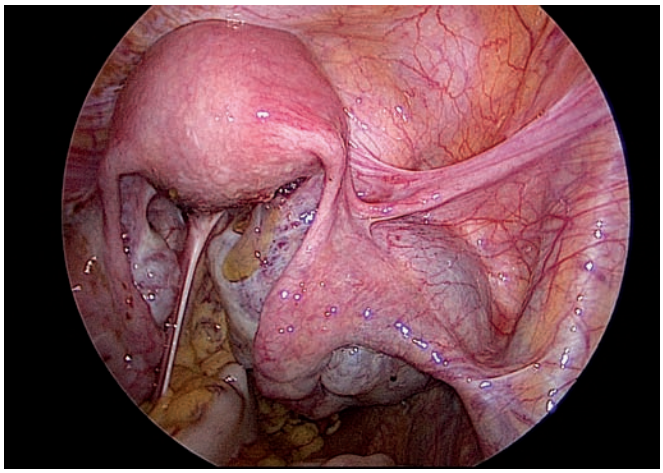


Figure 30.10 Laparoscopic view of adenomyosis of the uterus. (courtesy: Dr Vivek Marwah, New Delhi.)

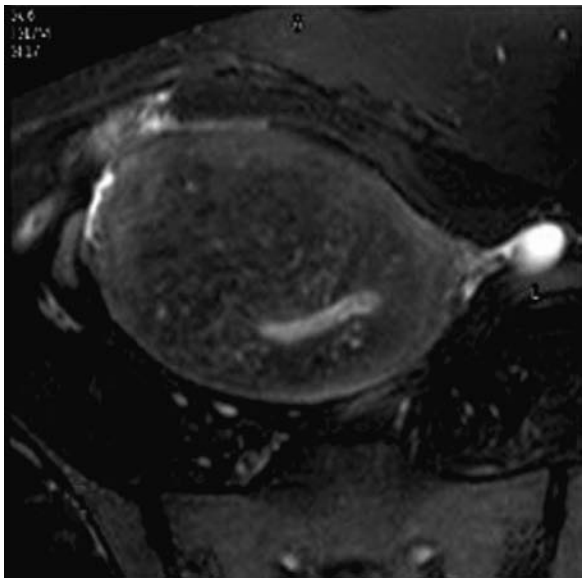


Figure 30.11 MRI showing adenomyosis of the uterus. (Courtesy: Dr Parveen Gulati, New Delhi.)

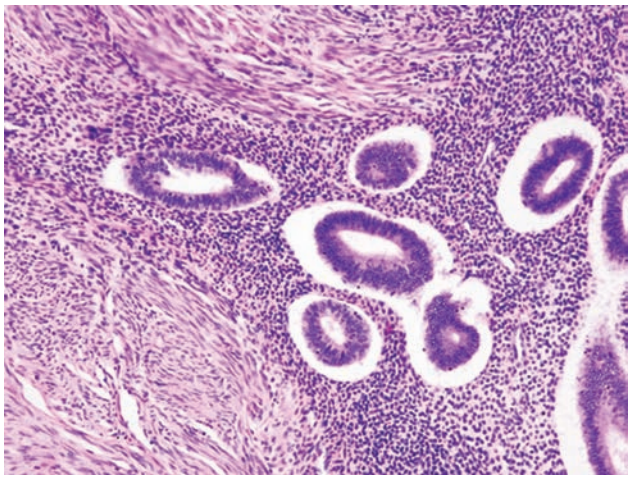


Figure 30.12 Adenomyosis uteri. Note the island of endometrial glands with associated stroma deep in the myometrium (×33). (Source: Wikimedia commons.)

menorrhagia and progressively increasing dysmenorrhoea. Pelvic discomfort, backache and dyspareunia are the other symptoms of adenomyosis. Clinical examination reveals a symmetrical enlargement of the uterus if the adenomyosis is diffuse and the uterus is tender. The uterine enlargement rarely exceeds that of a 3-month pregnancy and is often mistaken for a myoma. If a patient gives a history of menorrhagia with accompanying dysmenorrhoea, one should always consider the possibility of adenomyosis. If the adenomyosis is localized, the enlargement is asymmetrical and the resemblance to a myoma is more close. A myoma of this size is rarely painful. Therefore, a painful, symmetrical enlargement of the uterus should suggest the correct diagnosis. MRI is superior to ultrasound showing hypo- or anechoic area in the uterine wall. Ultrasound shows ill-defined hypoechoic areas, heterogeneous echoes in the myometrium, asymmetrical uterine enlargement and subendometrial halo thickening (Figure 30.13). It also shows endometrial infiltration into the myometrium.

Treatment (Figure 30.14)

A diagnostic hysteroscopy combined with a curettage is the initial step in the management of adenomyosis because of menorrhagia. Since most women are elderly and past the age of childbearing, total hysterectomy is the treatment. In younger women, in whom a localized adenomyosis is found confined to one part of the uterus, a localized excision is sometimes feasible, and this conservative resection is reasonable if the patient is particularly anxious to have a child. The possibility of scar rupture should be borne in mind.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal therapy are employed with some success in women reluctant to undergo hysterectomy, but the overall results are not satisfactory. Drugs used are danazol, GnRH and Mirena IUCD for menorrhagia and pain. Transcervical

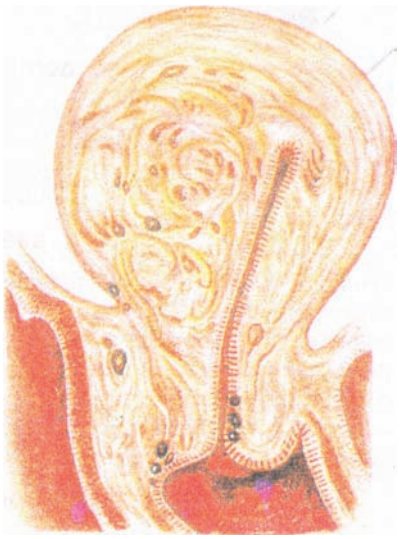


Figure 30.13 Adenomyosis. Note the absence of capsule and presence of dark spots.

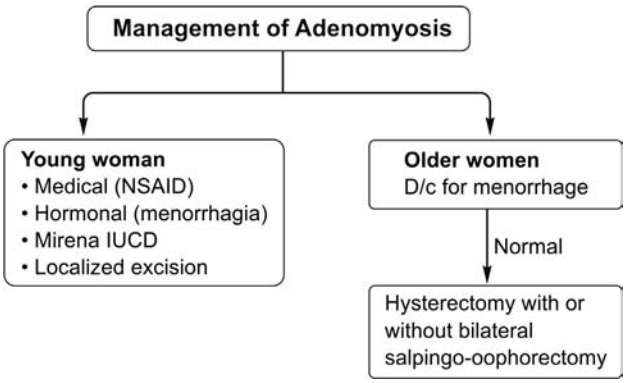


Figure 30.14 Management of adenomyosis.

resection of endometrium (TCRE) is effective for about 2 years. Unlike fibroid, uterine artery embolization has no effective role in adenomyosis. Mirena has been increasingly used in adenomyosis.

Lately, danazol IUCD is under trial (Danazol containing 300–400 mg IUCD).

MRI guided ultrasonic focused surgery and resection is under trial, and is desirable in young women.

Stromal Endometriosis

It is a rare type of endometriosis, when only stromal tissues without glandular elements are present in ectopic sites. The stromal cells penetrate the uterine wall and spread via lymphatics and veins into the broad ligaments. The symptoms are similar to endometriosis and the uterus appears enlarged. Hysterectomy is recommended. The ovaries may be retained. Local recurrence is common and the tumour behaves like a malignancy. In case it recurs, radiotherapy is the treatment of choice.

New drugs under trial:

- Aromatase inhibitors and selective oestrogen receptor modulator (SERM)
- Dopamine agonist cabergoline, pentoxiphylline

Key Points

- Endometriosis refers to the presence of ectopic endometrial tissue outside the cavity of the uterus.
- Theories of origin include retrograde implantation of menstrual blood into the peritoneal surfaces and organs, coelomic metaplasia, vascular embolization and lymphatic permeation.
- Endometriosis manifests as islands of flame-shaped chocolate deposits or appear like powder-burn marks. It can cause extensive adhesions between the ovaries, back of the uterus and the pouch of Douglas, obliterating the same and causing dense rectal adhesions. Many appear as a cystic ovarian enlargement or ovarian endometriomas (chocolate cyst).
- The patient presents with pelvic pain, dysmenorrhoea, dyspareunia, menstrual disturbances and infertility. Symptoms related to other organs depend on the extent of spread of the disease.
- Ultrasonography and laparoscopy are useful tools in establishing the diagnosis.
- Medical treatment consists of analgesics to control pain. Hormonal therapy and GnRH analogues provide relief from pain and help regression of disease, but delays fertility. For women desirous of childbearing, operative laparoscopy with electrocauterization/laser ablation of endometriosis, evacuation of large endometriomas with cautery, peeling out of its lining and surgery to restore tubo-ovarian relationship help to improve fertility status.
- Medical treatment is the first line of treatment in mild and moderate endometriosis. All hormones are equally effective. One should choose the drug that is cost-effective and has less sides.
- Dydrogesterone does not prevent ovulation and is preferred in infertile women.
- Pre- and postoperative hormonal therapy relieve pain and symptoms, but do not improve fertility rate.
- Laparoscopy causes less postoperative pelvic adhesions and is preferred over laparotomy in young women.
- For adenomyosis and extensive disease, a hysterectomy with or without bilateral salpingo-oophorectomy brings relief to middle-aged patients.
- The relationship between mild endometriosis and infertility cannot be explained.
- Both laparoscopy and laparotomy yield similar pregnancy rate, but laparoscopy has less morbidity and causes less postoperative adhesions.
- Infertility is best treated surgically. IVF has a therapeutic role when other measures fail.
- Rectovaginal endometriosis is a separate entity and requires surgery but Mirena is also found useful.
- Malignancy kills a woman; endometriosis cripples her.

Self-Assessment

1. Discuss the clinical features and management of pelvic endometriosis in a young nulliparous woman.
2. A woman, para 1, presents with dysmenorrhoea, menorrhagia and chronic abdominal pain. A tender mass is felt in the right fornix. How will you investigate and manage the case?
3. A 35-year-old woman presents with menorrhagia, dysmenorrhoea. The uterus is 14 weeks enlarged. Discuss the differential diagnosis and management.
4. Short notes on:
   - Chocolate cyst of ovary
   - Endometriosis of rectovaginal septum.

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Chapter

31

Disorders of the Broad Ligament, Fallopian Tubes and Parametrium

CHAPTER OUTLINE

Broad Ligament Cysts

Broad ligament cysts are fairly common. However, they are small and are of no clinical importance except the parovarian cyst which may attain a huge size and undergo torsion.

Anatomical Considerations

Vestigial remnants of the Wolffian duct (mesonephric duct) are seen in the broad ligament, lying between the fallopian tube and the hilum of the ovary. The mesonephric duct extends from the outer aspect of the ovary, parallel to the fallopian tube in an inward and downward direction until it enters the myometrium in the region of the cervix. Its lowermost limit is the region of the hymen. It should be remembered that what is known as Wolffian duct is the same as the mesonephric duct or Gartner's duct.

Associated with the mesonephric duct and opening into it are the tubules of the upper part of the Wolffian body, the epoophoron or parovarium (sometimes called the organ of Rosenmüller). They are situated in the broad ligament adjacent to the hilum of the ovary. These mesonephric tubules are sometimes called Kobelt's tubules. Besides these, a number of blind isolated tubular remnants are seen near the inner border of the ovary and are known as paroophoron.

The lining of the mesonephric duct is a nonciliated, low columnar epithelium. While, the lining of the mesonephric tubules is low columnar or cuboidal; both ciliated and nonciliated cells are present in it.

Cysts may arise in the broad ligament from both the mesonephric duct and its tubules. These cysts are either small, pedunculated or intraligamentary, lying between the layers of the broad ligament where they may attain a considerable size. Mesonephric duct cysts are never lined with ciliated epithelium, whereas cysts of the mesonephric tubules may be. These cysts of mesonephric origin lie between the ovary and the fallopian tube, but are always separate and easily defined from the ovary itself.

Parovarian Cysts

Parovarian cysts are extraperitoneal cysts lying in the broad ligament adjacent to the ovary, below the fallopian tube. The tube is stretched and flattened over the top of the cyst which tends to enlarge in a lateral direction so that it may lie to the side of and above the ovary. Small parovarian cysts are extremely common and are often found at operation without their presence having previously been suspected. They sometimes form a cyst as large as 15–30 cm in diameter. The cyst is usually unilocular, and contains clear fluid. Its wall is smooth, thin and translucent. Sometimes, a few loculi are present, and papilloma, similar to the stationary papillomas of papillary cystadenomas of the ovary, may be scattered over the inner surface of the cyst. Unlike the ovarian cyst, the wall of a parovarian cyst frequently contains smooth muscle as do the mesonephric tubules. It is therefore possible to establish the origin of these cysts by histological examination.

Parovarian cyst is clinically diagnosed as an ovarian cyst, and at laparotomy, it is identified as a broad ligament cyst. An ovarian cyst can also burrow into the broad ligament

but in such a case, the normal ovary is not identifiable as in a parovarian cyst. Histological identification of the muscle in a cyst establishes the correct diagnosis.

The parovarian cyst is seen in young women. It displaces the uterus to the opposite side, and may be fixed in between the two layers of the broad ligament. As these cysts can undergo torsion, they are sometimes misdiagnosed as twisted ovarian cysts (Figure 31.1).

Treatment

Surgical removal of the parovarian cyst becomes necessary when it attains a large size. A delicate incision is made in the peritoneum over the cyst from which it is reflected by blunt dissection. A finger is then swept round the cyst between it and its bed until it is sufficiently free to be enucleated. Only a few small vessels will need ligation in the cyst bed, hence it is unnecessary to provide drainage. The ureter is found very close to the cyst and may be easily damaged. It is mandatory therefore to identify it or trace it down from the pelvic brim before any structure is cut or clamped.

Tumours of the Fallopian Tubes

Neoplasms of the fallopian tubes are extremely rare and often malignant. See Chapter 37 for more details on this condition.

Affections of the Broad Ligament and Parametrium

Haematoma

Haematoma of the broad ligament and parametrium may result from ectopic gestation which ruptures extraperitoneally into the broad ligament. A large haematoma may develop following rupture of the uterus or cervical laceration during childbirth. Haematoma may follow dilatation of the cervix, if the cervix gets split and uterine vessels get torn. The condition may also develop in cases of concealed accidental haemorrhage. A broad ligament haematoma tends to spread extraperitoneally. It may track upwards and cause a swelling above the Poupart's ligament and may even spread to the perinephric region. A haematoma may sometimes be encountered following abdominal and vaginal hysterectomy when a vascular pedicle slips and retracts into the cellular tissue. Pain, tachycardia and haemorrhagic shock ensue. A painful lump is felt in the lower abdomen. Prophylactic or therapeutic anticoagulants in the postoperative period can also produce a haematoma. A small haematoma resolves with conservative treatment, but a large one requires drainage and ligation of the bleeder.

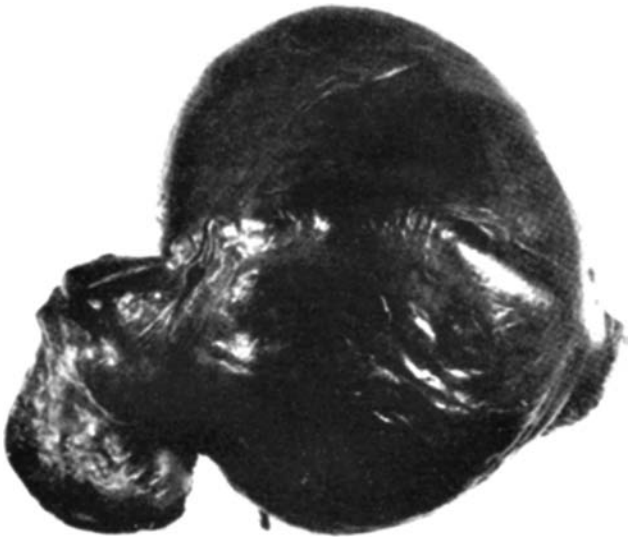

Figure 31.1 A parovarian cyst which had undergone torsion involving also the appendages. Note the ovary to the left and the fallopian tube over the cyst.

Parametritis

Parametritis, first described by Matthews Duncan, is a cellulitis of the tissues of the parametrium. Well-marked parametritis almost invariably follows childbirth or abortion, when the parametrium is infected from lacerations of the vaginal portion of the cervix, the vaginal vault or from lacerations of the lower uterine segment. Some degree of parametritis is present in all acute infections of the uterus and fallopian tubes and in advanced carcinoma of the cervix. The cases which are of clinical importance are those complicating childbirth and abortion. The condition causes symptoms at the beginning of the second week when the patient complains of pain in the hypogastrium and back. The temperature rises to about 102°F; the pulse rate is raised in the same proportion. The inflammation of the pelvic cellular tissue leads to the development of a large indurated swelling in the pelvis. In the early stages, the uterus is pushed to the opposite side and the indurated swelling of the parametrium extends from the uterus to the lateral wall of the pelvis, and fixes the uterus in the pelvis. It is impossible to separate the uterus from the swelling, because the parametrium extends to the wall of the uterus. The parametric effusion spreads backwards along the uterosacral ligaments, and it may also track upwards and point above Poupart's ligament. On rare occasions, the effusion may point in the perinephric region, in the ischiorectal fossa and even in the buttock, having tracked through the greater sciatic foramen. Suppuration in parametric effusion is uncommon, and even if the effusion points and has to be incised, it is rare for frank pus to be evacuated. As the effusion is extraperitoneal, symptoms of peritoneal irritation are absent, but rectal symptoms may arise as the result of inflammation involving the rectum.

Most parametric effusions subside under conservative antimicrobial treatment, but they are followed by scarring of the parametrium and this causes chronic pelvic pain. The scarred tissue draws the uterus over to the

affected side and the thick scar tissue is readily palpated on bimanual examination. Ureteric kinking can cause hydronephrosis.

Parametritis is often complicated by some degree of pelvic thrombophlebitis with its risk of pyaemia, pulmonary infarction and extension to the lower extremities to produce a 'white leg'. This clinical syndrome is especially common if the responsible organism is the anaerobic *Streptococcus*. Almost all parametritic effusions lie lateral to the uterus and vagina, where the parametrium is most plentiful. However, on rare occasions, an anteroposterior parametritis develops situated between the cervix and the rectal wall posteriorly, and the bladder and urethra anteriorly. The *treatment* of parametritis consists of bed rest, local heat and a full course of the appropriate antibiotic—similar to that described in the treatment of acute salpingo-oophoritis.

Tumours of the Broad Ligament and Parametrium

Myoma

The most common tumour is a myoma. It may be primary, when it arises from the uterosacral or round ligament, and tissues in the broad ligament, or secondary, when it arises low in the lateral wall of the uterus or the cervix but grows laterally between the two layers of the broad ligament. In the latter, the myoma retains its attachment to the uterus, and the uterine vessels as well as the ureter lie lateral to the tumour. In case of a primary myoma, the uterine vessel is medial to the tumour, but the ureter may lie anywhere in relation to it though usually it is beneath the tumour. Primary myoma is also known as true broad ligament myoma and secondary myoma as false broad ligament tumour.

Sarcoma

Sarcoma is very rare. It presents the clinical features of a myoma. In the early stage, surgery is feasible, but in advanced stages, it can be treated only by radiation.

Lipoma

Lipoma is rare and can be enucleated without difficulty.

Retroperitoneal Tumours

Retroperitoneal tumours are included here because they are often mistaken for an ovarian tumour or a broad ligament tumour, and their exact nature is revealed only at laparotomy. These tumours are classified as:

- Congenital: Ectopic pelvic kidney should be suspected when a fixed pelvic mass is associated with the absence or malformation of the genital tract. Intravenous pyelography reveals its true condition.
- Dermoid: A rare tumour.
- Tumours of neurogenic origin, neurofibromas and tumours arising from the spinal meninges.
- Solid tumours arising from the bony pelvis, viz., osteoma, chondroma and sarcoma.

When faced with a retroperitoneal tumour, the most thorough pre-operative investigations, viz., IVP and barium enema, CT and MRI are indicated. Diagnostic laparoscopy and biopsy are essential. The ultrasound will indicate its location. Two dangers are encountered during removal of the retroperitoneal tumour:

- The ureter may be close to the tumour and be cut or ligated unless it is identified at the start of the surgery.
- Large vessels of the hypogastric system may obtrude into the operative fields and these must be secured.

In case of inoperable fixed growth, radiotherapy is an alternative.

The different types of abdomen lumps encountered in gynaecology is illustrated in Table 31.1

Key Points

- Remnants of the Wolffian body and the mesonephric duct are present in the broad ligament between the fallopian tube and the ovary; these can enlarge and cause cystic neoplasms. The parovarian cyst can grow to a large size. It can undergo torsion or rupture.

TABLE 31.1 Lumps in the abdomen

Adolescents	Reproductive Age	Menopause
• Haematocolpos • Haematometra • Ovarian tumour • Uterine fibroids (rare) • Tubercular mass • Pelvic kidney	• Pregnancy • Ectopic pregnancy • Full bladder—RVRF, gravid uterus • Fibroid or ovarian tumour associated with pregnancy • Uterine fibroid • PID • Ovarian tumour	• Pyometra • Endometrial carcinoma • Ovarian tumour • Fallopian tube cancer • Uterine sarcoma • Rectal tumour • Chronic retention of urine

- The parametrium can be the site of a haematoma or infection causing parametritis.
- The connective tissue in the broad ligament can be the site of a true broad ligament fibroid.
- Retroperitoneal tumours mimic broad ligament neoplasms.
- The nature of the abdominal tumours vary according to the age.

Self-Assessment

1. Describe the different abdominal tumours encountered in gynaecology.
2. Write short notes on:
   a. Haematoma of the broad ligament
   b. Retroperitoneal tumours

Suggested Reading

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Chapter 32 Disorders of the Ovary

CHAPTER OUTLINE

Ovarian enlargements, cystic or solid, may occur at any age. Functional and inflammatory enlargements of the ovary develop almost exclusively during the childbearing years. They may be asymptomatic or produce local discomfort, menstrual disturbances, infertility, or in rare cases cause acute symptoms due to complications like haemorrhage, rupture or torsion.

The ovary is complex in its embryology, histology, steroidogenesis, and has the potential to develop malignancy. Therefore, ovarian neoplasms exhibit a wide variation in structure and biological behaviour. Unlike the cervix and uterus, the ovaries are not clinically accessible, and therefore, easy screening methods for detecting ovarian neoplasms are not available. The ovary, after the uterus, is the second most common site for development of gynaecological malignancy, and the prognosis remains poor.

Ovarian tumour may occur at any age.

In adolescents, the ovarian tumour is mostly malignant, so also in menopausal women.

In the childbearing periods, 70% are functional, 20% are neoplastic (mostly benign) and 10% are endometriomas.

Non-Neoplastic Enlargements of the Ovary (Table 32.1)

Such an ovarian enlargement may be the result of ovarian congestion due to adnexal inflammatory states, ovarian endometriosis causing a chocolate cyst or persistence and enlargement of physiological structures in the ovary like the Graafian follicle or corpus luteum. The lesions due to inflammatory conditions are discussed in the chapter on pelvic inflammatory disease, and endometriosis affecting the ovary is dealt with in Chapter 30. The discussion in this chapter will be restricted to non-neoplastic functional distension cysts of the ovary, and polycystic ovarian syndrome. *To define a functional cyst, its size must be at least 3 cm*, but not more than 7 cm.

Follicular Cysts

Follicular cysts are not uncommon. They may be single or multiple, may be bilateral and vary in size from small blebs to cysts of large size but generally do not exceed 5.0 cm in diameter (Figure 32.1). They are the result of failure of absorption of the fluid in an incompletely developed follicle or anovulation. They are usually asymptomatic unless haemorrhage, rupture or torsion supervenes, in which case symptoms and signs of an acute abdomen develop.

Large and multiple cysts may cause pelvic pain, dyspareunia and irregular bleeding. The enlarged ovary may be recognizable clinically or documented on sonography.

Ovarian neoplasms, inflammatory adnexal enlargement and endometriosis must be considered in the differential diagnosis.

Most follicular cysts disappear spontaneously within a few weeks to months. When symptoms like amenorrhoea are prolonged, stimulation of postovulatory change by administering oral medroxyprogesterone 10 mg three times a day over a period of 5–7 days will generally bring on menstruation. Primolut N 5 mg tid for 3 days also induces menstruation. Clomiphene citrate 50 mg given orally for five consecutive days helps to induce ovulation and brings about menstruation, or pregnancy. Oral combined pills administered for 3 months also resolve the cyst in most cases.

If any cyst persists for longer than 3 months, or size increases to >7 cm, the possibility of a neoplastic cyst must be kept in mind, and the patient investigated.

Follicular Haematomas

Small follicular haematomas are common. To the naked eye, the ovary contains haemorrhagic cysts. Old cysts appear to contain tarry material and are likely to be mistaken for endometriosis. Many of these are asymptomatic and of no clinical significance except for the rare case, when the cyst bursts into the peritoneal cavity causing acute abdomen, and is mistaken for an ectopic pregnancy.

TABLE 32.1 Clinical features of polycystic ovarian syndrome

Clinical Features	Hormonal	Sequelae

• Young woman
• Central obesity
  • BMI >30 kg/cm^2
  • Waist line >88 cm
• Oligomenorrhoea, amenorrhoea
• Infertility (20%)
• Hirsutism
• Acanthosis nigra due to insulin resistance. Thick pigmented skin over the nape of neck, inner thigh and axilla
• Most androgens from ovary
• ↑ fasting insulin >10 mIU/L
	• ↑ E_2 level
	• ↓ FSH ↑ LH >10 IU/mL
	• ↓ FSH/LH ratio
	• ↑ Androgens
	• Testosterone, epiandrostenedione, ↑ dehydroepiandrosterone ↑
	• 17-α-hydroxyprogesterone >300 ng/dL
	• Testosterone >2 ng/mL
	• Prolactin ↑
	• Sex hormone binding globulin (SHBG) ↓
	• ↓ E_2/oestrone (E_1) ratio
	• F. glucose/insulin ratio < 4.5
		• Diabetes (15%)
		• CVS disorder
		• Lipidaemia
		• Hypertension
		• Endometrial cancer
		• Breast cancer
		• Premature ovarian failure following surgery

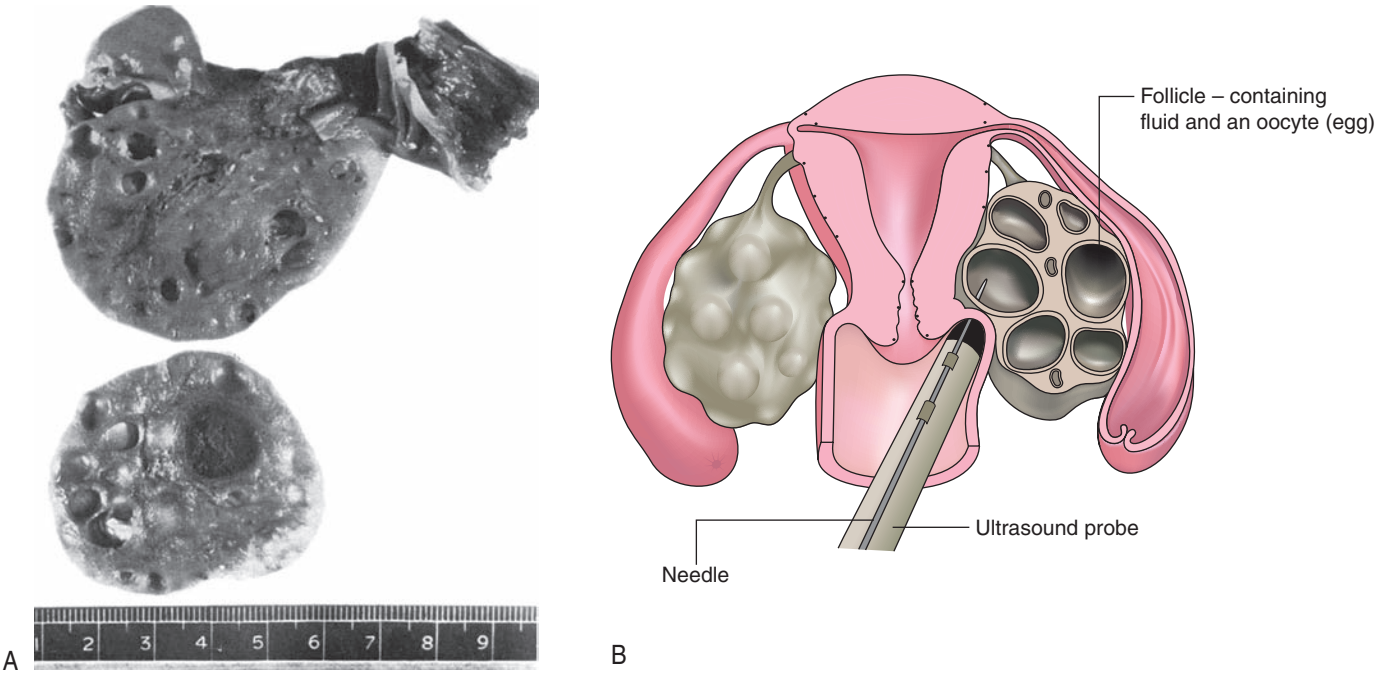

Figure 32.1 (A) Multiple follicular cysts of the ovaries. **(B)** Transvaginal ultrasound showing polycystic ovary. (Source: Rao, KA. *Textbook of Gynaecology,* India: Elsevier, 2008.)

Lutein Cysts of the Ovary

Two types of lutein cysts are recognized:

- Granulosa lutein cysts found within the corpus luteum.
- Theca lutein cysts associated with trophoblastic disease and chorionic gonadotropin therapy.

Corpus Luteum (Granulosa Lutein) Cysts

Corpus luteum cysts are functional, non-neoplastic enlargements of the ovary. Persistent corpus luteum cysts may cause local pain, tenderness or delayed menstruation. These cysts are often palpable clinically. Unless complications like torsion or rupture lead to an acute abdomen requiring surgical treatment, most cysts will resolve in due course of time. Hence observation is recommended whenever this condition is suspected, because it resembles unruptured ectopic pregnancy. Sonography and serum quantitative estimations of β-hCG help to resolve the diagnosis.

Ultrasound reveals spider-web-like structure with or without a clot. Doppler shows rich vascularization with high blood flow velocity.

Theca Lutein Cysts

These cysts can sometimes enlarge to several centimetres in diameter. They are usually bilateral and filled with straw-coloured fluid. Theca lutein cysts are often found in association with hydatidiform moles, choriocarcinoma and gonadotropin (hCG) or clomiphene therapy. The

cysts spontaneously regress after elimination of the mole, therapeutic curettage, treatment of choriocarcinoma or discontinuation of gonadotropin therapy.

Functional cysts are distinguished from neoplastic cysts by *the fact that they never grow more than 7 cm in size, are unilocular with clear fluid, and regress after some time*. The hyperstimulation syndrome by clomiphene therapy has been described in the chapter on hormonal therapy.

Multiple Functional Cysts

Multiple functional cysts are caused by the following:

- FSH secreting pituitary adenoma
- Ovarian hyperstimulation syndrome (OHSS)
- Polycystic ovarian syndrome (PCOS)

In pituitary adenoma, ovarian cysts measure more than 1 cm; FSH and oestrogen levels are raised, but LH level is low. Other signs of hyperstimulation such as haemoconcentration and coagulation profile are not affected.

Ovarian hyperstimulation syndrome is caused mainly by human chorionic gonadotropin hormone; the follicular size is more than 3 cm.

PCOS is characterized by multiple small cysts less than 1 cm; LH is raised and LH/FSH ratio is ≥ 2.

Amenorrhoea, oligomenorrhoea and infertility are the clinical features. Pituitary adenoma may requires transphenoidal excision of the adenoma, but no surgery is required for the ovarian cysts. These eventually resolve.

Polycystic Ovarian Syndrome (PCOS) or Disease (PCOD)

Polycystic ovarian disease is a heterogeneous, multisystem endocrinopathy in women of reproductive age with the ovarian expression of various metabolic disturbances and a wide spectrum of clinical features such as obesity, menstrual abnormalities and hyperandrogenism. This disease was discovered by and named as Stein–Leventhal syndrome in 1935. To diagnose PCOS, adrenal and androgen secretory ovarian tumour should be excluded.

Incidence

Current incidence of PCOS (5–6%) is fast increasing lately due to change in lifestyle and stress. It is also becoming a common problem amongst adolescents, developing soon after puberty. Amongst infertile women, about 20% infertility is attributed to anovulation caused by PCOS. Some of the women who develop cardiovascular disease, hypertension, endometrial cancer and type 2 diabetes later in life appear to have suffered from PCOS in earlier years.

Aetiology and Pathogenesis

PCOS has been attributed to several causes including change in lifestyle, diet and stress. Initially, the ovaries were thought to be the primary source which set the changes in the endocrine pattern. Genetic and familial environment factors (autosomal dominant inherited factors) were later added as aetiological factors in the development of PCOS. The environment factor may function in the utero or in early adolescent life, manifesting clinically a few years later as PCOS. CYP_{21} gene mutation has been discovered in this connection. Familial occurrence has been reported. X-linked dominant mode of inheritance is also involved.

Another view held for occurrence of PCOS is enhanced serine phosphorylation unification activity in the ovary (hyperandrogen) and reduced insulin reception activity peripherally (insulin resistance).

Obesity is related to PCOS. The adipose tissue (fat) is considered an endocrine and immunomodulatory organ; it secretes leptin, adiponectin and cytokines which interfere with *insulin signalling* pathways in the liver and muscle resulting in *insulin resistance*, and *hyperinsulinaemia*. Increased birth weight in obese and PCOS mothers can also cause PCOS in adolescent daughters.

Raised LH secretion by insulin can cause infertility or miscarriage through improper oocyte maturation.

Obesity is characterized as the condition when body mass index >30 kg/m^2 and waist line >88 cm prevails.

Waist/hip ratio >0.85.

Endogenous β endorphin also stimulates insulin release and may contribute to insulin resistance.

Hyperandrogenism and resulting anovulation was initially thought to arise primarily in the ovaries.

It is now proved that insulin resistance with resultant hyperinsulinaemia initiates PCOS in 50–70% cases, though hypothalamic–pituitary–ovarian axis and adrenal glands are also involved to some extent.

Insulin induces LH to cause thecal hyperplasia and secrete androgens, testosterone and epi-androstenedione which are converted to oestrogen in the granulose cells. Epi-androstenedione is converted in the peripheral fat to oestrone. This leads to rise in the oestrogen and inhibin level. These in turn cause high LH surge.

While oestrone level increases, oestradiol level remains normal with the result that the oestrone/oestradiol ratio rises.

Hyperandrogenism lowers the level of hepatic sex hormone binding globulin (SHBG), so that the level of free testosterone rises leading to hirsutism. *Androgen also suppresses the growth of the dominant follicle and prevents apoptosis of smaller follicles which are normally destined to disappear in the late follicular phase.*

Polycystic ovarian syndrome may set in early adolescent life, but clinically manifest in the reproductive age with long-term implications of diabetes, hypertension, hyperlipidaemia and cardiovascular disease; this cluster of disorders is known as the 'X syndrome'.

Endocrinological changes are as follows:

1. Oestrone/E_2 level rises.
2. LH level is raised over 10 IU/mL.
   FSH level remains normal, but FSH/LH ratio falls.
3. SHBG level falls due to hyperandrogenism.
4. Testosterone and epi-androstenedione levels rise.
5. Fasting blood glucose/fasting insulin <4.5 suggests insulin resistance.

6. Triglyceride level >150 mg/dL-hyperlipidaemia HDL <50 mg/dL.
   Testosterone >2 ng/mL, free T >2.2 pg/mL (Normal level 0.2–0.8 ng/mL)
   Normal androstenedione level is 1.3–1.5 ng/mL.
   DHEA >700 ng/mL suggests adrenal tumour.
7. Prolactin is mildly raised in 15% cases.
8. Fasting insulin is more than 10 mIU/L in PCOS in 50–70/cases.
9. Thyroid function tests may be abnormal (hypothyroidism).
10. 17-α-hydroxyprogesterone in the follicular phase >300 ng/dL suggests adrenal hyperplasia due to 21-hydroxylase deficiency.
11. Urinary cortisol <50 µg/24 h.

Pathology

Macroscopically, both ovaries are enlarged, though one PCOS ovary is also diagnostic. The ovary shows a thick capsule of tunica albuginea. The ovarian surface may be lobulated but the peritoneal surface free of adhesions.

Multiple cysts (12 or more) of 2–9 mm size are located peripherally along the surface of the ovary giving it a 'necklace' appearance on ultrasound. These are persistent atretic follicles. Theca cell hyperplasia and stromal hyperplasia account for the increase in the size of the ovary which amounts to more than 10 cm^3 in volume. The laparoscopic view of the polycystic ovarian disease is shown in Figure 32.2.

Clinical Features (Table 32.1)

The pathogenesis appears to be initiated in utero or early adolescent period. Early adrenarche in the form of early pubertal hair and early menarche is observed in a few girls. Menstruation for a couple of years may be normal, but clinical features of PCOS develop early with oligomenorrhoea (87%) or with a short period of amenorrhoea (26%) followed by prolonged or heavy periods (a common complaint in a majority of cases). Dysmenorrhoea is absent.

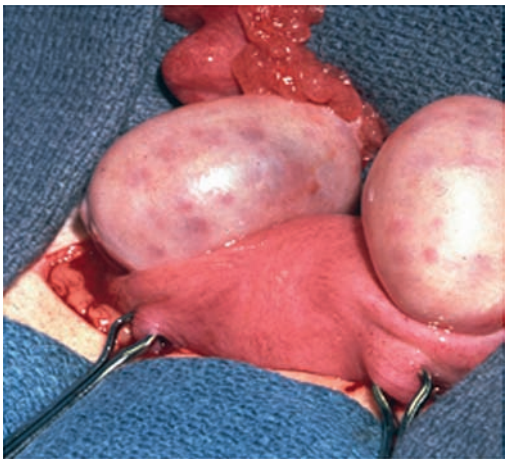

Figure 32.2 Bilateral enlarged ovaries with a smooth and thickened capsule. (From Figure 22.3A. R. Jeffrey Chang: Polycystic Ovary Syndrome and Hyperandrogenic States. Jerome F Strauss and Robert L Barbieri: In: Yen & Jaffe's Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management, 7th Edition. Saunders: Elsevier, 2014.)

In the reproductive years, infertility accounts for about 20% cases. This is due to anovulatory cycles. During pregnancy, if the woman conceives, carbohydrate intolerance, diabetes and hypertension may develop. Pregnancy loss occurs in 20–30%.

Hyperandrogenism appears in the form of acne (30%) and hirsutism. Facial hair appears over the upper lip, chin, breasts and thighs. Baldness is sometimes noted, but virilism does not develop.

History of lifestyle, diet and smoking and exogenous hormone administration should be inquired into. Family history of diabetes and hypertension should be asked. *Excessive exercise, history of tuberculosis and thyroid are important in menstrual disorder.*

Examination

Look for

- Obesity, especially waistline. Waist over hip ratio >0.85 is abnormal; 50% women are obese.
- Body mass index between 25 and 30—overweight; and above 30—obesity.
- Thyroid enlargement.
- Hirsutism and acne.
- Hyperinsulinaemia which may manifest as acanthosis nigra (5%) over the nape of the neck, axilla and below the breasts; 75% obese women reveal hyperinsulinaemia.
- Blood pressure in obese women.

Pelvic findings are normal, and it is not common to palpate the enlarged ovaries.

For the diagnosis of PCOS, the Rotterdam criteria (2003) suggests that at least two out of three criteria should be present. These criteria are:

- Oligo/amenorrhoea, anovulation, infertility
- Hirsutism–acne
- Ultrasound findings (see below under 'Investigations')

Differential Diagnosis

Though the diagnosis is easy in most cases, congenital or adult adrenal hyperplasia, Cushing's disease and ovarian masculinizing tumours should be considered in extremely obese women with virilism. With irregular cycles in young girls, hormonal assays will identify hypothalamic–pituitary–ovarian dysfunction. Thyroid function tests may be called for in a few cases.

Investigations

Ultrasound is diagnostic of PCOS.

- It confirms the enlarged ovaries, their size and increased stroma. Ovarian volume will be more than 10 mm^3.
- It shows 12 or more small follicles each of 2–9 mm in size placed peripherally.
- It rules out ovarian tumour.
- It shows endometrial hyperplasia if present.

In case of doubt, abdominal scan will reveal adrenal hyperplasia or tumour. Ultrasound should preferably be performed in the early follicular phase. Increased blood flow is sometimes revealed on Doppler ultrasound. Ultrasound is also used to watch the response of medication and to decide when to stop the drug therapy. Sometimes, only one ovary is involved. These ovarian changes are not applicable if the woman is on combined oral pills, as these pills change the ovarian morphology.

- Hormonal study mentioned earlier is not performed routinely, but specific hormonal studies are undertaken in a woman as and when required. All hormonal studies are not needed as a routine.
- Thyroid function tests in obese woman.
- Laparoscopy is reserved for therapeutic purpose, now that the diagnosis can be confirmed on ultrasound findings. Laparoscopy reveals enlarged bilateral ovarian cysts.

Treatment

The purpose of treatment is

- to cure a woman with menstrual disorders
- to treat hirsutism
- to treat infertility
- to prevent long-term effects of X syndrome in later life.

The treatment therefore is catered to the requirement of the woman.

- **Weight loss.** Weight loss of more than 5% of previous weight alone is beneficial in mild hirsutism; it restores the hormonal milieu considerably. Weight loss increases the secretion of the sex hormone binding globulin, reduces insulin level and testosterone level.
- **Lifestyle.** Cigarette smoking should be abandoned. It lowers E_2 level and raises DHEA and androgen level.
- Hormones to control menstruation are:
  - Oral combined pills (OC)
  - OC and cyproterone acetate; OC and spironolactone
- Ketoconazole 200 mg daily reduces testosterone secretion.

Oestrogen suppresses androgens and adrenal hormones (DHEA). It raises the secretion of SHBG in the liver, which binds with testosterone, thus reducing free testosterone. It also suppresses LH. It is best given as low-dose combined pills, having progestogen with lesser androgenic effect. Fourth generation of combined pills which contains 30 μg E_2 and 2–3 mg drospirenone (progestogen with anti-androgenic action) is best for PCOS (Yasmin, Janya, Tarana). It helps to reduce acne and further development of hirsutism. It prevents water retention and reduces weight; it maintains lipid profile.

- Progestogen may be required to induce menstruation in amenorrhoeic woman prior to initiating hormonal cyclical therapy.
- OC with cyproterone is prescribed if the woman has hirsutism (see Chapter 10).
- Epi-ornithine HCl topically prevents hair growth.

Hirsutism. Anti-androgens used are described in detail in Chapter 8. Acne can be managed by clindamycin lotion 1% or erythromycin gel 2% if pustules form. For severe acne, isotretinoin is used, but it is teratogenic and pregnancy should be avoided while on this medication. *The drugs take 3–6 months before the effect on hirsutism is noted.*

Dexamethasone (0.5 mg) at bedtime reduces androgen production, and is used in some infertile women with clomiphene if DHEA-S is raised above 5 ng/mL.

Infertility. *Clomiphene is the first line of treatment if PCOS woman is to be treated for infertility*. It induces ovulation in 80% and 40–50% conceive, but 25–40% abortion rate is caused by corpus luteal phase defect. Hyperstimulation occurs in 10% cases. Clomiphene with dexamethasone improves fertility rate. In a resistant case, tamoxifen 20–40 mg daily for 5 days or off-label letrozole (2.5 mg daily for 5 days or 20 mg single dose on day 3) should be tried. Failure after the above therapy calls for FSH, LH or GnRH analogues. A woman with insulin resistance requires, in addition, metformin.

This woman also shows raised level of homocysteine in which case *N*-acetyl-cysteine 1.2 g may be added to clomiphene therapy. *N*-acetyl-cysteine (NAC) is a mucolytic drug and an insulin sensitizer.

Metformin. Metformin treats the root cause of PCOS, rectifies endocrine and metabolic functions and improves fertility rate. It is used as an insulin sensitizer. It reduces insulin level, delays glucose absorption and liver production of glucose (liver neoglycolysis). It also improves peripheral utilization of glucose; liver and renal function tests should be performed prior to metformin administration.

Besides reducing the level of insulin, metformin also reduces the level of total and free testosterone and increases the sex hormone binding globulin. Ovulation occurs in 70–80%, and pregnancy in 30–40%. It does not cause hypoglycaemia and does not reduce weight. It is contraindicated in hepatic and renal disease, and causes gastrointestinal disturbances and lactic acidosis. Therefore, starting with 500 mg daily, the dose is gradually increased to 500 mg three times a day. Metformin should not be administered for more than 6 months. One gram tablet is also available to be taken once at night (riomet 1 g). If metformin is contraindicated, acarbose 300 mg daily can replace it. Octequitide is a peptide hormone secreted by hypothalamus which inhibits the growth hormone and insulin. It enhances ovulation in clomiphene-resistant infertility.

Lately, to improve the pregnancy rate in PCOS, instead of metformin, some gynaecologists have started using *N*-acetyl cysteine with micronutrients. This reduces the homocysteine level. The micronutrients include vitamin D, minerals, chromium, selenium, inositol and folic acid (ovacare, one tablet twice daily).

It is important to inform the patient that PCOD can recur. Any form of treatment is likely to give temporary relief and may be required to be repeated and varied at various times during her reproductive years. The treatment will also ensure that in the long term, diabetes and endometrial cancer do not develop.

Surgery

Surgery is reserved for those in whom

- Medical therapy fails
- Hyperstimulation occurs
- Infertile women
- Previous pregnancy losses

Surgery comprises laparoscopic drilling or puncture of not more than four cysts in each ovary either by laser or by unipolar electrocautery (Figure 32.3).

Surgery restores endocrine milieu and improves fertility for a year or so. Thereafter, pelvic adhesions caused by surgery may again reduce fertility rate. Hydrofloatation reduces adhesion formation.

Advantages of surgery are as follows:

- Tubal testing with chromotubation can be performed simultaneously.
- Other causes of infertility, i.e. endometriosis looked for.
- One-time treatment.
- Intense and prolonged monitoring not required.
- Cost effective compared to IVF.
- Reduces androgen and LH production
- Following surgery, single ovulation occurs with drugs, and hyperstimulation and multiple pregnancy are avoided.
- Ovulation occurs in 80–90% and pregnancy in 60–70%.

Disadvantages of surgery are as follows:

- Surgery involves anaesthesia and laparoscopy.
- Adhesions may form postoperatively.
- Premature ovarian failure due to destruction of ovarian tissue if cautery is used. For this reason, many now prefer simple puncture of the cysts.

Lately, a Chinese group has performed ultrasound-guided laser coagulation of ovarian cysts, under heavy sedation. This requires more study. While avoiding laparoscopic surgery and postoperative adhesions, it occasionally causes skin burn; bowel burn is also reported.

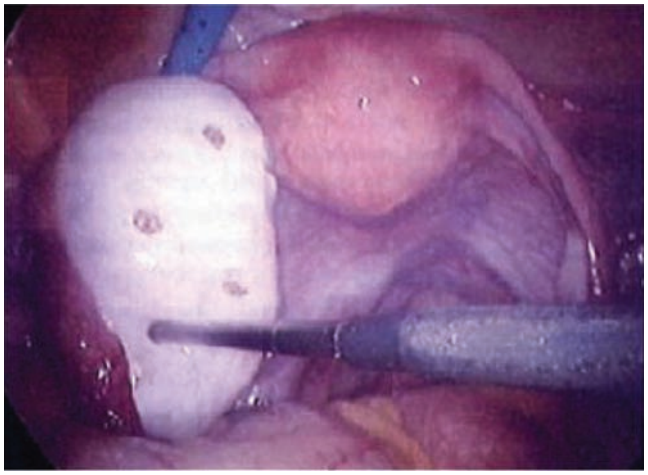

Figure 32.3 Laparoscopic ovarian drilling. (From Figure 2. Suresh Kini: In: Polycystic ovary syndrome: diagnosis and management of related infertility practice points. Obstetrics, Gynaecology and Reproductive Medicine. Vol 22(12): 347–353, 2012.)

Prevention

With the knowledge that PCOS has long-term adverse effects (threefold) on the health of the woman, such as diabetes, hypertension, cardiovascular disease and hyperlipidaemia, endometrial cancer, it is now suggested that PCOS should be adequately treated at the earliest. This woman should be observed for these ailments in later life. Obesity in adolescents needs to be avoided and corrected. Lifestyle changes should be recommended.

Key Points

- Polycystic ovary is a multisystem endocrinopathy with features of oligomenorrhoea, non-ovulation, obesity and hirsutism. It is a disease of young women.
- PCOS originates from insulin resistance; hyperinsulinaemia and obesity are linked.
- PCOS causes oligomenorrhoea, hirsutism and infertility.
- Ultrasound is the gold standard investigation in the diagnosis of PCOS. Hormonal study is performed only if required.
- Decrease in weight and change of life style improves the condition considerably.
- Hormone therapy is catered to the individual requirement.
- Surgery is performed if medical therapy fails and to improve fertility rate.
- Complete cure should be ensured to avoid late sequel such as diabetes, hypertension, cardiovascular disease and hyperlipidaemia.
- Raised E_2 level, LH level and androgens with low or normal FSH characterize this syndrome.
- Clomiphene remains the first line of treatment for infertility in PCOS. Resistant cases require laparoscopic puncture or gonadotropins and metformin.

Self-Assessment

1. Describe the clinical features of polycystic ovarian syndrome.
2. Discuss the management of PCOS.
3. A young 22-year-old nullipara presents with 6 weeks amenorrhoea, acute abdominal pain and slight vaginal bleeding. Ultrasound shows a cystic mass 3 × 3" in the right fornix. Discuss the differential diagnosis and management.

Suggested Reading

Bonnar J. Recent Advances in Obstetrics and Gynaecology Vol 19: 121, 1995.
Bonnar J. Recent Advances in Obstetrics and Gynaecology 21: 111, 2001.
Studd J. Progress in Obstetrics and Gynaecology 11: 851, 1994.
Studd J. Progress in Obstetrics and Gynaecology 2005; Vol 16: 227.

Chapter

33

Ovarian Tumours

CHAPTER OUTLINE

Ovarian tumour is not a single entity, but a complex wide spectrum of neoplasms involving a variety of histological tissues ranging from epithelial tissues, connective tissues, specialized hormone-secreting cells to germinal and embryonal cells. The most common are epithelial tumours forming 80% of all tumours. Eighty per cent are benign tumours and 20% malignant. Of all the malignant tumours, 90% are epithelial in origin, 80% are primary in the ovary and 20% secondary from breasts, gastrointestinal tract and colon. Benign tumours can become secondarily malignant. Mucinous cyst becomes malignant in 5% but papillary cyst adenoma becomes malignant in 50% if left untreated.

Unfortunately, patients with ovarian tumours are often symptom-free for a long time, and the signs are often non-specific. By the time ovarian malignancy is established, about two-thirds of these are already far advanced and the prognosis in such cases is unfavourable.

An ovarian tumour in adolescent and post-menopausal women is more often malignant. In the reproductive age, it is mostly benign. Most germ cell tumours occur in young girls (Table 33.1).

Pathology

In an attempt to standardize the nomenclature used in describing the diverse varieties of tumours, the World Health Organization (WHO) devised a classification listing nine major groups for benign and malignant tumours (Table 33.2).

Epithelial ovarian neoplasms arise from the mesoepithelial cells on the ovarian surface. Epithelial cancers constitute about 80% of all ovarian cancers. The most common histologic type is the papillary serous cystadenomas and carcinomas accounting for almost 50% of all epithelial

TABLE 33.1 Varieties of cystic/neoplastic enlargements of the ovaries

1. Functional cysts	• Follicular cysts • Lutein cysts • Multiple functional cysts • Corpus luteal cyst (PCOS)
2. Inflammatory	• Salpingo-oophoritis • Puerperal, abortal, IUCD related
3. Metaplastic	• Endometrioma
4. Neoplastic benign and malignant	• Premenarchal years: 10% are malignant—mostly dysgerminoma teratoma • Reproductive period—15% malignant • Premenopausal—50% malignant

TABLE 33.2 WHO classification of ovarian tumours (major groups)

I. Common epithelial tumours:
- Serous tumours
- Mucinous tumours
- Endometrioid tumours
- Clear cell (mesonephroid tumours)
- Brenner tumours
- Mixed epithelial tumours
- Undifferentiated carcinoma
- Unclassified epithelial tumours

II. Sex cord (gonadal stromal) tumours:
- Granulosa stromal cell tumours, theca cell tumours
- Androblastomas: Sertoli–Leydig cell tumours
- Gynandroblastomas
- Unclassified

III. Lipid (lipoid) cell tumours

IV. Germ cell tumours:
- Dysgerminoma
- Endodermal sinus tumour
- Embryonal carcinoma
- Polyembryoma
- Choriocarcinoma
- Teratoma
- Mixed forms

V. Gonadoblastoma:
- Pure
- Mixed with dysgerminoma or other germ cell tumours

VI. Soft tissue tumours not specific to ovary

VII. Unclassified tumours

VIII. Secondary (metastatic) tumours

IX. Tumour-like conditions

tumours. Mucinous cysts account for 12–15%, clear cell and endometrioid combined about 10%, and the unspecified types 25–27% of the cases.

The degree of cellular differentiation of the epithelial ovarian neoplasm expressed as histologic grade has an important prognostic significance as well as in identifying malignancy.

The criteria of grading used include mitotic count, stratification, cellular pleomorphism, nuclear atypism and proportion of solid areas within the tumour.

Grade '0' tumours, also known as borderline malignancies or tumours of low malignant potential (LMP), may demonstrate papillary tufting, stratification, epithelial atypia, exfoliation of cellular clusters, minimal mitotic activity, but no stromal invasion. The 5-year survival of patients with Stage I Grade '0' tumours is more than 90% compared to 54% survival for patients with Stage I Grade 3 serous cystadenocarcinomas.

Besides histological tumour grading, flow-cytometry analysis of tumour DNA content provides another method of assessing tumour differentiation and prognosis.

Borderline Ovarian Tumours

Borderline ovarian tumours or ovarian epithelial tumours of low malignant potential (LMP) were first described by Taylor in 1929. There is a broad agreement that a category of borderline tumour exists. Histologically, these tumours are intermediate between truly benign neoplasms and those with invasive characteristics.

They are prevalent in 2.5/10,000 women and account for 10–20% of all epithelial tumours. No matter how malignant the epithelial cells appear, unless they invade the stroma or are at least four cells high in the mucinous tumour, they must be classified as of LMP. Mitotic figures should be less than 4 per 10 high-power field.

Characteristics of Borderline Ovarian Tumours

- Patients have a high survival rate of 90%.
- Tumours run a typical indolent course. It may however progress to malignancy.
- Spontaneous regression of peritoneal implants is known to occur.
- Diagnosis must be based exclusively on the examination of the ovarian tumour.
- Multiple sections must be examined to exclude invasion.

Nonepithelial tumours (germ cell and gonadal stroma) do not lend themselves to a diagnosis of LMP tumour. Borderline malignant tumours occur in younger women (35–55 years), 10 years younger than their malignant counterparts.

Risk Factors

Low parity infertility and failure to lactate increase the risk of developing these tumours. Unopposed oestrogen and obesity are also likely risks. Smokers are prone to LMP tumours. Induction of ovulation may also be a risk factor. *Oral combined pills do not provide any protection against development of a borderline ovarian tumour.*

Pathology

Borderline ovarian tumours are mainly serous (endosalpinx and endocervical type) and mucinous, the former being more common than the latter.

The clinical features are similar to those of benign ovarian tumours; so also are the investigations. The diagnosis is entirely dependent on several sections studied histologically; frozen section is necessary in young women.

Management is individualized according to age, parity and desire to conserve the fertility function. Conservative surgery in the form of ovarian cystectomy, ovariotomy or salpingo-oophorectomy are performed. In mucinous borderline tumour, it is prudent to perform appendicectomy as well, because many believe this ovarian tumour is secondary to the appendix. Appendicectomy avoids occurrence of pseudomyxoma peritonei. No adjuvant chemotherapy or radiotherapy is necessary, but follow-up is mandatory, as recurrence of 10–30% is reported. Routine lymphadenectomy is also not required.

Tumours of the Surface Epithelium

Serous Cystadenoma and Cystadenocarcinoma

Serous cystadenoma and cystadenocarcinoma are amongst the most common of cystic ovarian neoplasms, accounting for about 50% of all ovarian tumours; of these, 60–70% are benign, 15% borderline and 20–25% are malignant.

Serous cystadenomas occur in the third, fourth and fifth decades of life; malignant cystadenocarcinomas tend to occur more frequently with advancing age. In about half of the cases, they are bilateral.

Delicate papillary excrescences may be seen on the surface and within the loculi in a benign cyst. In case of serous cystadenocarcinoma, coarse papillary growths spread to the peritoneal surfaces. The papillae are friable unlike their benign counterparts. Histologically, the benign variety shows cystic spaces, and the lining of the tumour consists of tall columnar ciliated epithelium resembling the endosalpinx. The loculi contain a serous straw-coloured fluid, which may be blood stained when malignant transformation occurs. Unless cellular atypia exceeds four-cell layer thickness or stromal invasion occurs, the tumour is classified as borderline or benign (Figure 33.1).

Mucinous Tumours

Mucinous tumours are multiloculated cysts lined by epithelium resembling the endocervix (Figures 33.2 and 33.3). Formerly, they were referred to as pseudomucinous cysts, but their contents are not chemically true mucin. The cut surface shows multiloculi and honeycombed appearance. The tumours are not infrequent, can grow to a large size and often weigh as much as 5–10 kg; they are often pedunculated. These may be combined with a dermoid cyst or a Brenner tumour (Figure 33.4). They are usually unilateral; only 5% are bilateral. The tumours are essentially benign, only 5–10% become malignant and 10–15% are of LMP. Bilateral tumours are often metastatic from the gastrointestinal tract, mainly mucocele of appendix or primary adenocarcinoma of appendix.

Mucinous tumours occur in women between 30 and 60 years. They have a glistening surface, and the cut section reveals loculi filled with mucinous contents (Figure 33.5). If the tumour ruptures, it may lead to formation of pseudomyxoma peritonei and the viscera show extensive adhesions. Appendicectomy at the time of primary surgery prevents pseudomyxoma peritonei, as often mucocele of appendix is known to cause this complication.

Endometrioid Tumour

Endometrioid tumours are mostly malignant and account for about 20% of all ovarian cancers. They are lined by a glandular epithelium resembling the endometrium. The tumours are of moderate size, and are essentially solid, with cystic areas in between filled with haemorrhagic fluid. In 15% of cases, ovarian endometriosis may coexist. They are associated with endometrial cancer in 20%.

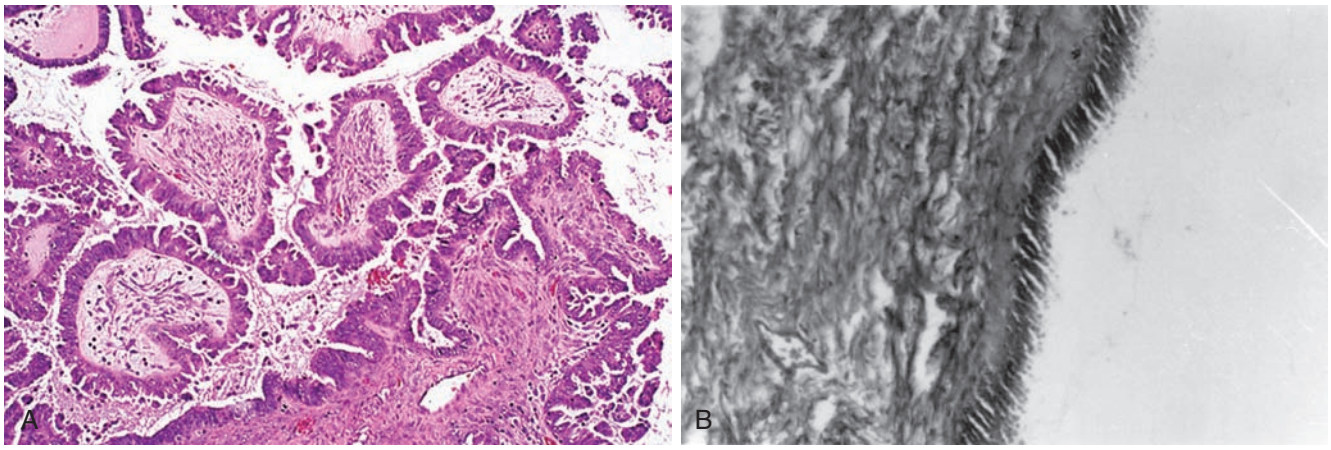

Figure 33.1 **(A)** A papillary form of serous cystadenoma of the ovary. The epithelium, though hyperplastic, is undoubtedly benign (×60). **(B)** High-power serous cystadenoma. (Source: Rao, K.A: *Textbook of Gynaecology*, India: Elsevier, 2008.)

Figure 33.2 Mucinous tumour. (From: Sengupta, Chattopadhyay and Varma: *Gynaecology for Postgraduates and Practitioners,* 2nd Ed. India: Elsevier, 2007.)

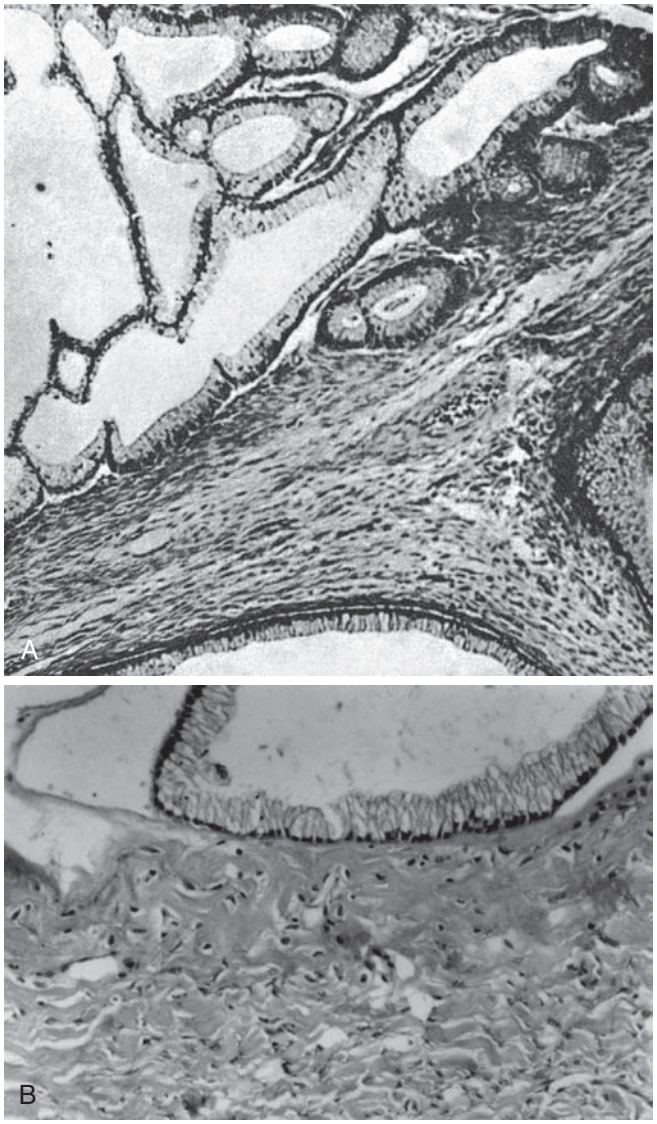

Figure 33.3 **(A)** Mucinous cystadenoma. **(B)** Mucinous cystadenoma. High power shows cells resembling endocervix.

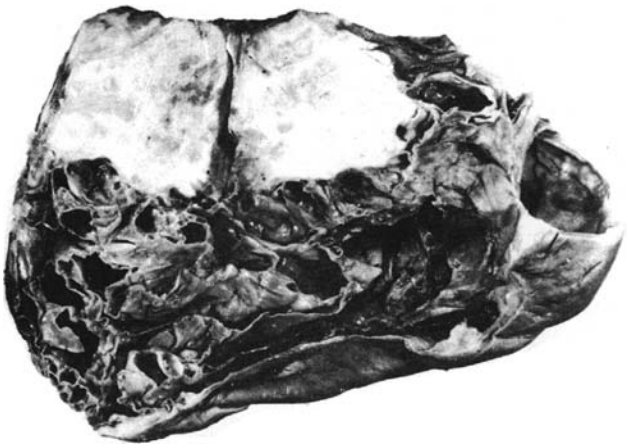

Figure 33.4 A combined Brenner tumour (solid area) and multilocular mucinous cystadenoma.

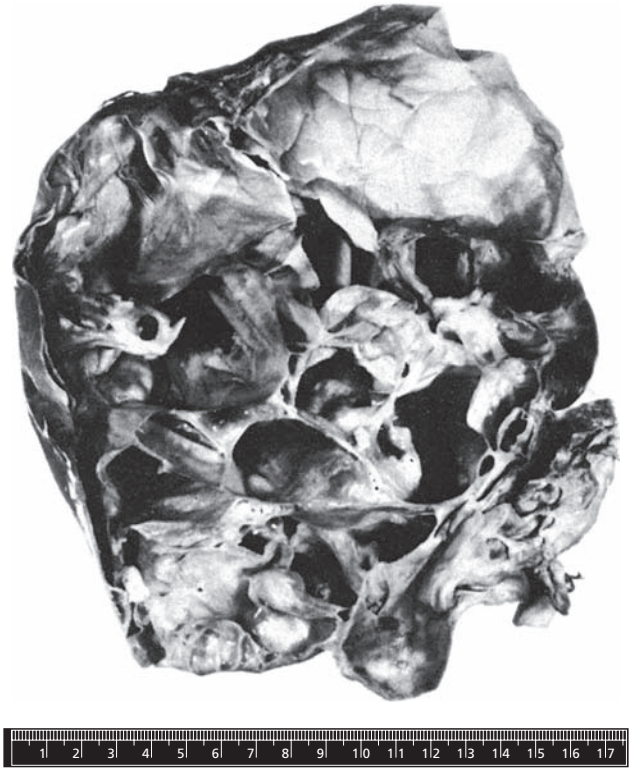

Figure 33.5 A mucinous cystadenoma with many loculi, several of which intercommunicate.

Mesonephroid Tumour

Mesonephroid tumour, also called clear cell carcinoma, is an uncommon tumour of the ovary. It is composed of large cuboidal epithelial cells with abundant clear cytoplasm characteristically forming tubules, glands, small cystic spaces lined by clear cells showing large dark nuclei protruding into the lumen (hobnail cells). The tumour is highly malignant.

Brenner Tumour

Brenner tumour is an uncommon solid fibro-epithelial tumour accounting for about 1–2% of all ovarian neoplasms.

On gross appearance, it resembles a fibroma of the ovary (Figure 33.4), its cut surface appears gritty and yellowish grey. It is generally unilateral, small to moderate in size, essentially benign and has no endocrine function.

The tumour is generally seen in women around menopause, and causes post-menopausal bleeding. Occasionally, it may be associated with ascites and hydrothorax (pseudo-Meigs syndrome). In rare cases, it becomes malignant.

Histologically, the tumour shows a background of fibrous tissue—interspersed within it are nests of transitional epithelium (Walthard cell rests). These cells demonstrate a longitudinal groove resembling puffed wheat. As mentioned earlier, this tumour may be combined with a mucinous adenoma of the ovary.

Spread of Epithelial Tumours of the Ovary

Sometimes, these tumours become malignant and extend through the capsule and may be seeded on to the peritoneal surface, omentum, intestinal viscera and by transcoelomic spread reach the sub-diaphragmatic space. The ascitic fluid is often blood-stained and shows presence of clusters of tumour cells. The tumour cells may spread to the para-aortic lymph nodes, and metastasize to the liver, lungs, gastrointestinal tract and other areas. In over half the cases, the opposite ovary is also involved.

Germ Cell Tumours

Incidence

Germ cell tumours account for 15–20% of all ovarian tumours. The majority of tumours (about 95%) are benign cystic teratomas, also called dermoids. Below the age of 20 years, 60% of the tumours are of the germ cell origin, and in girls under the age of 10 years, almost 85% belong to this group and are invariably malignant.

Teratoma

All germ cell tumours show differentiation along embryonic rather than extra-embryonic pathways. These are grouped together as teratomas, and divided into three categories: (i) mature (benign), e.g. dermoid cyst, (ii) immature (essentially malignant), e.g. solid teratoma and (iii) monodermal or highly specialized, e.g. struma ovarii.

Dermoid Cysts

Of all cystic tumours of the ovary, 5–10% are dermoids. A dermoid cyst is usually unilocular with smooth surface, seldom attaining more than 15 cm in diameter. It contains sebaceous material and hair, and the wall is lined in part by squamous epithelium which contains hair follicles and sebaceous glands. Teeth, bone, cartilage, thyroid tissue and bronchial mucous membrane are often found in the wall (Figure 33.6). Sometimes, the sebaceous material collects together in the form of small balls, and as many as 1000 sebaceous balls have been recovered in a dermoid cyst. The inner surface is called a 'focus' or 'embryonic node' from which the hair project and in which the teeth and bone are usually found. The nomenclature 'dermoid cyst' is inaccurate, for in addition to ectodermal tissues, tissues from both the mesoderm and endoderm are also seen in some part of the tumour. Moreover, though squamous epithelium usually lines the cyst, columnar and transitional types are also found. It is extremely rare for pancreas, liver tissue and intestinal mucous membrane to be present in the wall of a dermoid cyst (Figures 33.7 and 33.8).

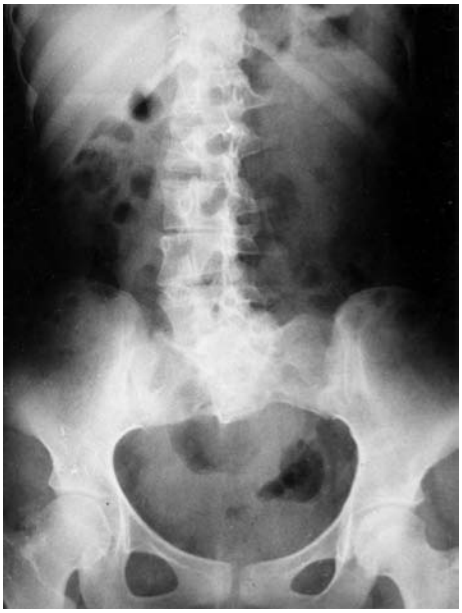

Figure 33.6 Dermoid cyst showing a tooth.

Dermoid cysts frequently arise in association with mucinous cystadenomas to form a combined tumour, part of which consists of a dermoid cyst while the rest has the characteristic structure of a mucinous cystadenoma. Perhaps as many as 40% of dermoid cysts are combined tumours of this kind. This association suggests the common origin of the two forms.

Multiple dermoid cysts in the same ovary are well recognized and it is not uncommon to find 2–3 separate dermoids. Extraovarian dermoid cysts arise occasionally in the lumbar region, uterovesical area, parasacral region and rectovaginal septum. Combined tumours tend to arise in patients between the ages of 20 and 30 years, while simple dermoid cysts have a maximum age incidence between 40 and 50 years. Tumours may, however, arise at any age. Dermoids are bilateral in 12–15%.

Dermoid cysts are innocent ovarian tumours but epidermoid carcinoma occurs in 1.7% and sarcomatous changes have been described. Usually, a squamous cell carcinoma develops from the ectodermal tissues but mammary carcinomas and malignant thyroid tumours have also been described (Figure 33.9).

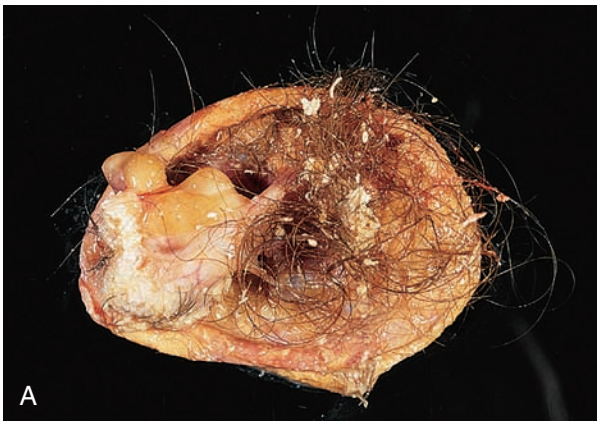

Figure 33.7 (A) Gross appearance of a cut-open dermoid cyst. Note the presence of hair-bearing skin. (Source: Hacker NF, Gambone JC, Hobel CJ, *Hacker and Moore's Essentials of Obstetrics and Gynecology, 5th ed.* Philadelphia: Elsevier, 2010.)

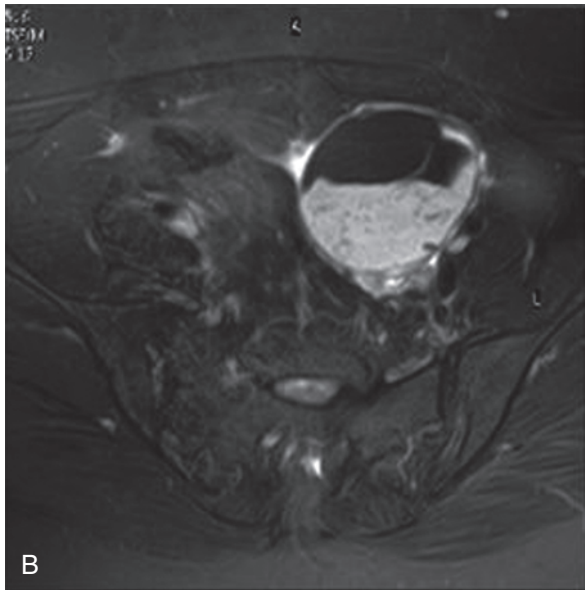

Figure 33.7 (B) MRI showing a dermoid cyst. (Courtesy: Dr Parveen Gulati, New Delhi.)

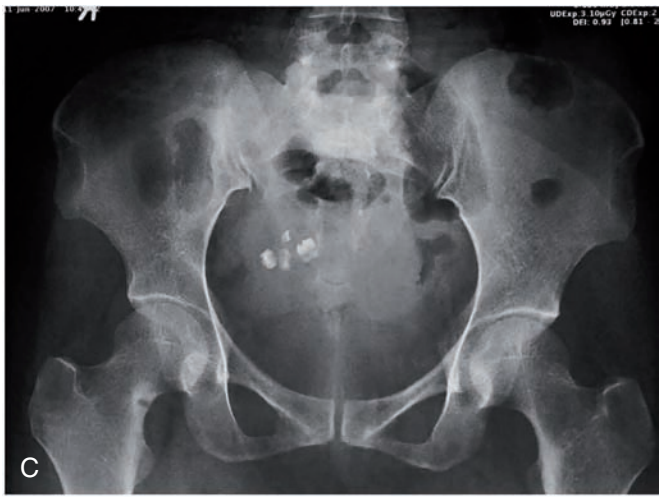

Figure 33.7 (C) Tooth like calcifications seen in the right hemipelvis suggestive of dermoids. (Courtesy: Dr KK Saxena, New Delhi.)

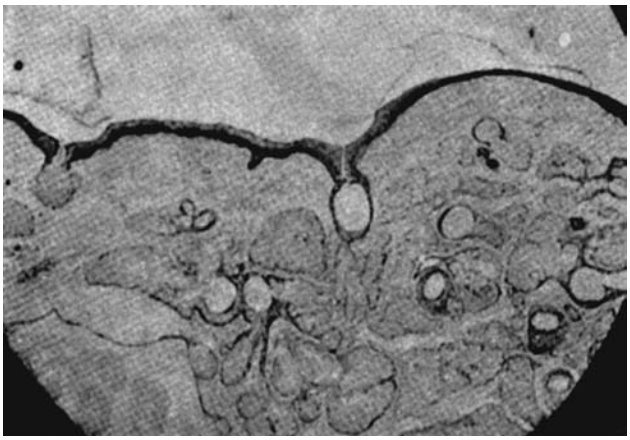

Figure 33.8 Dermoid cyst of the ovary. The cyst is lined by squamous epithelium. Sebaceous glands open into the cavity of the cyst. Hair follicles are also present.

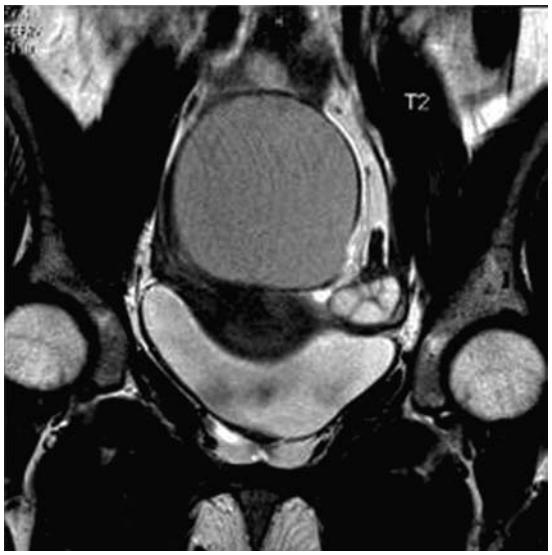

Figure 33.9 MRI showing right ovarian cyst. (Courtesy: Dr Parveen Gulati, New Delhi.)

Solid Teratoma of the Ovary

These tumours are very rare. They are mostly solid and the cut surface has a peculiar trabeculated appearance. Invariably large loculi are found beneath the capsule. The solid part of the tumour contains cartilage and bone, while hair and sebaceous material are found in the cystic spaces. The solid area also contains plain muscle, brain tissue, glia, pia mater and intestinal mucous membrane. The attempted formation of a rudimentary eye has been described and even the recognizable pattern of a fetus has been simulated, the so-called embryoma. As a rule, however, the formation is a conglomerate, without order or arrangement. Most solid teratomas of the ovary are malignant tumours because of sarcomatous change, but about 20% are innocent (Figure 33.10).

Struma Ovarii

Struma ovarii (Figure 33.11) consists of thyroid tissue similar to that of a thyroid adenoma. The tumour is solid,

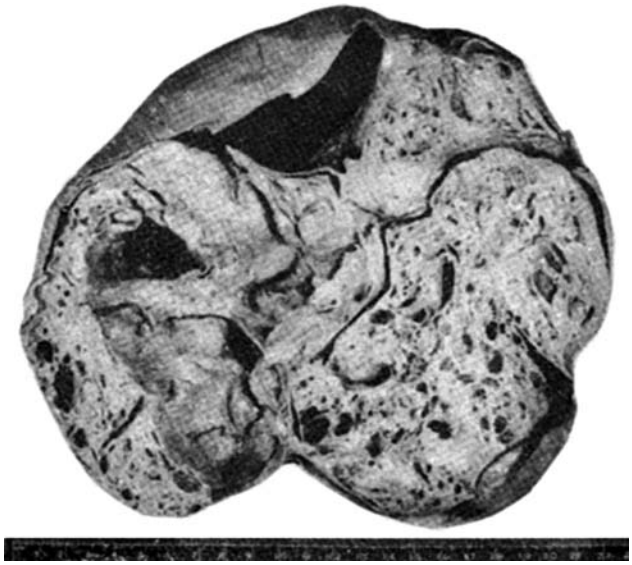

Figure 33.10 A solid teratoma of the ovary.

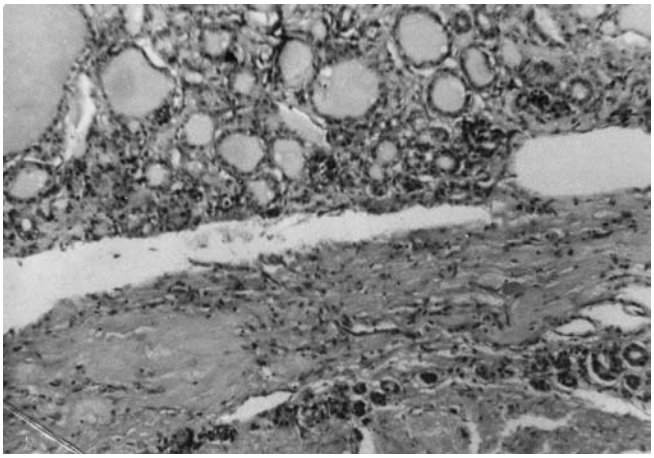

Figure 33.11 Struma ovarii showing space filled with colloid.

consisting almost entirely of thyroid tissue and should be clearly distinguished from a dermoid cyst with thyroid tissue in its wall. To the naked eye, the tumour resembles a small mucinous cystadenoma, but the material contained in the vesicles is colloid and gives reaction to iodine. Some cases develop thyrotoxicosis. Most of the tumours are innocent, but malignant thyroid tumours have been recorded. The histogenesis is supposedly a dermoid in which the thyroid tissue dominates at the expense of the other elements.

Carcinoid Tumours

An interesting tumour of the ovary, sometimes primary and sometimes metastatic, is the argentaffinoma. It occurs as a malignant change in a benign dermoid cyst and presents as a solid yellow tumour with the histological property of reducing silver salts derived from the specialized Kulchitsky cells of the intestine. It produces 5-hydroxytryptamine which causes attacks of flushing and cyanosis.

Dysgerminoma

Dysgerminoma corresponds to the seminoma of the testis and accounts for 3–5% of all ovarian tumours. It usually arises in young women or in children, with an average incidence at the age of 20. The tumour is solid with a peculiar elastic rubbery consistency and a smooth, firm capsule. The cut surface is yellow or grey with areas of degeneration and haemorrhage. The size is variable, usually moderate, though large tumours have been described. It is usually unilateral, bilateral in 10%, occasionally undergoes torsion and may, like all solid tumours, be associated with ascites. The tumour consists of large cells arranged in bunches or alveoli. Lymphocytes and giant cells are always found amongst the tumour cells. This appearance of large dark-staining nuclei with clear, almost translucent, cytoplasm and lymphocytic infiltration of the fibrous septa is diagnostic (Figure 33.12). The tumour is neutral and does not secrete either male or female sex hormones but placental alkaline phosphatase (PLAP), lactate dehydrogenase (LDH) and β-hCG. A number of patients with a dysgerminoma of the ovary have been reported to show genital abnormality, with hypoplasia or absence of some part of the genital tract. It has been reported in pseudohermaphrodites. Such congenital abnormalities are not caused by the dysgerminoma and its removal has no beneficial effect upon them. The malignancy rate is 30–50% and depends largely on the findings at laparotomy:

- A unilateral tumour confined to one ovary is relatively benign.
- The presence of active invasion of the pelvic viscera is of poor prognosis.
- The presence of extra pelvic metastases in the general peritoneal cavity, lymph glands, omentum or liver renders the outlook hopeless.

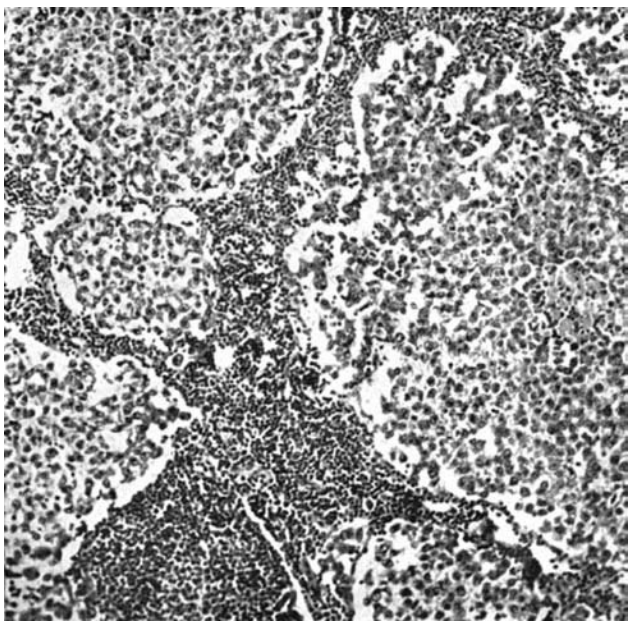

Figure 33.12 Ovarian dysgerminoma. Note the lymphocytic infiltration amongst the masses of large tumour cells (×120).

Conservative surgery is recommended in young girls. Though highly radiosensitive, ovarian destruction contraindicates the use of radiotherapy in young girls. Postoperative chemotherapy yields 90% success. Chemotherapy comprises:

- Injection bleomycin 15 mg IV or IM weekly for 12 weeks.
- Injection etoposide 100 mg/m^2 1–5 days every 3 weeks.
- Injection cisplatin 20 mg/m^2 1–5 days every 3 weeks.

Alternate chemotherapy are as follows:

- VAC (vincristine, adriamycin and cyclophosphamides) for 12 cycles cure 86% in Stage I disease.
- VBP (vincristine, bleomycin and cisplatin) is also effective.
- Carboplatin and ifosfamide combination is better and less toxic than cisplatin.
- Radiotherapy is employed only for residual and recurrent tumour.

Mixed Germ Cell Tumour

Mixed germ cell tumours contain two or more recognizable germ cell entities, e.g. combination of dysgerminoma, gonadoblastoma, teratoma, endodermal sinus tumours and choriocarcinoma. Gonadoblastoma contains calcified elements, and Y chromosome is detected in 90% tumours. Fifty per cent turn malignant.

Sex Cord Stromal Tumours

Sex cord stromal tumours originate either from the sex cords of the embryonic gonad (before the differentiation of the gonadal mesenchyme into male or female) or from the stroma of the ovary. Since theca cells are the source of ovarian steroids, many of these are functional and exert feminizing effects. The embryonic sex cords may differentiate along the male line, giving rise to Sertoli or Leydig cell tumours called androblastomas. The sex cord tumours are also referred to as *mesenchymomas*.

Feminizing Functioning Mesenchymoma

Granulosa Cell Tumour

Granulosa cell tumours are interesting growths of the ovary composed of cells closely resembling the granulosa cells of the Graafian follicle.

Clinical Features

Granulosa cell tumours are fairly common and represent 10% of all solid ovarian tumours. They can occur at any age. The tumour is observed in 80% of women over 40 years and in 5% of prepubertal girls. The main clinical features depend upon the oestrogenic activity of the tumour and only the larger ones cause pain and abdominal swelling. Feminizing tumours secrete oestrogen.

- When occurring before puberty, a precocious puberty (see Figure 4.5) results with development of secondary sexual characteristics, hypertrophy of breasts and external genitalia, pubic hair and myohyperplasia of the uterus. The endometrium shows an oestrogenic, anovulatory pattern. Removal of the tumour causes regression of all these manifestations.
- When occurring in adult life, the oestrogenic effect is less marked than in the prepubertal stage. There is no change in the secondary sexual characteristics since these are already established. The effect on the endometrium is that of hyperoestrogenism in general, i.e. an exaggerated proliferative pattern with cystic glandular hyperplasia (Figure 33.13). Superthreshold level of blood oestrogen may lead to amenorrhoea, followed by prolonged bleeding. In fact, the behaviour of the endometrium closely resembles that of metropathia haemorrhagica.
- In the post-menopausal patient, the most remarkable feature is post-menopausal bleeding (Figure 33.13). The secondary sexual characteristics are less affected though hypertrophy of the breast is sometimes seen. The uterus shows myohyperplasia and cystic glandular hyperplasia exactly as in metropathia. Removal of the tumour causes regression of all these symptoms.

Macroscopic Features

The tumour varies in size from tiny to gross, the average being 10 cm in diameter. The shape is oval and the consistency soft. The cut surface is reticular or trabeculated with areas of interstitial haemorrhage, and shows yellow areas. The outer surface is smooth and lobulated.

The cells are arranged either in cords or in trabeculae, and are often surrounded by structureless hyaline tissue, which resembles the glass membrane of an atretic follicle. Moreover, small Call–Exner bodies can usually be found in some part of the tumour. These small cyst-like spaces are

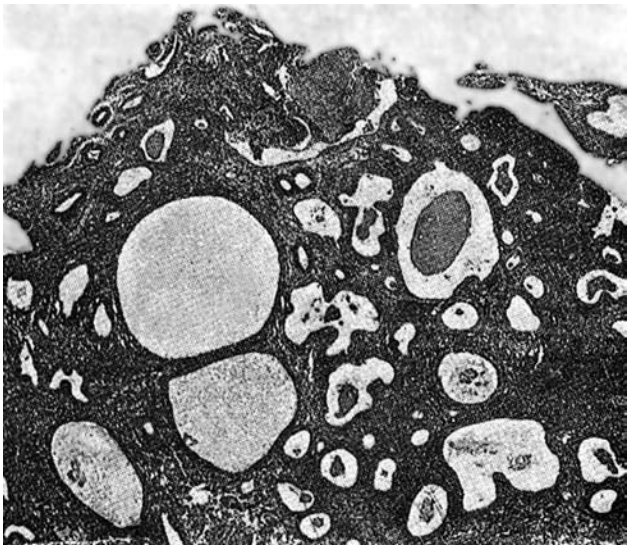

Figure 33.13 Cystic glandular hyperplasia of endometrium resulting from a granulosa cell tumour. The patient, aged 79, has post-menopausal bleeding (×33).

characteristic features of the granulosa cells of the Graafian follicle. Three histological types of granulosa cell tumours have been identified: (i) an early undifferentiated form which consists of a solid mass of granulosa cell, (ii) a trabecular form and (iii) a folliculoid type in which the granulosa cells are grouped around spaces filled with secretion (Figure 33.14). Most granulosa cell tumours are encapsulated and appear to be clinically benign. This appearance of the gross specimen and the histological picture may both be misleading as judged by the subsequent recurrence of the tumour. Recurrence may be delayed for many years. Kottmeier reported that malignant recurrence occurs in 50% of granulosa cell tumours and the term granulosa cell carcinoma is justified.

There is a certain correlation between the histological appearance and malignancy. A well-differentiated folliculoid appearance has 10% malignant potential while an anaplastic, almost sarcomatous appearance has 65% malignant potential.

The metastases are interesting, because the opposite ovary first becomes involved, then metastases develop in the lumbar region; secondary deposits become scattered in the mesentery, the liver and mediastinum.

Association of Carcinoma of the Endometrium with Granulosa Cell Tumours

There is a strong evidence that carcinoma of the endometrium may be associated with feminizing tumours of the ovary in postmenopausal women. It has been estimated that in one-fifth of oestrogenic ovarian tumours, an endometrial cancer will develop. A theca cell tumour is four times more commonly associated with endometrial cancer than the granulosa cell tumour, because of its high oestrogen secretion.

Theca Cell Tumour

This tumour is seen rarely and usually arises after menopause. It is nearly always unilateral and forms a solid mass. The cut surface is yellow in colour and, if stained selectively, lipoid material is characteristically present. The tumour consists of spindle-shaped cells reminiscent of an ovarian fibroma together with fat-laden polyhedral cells which resemble the theca lutein cells of the Graafian follicle. The tumour is intensely oestrogenic and causes postmenopausal haemorrhage. It is usually innocent, but malignant forms have been described. It has been shown that both granulosa cell tumours and theca cell tumours may show luteinization of their cells, with the result that progesterone is secreted and secretory hypertrophy can be demonstrated in the endometrium.

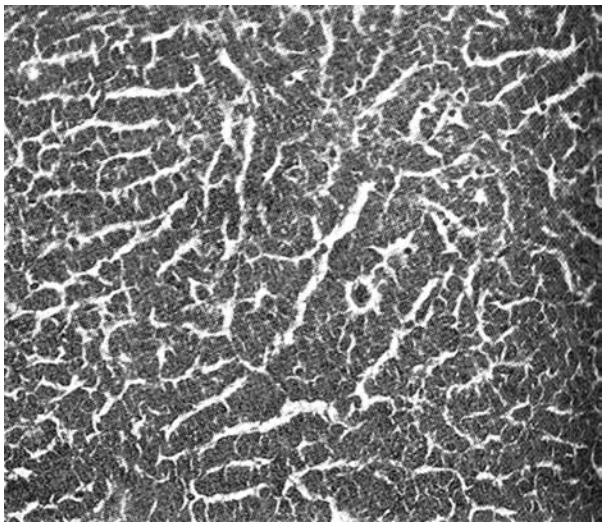

Figure 33.14 Granulosa cell tumour, folliculoid pattern. Note the arrangement of the cells into 'rosettes' (Call–Exner bodies) (×170).

Virilizing Mesenchymoma

Virilizing mesenchymoma and other virilizing tumours of the ovary are grouped together here for convenience.

Arrhenoblastoma

Arrhenoblastoma are rare tumours that secrete androgens which cause defeminization followed by masculinization. Women in the childbearing age may complain of altered body contours, flattening of the breasts, scanty and irregular menstruation ending ultimately in amenorrhoea. Later signs of masculinization like increased hair growth on the face (hirsutism) appear. Coarsening of the features, enlargement of the clitoris (Figure 33.15) and even breaking of the voice may occur. Removal of the tumour reverses the above features except the voice change.

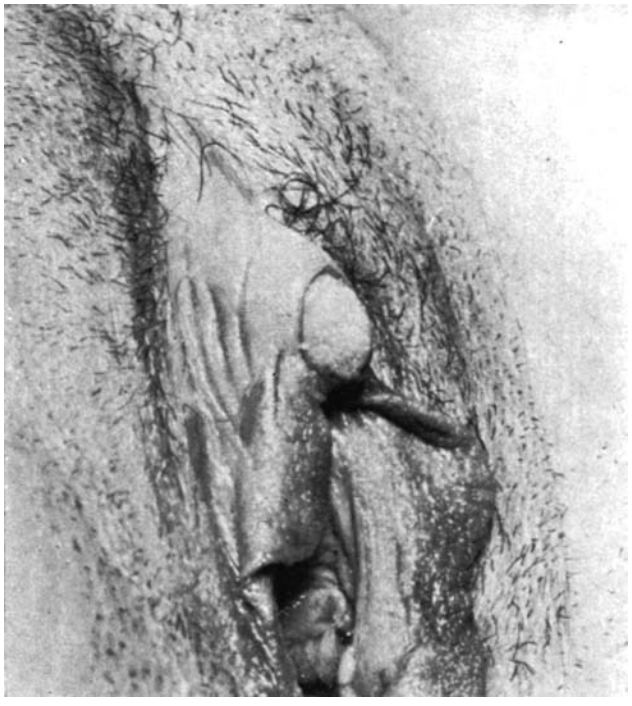

Figure 33.15 Hypertrophy of the clitoris in a patient with arrhenoblastoma.

The gross appearance of the tumour is like that of other mesenchymomas. Generally, only one ovary is affected. Its association with pregnancy has been reported. The incidence of malignant transformation is rated to be higher than with feminizing tumours.

Histologically, the tumour reveals all grades of differentiation from the testicular adenoma showing perfectly formed seminiferous tubules (Figure 33.16) to a sarcomatous anaplastic variety, wherein lipoid-containing cells are seen. The diagnosis is usually made on the basis of the endocrine behaviour of the tumour.

Adrenal Cortical Tumours of the Ovary

Adrenal cortical tumours of the ovary have some resemblance to the adrenal cortex when examined microscopically and have been called hypernephroma, masculinovoblastoma, virilizing luteoma or clear-celled tumour. These various appellations show that the constituent cells resemble the large clear cells of the adrenal cortex or lutein cells of the corpus luteum. Whatever their true origin, they are very rare tumours which are sometimes masculinizing.

Hilus Cell Tumour

A rare virilizing tumour arising from cells in the ovarian hilum has been described in women past menopause. One interesting feature of the hilus cell tumour is the presence of Reinke crystals in the cells, a distinguishing feature of the Leydig or interstitial cells of the testis.

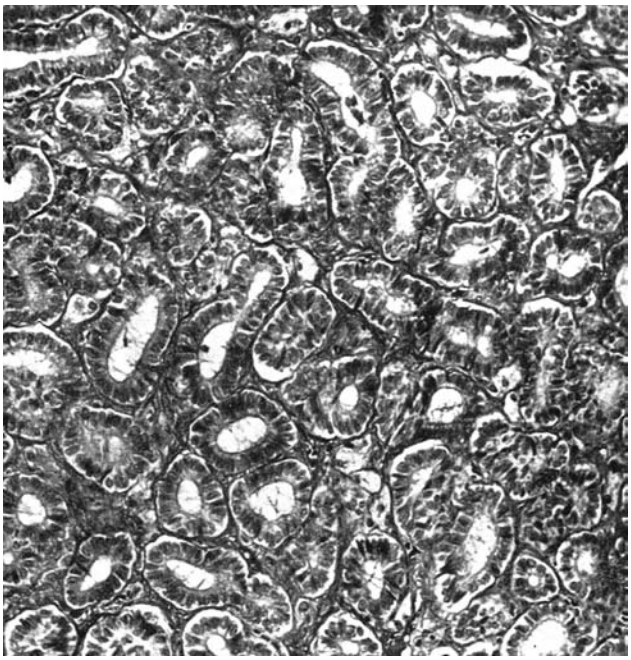

Figure 33.16 High-power magnification of arrhenoblastoma. Note the well-differentiated tubular structure simulating the seminiferous tubules of the testis (×170).

Gynandroblastoma

A gynandroblastoma combines the characteristics of the granulosa cell tumour and an arrhenoblastoma.

Tumours Arising from Connective Tissues of the Ovary

Of the innocent connective tissue tumours of the ovary, fibromas are the most common.

Ovarian Fibroma

Ovarian fibroma comprises about 3% of ovarian neoplasms and has no particular age incidence. The tumour is oval in shape with a smooth surface and large veins always noticeable in the capsule. The consistency is firm and harder than that of a uterine myoma. The tumour frequently undergoes degeneration so that cystic spaces are found towards the centre. Calcareous degeneration is not uncommon. The tumours are usually about 15 cm in diameter but sometimes become much larger than this and may weigh as much as 25 kg. Torsion may occur with the larger tumours.

Microscopic examination shows the tumour to be composed of a network of spindle-shaped cells which closely resemble the spindle cells of the ovarian cortex. The cellular pattern is strikingly uniform and there is no attempt at nuclear activity. The association of Brenner tumours with ovarian fibroma is known. In large tumours, the connective tissue cells are elongated and an intercellular matrix becomes prominent. The tumours are often accompanied by ascites. Sometimes, the patient has hydrothorax. The combination of an ovarian fibroma with ascites and hydrothorax, usually right-sided, is known as Meigs syndrome. It is now accepted that the diaphragm is porous either by reason of minute foramina or via the lymphatics. Meigs syndrome can occur with other solid ovarian tumours such as granulosa cell tumour and Brenner tumour.

Three type of fibromas are recognized. In the first, the tumour takes the form of a surface papilloma on the ovary. In the second type, there is a small encapsulated fibroma arising in an ovary so that normal ovarian tissue can be recognized at one pole of the tumour. In the third type, the fibroma replaces the ovary completely.

Histogenesis of Ovarian Tumours

Fibromas

Small ovarian fibromas form white rounded excrescences in the cortex of the ovary. The tumour arises from the stroma cells of the ovarian cortex. Histologically, a fibroma and a Brenner tumour have a close resemblance, apart from the inclusion of the epithelioid Walthard rests in the latter. With subsequent growth, a capsule becomes differentiated and the tumour grows at the expense of the normal ovarian

tissue, so that finally the ovary is completely replaced by the fibroma. The structure of a large ovarian fibroma is not unlike that of the stroma of the ovarian cortex, except that the constituent cells are more primitive in type.

Papillary Serous Cystadenoma

Papillary serous cystadenomas almost certainly originate from down growths of the surface epithelium of the ovary into the cortex. Small down growths of this sort are extremely common, even in normal ovaries, and small cysts, only recognized by microscopic examination, are fairly frequent. Papillary forms result from intracystic growths into these tumours. Papillary serous carcinomas of the ovary arise when the intracystic growths become malignant.

The origin of the tumours from down growths of the surface epithelium of the ovary is generally accepted and the tumours are regarded as examples of ovarian Müllerianosis, with epithelial cells resembling endosalpinx.

Granulosa Cell Tumours

Granulosa cell tumours consist of cells identical with the granulosa cells of Graafian follicles and theca cell tumours similar to the theca interna cell. As both types of tumours may arise after menopause, when there are no Graafian follicles in the ovaries, the tumours cannot be regarded as being derived from mature cells of this type. They are therefore regarded as originating in mesenchymal cells which are differentiated sexually. The arrhenoblastoma is regarded as being derived from mesenchymal cells of the male type. The theca cell is regarded as the master hormone producer in the ovary.

Teratoid Tumours

Teratomas probably arise from totipotent cells, i.e. cells which are capable of producing ectodermal, mesodermal and endodermal structure.

Mucinous Cystadenomas

The cells of the tumour resemble those of the cervix and the large intestine. The two present-day theories are: (i) the tumour represents an example of ovarian Müllerianosis, with metaplasia of the ovarian surface epithelium into cervical epithelium and (ii) the tumour arises from large intestine elements of a dermoid cyst.

Brenner Tumour

Brenner tumours are often associated with a mucinous cystadenoma, where there is probably some relation between their origins. The similarity to Walthard inclusions has already been noted and this suggests that Brenner tumours, like Walthard inclusions, are derived from the germinal epithelial layer of the ovary.

Complications of Ovarian Tumours (Table 33.3)

TABLE 33.3 Complications of an ovarian tumour

- Torsion
- Rupture
- Haemorrhage
- Infection
- Pseudomyxoma peritoneum
- Malignancy

Axial Rotation: Torsion

Torsion of an ovarian cyst is a very common complication, and occurs in about 12% cases. Chocolate cysts and malignant ovarian tumours are usually fixed by adhesions, so it is very rare for these ovarian tumours to undergo torsion. On the other hand, paraovarian cysts and broad ligament cysts are the most likely pelvic tumours to undergo torsion, probably because they develop in the outer part of the broad ligament and come to lie above the infundibulopelvic fold and above the pelvic brim so that they have a greater degree of mobility than other ovarian tumours. In most cases, the cyst is about 10 cm or over in diameter when it undergoes torsion. Because of the high incidence of mucinous cystadenomas, dermoid cyst torsion is most frequently seen with these tumours. There is no particular age incidence. The right and left sides are involved with equal frequency. Usually, the tumour rotates so that its anterior surface turns towards the patient's right side. It is not uncommon for the tumour to be rotated through three or more complete circles. As a result of rotation, the veins in the pedicle become occluded, the tumour becomes congested, and there is interstitial haemorrhage in the wall of the tumour and into the loculi. The increased tension causes severe abdominal pain and the signs of peritoneal irritation. Subsequently, adhesions form with surrounding structures, so that the omentum and intestines become attached to the tumour. On occasions, the cyst may become infected.

The most probable explanation of rotation of an ovarian cyst is haemodynamic. It is suggested that some violent movement, a history of which is almost invariably obtained, initiates the twist and as a result the ovarian artery itself becomes twisted. The pulsation in the vessel will then cause a series of tiny impulses to be transmitted to the pedicle, each of which will aggravate the twist. After a time, the degree of torsion will be such that the veins in the pedicle become occluded and the patient complains of severe abdominal pain (Figure 33.17).

Clinical Features of Torsion of Ovary

The woman often presents with acute abdominal pain, fever and vomiting. Sometimes, she complains of intermittent abdominal pain referred along the obturator nerve to along the medial aspect of the thigh.

Ultrasound shows a swollen oedematous ovary, globular in shape, and free fluid in the peritoneal cavity.

The pelvic findings reveal a tender mass separate from the uterus.

This is an emergency requiring urgent laparotomy. *The appearance of torsion of the ovarian tumour does not correlate*

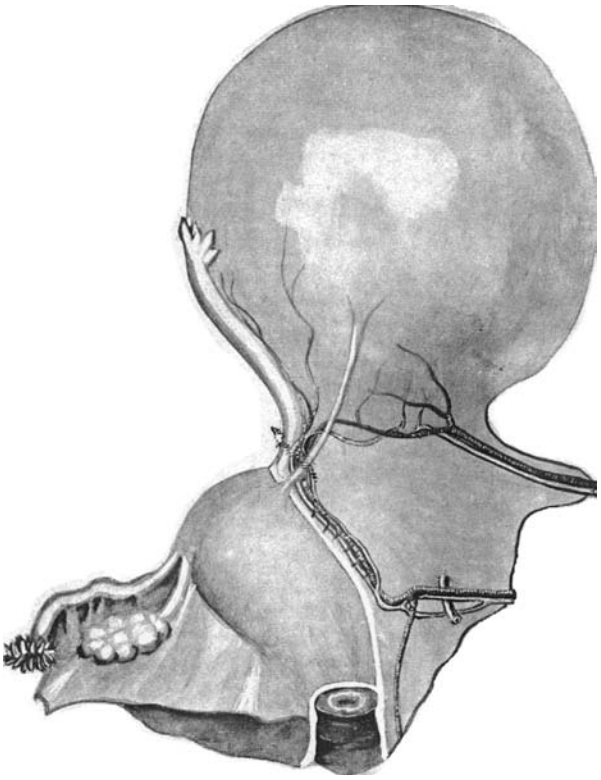

Figure 33.17 The pedicle of an ovarian cyst showing the relations of the ovarian vessels, the ovarian ligament and the fallopian tube, together with the anastomosing branch of the uterine artery.

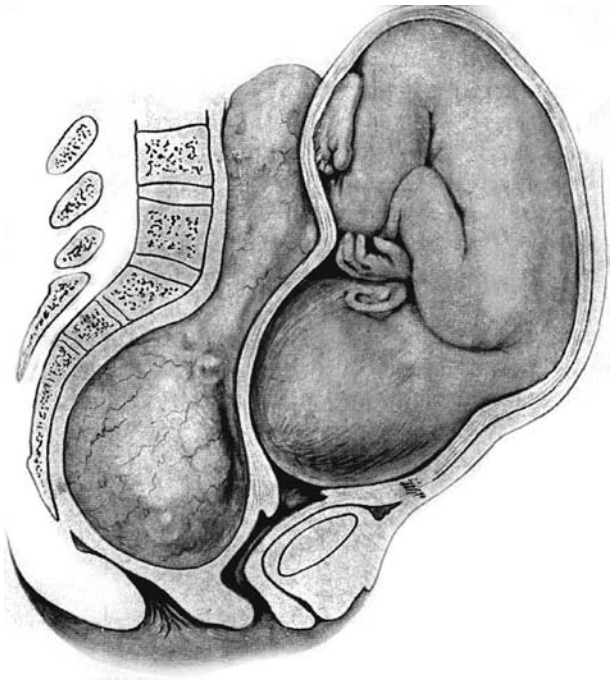

Figure 33.18 Ovarian cyst obstructing labour. (From: *Eden and Holland's Manual of Obstetrics*.)

with the ovarian viability, even when the tumour appears blackish. Therefore, one is advised to try and conserve the ovary if possible, unless gangrene has set in. De-torsion of the ovary and ovariopexy, after removal of the tumour should be attempted.

The ovary should be observed for colour change from bluish black appearance to its normal appearance. The theoretical risk of embolism with de-torsion does not normally occur. The ovary recovers and becomes functional. This is especially important in a young woman.

Rupture

Rupture of an ovarian cyst may be traumatic or spontaneous. Traumatic rupture results from direct violence to the abdomen. It may happen during labour when a cyst is impacted in the pouch of Douglas in advance of the presenting part (Figure 33.18). It is not uncommon for a small thin-walled retention cyst to rupture during bimanual examination.

Spontaneous rupture of an ovarian cyst is not uncommon. With malignant ovarian tumours, particularly those of the papillomatous type, the carcinoma cells infiltrate through the connective tissue capsule to ulcerate into the peritoneal cavity. With innocent papillomatous serous cystadenomas, a similar process takes place. The most interesting cases of spontaneous rupture are those arising with actively growing mucinous cystadenomas. The epithelial elements of the growth grow so rapidly that the connective tissue of the capsule are unable to keep up with them, and spontaneous rupture of the tumour is the result. The mucinous material is discharged into the peritoneal cavity. In most cases with a small leak there is no serious after-effect, but in rare cases, the condition called pseudomyxoma of the peritoneum develops.

Haemorrhage

Haemorrhage follows torsion and rupture. The woman develops abdominal pain and may vomit. Depending upon the quantity of bleeding, the general condition varies. Large haemorrhage can cause haemorrhagic shock. Ultrasound shows clots in the cyst and free blood in the pouch of Douglas. A small haemorrhage is treated conservatively. A large haemorrhage requires laparotomy, removal of the tumour and resuscitation.

Pseudomyxoma of the Peritoneum

In this condition, the peritoneal cavity is filled with coagulated mucinous material adherent to the omentum and intestines. The findings at laparotomy almost exactly resemble a boiled sago pudding. The material cannot be removed completely at operation because of its attachment to the bowel, and the condition tends to recur after operation. Pseudomyxoma of the peritoneum usually occurs with a mucinous cystadenoma of the ovary, but it has also been reported with a mucocele of the appendix and carcinoma of the large intestine in men. In pseudomyxoma of the peritoneum, the mesothelium of the peritoneum is converted, in part, into high columnar cells which are histologically similar to those lining a mucinous cystadenoma of the ovary, and these cells secrete mucinous material into the peritoneal cavity. The prognosis in pseudomyxoma of the peritoneum is bad, even after the ovaries and the appendix are removed. It is now believed that mucocele of

the appendix may induce secondary ovarian tumour. *Therefore, there is a tendency amongst gynaecologists to remove the appendix as well, when encountered with mucinous ovarian tumour, and avoid pseudomyxoma of the peritoneum*. Pseudomyxoma is treated with palliative chemotherapy.

Infection

Infection of an ovarian tumour is infrequent. Most cases follow acute salpingitis or when the cyst becomes infected during the puerperium as part of an ascending genital tract infection. Infection may also follow torsion when, as the result of adhesions to the intestine, the tumour becomes directly infected. Infection by the blood stream is very uncommon. Infected ovarian tumours are always adherent to adjacent viscera and occasionally discharge their contents into the rectum. Sebaceous material in a dermoid cyst also causes infection in the tumour; it may also cause peritonitis.

Extraperitoneal Development

Some ovarian tumours burrow extraperitoneally during their development and may spread upwards into the perinephric region. The removal of these tumours is extremely difficult and there is danger of injuring the ureter. During dissection and removal of such a cyst, large vessels may be torn in the retroperitoneal space and subsequent leakage of blood will form a retroperitoneal haematoma. Such a haematoma gives rise to considerable shock and requires drainage. Transfusion will also be necessary.

Secondary Malignancy

Secondary malignant changes occur in 50% serous cystadenomas, 5% in mucinous cystadenomas, but only in 1.7% of dermoid cysts.

Benign Ovarian Tumours

Symptoms

Although benign ovarian cysts frequently produce enormous tumours, they cause relatively few symptoms. Indeed, in innocent ovarian tumours, the patient's attention is first directed to the abdominal swelling. The average pseudomucinous cystadenoma removed at operation is about the size of a football, and it is not until the tumour has reached this size that it causes sufficient abdominal enlargement to make the patient realize that something is wrong (Figures 33.19 and 33.20; Table 33.4).

Menstrual Cycles

Ovarian tumours, even bilateral, do not generally affect the menstrual cycles. The only tumours causing menorrhagia are granulosa and theca cell tumours by virtue of their oestrogen hormone secretion. Similarly, masculinizing tumours cause amenorrhoea and virilization. Postmenopausal bleeding occurs in benign Brenner and feminizing tumours.

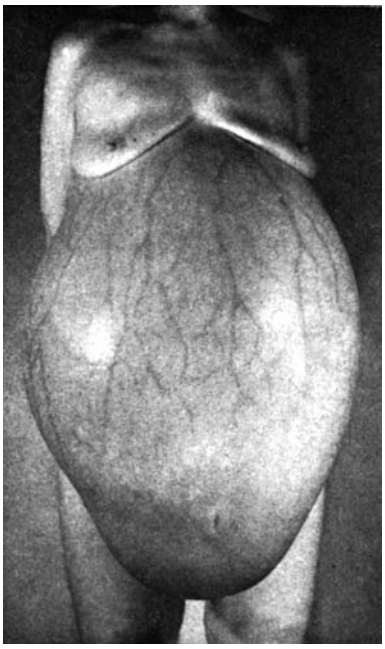

Figure 33.19 A very large benign mucinous ovarian cyst which weighed about 50 kg. Note the prominent veins, displacement of the umbilicus and oedema of the lower abdomen.

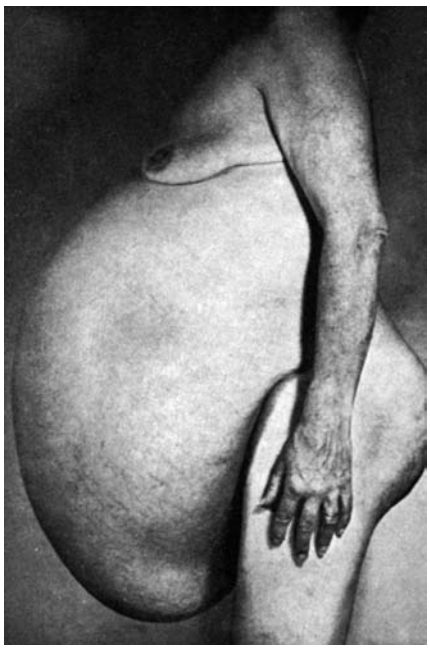

Figure 33.20 A lateral view of the same patient as in Figure 33.19. Note the lumbar lordosis.

Pressure Symptoms

The ovarian tumour placed in the uterovesical pouch anterior to the uterus and those impacted in the pouch of Douglas may cause increase in frequency of micturition and even retention. Pressure on the rectum is hardly ever noticed. Mammoth tumours such as mucinous tumours may cause dyspnoea and palpitation, and bilateral pitting oedema of the feet.

TABLE 33.4 Features of benign and malignant ovarian tumours

Benign Ovarian Tumours	Malignant Ovarian Tumour
History	
• Not related to age or parity, though most common during childbearing period • Slow-growing tumour, no pain. No menstrual disorder unless it is a feminizing tumour or masculizing tumour	• Seen most commonly in adolescents and elderly women—mostly after 50 years of age. Low parity or infertile woman • Rapidly growing tumour, pain in advanced stage. Post-menopausal bleeding • Family history of breast, ovarian or colonic cancer
Examination	
• Usually unilateral, cystic, well-defined and mobile. No ascites (except in Meigs syndrome.) No nodules in the abdomen or pouch of Douglas	• May be bilateral and solid, fixed. Ascites may be present. Metastatic nodules may be felt per abdomen. Nodules in the pouch of Douglas
Ultrasound	
• Cystic well-defined with or without echoes. No ascites (except in Meigs syndrome)	• Often solid and bilateral fixed with internal echoes, ascites may be present. Metastatic nodules may be seen
Doppler ultrasound	
• No increased vascularity	• Increased vascularity • Pulsatile index <1 • Resistance index <0.4
MRI and CT	
• Similar to ultrasound findings • CA-135 normal	• Metastatic and enlarged lymph nodes may be detected • CA-125 raised more than 35 IU/mL
Operative findings	
• Well-defined ovarian cystic or solid tumour. No ascites or metastatic nodule. Often mobile	• Fixed solid tumour, often bilateral—with blood-stained ascites. Metastatic growth over the omentum and peritoneal cavity. Lymph nodes may be enlarged

Pain

Normally, benign ovarian tumours cause no abdominal pain and are comfortably placed in the abdominal cavity which is distensible. The mammoth tumour may however cause abdominal discomfort and difficulty in walking. Acute abdominal pain develops if the ovarian tumour undergoes torsion, rupture or haemorrhage. An infected dermoid cyst is likely to develop pain and fever.

With torsion, the woman develops acute abdominal pain, vomiting and at times low-grade fever. The patient may be in shock, with thready pulse. The abdomen is distended, and moves poorly with respiration. The cyst is tense and tender. Immediate laparotomy is required to remove the tumour.

The germ cell tumours occurring in adolescent and young women grow rapidly and cause abdominal pain, which may be the first symptom noticed by these young girls.

Physical Signs

The typical ovarian cyst forms an abdominal swelling detected by inspection. The abdominal wall can be seen to move over the swelling when the patient takes a deep inspiration. The tumour is symmetrically situated in the abdomen. On palpation, the upper and lateral limits of the tumour can be defined, but it is impossible to identify the lower pole of the tumour except in case of a relatively small cyst with a long pedicle. The surface of the tumour is smooth, although it may be slightly bossed with multilocular cysts. Small cysts are usually movable from side to side, but large tumours filling the abdomen and tumours which have burrowed extraperitoneally are fixed. The consistency of the cystic tumour is tense and cystic and a fluid thrill can be elicited. Sometimes, a cyst is flaccid, when a well-marked fluid thrill is obtained. It is not uncommon for hard areas to be palpated, even in large ovarian cysts. These areas in mucinous cystadenomas are composed of small loculi which give the tumour an almost solid feeling on palpation. All patients with an ovarian cyst should be examined carefully for ascites, since the presence of ascites is a strong evidence that the tumour is malignant. Exception is the Meigs syndrome associated with fibroma, Brenner tumour and occasionally granulosa cell tumour. On auscultation, an ovarian tumour is silent and on percussion it is dull over the centre of the tumour but resonant in the flanks which are occupied by the displaced large and small bowel. This sign is reversed in ascites. The legs should be examined for oedema (Figure 33.21).

The physical signs on bimanual examination vary according to the size of the tumour. With small tumours, the uterus can be identified without difficulty, and the ovarian cyst outlined bimanually, so that the whole of the surface of the cyst can be palpated. The cyst usually displaces the uterus to the opposite side. With large cysts, it may be difficult to outline the uterus. Even with a large cyst, the lower pole of the tumour should be palpable through one of the fornices. The firm rounded lower pole of the tumour has a characteristic feel, and fluctuation can usually be detected

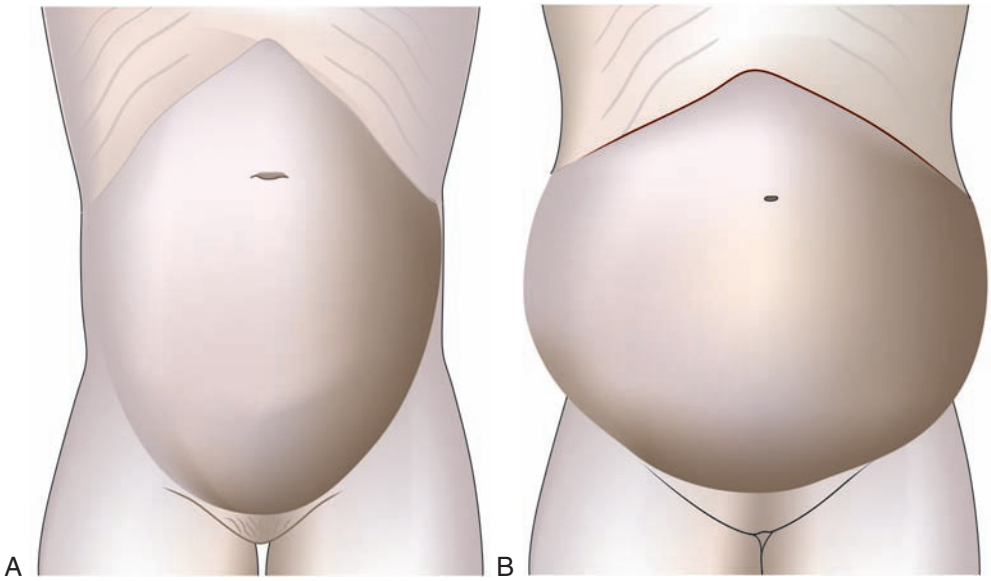

Figure 33.21 On the left is a case of ovarian cyst, while on the right is the abdomen of a case of ascites. In ascites, the abdomen spreads much more laterally than in the case of an ovarian cyst.

between the fingers placed in the vagina and the external hand. It is important to identify the position of the uterus if possible, as mistakes in diagnosis with innocent ovarian cysts are almost always due to failure to identify the body of the uterus separate from the tumour. An ovarian cyst may simulate very closely a cystic degenerated myoma and the diagnosis cannot be made with accuracy unless the position of the body of the uterus is established. The cardinal sign that distinguishes a mobile ovarian tumour from a uterine tumour is when the ovarian tumour is raised up by the abdomen and the cervix remains stationary to the vaginal fingers. In all cases, the pouch of Douglas should be examined carefully as the presence of hard nodules is a strong evidence that the tumour is malignant.

Differential Diagnosis

The abdominal physical signs of an ovarian cyst may be simulated by a full bladder, a pregnant uterus, a myoma, ascites and other abdominal tumours such as hydronephrosis, mesenteric cyst, retroperitoneal tumour and tuberculous peritonitis, especially if encysted by coils of adherent intestines.

Full Bladder

Full bladder is tense and tender, fixed in position, anterior to the uterus, projecting anteriorly more than an ovarian cyst, and a catheter should be passed to establish the diagnosis.

Pregnant Uterus

A pregnant uterus should be thought of whenever a tumour is found arising from the pelvis. The exclusion of pregnancy offers no difficulty if a careful bimanual examination is made and signs of pregnancy looked for. Appropriate investigations such as ultrasonic examination and a pregnancy test will confirm or refute the diagnosis. Mistakes are made because the possibility is not considered, especially in an unmarried girl who denies history of amenorrhoea.

Myoma

A myoma is usually hard or firm, without the tense cystic consistency of a typical ovarian cyst. Pedunculated and degenerated fibroid may however be mistaken for an ovarian tumour. Removal of the tumour is indicated in both these conditions.

Ascites

Sometimes great difficulty is felt in distinguishing between a large ovarian cyst and ascites. With a large ovarian cyst, the percussion note over the tumour is dull, whereas both flanks are resonant. In ascites, the note is dull over the flanks, while the abdomen is tympanitic in the midline. Moreover, the physical signs of shifting dullness may be obtained. Even with large ovarian cysts, the lateral borders of the tumour may be palpable and the tumour may have some degree of mobility (Figures 33.21 and 33.22). Ultrasound distinguishes these two conditions.

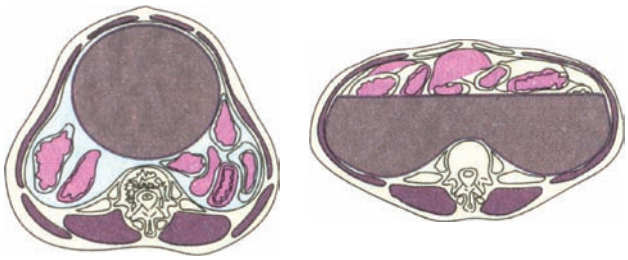

Figure 33.22 On the left, a cross-section of the abdomen is shown from a case of an ovarian cyst, while on the right is a cross-section from a case of ascites. With an ovarian cyst, the intestines are displaced dorsally while with ascites, the intestines lie immediately beneath the abdominal wall.

The most difficult cases are those of encysted tuberculous peritonitis with ascites. Often, a history of oligomenorrhoea or amenorrhoea can be elicited. The tympanic note over the tumour suggests intestinal adhesions over the cyst. The cyst is also fixed. In most cases of tuberculous peritonitis, the patient has lost weight, is pyrexial and there may be other signs of tuberculosis in the body. A diagnostic curettage may reveal tuberculous involvement of the endometrium.

In rare cases, obesity can be mistaken for an ovarian cyst. The surest method of excluding an ovarian cyst is to percuss the abdomen below the level of the umbilicus. If the note is tympanitic, an ovarian cyst can be excluded. An ultrasound scan may be necessary in a few cases.

Other Tumours

Other tumours may cause difficulty in diagnosis. For example, a large hydronephrosis may project forwards into the abdomen. Such a tumour always penetrates back into the loin and is situated high up in the abdomen, well above the pelvis. Investigations by intravenous or retrograde pyelography will establish the diagnosis. Other tumours such as enlarged spleen, mesenteric cyst, mucocele of the appendix or gall bladder, hydatid cysts and pancreatic cysts should be considered if the physical signs of an ovarian cyst are atypical, and if the tumour lies in mid or upper abdomen.

Small ovarian cysts which lie in the pelvis are palpated without much difficulty. They are movable, with a tense consistency and a smooth rounded surface. It may be difficult to establish the diagnosis with accuracy if the tumour is fixed when such conditions as ectopic gestation, hydrosalpinx and pyosalpinx have to be excluded.

Investigations

- **Ultrasound**. Transabdominal transducer is employed if the tumour is abdominal. Otherwise transvaginal ultrasound (TVS) gives more detailed features of the tumour.
- A benign cyst is characteristically unilateral, unilocular or multilocular with a thin wall and thin septa of less than 5 mm in a multilocular cyst. The cavity is nonechogenic. These findings along with normal CA-125 level below 35 U/mL indicate the benign nature of the epithelial tumour in 95% cases.
- A raised CA-125 level is also reported in abdominal tuberculosis and pelvic endometriosis. On the other hand, only 50% Stage I epithelial ovarian malignant tumours present raised levels.
- A solid tumour suggests malignancy except in a fibroma and Brenner tumour. Dermoid can be identified by solid areas in a cystic tumour and occasional presence of a tooth on ultrasound scanning.
- A menopausal ovary measures not more than 2 × 1.5 × 1 cm in size (volume 8 mL). A size more than this is suspicious of an ovarian growth.

A malignant ovarian tumour is suspected if ultrasound reveals bilateral (may be unilateral) or a solid tumour with ascites. The tumour wall is thick with echogenic areas within the tumour. The septum is more than 5 mm thick with papillary projections from its wall. Except in Meigs syndrome, the presence of ascites as shown on ultrasound strongly points to the malignant nature of the tumour.

Colour flow Doppler technology, which adds further information of neovascularization, indicates increased blood flow to the tumour and probability of the tumour being malignant. Low pulsatile index also suggests increased blood flow in a malignant tumour.

Additional information may be provided by:

- Radiograph of abdomen/pelvis which may demonstrate a soft tissue shadow, or teeth in a dermoid (molar tooth).
- Diagnostic laparoscopic examination may be needed in a few cases.
- Intravenous pyelography will exclude a hydronephrosis. Ultrasound can also diagnose it.
- In all suspected metastatic ovarian cancers, a barium meal should be performed to exclude gastrointestinal primary carcinoma.
- Radiograph of chest will rule out pulmonary metastasis and also hydrothorax in case of Meigs syndrome.
- Breast examination will rule out pregnancy as well as detect a metastatic growth.

CT and MRI are useful in identifying a dermoid cyst, haemorrhagic cyst, fibroma, endometriosis and hydrosalpinx (Figure 33.9).

In a malignant tumour, CT, MRI recognize the spread of the tumour, enlargement of pelvic and para-aortic lymph nodes more than 1 cm. This helps in planning surgery and postoperative radiotherapy or chemotherapy.

Tissue markers such as CA-125 and NB/70k are useful mainly in the follow-up of certain tumours. CA-125 is a glycoprotein and surface cell antigen which is secreted by the malignant epithelial tumours. A level more than 35 U/mL suggests malignant and residual tumour, and indicates the need for chemotherapy. CA-125 is also raised in abdominal tuberculosis and endometriosis. CEA (carcinoembryonic antigen) more than 5 mg/L is seen in mucinous ovarian tumour. It should be emphasized that CA-125 is raised in only 50% cases in Stage I and 90% in Stage II ovarian cancer.

Germ cell tumours produce hCG, alpha-fetoproteins, placental alkaline phosphatase (PLAP) and LDH, and when combined with ultrasound improve predictability of the type of tumour.

Cytological study of ascitic fluid or aspirated cyst fluid either laparoscopically or under ultrasound guidance may reveal malignancy, but false-negative reporting is also high. Fine-needle aspiration cytology (FNAC) of a solid tumour may give a clue to the nature of the tumour.

Treatment

A simple unilocular cyst less than 7 cm is often a functional cyst and should be observed. Most functional cysts resolve spontaneously over 4–6 months. A repeat ultrasound will

pick up a persistent cyst which requires removal. To expedite its resolution, oral combined pills may be prescribed for 3–4 months in woman of reproductive age as this may help in its resolution.

Simple aspiration of a cyst is not advisable, because of the high risk of recurrence. Besides, if the cyst proves malignant, the outcome will be disastrous.

Laparotomy or laparoscopy is required in other cases to obtain the specimen for histology and for definitive treatment of its removal. Even a benign ovarian tumour more than 7 cm requires removal; otherwise, it may grow in size, undergo complications or turn malignant.

Open laparotomy is preferred to laparoscopic excision, though lately some expert laparoscopists are carrying out surgery for an ovarian tumour laparoscopically.

Prophylactic Oophorectomy

Bilateral removal of ovaries at hysterectomy is also desirable in a high risk woman with a family history of ovarian cancer, colonic and breast cancer, previous hyperstimulation of ovaries in infertility, and in a woman carrying BRCA-1 and BRCA-2 genes. The premenopausal woman having undergone bilateral oophorectomy may require supportive hormone replacement therapy.

The exact age when prophylactic oophorectomy is beneficial is difficult to decide and depends upon the following considerations:

- At what age the ovary ceases to function? This is difficult to determine.
- Does the preserved ovary continue to function after hysterectomy? It is observed that following hysterectomy, ovarian blood supply is compromised and at best it may retain its function for about 4 years.
- Following oophorectomy, is HRT effective? Though effective, it is advisable not to continue HRT for more than 5 years because of the risk of breast cancer.
- It can cause ovarian remnant syndrome.
- Very recently, ovarian grafting is attempted using epigastric artery and external iliac vein. Further trial will reveal the success rate.

Benign Ovarian Tumours

The treatment comprises:

- Abdominal hysterectomy and bilateral salpingo-oophorectomy
- Unilateral ovariotomy
- Ovarian cystectomy
- Laparoscopic cystectomy–ovariotomy
- Laparoscopy/ultrasound-guided aspiration and removal of the cyst.

Abdominal hysterectomy and bilateral salpingo-oophorectomy is recommended in a perimenopausal women, even if the tumour is benign and unilateral. The probability of discovering microscopic evidence of malignancy in histological specimens and thereby the need for second surgery can be avoided.

Ovariotomy/cystectomy. In a young woman, irrespective of parity, conservation of a healthy ovary is highly desirable. Therefore, the ovarian tumour should be enucleated (cystectomy), and if this is not possible, ovariotomy should be done by clamping the infundibulopelvic ligament laterally, mesovarium in the middle and fallopian tube, ovarian ligament medially. It is important to be certain that the tumour is benign and the other ovary healthy by frozen-section biopsy.

Laparoscopic cystectomy–ovariotomy is a minimal invasive surgery in vogue for small cysts.

Because of the risk of spillage of cyst content in a dermoid cyst resulting in peritonitis and mucinous material spillage causing pseudomyxoma peritonei in a case of mucinous cyst, some prefer open surgery. In a laparoscopic surgery, retrieval of the tumour in a plastic bag reduces the risk of spillage of cyst contents.

Laparoscopy carries a low morbidity and allows a quick recovery without a conventional abdominal scar.

Laparoscopic ovarian cystectomy is performed by first aspirating the cyst fluid followed by dissection of the cyst wall or by ablation. Mere aspiration of fluid is not recommended on account of recurrence of the tumour. Aspirated material/cyst wall should be subjected to histopathology and cancer ruled out.

Ablation of the cyst wall carried out with cautery or laser carries the risk of recurrence of the cyst. While dissection or peeling off of the cyst wall avoids recurrence, bleeding during dissection, adhesion formation and reduction in the ovarian reserve (due to destruction of a portion of the ovary) are the disadvantages.

Ovarian Tumours Associated with Pregnancy

The ovarian tumour discovered during pregnancy is an enlarged corpus luteal cyst, a benign as well as a malignant tumour. An asymptomatic tumour is discovered during routine ultrasound scanning in early pregnancy. Symptomatic tumour however presents with abdominal pain in pregnancy.

Corpus luteal cyst regresses after the 12th week and can therefore be observed. The benign tumour should be removed in the second trimester between the 14th and 16th week. Earlier surgery may increase the risk of abortion, whereas laparotomy in the third trimester increases the surgical difficulty because of the growing uterus; preterm labour is also a possibility. The tumour discovered late in pregnancy should be removed in early puerperium to avoid torsion and infection. The malignant ovarian tumour requires laparotomy at the earliest, irrespective of the duration of pregnancy.

Ovarian Cyst in a Menopausal Woman

A simple unilocular cyst measuring less than 5 cm can be observed with repeat ultrasound and CA-125 every

3 months. Many resolve in 6 months. A persistent cyst calls for its removal laparoscopically or by laparotomy. Aspiration of the cyst is contraindicated because of low yield of malignant cells (false-negative) and possibility of spread of malignancy if the cyst proves malignant histologically. Many perform bilateral oophorectomy and hysterectomy in perimenopausal women.

Ovarian Remnant Syndrome

Ovarian remnant syndrome follows hysterectomy in 1.4% cases. It is caused by ovarian adhesions to the vaginal vault, and causes cyclical abdominal pain and deep dyspareunia. It requires oophorectomy. The retained ovary may also develop malignancy in 1% cases. Apart from these, it is also observed that many ovaries atrophy prematurely (within 4 years) following hysterectomy, if the ovarian vessels get kinked and obliterated during hysterectomy. The conservation of ovaries at hysterectomy for benign tumour therefore remains a debatable issue at present.

Recent belief is to remove the ovaries at the time of hysterectomy and give hormone replacement therapy thereafter.

Ovarian Tumours in Adolescents (Figure 33.23)

Ovarian tumours account for 4–5% of all genital tumours, of which 25% are primary malignant tumours. Before the age of 20 years, 60% are germ cell tumours and 65% of these are malignant.

Since epithelial tumours are related to ovulation (combined oral contraceptives therefore protect against ovarian cancers in 40–50%) and ovulation occurs only after puberty, epithelial tumours are extremely rare (0.5%) during adolescent period. Dysgerminoma is the commonest tumour and causes amenorrhoea. Clinically, 'Grade 0' epithelial tumour may occasionally be encountered.

Conservative surgery followed by chemotherapy is effective and has replaced the older treatment of hysterectomy with bilateral salpingo-oophorectomy and radiotherapy in young girls.

Adnexal Mass

The ovary and the fallopian tube form the adnexa along with a rare tumour in the broad ligament. It is at times difficult clinically to identify the site of adnexal mass. Ultrasound, MRI and at times laparoscopy may be required to diagnose the condition.

Adnexal Mass in Premenarchial Age

- Mainly an ovarian tumour, i.e. germ cell tumour, dysgerminoma, teratoma, granulose cell tumour; 25% of them are malignant tumours.
- Tubercular pelvic mass.
- In rare cases, a pelvic kidney.

During Reproductive Age

- Functional ovarian cysts.
- Pelvic inflammatory disease.

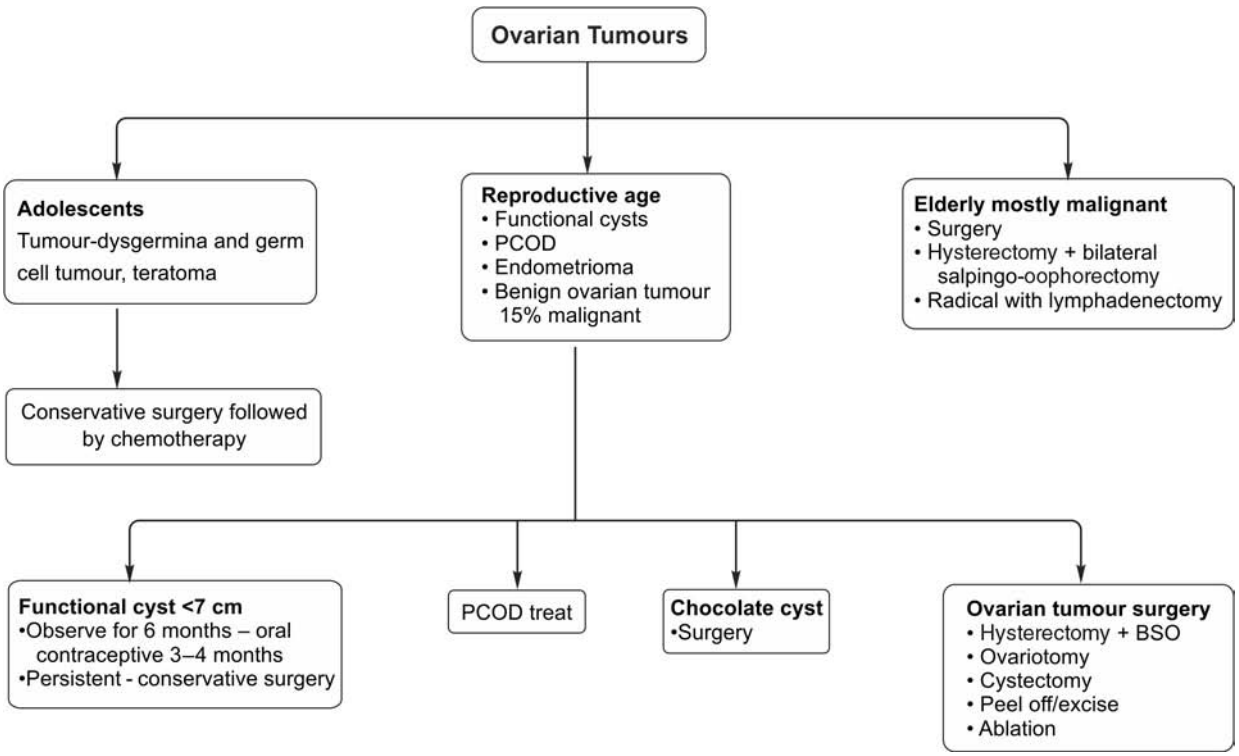

Figure 33.23 Ovarian tumours.

- Ectopic pregnancy.
- Endometrioma.
- Broad ligament tumour.
- Tubercular mass.
- Ovarian tumour, mostly benign.
- Pedunculated uterine fibroid.

PostMenopausal

- Malignant ovarian tumour 50%.
- Benign ovarian tumour.
- Pedunculated uterine fibroid.
- Colonic tumour

Correct diagnosis by clinical history examination, ultrasound, CT, MRI and if required laparoscopy is required, and the disorder treated by appropriate therapy.

Key Points

- A wide variety of diverse ovarian tumours are known to arise from the ovary. Many of these harbour a malignant potential. The tumours are often asymptomatic to begin with, and are often far advanced by the time they are diagnosed.
- Sex cord tumours have a potential to secrete hormones which may manifest clinical symptoms like precocious puberty, menstrual disturbances and postmenopausal bleeding. Virilizing effects may be observed in masculinizing tumours.
- Bilateral tumours, rapidly growing tumours and presence of ascites are suggestive of malignancy and require investigations.
- Tumour markers like CA-125 are particularly useful in postmenopausal women suspected of having a malignant epithelial cell tumour. Markers like CEA, alpha-fetoproteins, LDH and hCG are useful in germ cell tumours.
- Imaging modalities like ultrasonography, CT scan and MRI help to detect ovarian neoplasms, and assist in staging of ovarian cancers.
- It is important to differentiate between benign and malignant enlargements of the ovary to institute timely and effective treatment without undue delay.
- Benign ovarian tumour is surgically dealt with by ovarian cystectomy, ovariotomy, laparoscopic dissection of the cyst in a young woman and hysterectomy with bilateral removal of adnexa in an older woman.

Self-Assessment

1. A girl, 18-year-old, presents with an abdominal tumour and slight abdominal pain. Discuss the differential diagnosis and management.
2. A parous woman, 36-year-old, presents with an abdominal lump. Discuss the differential diagnosis.
3. A 30-year-old woman, para 2, presents with menorrhagia of 6 months duration. An abdominal tumour is palpable abdominally. Discuss the differential diagnosis and management.
4. Write short notes on:
   - Brenner tumour
   - Mucinous epithelial tumour
   - Arrhenoblastoma
   - Theca cell tumour

Suggested Reading

Sengupta S, Chattopadhyay, Varma. Gynaecology for Postgraduate and Practitioners, 2nd Ed. Elsevier, 2007.
Studd J. The adnexal mass In: Progress in Obstetrics and Gynaecology 17: 306, 2006.

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Chapter 34 Breast

CHAPTER OUTLINE

The breast is an essential part of gynaecological examination and should be included in the general examination of every woman coming with a gynaecological problem.

A routine breast examination may discover a breast lump, hitherto not recognized by the woman. Breast examination becomes mandatory in an ovarian tumour suspected to be a metastatic growth. During infertility work-up, galactorrhoea may point to hyperprolactinaemia as a cause for infertility. In primary amenorrhoea, ill-developed breasts suggest hypothalamic–pituitary cause whereas well-developed secondary sex characters indicate a local genital cause for amenorrhoea. Regular breast examination is essential in a woman on hormonal replacement therapy (Figures 34.1–34.3).

Hormonal Effects on the Breasts

Breast tissues, glandular, ductal as well as the stroma, respond to and remain sensitive to ovarian hormones throughout the reproductive period and also after menopause. Therefore, excess of ovarian hormones and antihormones play a major role in breast diseases.

Congenital Deformities

Congenital deformities include an absent or an extra nipple, supernumerary breasts, aplasia or hypoplasia sometimes unilateral.

In Turner's syndrome, and some cases of primary amenorrhoea, oestrogen therapy may develop the breasts and reduce the risk of osteoporosis.

Trauma and infection are mainly confined to breastfeeding puerperal women. Cracked nipples will be healed with Masse cream. Mastitis requires analgesic, hot fomentation and antibiotics. An abscess will require incision and drainage.

Mastalgia

Painful breast seen in young women is often cyclical but in older women it is usually acyclical. Cyclical mastalgia is the breast pain occurring for a few days before menstruation. Severe mastalgia lasts more than 7 days, requires drugs and interferes with the woman's activities. Chronic mastalgia is described when pain lasts for more than 6 months, and requires investigations.

Treatment

Treatment (Figure 34.4) comprises:

- Analgesics—nonsteroidal anti-inflammatory drugs (NSAIDs).
- Evening primrose oil capsule (well-women capsule) containing gamma linoleic acid or Efamast 3 g daily relieves pain in 70%. Occasional nausea and headache are the side effects.
- Danazol 100 mg bid produces severe androgenic side effects in some, and is expensive. Though 70% effective, cost and side effects may preclude some woman taking them. Vitamin B_6 benefits few women.
- Bromocriptine 2.5 mg bid. Nausea, vomiting and giddiness may occur, and because of these side effects, compliance is poor with danazol and bromocriptine. Forty-five per cent success is reported. *Cabergoline is long-acting with less side effects*. (Dostinex 0.25 mg twice a week).
- Tamoxifen 10 mg has less side effects, but endometrial hyperplasia and in rare cases, cancer has been reported.
- GnRH analogue (goserelin) 3.6 mg monthly depot injection is effective, but influences the menstrual cycle (amenorrhoea) and causes osteoporosis on prolonged use. Short-term therapy is useful, but very expensive.
- Testosterone undecanoate (Restandol) 40 mg bid is effective. Androgenic side effects after 3 months of treatment are often the limiting factor in its use.

Noncyclical mastalgia is seen in older women and may be a symptom of breast cancer. This requires investigations to find out the underlying cause. Some women suffer from chest wall pain (Tietze's syndrome). If this is the cause, NSAIDs usually relieve pain. If not, injection with an anaesthetic–steroid combination locally has shown 75% response.

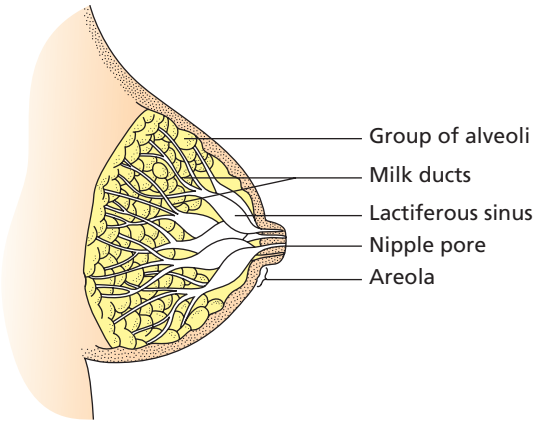

Figure 34.1 Milk-producing structures and ducts in the human breast (simplified cross section).

Breast Lump

Less than 10% of women presenting with a breast lump have breast cancer. Nevertheless, systematic examination and investigations are required to rule out malignancy. *Symptomatic lump (pain or growing) requires surgery*.

Cystic swelling. A single cyst is often benign. Multiple cysts can become malignant. Fine-needle aspiration cytology (FNAC), mammography and ultrasound will identify the cyst. *Blood-stained fluid, recurrence after aspiration and multiple cysts should be treated surgically. In young women, simple aspiration and cytology will be adequate.*

Periductal mastitis occurs in older women. Nipple discharge and retracted nipples are clinical features often associated with smoking, though the cause is not clear. Perhaps it alters the bacterial flora in the ducts, with a preponderance of *E. coli* and anaerobic organisms, and this leads to infection. Another possibility is direct toxic action of smoking on the vascular structure of ductal epithelium. Antibiotics and excision of the lesion are required.

Nipple discharge can be hormonal but blood-stained discharge is due to ductal papilloma and periductal mastitis, rarely malignancy. Cytology and mammography are not always useful. Resection of the lobe is the recommended treatment.

Galactorrhoea

Galactorrhoea is caused by hyperprolactinaemia and pituitary adenoma. Prolactin level more than 25 ng/mL can cause galactorrhoea, but not all hyperprolactinaemias produce galactorrhoea. The condition is associated with amenorrhoea, oligomenorrhoea and infertility. The macroadenoma can cause pressure on the optic nerve. The management of galactorrhoea is described in Chapter 23.

Other causes are hypothyroidism, chest wall injury, herpes zoster, stress and oestrogen and dopamine receptor blocking agents.

Benign Tumours

Fibroadenoma

This is a benign tumour and occurs at any age. It is usually a single tumour, rarely grows more than 5 cm and accounts for 15% of all breast tumours. Before the age of 30 years, the tumour runs a benign course, and if the investigations prove the benign nature of the tumour, it is safe to leave it behind. However after this age, the possibility of malignant change cannot be ruled out, and excision biopsy is recommended. If the benign tumour in a young woman becomes tender or increases in size, surgery is a wise decision.

Fibroadenosis in young women responds to danazol.

Progestogen-only pill (mini pill) reduces the incidence of benign breast disease by 35–40%, but increases the risk of cancer.

Duct papilloma causes blood-stained discharge. The cytology of the discharge, mammography and ultrasound locate the lesion. Ductoscopy confirms the nature of the lesion. It can turn malignant and requires excision.

Premenstrual Mastalgia

It is treated with toremifene, which is an anti-oestrogen and belongs to the tamoxifen group of drugs; 60 mg daily is given only in the luteal phase. It improves mastalgia in 60%

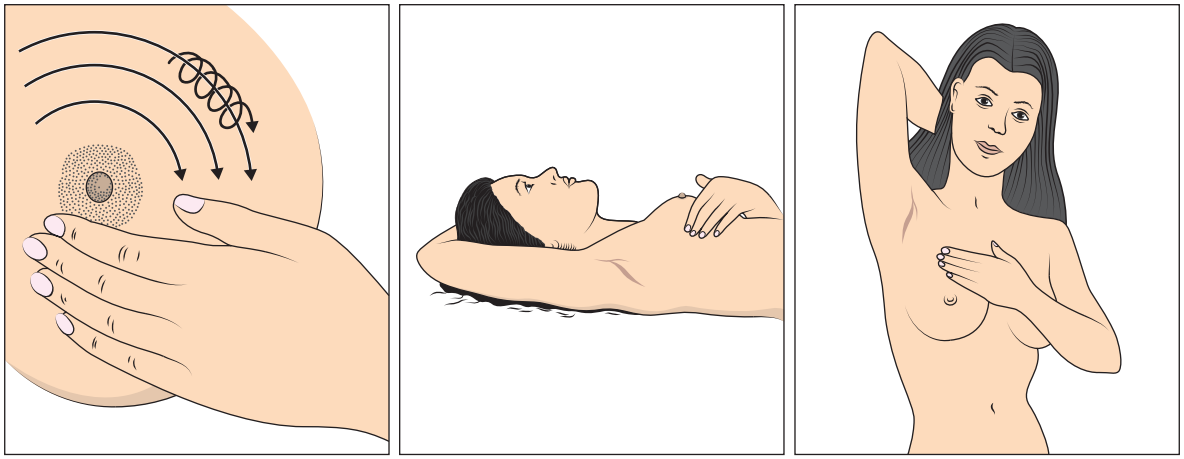

Figure 34.2 Self-palpation of breasts.

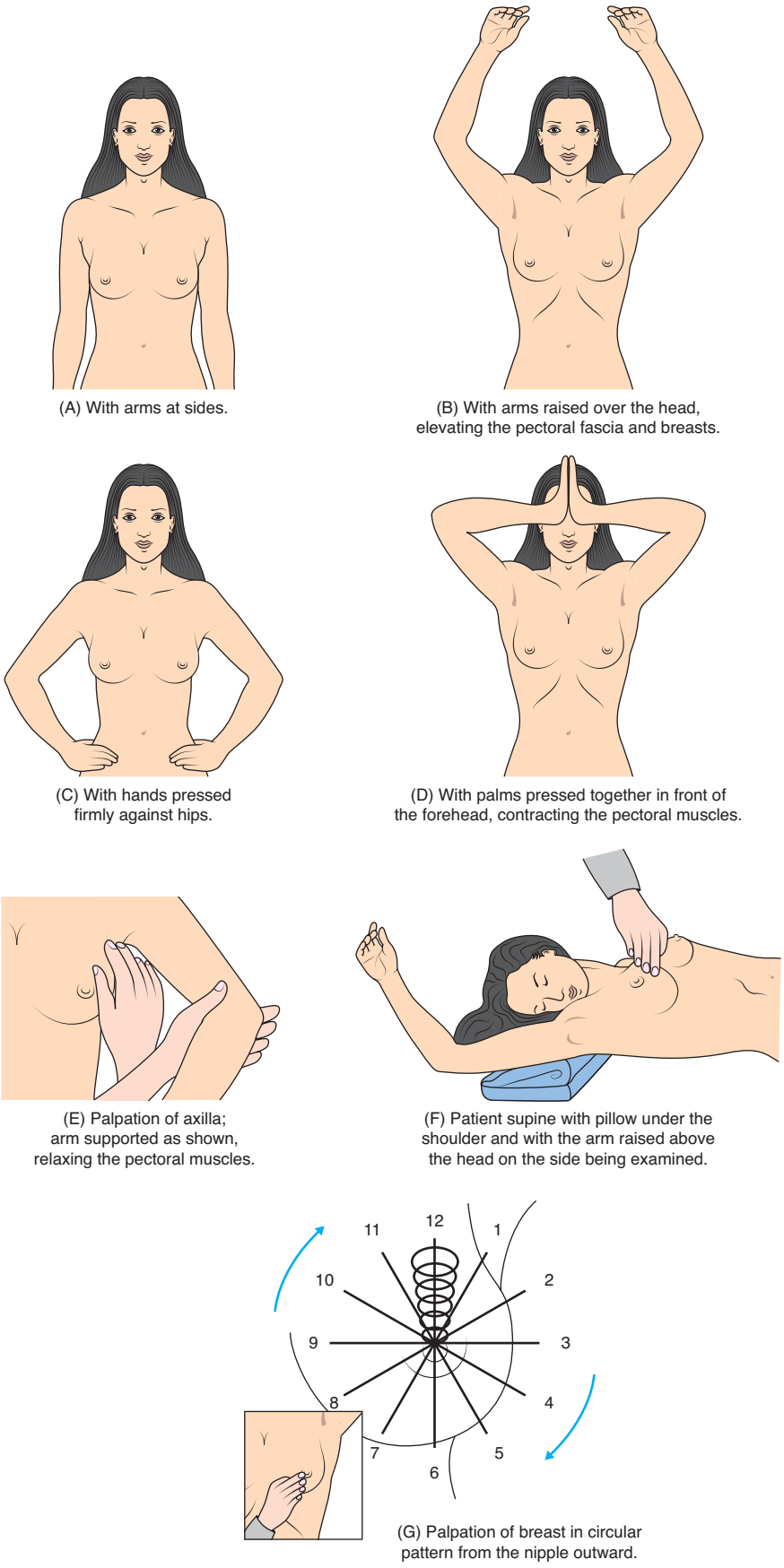

Figure 34.3 Breast examination. Positions include patient seated or standing. (Source: Rao, KA: *Textbook of Gynaecology,* India: Elsevier, 2008.)

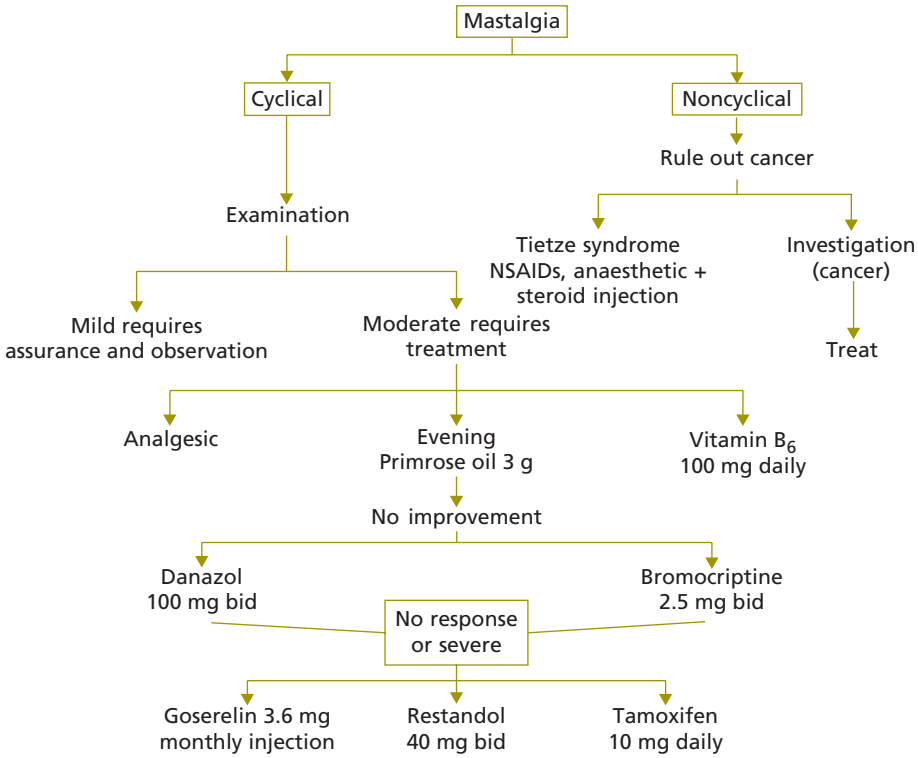

Figure 34.4 Treatment of mastalgia.

cases. It has lesser side effects as compared to tamoxifen (Figure 34.4).

Breast Cancer

Breast cancer is the commonest cancer in a woman and accounts for 10% of all breast problems presenting at the clinic. Breast carcinoma is more prevalent in elderly women, and needs prompt investigations and treatment, comprising surgery followed by radiotherapy and chemotherapy as the need be. Certain high-risk cases have been recognized which will need regular screening. These are:

- **Familial history** suggests that genetic factor is responsible ($BRCA_1$ and $BRCA_2$ genes mutation 5–8%). Individual risk factor is 0.08.
- A woman with ovarian cancer is at a high risk for breast cancer and vice versa. Both malignancies share common aetiological factors and have a common oncogen.
- A woman with ovarian cancer should be screened for breast tumour, as the ovarian tumour could be a metastasis from the breast.
- **Age**. After the age of 60 years, 50% breast lumps prove to be malignant. Fifteen per cent occur during childbearing age.
- **Parity**. Nulliparity, late first pregnancy after 30 years of age and nonlactation are the high-risk factors.
- Obese women too have a propensity to breast cancer.
- Early menarche and late menopause with greater number of menstrual cycles and shorter cycles expose the breast tissues to oestrogen hormones and make them susceptible to the development of breast cancer. Endogenous as well as exogenous oestrogens are carcinogenic. Lately, progestogens also have proved carcinogenic.
- The risk of breast cancer is high in young women on oral contraceptive pills. The risk decreases 10 years after stoppage of the hormones. However, cancer is well-differentiated in these women.
- **Smoking** encourages periductal mastitis and atypical growth. It is also immunosuppressive. Alcohol too may be a factor.
- **Hormones.** It is strongly suspected that combined oral contraceptives (COC) containing high-potency progestogen given for more than 4 years to a young woman below 25 years and before her first pregnancy may predispose her to breast cancer at a later age and the risk is two- to fivefold. One should be careful in prescribing COC to young women. Progestogen-only pill (POP) while protecting against benign tumours increases the risk in elderly women. The risk decreases after 10 years of stoppage of OC pills. Low-dose COC may have a lower risk. The risk is related to duration of COC intake. Lately, COC is considered a higher risk than oestrogen alone, because of the progestogen content.

Breast cancer is the main concern while prescribing hormone replacement therapy (HRT) to a menopausal woman. A woman on HRT should be screened regularly for breast lump and mammography should be done every 1–2 years. HRT should not be administered for more than 10 years. Fortunately breast cancer following HRT is of low malignancy with good prognosis.

It may be prudent not to recommend HRT to a woman treated for breast cancer. It is equally important to carefully monitor a woman on tamoxifen for breast and uterine cancer. It is suggested that vitamin A may be protective. Obesity increases the risk of cancer because of peripheral conversion of oestrogen. Raloxifene is safe against endometrial cancer, but causes thrombosis.

Clinical Features

Very often, the first thing a woman feels is a lump in her breast. Nipple discharge and pain come later.

The lump feels firm, irregular and fixed in the later stage. Axillary lymph nodes become palpable in the advanced stage. The other breast should also be palpated.

Investigations (Figure 34.5)

Clinical palpation is not 100% accurate in detecting cancer. Below the age of 40 years, 50% cases can be missed. Between 40 and 49 years, accuracy is 80%; between 50 and 59 years, 90%; and over 60 years, accuracy is 95%. Self-examination increases the awareness in a woman and brings her to the doctor at an early stage for the treatment. Examination by the physician supplements self-examination (Figures 34.2 and 34.3).

Mammography is indicated in the following cases:

- Older and high-risk women.
- To assure normality when a woman has cancer phobia.
- If a lump is present.
- Prior to HRT. Yearly/2-yearly screening between 45 and 60 years is cost effective.

Contraindication. Mammography is contraindicated in pregnancy because of the risk of radiation.

Using only mammography as the investigation tool is unreliable in 50% women below 40 years, because of dense breast tissue. Mammography identifies cancer in 75% cases between 40 and 49 years, and reliability increases with age. It must be mentioned that interpretation of mammography findings may be difficult if a woman had previous breast surgery. Similarly, HRT also interferes with mammographic screening. Mammography should include two views of both breasts: mediolateral side view and cranio-caudal view. Regular mammography can reduce the mortality of cancer by 30%. The findings include:

- Alteration in density of breast tissue
- Microcalcification
- Thickening of skin
- Presence of fibrous streaks
- Nipple alteration
- Detection of fibroadenoma, lymph nodes, galactocele
- Cysts and solid tumour.

Ultrasound imaging, using 10 MHz probe, is useful in all age groups, especially before the age of 35 when mammography may not be reliable. Ultrasound differentiates cystic from solid malignant tumour. It is required in young women, pregnant and lactating woman, and in duct papilloma. Ultrasound however fails to identify microcalcification, which is the hallmark of early cancer. In cancer of the breast, ovarian screening by ultrasound is important, as one cancer spreads to the other.

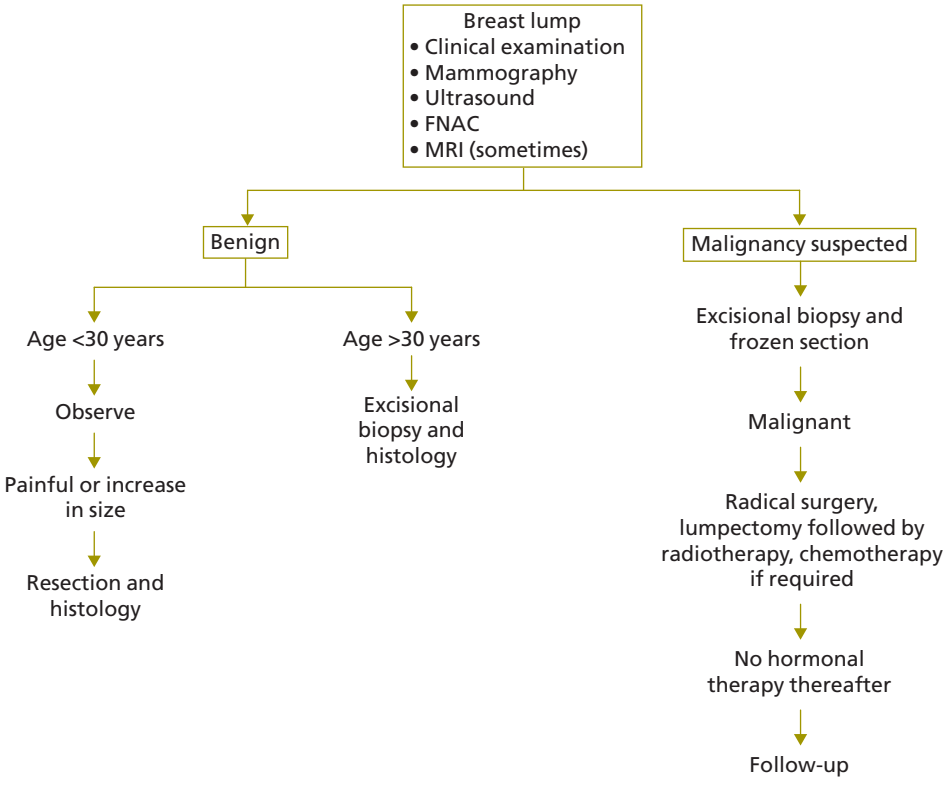

Figure 34.5 Investigation and treatment of breast lump.

Doppler ultrasound displays vascular pattern of a tumour and indicates the probability of malignancy.

Computer-aided detecting diagnosis (CADD) and electrical impedance imaging are new technologies.

Ductoscopy and cytology when duct papilla is suspected.

X-ray chest, CT brain and abdominal ultrasound for metastasis.

MRI gives the most accurate measurement of the tumour size of invasive cancer and helps in staging. It also predicts the response to primary chemotherapy. It is useful in young women and in a woman who had previous breast surgery.

FNA cytology under ultrasound or clinical guidance yields cellular study of the lump. Ultrasound/ mammography should be performed prior to FNAC, because haematoma sometimes caused by aspiration can obscure the image (90–95% specific).

Clinical examination, combined with mammography, FNAC, and ultrasound can identify cancer in 99.5% cases.

Tru-cut biopsy removes a core of tissue for the frozen section, histology and receptor study. A big tumour requires excisional biopsy.

Treatment

Treatment comprises:

- Excisional biopsy and frozen section followed by definitive surgery as required
- Lumpectomy
- Simple mastectomy
- Radical mastectomy
- Postoperative radiotherapy and chemotherapy

Lumpectomy yields similar results as radical mastectomy. Axillary lymph nodes are removed in the advanced stage.

Radiotherapy may be required as adjunct in advanced cases. Reconstructive prosthesis is done in the same sitting or at a later date.

Adjuvant chemotherapy reduces the risk of recurrence by 30%. Tamoxifen 20 mg daily or raloxifene 60 mg daily reduces the risk of recurrence in the contralateral breast by 50% for about 5 years, but is teratogenic in pregnancy and causes atropic vaginitis. Anastrozole (aromatase inhibitor) is better tolerated than tamoxifen (1–2 mg).

Chemotherapy

- Four cycles of adriamycin and cyclophosphamide
- Six cycles of 5-FU, adriamycin and cyclophosphamide
- Six cycles of 5-FU, epirubicin and anthracycline

Taxane improves survival. A woman should not conceive for 2 years after stoppage of chemotherapy.

Prognosis

Prognosis is based on staging, E_2 receptors in the tissues and axillary lymph node involvement. Metastasis is treated with chemotherapy.

Ovarian ablation may be required to prevent recurrence.

HRT and COC are contraindicated in a woman who is treated for breast cancer. However, severe menopausal symptoms may require a low-dose therapy. Under supervision, raloxifene is safe, does not cause endometrial hyperplasia and osteoporosis, though risk of thrombosis needs to be watched for. Lactation is also contraindicated in a woman treated for breast cancer, because of the risk of developing cancer in the opposite breast.

Breast cancer occurring during pregnancy is known. Surgery and radiotherapy are not contraindicated during pregnancy, provided adequate shielding is provided. If, however, chemotherapy is considered postoperatively, termination of early pregnancy is necessary because of teratogenicity of the drugs. Late in pregnancy, chemotherapy can be delayed until after delivery.

Prophylaxis

Tamoxifen and raloxifene for 5 years:

- Reduce the incidence of contralateral breast cancer by 50%.
- Prolongs disease free interval.
- Reduces the risk of recurrence.

Key Points

- Examination of the breasts should form part of the routine examination of all patients undergoing gynaecological examination.
- Examination may reveal congenital developmental anomalies like absent or extra nipple, hypoplasia, mastalgia, mastitis in nursing mothers, cracked nipples, galactorrhoea of significance in infertile women, presence of benign neoplasms like freely mobile fibroadenomas, presence of cysts like galactocele, irregular nodularity in chronic cystic mastitis, hard indurated nodule suggestive of breast cancer or the presence of blood-stained nipple discharge indicative of a possible underlying cancer.
- Breast lumps may be benign or malignant. Mammography and ultrasound examination, Doppler studies and MRI reveal presence of solid or cystic neoplasms. FNAC and cytological examination of the aspirate may help to establish early diagnosis of cancer.
- Breast cancer carries a worse prognosis if it occurs during pregnancy and lactation because of immunosuppressive condition.
- HRT is contraindicated in a woman treated for cancer of the breast. However, tibolone and bisphosphonates can be offered to prevent osteoporosis.
- Tamoxifen is teratogenic.
- Increasing awareness amongst clinicians of the importance of breast examination and teaching patients about the art of self-examination promote early diagnosis of cancer.
- A baseline mammography in all menopausal patients starting HRT is a desirable precaution. Use of oestrogens and progestogens should be withheld in women with a strong family history of breast cancer.

Self-Assessment

1. Describe the benign lesions of the breast.
2. A 50-year-old woman presents with a lump in the left breast. How will you manage this case?
3. A 22-year-old nullipara presents with galactorrhoea. How will you manage this case?

Suggested Reading

Studd J. Progress in Obstetrics and Gynaecology 11: 427, 1994.
Studd J. Progress in Obstetrics and Gynaecology 17: 306, 2006.

Chapter

35

Acute and Chronic Pelvic Pain

CHAPTER OUTLINE

Pelvic pain is not an uncommon complaint in women, and its diagnosis and management can be taxing at times.

Acute pelvic pain is an emergency and requires prompt and selective investigations to deal with the condition. Treatment is either medical or surgical.

Chronic pelvic pain can be very debilitating. In some cases, even after extensive investigations, the diagnosis may not be arrived at, and the treatment remains empirical. While chronic pelvic pain mainly affects women in the reproductive age group, acute pain can occur at all ages.

Acute Pelvic Pain

Premenarche

- Congenital causes: haematocolpos and haematometra (Chapter 9)
- Ovarian cyst: Torsion, rupture haemorrhage and malignancy (Chapter 33)
- Abdominal tuberculosis
- Nongynaecological causes

In young adolescents, most acute pains are of non-gynaecological origin. They may be related to urinary tract, gastrointestinal tract or abdominal tuberculosis.

Ovarian Tumour

The common ovarian tumours encountered in children and adolescents are dermoid cysts, teratoma dysgerminomas and germ cell tumours. Acute pain in a dermoid cyst occurs with infection, distension or torsion. The diagnosis is easy and laparotomy is required.

Reproductive Age Group

Acute pain may be due to obstetrical, gynaecological and non-gynaecological conditions.

Obstetrical Causes

- *Abortion*. Pain occurs in inevitable and septic abortion. Inevitable abortion is associated with severe vaginal bleeding and the diagnosis is obvious.
- *Septic abortion.* In septic abortion, the woman suffers from high fever, severe abdominal pain and vomiting. Foul smelling vaginal discharge may be present.
- *Ectopic pregnancy*. Acute ectopic pregnancy is associated with severe abdominal pain and short period of amenorrhoea with or without vaginal bleeding. Ultrasound reveals free fluid in the abdominal cavity and a pelvic mass. It requires emergency surgery.
- *Red degeneration of fibroid*. A woman in early pregnancy develops acute abdominal pain and sometimes vomiting. The uterus is more enlarged than the duration of pregnancy and is tender. Ultrasound reveals the presence of a fibroid. Treatment is conservative.
- *Twisted ovarian cyst.* This requires immediate surgery.
- *Acute hydramnios.* More common in a multiple pregnancy, acute hydramnios presents with unduly enlarged uterus in mid-pregnancy and abdominal pain. Ultrasound shows multiple pregnancy and hydramnios. Invariably, patient goes into spontaneous abortion.
- *Molar pregnancy*. Pain is due to sudden enlargement of the uterus, haemorrhage and perforation. Evacuation of the mole is required.
- *Retention of urine*. Retention occurs due to retroverted gravid uterus, haematocele of ectopic pregnancy fibroid or ovarian cyst impacted in the pelvis. It requires temporary catheterization in the retroverted gravid uterus and surgery for the other conditions.
- *Abruptio placentae.* Occurs after 20 weeks of pregnancy and associated with severe abdominal pain and vaginal bleeding.

Gynaecological Causes (Figure 35.1)

- *Dysmenorrhoea* is cyclical and related to menstruation. In early menarchal period, a young girl may be brought with acute abdominal pain. Pain is located in the lower abdomen and is often spasmodic. Antispasmodics relieve pain and no investigation is required.
- *Mittelschmerz* is a mid-cycle pain, not lasting more than 12–24 h, around ovulation. Pain is located in one of the iliac fossa and may be accompanied with slight vaginal bleeding. Analgesic may be required for severe pain.
- *Pelvic inflammatory disease (PID)*. Acute pain is felt in the lower abdomen, but may spread upwards if generalized peritonitis ensues. Pain is mostly bilateral, and abdomen is tender in acute PID.
- *Endometriosis*. Acute pain in endometriosis is either due to rupture of a chocolate cyst or due to leakage of blood into the peritoneal cavity. Ultrasound detects the cause. Laparoscopy or laparotomy is required.
- *Hyperstimulation of induction of ovulation.* The cause of acute pain is obvious, and its severity is related to endogenous or exogenous hCG. It is more severe if pregnancy (more so multiple pregnancy) results from IVF programme.
- It occurs 8–10 days following hCG hormone injection or early pregnancy. Severe case requires hospitalization, intravenous fluid and sedation (Chapter 43).
- *Uterine fibroid*. Normally, a fibroid does not cause acute pain unless a pedunculated fibroid undergoes torsion or the capsule vessel ruptures with intraperitoneal haemorrhage. Treatment is surgical.
- *Ovarian tumour*. Torsion, infection of a dermoid cyst and rupture cause acute pain in the abdomen. A malignant tumour is mostly 'silent' until in an advanced stage (Chapter 33).

Non-gynaecological Causes

- *Retention of urine* in gynaecology occurs when a tumour gets impacted in the pouch of Douglas. Acute cystitis and bladder stone cause severe pain in the suprapubic region. A ureteric colic is felt along the ureter on one side.
- *Gastrointestinal pain* is often colicky and associated with gastrointestinal symptoms. Appendicitis can confuse the diagnosis, but the pain is localized in the right iliac fossa.
- *Abdominal tuberculosis*.

Menopausal and Postmenopausal Women

- *Pyometra* occurs in endometrial cancer following radiotherapy, when the cervix gets stenosed or due to tubercular and senile endometritis. The pain is localized in the central portion of the lower abdomen and may or may not be accompanied with fever. Ultrasound shows an enlarged uterus with fluid. Treatment is cervical dilation and drainage. Endometrial curettage later will reveal tuberculosis or cancer.
- *Ovarian tumour* is invariably malignant in an old woman and is of late occurrence (Chapter 33).
- *Sarcoma in a fibroid* is diagnosed when the fibroid starts growing rapidly with pain and sometimes postmenopausal bleeding (Chapter 29).
- *Retention of urine* occurs in a menopausal woman due to bladder neck obstruction and requires drainage and appropriate management.

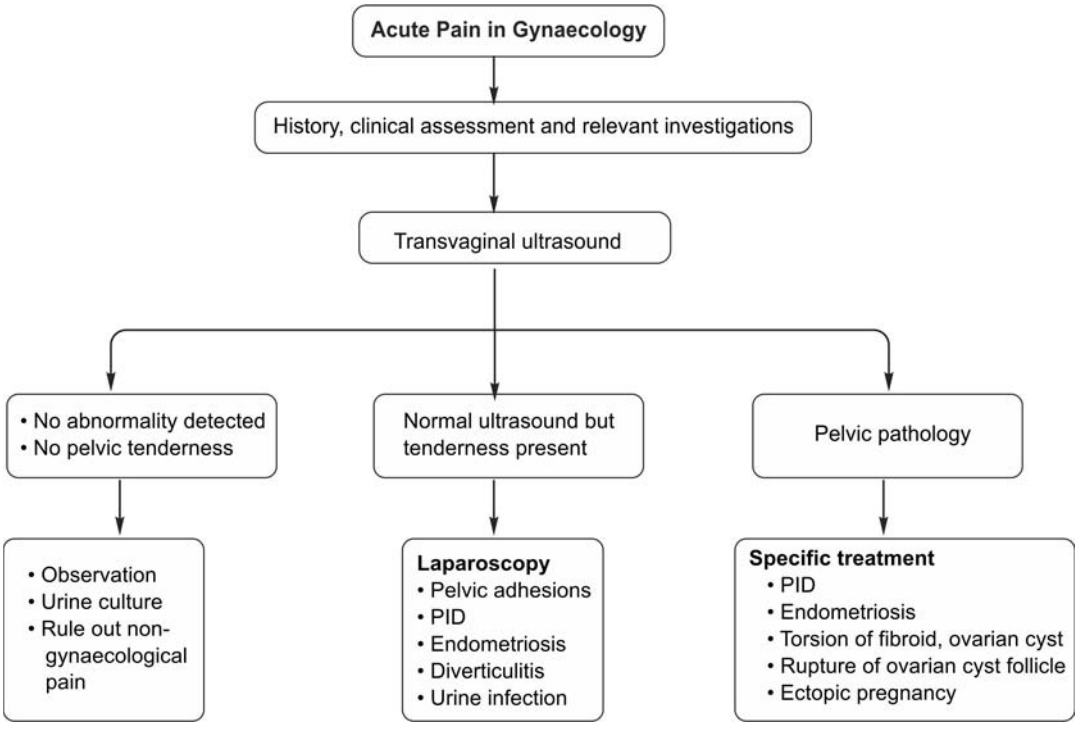

Figure 35.1 Acute pain in gynaecology.

History and Clinical Examination

- Age, parity and menstrual history should be recorded. The mode of onset pain, its location, severity, duration and radiation to other areas should be inquired into. The relation to menstrual history is important. History of fever, vomiting, diarrhoea as well as urinary symptoms are also relevant while making a clinical diagnosis.
- Clinical examination and relevant investigations should be undertaken.
- Management : Treat the cause.

Chronic Pelvic Pain

Chronic pelvic pain (CPP) refers to acyclical pelvic pain of more than 6 months duration. This type of pain has been a recognized symptom of organic lesions such as endometriosis, PIDs, adhesions and uterine fibroids. It is dealt with appropriate medical and surgical management.

It has been observed that some women suffer from chronic pelvic pain without any clinical evidence of pelvic pathology. It is easy to attribute this to neurosis, as many of these women present with neurotic personality. However, it is now confirmed that neurosis is the result and not the cause of this protracted pain, and chronic pelvic pain syndrome (CPPS) does exist. It is important therefore to elucidate the cause of CPPS by investigations such as ultrasound and diagnostic laparoscopy.

Laparoscopy reveals minute areas of endometriosis and pelvic adhesions which are invariably missed on pelvic examination. The absence of pelvic pathology and findings of normal pelvic organs is assuring to the woman as well as the doctor that no serious disease such as cancer exists. At times, the congestion and dilatation of pelvic veins is the only abnormal finding, and this is hard to treat.

Incidence

About 15% of women complain of chronic pelvic pain. Ten per cent women visit the gynaecologists. In some centres, as many as 30–40% diagnostic laparoscopies are performed for CPP.

Aetiology (Table 35.1)

The causes of chronic pelvic pain are diverse. They may be gynaecological and nongynaecological such as gastrointestinal tract, renal tract, skeletomuscular and peritoneal.

1. *Gynaecological causes* are often organic but can be functional.

   The well-recognized organic lesions are:

- Pelvic endometriosis, chocolate cyst of the ovary (30–35%)
  - Ovaries—ovarian adhesions, polycystic ovarian disease, residual ovarian syndrome, ovarian tumours (benign and malignant)
  - Tubal—chronic PID, tubal adhesions, postoperative adhesions, parametritis due to infection or malignancy (24%)
  - Pelvic tuberculosis and adhesions
  - Uterine—uterine fibroids and adenomyosis, pyometra in menopausal women, fixed retroverted uterus

2. *Functional causes* include:
   - Congestive dysmenorrhoea, Mittelschmerz and postcoital pain
   - CPPS, pelvic varicose or dilated veins (30%)
3. *Nongynaecological causes* are:
   - Intestinal tuberculosis, diverticulitis, colitis, appendicitis, irritable bowel syndrome which account for 20% cases
   - Carcinoma rectum
   - Chronic intestinal obstruction

TABLE 35.1 Correlation of history of pelvic findings and the possible diagnosis

History	Physical Finding	Diagnosis
Progressive worsening of dysmenorrhoea and dyspareunia	Tenderness and nodules in the posterior fornix and uterosacral ligaments	Pelvic endometriosis
Pelvic pain (postoperative)	Restricted mobility of pelvic viscera	Pelvic adhesions
Menorrhagia, dysmenorrhoea	Bulky uterus	Uterine fibroid or adenomyosis
Shifting pain on body movement	Normal pelvic findings	Pelvic venous congestion
Dyspareunia, post-coital pain following surgery	Tender ovaries at the vault	Residual ovarian syndrome
Pain and bulge over the abdomen or scar	Hernia	Hernia scar endometriosis
Urinary frequency, dysuria urgency, pain suprapubic	Bladder distension or empty bladder	Cystitis
Pain left iliac fossa	Tender colon	Colitis
Pain right iliac fossa	Tender McBurney point	Chronic appendicitis
Referred pain, localized pain on trigger points	Trigger points	Nerve and muscle pain

- Renal—ureteric colic, bladder stone, urinary tract infection, cystitis, chronic retention of urine.
- Skeletomuscular—joint pains (referred pain).
- Hernias
- Sickle cell disease, porphyria
- Neurological—herpes zoster, nerve entrapment, nerve compression, referred pain
- Scar—scar pain, scar endometriosis

Nerve entrapment in Pfannenstiel incision can cause chronic pain which sometimes last as long as two years.

No Cause of CPP Found

In quite a few cases, no cause of CPP can be detected (35%). Even laparoscopic findings appear normal, and extensive investigations undertaken do not reveal a definite cause. It is also observed that even when a lesion is detected, it may not be the cause of the chronic pelvic pain, i.e. loose peritoneal adhesions, mainly postoperative adhesions do not cause chronic pain, and adhesiolysis does not cure the symptom.

Clinical Features

Endometriosis, Chocolate Cyst of Ovary

Endometriosis presents as dull lower abdominal pain associated with dysmenorrhoea, menorrhagia and dyspareunia. It is important to note that small lesions with fibrosis may cause only dull chronic pain. Tender nodules felt in the posterior fornix and tender pelvic masses with the above history may help to recognize the clinical condition of endometriosis. Ultrasound confirms the presence and extent of the pelvic mass. Laparoscopic examination is useful not only to confirm the unsuspected clinical diagnosis but also to coagulate the lesion and to excise and drain the chocolate cyst with the help of laparoscopy.

Surgical removal of chocolate cyst by laparotomy may be necessary if the cyst is huge.

Correlation of macroscopic findings with histological and clinical findings is rather poor and not related to severity of pain and other symptoms.

Ovarian Adhesions and Polycystic Ovarian Disease

Ovarian adhesions and polycystic ovarian disease cause dyspareunia besides CPP. Laparoscopy confirms ovarian adhesions causing CPPS. The adhesions can be divided and cysts punctured by laparoscope coagulation.

Chronic Pelvic Inflammatory Disease

Chronic PID causes chronic persistent lower abdominal pain, dyspareunia, dysmenorrhoea, menorrhagia and infertility. The uterus is retroverted, fixed. Thickened and slightly tender masses may be felt in the pelvis. If medical treatment fails, removal of adnexa or hysterectomy would be justifiable. If the ovaries need removal, the woman should be offered hormone replacement therapy (HRT) to prevent menopausal sequelae.

Peritoneal and Postoperative Adhesions

Not all adhesions cause pain. Loose adhesions which do not restrict mobility of abdominal viscera remain asymptomatic and do not require adhesiolysis. Rather, breaking these adhesions may result in re-formation of denser adhesions which may cause persistent chronic pelvic pain later. Dense adhesions and adhesions which restrict visceral mobility will lead to CPP. If these adhesions entrap the ovaries, pain can result. It is observed that some adhesion tissue contain nerve fibres, and these adhesions when stretched during movement of viscera can elicit pain.

Pelvic Tuberculosis

Pelvic tuberculosis is not rare in India. Apart from chronic pain, the woman often suffers from amenorrhoea, oligomenorrhoea and infertility. Endometrial curettings may in some cases reveal the tubercular nature of the infection. Laparoscopy may be necessary to confirm the diagnosis. Anti-TB treatment is needed. PCR stains diagnose tuberculosis when histology fails to do so.

Uterine Fibroids and Adenomyosis

Uterine fibroids and adenomyosis cause dysmenorrhoea and menorrhagia. Dull abdominal pain is due to heaviness and pelvic congestion, and at times due to associated PID. Submucous fibroid can cause colicky pain. Interstitial fibroids cause dysmenorrhoea more than subserous fibroids which cause more of heaviness and dull pain. Bimanual examination and ultrasound will reveal the cause of the pelvic pain.

Polycystic ovarian disease associated with pelvic congestion can cause chronic pelvic pain.

Ovarian Cyst or Tumour

Ovarian cyst or tumour does not normally cause chronic pelvic pain unless the cyst or tumour is large, in which case, the patient notices the swelling first. A dermoid cyst may cause dull pain due to infection and gradual torsion of its pedicle. Malignant tumour is a silent tumour causing pain only in the advanced stage.

Residual Ovarian Syndrome

Residual ovarian syndrome is seen when one or both ovaries left at the time of hysterectomy develop adhesions; this causes chronic pelvic pain and dyspareunia. Extensive and dense adhesion may require surgical removal of the ovaries and HRT. With the availability of HRT, some believe in removing both ovaries at the time of hysterectomy to avoid occurrence of residual ovarian syndrome and the remote possibility of ovarian cancer in a woman over 40 years.

Dysmenorrhoea

Congestive dysmenorrhoea is present in endometriosis, PID and uterine fibroids. It is felt as a dull ache in the lower abdomen a few days before menstruation and is relieved following menstrual flow. The woman may also complain of backache and heaviness, in the lower abdomen. Dysmenorrhoea is related to menstrual cycles.

Ovulation Pain (Mittelschmerz)

Ovulation pain occurs in mid-cycle, is often acute, but at times, a sharp pain is followed by a dull pain lasting for several hours. It may be due to rupture of a Graafian follicle, but is often felt at the time of LH peak, 24 h before ovulation. It is postulated to be due to contractility of ovarian perifollicular smooth muscle mediated through $PGF_{2\alpha}$ in which case anti-inflammatory drugs are effective.

Chronic Pelvic Pain Syndrome

Chronic pelvic pain syndrome is a condition not associated with any clinical evidence of pelvic pathology. At laparoscopy, pelvic veins are seen dilated and some are associated with venous stasis. The woman is often of reproductive age and complains of dull aching pain in the lower abdomen; in rare cases, severe pain which responds to postural adjustment. Lying flat relieves or reduces pain, whereas standing, walking or bending worsens it. Other associated symptoms are congestive dysmenorrhoea (60–70%), dyspareunia and postcoital ache. Polycystic ovary syndrome (PCOS) is seen in 50%, and menorrhagia is present in half the number of cases. Shifting of location pain with body movement is characteristic of this syndrome. Doppler ultrasound and venography help in the diagnosis.

Intestinal

Chronic lower abdominal pain related to intestines and sigmoid colon is associated with irritable bowel syndrome and bowel symptoms such as constipation, chronic diarrhoea and colicky pain. Sigmoid colon pain is felt in the left iliac fossa, lasts for a few minutes to a few hours. Intestinal colic is often related to food and accompanied by flatulence. Appendicitis may present with chronic pain in the right iliac fossa. Irritable bowel syndrome and inflammatory bowel diseases are not uncommon in women between 30 and 40 years, and may be associated with pelvic vein congestion (20%).

Stool examination for amoebiasis, sigmoidoscopy, colonoscopy and barium enema may reveal the cause of abdominal pain. Irritable bowel syndrome responds to drotaverine and mebeverine.

Urinary Tract

Infection, cystitis and bladder stones cause chronic pelvic pain, but are associated with urinary symptoms. Chronic retention of urine caused by bladder neck obstruction or a pelvic tumour causes chronic pain in the suprapubic region and difficulty in passing urine. A full bladder is palpable in the suprapubic region. Catheterization will empty the bladder and relieve the discomfort. Urine culture, cystoscopy, radiography of pelvis for stone and ultrasound are useful diagnostic procedures.

Psychological Factors

Some women with chronic pelvic pain appear neurotic and this was considered to be the cause in women with CPP. As mentioned before, now it is proved, that in many cases, neurosis is the result of CPP and not vice versa. Some elements of neurosis may eventually contribute to exaggeration of symptoms. Anti-depressants do not relieve pain in majority of these women, though when given along with medications do alleviate neurosis. Psychotherapy may also help.

Skeletomuscular Pain

It can cause CPP. Ilioinguinal nerve may be trapped in a wide Pfannenstiel incision. Postoperative muscle pain is also possible. Trigger points can be located by pressing a finger where the woman complains of pain. Pain following surgery and accidents are the obvious causes of chronic pain. Referred pain from the spine is an identifiable cause of chronic pain (Table 35.1).

History

Chronic pelvic pain is common in reproductive years. The onset, type, duration and location of pain will provide guidance to the probable cause of the pain. Radiation of pain and its relation to menstruation is important. Obstetric and sexual history are significant. History of intrauterine contraceptive device suggests pelvic infection. Associated urinary and bowel symptoms should be inquired into. Some women with chronic pelvic pain also complain of dysmenorrhoea and dyspareunia.

Past history of tuberculosis and psychiatric problem will help. History of cancer in the family will suggest probable cancer phobia in the woman.

General examination will reveal lymphadenopathy (tuberculosis), anaemia and swelling of feet. Abdominal mass, ascites and tenderness suggest organic lesion.

Vaginal discharge is seen in PID. Bimanual pelvic examination is necessary to rule out organic pelvic lesion. A full bladder is felt anterior to the uterus and is tender on palpation. Rectal examination may reveal a mass or stricture. Pain and restriction of joint movements suggest referred pain to the pelvis. Tenderness in the pelvis is caused by endometriosis, adenomyosis, pelvic adhesion, PID diverticulitis and urinary infection.

Ovarian pain is located at the junction of the middle and inner two-third of a line between the anterior superior iliac spine to the umbilicus, and tenderness can be elicited here.

Investigations

A firm diagnosis and cause of pain cannot always be elicited clinically. Ultrasound, diagnostic laparoscopy, Doppler ultrasound for pelvic congestion, urine tests, barium enema, colonoscopy, sigmoidoscopy, radiography of joints and intravenous pyelography (IVP) will be needed in accordance with the patient's history and examination. CT and MRI may be helpful in some cases. MRI can miss a small nodule, but it picks up rectovaginal endometriosis.

Laparoscopy detects small nodules of endometriosis which are undetected clinically. It can detect pelvic adhesions and

small inflammatory masses apart from obvious pelvic pathology. Therapeutic treatment can be applied in the same sitting such as adhesiolysis and cauterization of endometriosis. Pelvic venous congestion and dilated vessels are not always revealed because of head low position and pressure of pneumoperitoneum.

A poor correlation between macroscopic view and histological evidence exists at laparoscopy and the diagnosis can be missed if peritoneal biopsies are not taken. The burnt-out healed areas of endometriosis can also cause chronic pelvic pain due to fibrosis and entrapment of nerve fibres.

Even if a pelvic pathology is detected at laparoscopy, i.e. fibroid or a small ovarian cyst, adhesions, it may not be the real cause of chronic pelvic pain; it could be just a co-incidental finding. '*Conscious pain mapping' at diagnostic laparoscopy under local anaesthesia is useful in deciding the cause and location of chronic pain.*

When laparoscopy fails to reveal any pathology and pelvic venous congestion is suspected to be the cause of pelvic pain, transuterine pelvic venography is performed by injecting the dye myometrially or pelvic venography using contrast medium. In pelvic congestion syndrome, dilated ovarian and uterine vessels with delayed clearance of dye are observed. Hysteroscopy picks up intra-uterine lesions.

Management

The detection of pelvic pathology or cause for pain determines the therapy appropriate to the cause. Negative investigations at least assure the woman that no serious condition prevails, and cancer phobia can be eliminated. *Diagnostic laparoscopy remains the gold standard when a woman fails to respond to hormones.*

The problem however remains when no cause is found. Doppler ultrasound or pelvic venography will demonstrate the dilated veins. Treatment comprises progestogen therapy or hysterectomy. NSAIDs (nonsteroidal anti-inflammatory drugs) are effective in mild cases. GnRH can shrink the endometriosis and the pelvic veins.

The rationale behind progestogen treatment is that oestrogen causes dilatation of pelvic vessels and progestogens, by their anti-oestrogenic effect, constrict the veins, reduce the blood flow, and suppress ovulation. Medroxyprogesterone acetate (MDPA) up to 30 mg daily (Provera) given for 9–12 months relieves pelvic pain. Unfortunately, pain may recur after stoppage of the drug and prolonged therapy can produce side effects such as increase in body weight, pain, bloating and menstrual irregularity; thus, it is not desirable. Breast cancer may be related to prolonged progestogen therapy.

Micronized progesterone is a natural progesterone available in India as utrogestan 100 mg oral and vaginal tablet. Oral tablets are toxic to the liver and in a woman with liver damage, vaginal tablets are preferred. Because it causes dizziness in a few cases, one tablet daily is advocated at bed time for 10 days in the premenstrual phase. For premenstrual tension, one tablet twice daily is recommended for 10 days premenstrually.

Alternative to prolonged progestogen therapy which can cause systemic side effects, besides inconvenience of daily administration, Mirena IUCD can be inserted. Mirena is very effective in relieving pain and effective over 5 years if needed. Besides, it acts as a contraceptive when the woman is not desirous of pregnancy.

Selective serotonin re-uptake inhibitor fluoxetine 10–60 mg daily, or sertraline 50–200 mg daily are drugs useful in some cases.

The diameter of pelvic veins was reduced and pain relieved for 48 h after intravenous injection of diethyl ergotamine. Further trials are necessary to find out whether oral tablets will lead to permanent cure. Diethyl ergotamine causes vasoconstriction of veins and reduces pelvic congestion. Ligation of ovarian veins has been attempted with variable results. Hysterectomy and bilateral salpingo-oophorectomy may be resorted to if drug therapy fails in elderly women.

Psychotherapy alone or combined with drugs will be useful in pelvic pain syndrome and irritable bowel syndrome.

Acupuncture and short-wave diathermy are adjuvants, and are effective in some women. Presacral neurectomy and laparoscopic uterosacral nerve ablation (LUNA) are recommended in intractable pain in young women.

LUNA is sometimes associated with prolapse and bladder dysfunction. Ureteric damage can also occur. Presacral neurectomy causes bleeding and haematoma.

Static magnetic therapy for 4 weeks or transcutaneous nerve stimulation helps in some cases.

Conscious pain mapping. Varicosity of pelvic veins have been treated with embolization of ovarian vessels or laparoscopic injection of sclerosing agents (sclerotherapy) using 5% ethanolamine maleate. Gel foams and coils are also used.

Conscious pain mapping involves laparoscopy under local anaesthesia and interaction with the woman on touching individual organs to localize the organ of pain. This will improve diagnostic accuracy.

Backache is one of the accompanying symptoms in the following gynaecological diseases.

- Pelvic endometriosis
- Pelvic adhesions
- PID and fixed retroverted uterus
- Prolapse genital tract
- Uterine fibroids
- Orthopaedic cause in the absence of the above backache due to gynaecological causes is limited to below the fourth lumbar spine; it is diffuse and cannot be pinpointed to a spot

History—onset, severity, duration, location
Examination—pelvic examination
Ultrasound—gynaecological pathology
X-ray spine—orthopaedic cause

Key Points

- Acute pelvic pain is an emergency, and requires quick investigations and treatment.
- Chronic pelvic pain is a recognized entity in clinical practice.
- The pain may be of functional origin without any recognizable evident pathology.
- Amongst the common underlying causes of chronic pain are PID, pelvic adhesions, endometriosis and adenomyosis, uterine fibroids, fixed uterine retroversion, ovarian enlargements and neoplasms, genital tuberculosis and residual ovarian syndrome following hysterectomy.
- Blood investigations, ESR, pelvic ultrasonography with colour Doppler, CT/MRI scan, laparoscopy, hysteroscopy may be necessary in occasional cases.
- Treatment consists of proper counselling, antibiotics, and anti-inflammatory drugs like NSAIDs, analgesics, hormones, short-wave diathermy and surgery in selected cases.
- Presacral neurectomy and laparoscopic uterosacral nerve ablation are reserved for intractable pain in young women.

Self-Assessment

1. Discuss the causes of chronic pelvic pain.
2. A 30-year-old woman, para 1+0, presents with chronic pelvic pain for 6 months. How will you manage?
3. A 28-year-old woman, nulliparous, complains of dysmenorrhoea, menorrhagia and chronic pelvic pain. How will you manage this case?
4. A woman, 32-year-old, presents with acute abdominal pain and vomiting. A lump is felt per abdomen. Discuss the differential diagnosis and management.

Suggested Reading

Arulkumaran S. Clinics in Obstetrics and Gynaecology 20: 5, 2006.
Studd J. Acute abdominal pain. Progress in Obstetrics and Gynaecology 13: 311, 1998.
Studd J. Chronic pelvic pain. Progress in Obstetrics and Gynaecology 9: 245, 1991.

Chapter

36

Dysmenorrhoea, Premenstrual Syndrome

CHAPTER OUTLINE

Definition

Dysmenorrhoea means cramping pain accompanying menstruation.

Aetiology

Patients can be classified into groups for understanding the pathogenesis of this distressing condition.

Types

1. *Primary dysmenorrhoea* refers to one that is not associated with any identifiable pelvic pathology. It is now clear that the pathogenesis of pain is attributed to a biochemical derangement. It affects more than 50% postpubescent women in the age group of 18–25 years with ovulatory cycles.
2. *Secondary dysmenorrhoea* refers to the one associated with the presence of organic pelvic pathology, i.e. fibroids, adenomyosis, pelvic inflammatory disease (PID) and endometriosis. Unilateral dysmenorrhoea occurs in a rudimentary horn of a bicornuate uterus. It is also seen in some women wearing intrauterine contraceptive device (IUCD) and in cases of cervical stenosis.

Varieties

Dysmenorrhoea is described under three clinical varieties:

1. *Spasmodic dysmenorrhoea* is the most prevalent and manifests as cramping pains, generally most pronounced on the first and second day of menstruation.
2. *Congestive dysmenorrhoea* manifests as increasing pelvic discomfort and pelvic pain a few days before menses begin. Thereafter, the patient rapidly experiences relief in the symptoms. This variety is commonly seen in PID, IUCD wearers, pelvic endometriosis and fibroids. It is also experienced by women having varicosity of pelvic veins.
3. *Membranous dysmenorrhoea* is a special group in which the endometrium is shed as a cast at the time of menstruation. The passage of the cast is accompanied by painful uterine cramps. This is a rare variety.

Aetiology of Pain (Figure 36.1)

Spasmodic pain is attributed to myometrial contractions due to increased $PGF_{2\alpha}$ secreted under progesterone effect Increased peristaltic action is seen in the subendometrial zone on ultrasound scan and this causes myometrial activity. The pelvic venous congestion as recognized on Doppler ultrasound explains congestive dysmenorrhoea. The relief of dysmenorrhoea following cervical dilatation and vaginal delivery is attributed to damage to sympathetic nerves around the cervix.

Vasopressin by increasing $PGF_{2\alpha}$ secretion in primary dysmenorrhoea is also held responsible. Similarly, endothelin by increasing $PGF_{2\alpha}$ contributes to dysmenorrhoea.

Clinical Features (Table 36.1)

Primary dysmenorrhoea is widely prevalent; more than 50% of teenagers and 30–50% of menstruating women suffer from varying degrees of discomfort. The severe incapacitating type which interferes with a woman's daily activities affects only about 5–15% of the population. Its prevalence is higher amongst the more intelligent and sensitive working-class women. Both the local and systemic symptoms are apparently the result of increased levels of prostaglandins ($F_{2\alpha}$) in the menstrual fluid. This results in uterine cramping, nausea, vomiting, backache, diarrhoea, giddiness, syncope and fainting. It is responsible for the highest incidence of absenteeism, resulting in loss of work hours and economic loss.

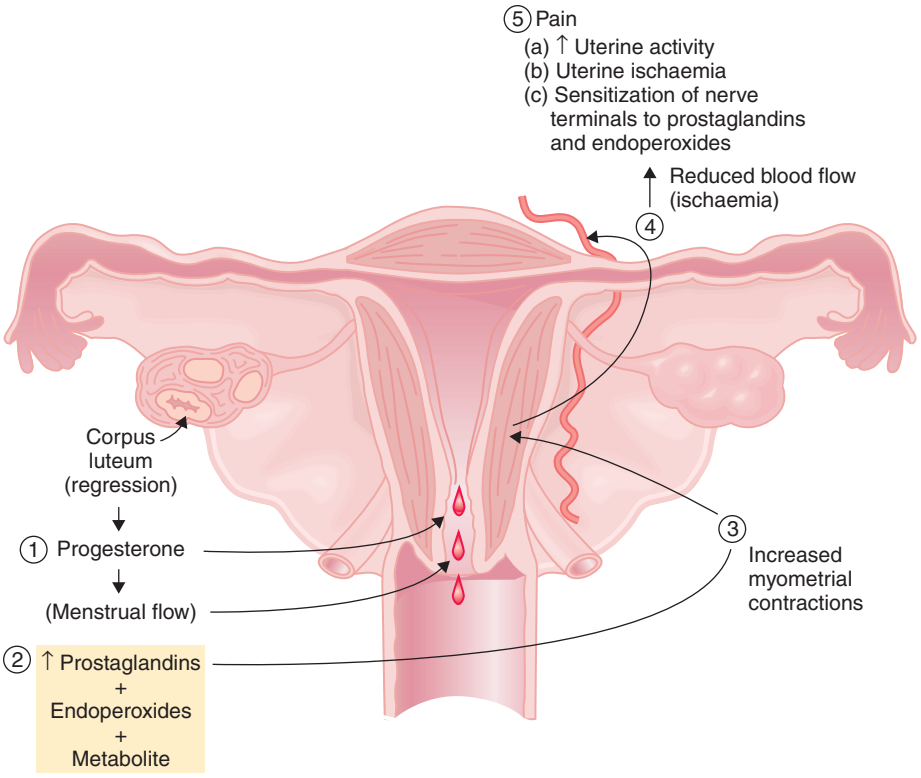

Figure 36.1 Postulated mechanism in the generation of pain in dysmenorrhoea. (Source: Hacker NF, Gambone JC, Hobel CJ, *Hacker and Moore's Essentials of Obstetrics and Gynecology*, 5th ed. Philadelphia: Elsevier, 2010.)

TABLE 36.1 Differentiating features of primary and secondary dysmenorrhoea

Differentiating Features	Primary	Secondary
Onset	Within 2 years of menarche	20–30 years, maybe pre- and postmenstrual
Description	Cramping—hypogastrium, back, inner thighs	Variable dull ache
Symptomatology	Nausea, vomiting, diarrhoea, headache, fatigue	Dyspareunia, infertility, menstrual disorders
Pelvic findings	Normal	Variable, depending on cause
Aetiology	Excessive myometrial contraction, ischaemia, excessive prostaglandin production	Endometriosis, PID, adenomyosis, fibroids, pelvic vein congestion
Management	Reassurance, analgesics, NSAIDs, antispasmodics, OC pills, in rare cases, surgery—Cotte's operation or laparoscopic uterosacral nerve ablation (LUNA)	Treatment directed to the cause

Primary dysmenorrhoea occurs in ovulatory cycles; hence, it makes its appearance a few years after menarche with at least 6–12 months of painless periods. It is most intense on the first day of menses and progressively lessens with menstrual flow. It often lessens with passage of time and after childbirth. Pelvis findings are normal. Pain may be accompanied by nausea, vomiting, headache, fainting.

Investigations

In women suffering from secondary dysmenorrhoea, tests to confirm the clinical diagnosis and unravel the extent and type of underlying pathology should be carried out. These commonly include the following:

- Pelvic sonography followed by CT scan or MRI scan, if indicated.
- Diagnostic hysterosalpingogram/sonosalpingography.
- Endoscopy—diagnostic hysteroscopy/laparoscopy.

Treatment

Treatment includes counselling, psychotherapy to modify patient's perception of her problem and alter behavioural attitude, medical measures and surgical interventions.

Medical Measures

Therapy for primary dysmenorrhoea consists of measures to relieve pain and to suppress ovulation if the woman desires contraception additionally.

- Analgesics like paracetamol 500 mg t.i.d./piroxicam 20 mg/b.i.d.
- Antispasmodics like hyoscine (Buscopan) compounds t.i.d./Camylofin (Anafortan) t.i.d./Drotaverine (Drotin) t.i.d., Trigan-D.
- Prostaglandin synthetase inhibitors are cyclooxygenase inhibitors. Nonsteroidal anti-inflammatory drugs (NSAIDs) like mefenamic acid 250–500 mg/q.i.d. provide relief in 80–90% cases. Indomethacin 25 mg three to six times daily

provides relief in 70% cases. Naproxen 275 mg/t.i.d. relieves about 80% cases/ketoprofen 50 mg/t.i.d. is successful in 90% cases. Ibuprofen 400 mg 6–8 hourly is also effective. The advantage of the above regimes is that medication is restricted to the symptom days alone, and it does not interfere with ovulation. Meloxicam has no gastric side effects. The side effects of these drugs are nausea, vomiting, blurred vision, nephrotoxicity and gastric ulcer on prolonged use.

- Glyceryl trinitrate (nitroglycerine), a nitric oxide donor, relieves pain by relaxing smooth muscles of the uterus.
- Progestogen containing IUCD (Mirena, Progestasert) relieves pain in addition to providing contraceptive measures and reducing bleeding.
- OC drugs administered cyclically suppress ovulation and are useful in relieving dysmenorrhoea. The advantages of regularity of periods, modest bleeding and desired contraception make this the treatment of choice in many young women. The drugs also cure Mittelschmerz pain.
- Pelvic endometriosis may be treated with increasing doses of danazol/OCs/GnRH antagonists (leuprolide, buserelin, nafarelin).
- Vitamin E 200 mg b.i.d. starting 2 days before and 3 days during periods claims to reduce dysmenorrhoea.

Surgery

Surgery is indicated if medical measures fail to provide relief and in women with secondary dysmenorrhoea to treat the underlying pelvic pathology. Surgical interventions may be diagnostic to begin with, followed by definitive treatment based on severity of symptoms, patient's age, desire for childbearing, menstrual functions and the patient's perception of her problem. Surgical interventions include the following:

- Diagnostic hysteroscopy followed by dilation and curettage (D&C), excision of polyp or uterine septum. Dilatation of cervix—it damages the nerves.
- Diagnostic laparoscopy followed by lysis of pelvic adhesions, myomectomy, draining of chocolate cyst, cautery or laser vaporization of islands of endometriosis, excision of adnexal masses, LUNA (laser-assisted uterosacral nerve ablation) for spasmodic dysmenorrhoea.
- Laparotomy followed by excision of chocolate cysts, eradication of endometriosis, myomectomy, excision of localized adenomyoma, presacral neurectomy (Cotte's operation).
- Hysterectomy in the elderly woman is the last resort.
- Transcutaneous electrical nerve stimulation (TENS) is effective in 45% cases.

Premenstrual Syndrome

Premenstrual syndrome (PMS), also described as premenstrual tension (PMT), is a symptom complex recognized primarily by cyclic changes associated with ovulatory cycles. It occurs 7–14 days prior to menstruation and spontaneously resolves after menses. It is frequently encountered in middle-aged women. It is important for two reasons, firstly because the symptoms of PMT are responsible for socioeconomic loss and secondly because of associated legal and women's rights issues that have arisen in conjunction with personal accountability during the premenstrual period. It comprises physical, psychological and behavioural changes not associated with organic lesion (Table 36.2). It is prevalent in 5% women.

Aetiology

The exact cause of PMS is not known. It has been postulated that it represents a syndrome which is the result of multiple biochemical abnormalities. Amongst these, the following have been implicated: (i) oestrogen excess or progesterone deficiency in the luteal phase; (ii) increased carbohydrate intolerance in the luteal phase; (iii) pyridoxine deficiency—this vitamin plays a role in oestrogen synthesis and also in dopamine and serotonin production; (iv) increased production of vasopressin, aldosterone, prolactin and systemic prostaglandins which adversely affect renal function and contribute to fluid retention and bloating; and (v) fluctuations in opiate peptide concentrations affecting endorphin levels. However, biochemical estimations do not bear these out. Hence, at present it is not yet clear whether PMS is an abnormal response to normal hormonal fluctuation or a result of hormonal abnormalities. *A woman with hysterectomy but conservation of ovaries may also suffer from PMT suggesting that the ovarian hormones have a role in PMT.*

Low level of β-endorphins (neurotransmitters) in the brain and low level of serotonin are probably responsible for psychiatric disorders. Genetic predisposition is also recognized in a few cases.

Clinical Features

The syndrome may be mild, moderate or severe.

Symptoms of PMS are myriad and not associated with organic lesion in the pelvis. The classic description includes increasing breast tenderness, abdominal bloating, headache, sleeplessness, fatigue, emotional lability, mood swings and depression, irritability, fluid retention and weight gain beginning 7–14 days prior to menses. As menstruation approaches, psychological abnormalities like irritability and hostility increase. The dominant symptom in different groups varies from anxiety, to depression, to fluid retention, bloating, headache and breast pain, to increased appetite and craving for sweet foods. Five per cent suffer from severe symptoms which influence daily activity. The body weight increases by 1 kg and breast volume by 20% due to oedema and increased vascularity. PMT

TABLE 36.2 Various symptoms of premenstrual tension

1. Pain	Headache, breast pain, abdominal cramps, muscle stiffness, backache, generalized body ache
2. Water retention	Breast pain, bloating, weight gain
3. Behavioural changes	Low performance, difficulty in concentration, irritability, depression, forgetfulness, low judgment, anxiety, loneliness, feel like crying
4. Autonomic changes	Dizziness, faintness, nausea, vomiting, hot flushes

does not occur before puberty, during pregnancy or after menopause. It may however occur if the post-menopausal woman goes on hormone replacement therapy (HRT).

Diagnosis

Diagnosis depends on history and careful questioning. Temporal correlation of symptoms with the premenstrual phase of the cycle as documented in a menstrual diary helps to arrive at a rational diagnosis. No organic pelvic lesion is detected, and no definite test is available to confirm the diagnosis.

Treatment (Table 36.3)

- For psychological symptoms (psychotherapy), counselling and reassurance alone suffice for the milder cases. Vitamins B_1 25–50 mg, B_6 100 mg and E 200 mg daily help.
- For breast symptoms alone—beneficial therapies include (i) Danazol 100–200 mg in divided doses during the luteal phase. However, adverse masculinizing effect following long-term usage is a drawback. (ii) GnRH analogues provide relief, but long use causes menopausal (antioestrogenic effects) symptoms and osteoporosis. Besides, the drugs are expensive. The following drugs are used:
  - Goserelin (Zoladex) 3.6 mg subcutaneously 4 weekly.
  - Leuprorelin acetate (Prostap) 3.75 mg IM 4 weekly.
  - Triptorelin (Decapeptyl) 3 mg IM 4 weekly.
  - Buserelin (Suprefact) 200–500 mg daily subcutaneously three times a day for 6 months. Oestrogen and progestogen as add back-up therapy to GnRH prevents side effects of oestrogen deficiency.
  - Bromocriptine 0.25–2.5 mg relieves breast tenderness, but has side effects like nausea, dizziness, weight gain and swelling.
- For bloatedness, weight gain, fluid retention and headaches, (i) salt and fluid restriction and (ii) spironolactones 100 mg and diuretics may help. Buspirone 7.5–15 mg daily or drospironolactone (Yasmin) contains 3 mg spironolactone and 30 μg EE_2. It is used cyclically as combined oral pills. Evening primrose oil (Primosa) 500 mg tid; It is non-hormonal and contains polyunsaturated essential fatty acids. It diverts harmful PGE_2 to PGE_1 and replenishes CNS PGE_1. By this. it suppresses irritability and depression, as well as reduces fluid retention and mastalgia. Gold prim contains primosa with vitamin and minerals (six capsules a day).
- *Prostaglandin inhibitors*: Mefenamic acid and naproxen improve mood and physical symptoms. These drugs cause gastrointestinal (GI) upsets and rashes. Cyclooxygenase inhibitor (cox-2) has less side effects than NSAID. Ibuprofen 400 mg 6–8 hourly is also useful.
- Anxiolytics (alprazolam) 0.25 mg and antidepressants (tricyclics) do provide some relief from PMS, but the benefits of therapy must be weighed against the side effects.
- γ-aminobutyric acid (GABA) suppresses anxiety level in the brain. Therefore, GABA agonists are effective. Selective serotonin re-uptake inhibitors (SSRI) like fluoxetine 20 mg daily and sertraline 50 mg have been beneficial in treating physical as well as behavioural symptoms (60% cured). The side effects include headache, drowsiness, insomnia, sexual dysfunction and GI disturbances.
- Sertraline 50–150 mg and citalopram 20–40 mg daily are also used in the premenstrual phase. Vitamin B_6 (60–100 mg) and magnesium (200 mg) are co-factors in the synthesis of neurotransmitters serotonin and dopamine. One gram calcium daily also helps to relieve neurological symptoms. Venlafaxine is a combination of sertraline and noradrenaline reuptake inhibitor.
- Micronized progesterone pessary 200–400 mg daily in the premenstrual phase. *Mirena IUCD is now used instead of oral progestogens.*
- OCs render the cycles anovulatory and provide relief.
- Oestrogen skin patch releasing 100 μg daily or 50 mg oestrogen implant with 100 mg testosterone is also employed.
- General measures like exercise, relaxation and hobbies, meditation and yoga are likely to be beneficial.
- Hysterectomy with removal of ovaries is a last resort. In a younger woman, oophorectomy will need IVF programme with donor eggs.
- Reassurance, counselling, psychotherapy and selective use of drugs help to control the symptoms.

In conclusion it may be stated that reassurance, counselling, psychotherapy and selective use of medications help to control these symptoms.

TABLE 36.3 Management of premenstrual syndrome

Psychosomatic	Vitamins B1, B6, E Selective serotonin reuptake Inhibitor, sertraline, citalopram anxiolytics
Breast pain	Danazol, bromocryptine GnRh
Pelvic pain and bloatedness	Yasmin, primrose Prostaglandin inhibitors OC, progestogen Mirena IUCD

Key Points

- Spasmodic dysmenorrhoea is common in adolescents and young women. Congestive dysmenorrhoea is often associated with pelvic inflammatory disease, fibroids and pelvic endometriosis.
- Acquired dysmenorrhoea is a manifestation of organic uterine pathology such as fibroids and adenomyosis.
- Premenstrual syndrome is a functional disorder found in educated and economically independent working middle-aged women and requires treatment.

Self-Assessment

1. Describe the management and clinical features of premenstrual syndrome.

Suggested Reading

Bonnar J. Recent Advances in Obstetrics and Gynaecology 15: 169, 2003.

Chapter 37 Vulval and Vaginal Cancer

CHAPTER OUTLINE

Cancers of the Genital Tract

Genital tract cancers are an important topic in gynaecology because of the high mortality, morbidity and shortening of lifespan in women. The detection of the pre-invasive and micro-invasive stages and the near-100% survival by conservative surgery now adds to the success story of genital tract cancers. While breast cancer predominates in the developed countries, genital tract cancers remain the main killers in developing countries, including India.

Table 37.1 shows that cancer of the cervix holds the prime position in developing countries, followed by that of the uterus, ovary, vulva, fallopian tube and vagina in that order of frequency and forms a major health problem despite it being potentially preventable.

Burden of gynaecologic and breast cancers in Southeast Asia: Nandakumar et al. (2000) reviewed the cancer burden amongst women living in the Indian subcontinent. Their findings have been briefly shown in Table 37.2 for quick comparison.

Table 37.2 shows that cancer of the cervix continues to be the leading cause of cancer in our subcontinent. Breast cancer comes up as the second most common cancer, except in Pakistan, where breast cancer leads the list of cancers in women. Fortunately, both these cancers are amenable to early diagnosis and cure.

Cancer of the Vulva

Cancer of the vulva is a rare entity and accounts for 1–5% of all genital cancers. In developing countries, incidence is 50% lower.

Malignant tumours of the vulva are grouped as follows:

1. Pre-invasive lesions—intraepithelial cancer VIN I, II, III
   Bowen disease
   Paget's disease
   Microinvasive
   Melanoma in situ

   } Intraepithelial carcinomas

2. Invasive lesions
   - Squamous cell carcinoma—most common 90%
   - Melanoma 1–5%
   - Adenocarcinoma 1%
   - Sarcoma 2%
   - Rodent ulcer or basal cell carcinoma 1%.

The vulva can also occasionally be the site of metastatic cancer. Cancer of the vulva and the cervix may coexist in case it is caused by papilloma virus. Most of these malignant lesions are located on the labia majora. In 5%, the lesions are multifocal, and are seen in younger women below 40 years.

A single lesion is seen in older women.

Pre-Invasive Lesions

Intraepithelial Vulval Carcinoma (VIN)

Definition. Intraepithelial vulval cancer is defined as a cellular abnormality limited to the epithelium of the vulval skin, excluding the keratinized layer. The presence of acanthosis, intraepithelial pearl formation at the rete pegs and inflammatory reaction in the dermis are the other characteristics of this lesion. The cancer cells are restricted by the basement membrane and do not spread to the dermis.

Classification. The classification is comparable to that of pre-invasive carcinoma of the cervix.

VIN I. The cellular abnormality is mild, limited to the basal layer, involving the lower one-third of the vulval epithelium.

VIN II. The cellular abnormality extends to the lower two-thirds of the vulval epithelium and involves the basal as well as the intermediate layer; it is often associated with HPV (human papilloma virus) infection.

VIN III *also in-situ vulva*. The entire thickness of the epithelial layer shows cellular abnormality, but there is no

TABLE 37.1 Incidence of genital tract cancers in developed and developing countries

Organ	Developed Countries	Developing Countries
Cervix	60%	80%
Uterus	25–30%	5%
Ovary	10%	10–15%
Vulva	4–5%	1–5%
Fallopian tube	0.3–0.5%	0.3%
Vagina	0.2%	0.2%

TABLE 37.2 Common gynaecologic cancers and breast cancer in Southeast Asian countries

Cancer Site	India (ASR)	Pakistan (ASR)	Bangladesh (ASR)	Sri Lanka (ASR)
Cervix	30.7	6.5	27.6	28.8
Corpus uteri	<1.5	5.8	<1.5	<1.5
Ovary	4.9	9.8	3.3	5.1
Breast	19.1	50.1	16.6	19.3
Others	<1.0	<1.0	<1.0	<1.0

ASR: Age-standardized. Rates per 100,000 female population.

vascular or lymphatic involvement, and the basement membrane is intact. It is most common.

Lately, VIN I is deleted because of lack of reproducibility of histopathology and difficulty in differentiating from the normal.

VIN III is of two types:

1. Young HPV-positive women presenting with multiple lesions—90% regress and 10% progress to invasive cancer.
2. Elderly women, HPV-negative with a single lesion associated with lichen sclerosis—often progressing to invasive cancer.

In a young woman, the period between CIN disease and the development of invasive carcinoma is about 8 years. *It is, however, important to remember that invasive cancer need not always be preceded by pre-invasive lesion and it can develop de-novo.*

Incidence. A rise in the incidence of VIN in recent times is attributed to greater awareness of its existence, better diagnosis and the longer survival of woman beyond the age of 70, when the carcinoma of the vulva prevails. The intraepithelial cancer also increasingly affects younger women below 40 years, who are often affected by sexually transmitted diseases and viral infections such as HPV (70–80%) and herpes simplex virus II (HSV). Human papilloma virus (16, 18, 31, 33) (HPV) as well as smoking predisposes one to cancer. Type 16 is the most common and is present in 60–90% cases.

Aetiology. The aetiological factors are similar to those of vulval dystrophy (see Chapter 27 on diseases of the vulva), and therefore it is not surprising to see the lesions of VIN amongst the dystrophic areas.

Chronic vulval irritation, immunosuppressive conditions like pregnancy, HIV infection and smoking suppress the immune system and predispose the patient to VIN lesions. Condyloma, sexually transmitted diseases and dystrophies are the other risk factors. Poor nutrition and hygiene, and local moisture are the contributing factors. The association with carcinoma of the cervix and breast cancer in the same woman indicates the common aetiological factors.

Fifty per cent VIN cases have sequential or concomitant neoplasia in the lower genital tract, especially cancer of the cervix.

The VIN lesions are observed in relatively young women below 40. Obesity, diabetes, chronic pruritus and dermatitis are often linked to this disease.

Histology. A loss of polarity, and stratification and dystrophic changes are confined to the epidermis, and the basement membrane remains intact.

Clinical Features. Many early lesions may remain asymptomatic for a long period, and VIN I is not visible macroscopically. Pruritus may be the only symptom in the early stage. It may be mistaken and treated for fungal infection. Later, soreness, dysuria and dyspareunia develop. Pre-existing leucoplakia, condyloma and dystrophic areas may now show white, or red, flat warty or papular lesions, single or multiple with well-defined edges. Multiple widespread lesions are more common in younger women, and occur in 5–25% cases. Some develop pigmentation. The lesions mainly affect the labia majora but may also be seen over the perineum and perianal regions. The clitoris and labia minora are not spared. The inguinal glands are not palpable (Figure 37.1).

Investigations. It is impossible to diagnose VIN and differentiate it from dystrophies without a biopsy. Exfoliative cytology does not yield satisfactory results because of keratinization and poor exfoliation of cells. Colposcopic study too does not

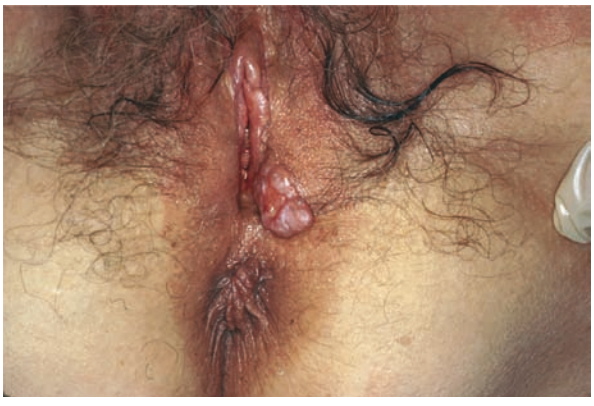

Figure 37.1 Basal cell carcinoma. (From Figure 8-30. Clinical Gynecologic Oncology. In: Invasive Cancer of the Vulva, 2007.)

always show punctuation, mosaic and abnormal vascular pattern if the vulval skin is hypertrophied and thick. Application of K-Y jelly improves visualization of the vasculature of vulval skin. Five per cent acetic acid causes white areas and staining the area with 1% toluidine blue marks abnormal areas royal blue, thus enabling selective biopsies from the dark-stained areas. Excisional biopsy of a localized lesion picks up VIN. Colposcopy and pap smear of the cervix are also required to rule out concomitant pre-invasive cancer of the cervix.

Proctoscopy and anoscopy may be required if the perianal region is involved in the lesion. This will show the extension into the anal wall. Vaginal and Pap smear become mandatory in the diagnosis as well as in the treatment of these multifocal lesions.

DNA study is useful so far as aneuploidy is concerned. Aneuploidy strongly suggests the possibility of VIN progressing to invasion and should be treated, whereas euploidy in young women can be observed over a period of 6 months, with a hope of regression.

Human papilloma virus DNA detection combined with cytology improves the detection test to 95%.

Vulvoscopy defines vascular pattern, but is not so clear because of keratinization. Condyloma which does not respond to treatment should be investigated for VIN.

Management (Table 37.3). The purpose of treating VIN lesions is threefold:

- To relieve the symptoms of pruritus and soreness.
- To prevent cancer developing in the area. *Five to ten per cent VIN III progress to invasive cancer within 8 years.*
- To avoid mutilating surgery and sexual dysfunction in young women; radical vulvectomy is mutilating and causes genital disfigurement and dyspareunia.

The treatment is therefore based on the age of the woman, sexual activity, site and extent of VIN and grading.

With more young women developing VIN, there is a tendency to shift from the earlier radical approach to a very conservative management with success of 90–94%. However, a long follow-up is required to watch for recurrence and progression to invasion.

TABLE 37.3 Management of VIN

- Observe young women with multiple lesions and HPV positive for 6 months. Persistent lesion requires treatment.

Excision
- Wide excision
- Skinning vulvectomy

Ablative
- CO_2 laser
- Photodynamic therapy

Surgery
- Simple vulvectomy in older women and in Bowen disease

Medical
- Local application of dinitrochlorobenzene, 5% testosterone cream, fluoroxacil (5-FU) mainly for local recurrence
- Lifelong follow-up

The management is as follows:

1. Young women with multiple focal lesions and showing euploidy on DNA study may be observed for up to 6 months, because such lesions often disappear by then. This occurs more commonly in young women who develop VIN during pregnancy, during an immunosuppressive period and following viral infection, especially HPV 16, 18.
2. With unifocal lesion, wide excision of the lesion going 2 cm beyond the margin is found adequate and vulvectomy is not warranted. The skin edges can be approximated with or without undermining the excised margins. Local recurrence is the risk to be watched for. Excision is performed with a knife, cautery or laser.
3. Persistent VIN and VIN III require excision, skinning vulvectomy (Rutledge and Sinclair) with split skin graft to avoid disfigurement of the introitus and dyspareunia. Skinning vulvectomy is desirable if the involved area is widespread. CO_2 laser vaporization (Townsend) or laser excision, cryosurgery, application of dinitrochlorobenzene, 5% testosterone cream and corticosteroids are also conservative treatment, but they do not guarantee against recurrence or invasion and need lifelong follow-up. Laser therapy avoids pain and scar formation without disfigurement; the cut heals in a few weeks. Periurethral and perianal lesions are however not amenable to laser, and require excision.

   Cryosurgery up to a depth of 2 mm can cause extensive sloughing. *Prophylactic HPV vaccine* is now available (refer to cancer cervix for vaccine)

   Photodynamic therapy (PDT) uses a tumour photosensitizer 5-amino-levulinic acid (ALA) combined with non-thermal light of appropriate wavelength to generate oxygen-induced cell death. Quick healing and minimal tissue destruction are its advantages.

   Conservative therapy requires that invasive lesion should be excluded by multiple or adequate biopsy.
4. Elderly women should be dealt with by simple vulvectomy.

   Lifelong follow-up is required in all cases.

Follow-Up. Recurrence around the excised lesion or fresh recurrence occurs in 20–30% of cases. Five to ten per cent progress to invasive cancer in 8 years, after which invasion is less likely, unlike that in carcinoma in situ of the cervix which may take 10–15 years to develop to invasive cancer. Pap smear, colposcopy 3–6-monthly and later yearly will be required. Recurrent tumour is treated with 5-FU.

Bowen Disease

Bowen disease is an intra-epithelial carcinoma of the vulva. It presents as a slow-growing hard reddish indurated patch. Initially, it is well circumscribed, with a dry or eczematous surface. This verrucous lesion rarely metastasizes. Pruritus is the main complaint. The biopsy reveals typical prickle cells invading the epidermis. The presence of giant cells and corps rond are characteristic of the lesion. The vagina and the cervix may also show similar

lesions in the colposcopically directed biopsy. The treatment consists of simple vulvectomy.

Paget's Disease

A rare extramammary disease, Paget's disease is comparable to intraductal carcinoma of the breasts, because the apocrine sweat glands are involved. It occurs in a postmenopausal woman as a sharply demarcated and slightly elevated white indurated or eczematous lesion and causes pruritus. The biopsy reveals the characteristic large pale vacuolated cells in the epidermis (Figure 37.2). Perianal and perineal areas are rarely involved. The Paget's cells are adenocarcinomatous mucus-secreting cells, round cells with pale cytoplasm and vesicular nuclei. Mitosis is rare. Unlike Paget's disease of the breast, the underlying carcinoma is reported in only 20% due to adenocarcinoma of the Bartholin's gland. In the perianal region, it is associated with adenocarcinoma of the anus. It is important to search for the underlying malignancy which may be involved in 30% cases. The treatment is local excision or vulvectomy if no underlying lesion is detected. With underlying lesion, treatment is as of invasive cancer. Radiotherapy is employed for women unfit for surgery but prolonged follow-up for recurrence is obligatory. Local and systemic 5-FU and bleomycin is also tried. The tumour recurs in 20%.

Microinvasive Cancer

Microinvasive melanoma is rare and detected only histologically.

Superficially invasive vulval cancer (microinvasive-SIVC) is defined as a single lesion measuring 2 cm or less in the maximum diameter with a depth of invasion not greater than 1 mm. It represents Stage IA of the FIGO classification. Multiple foci even of depth less than 1 mm do not fall under this classification. Avoiding radical surgery while maintaining the same survival rate has reduced the surgical morbidity of extensive lymphadenectomy and improved sexual and general quality of life. Sentinel lymph node mapping and accurate staging is therefore very necessary. Wide excision or vulvectomy is done.

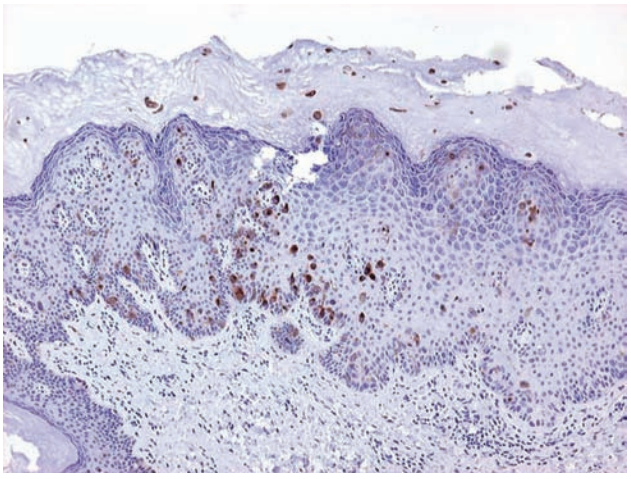

Figure 37.2 Paget's disease of the vulva. (Source: David Dabbs, University of Pittsburgh School of Medicine, Department of Pathology.)

When the lymph nodes are involved, surgery is better than radiation for groin lymph nodes. However, radiotherapy yields better survival rates for pelvic lymph nodes.

Invasive Carcinoma of the Vulva

Epidemiology

Vulval cancer accounts for 2–4% of all malignancies of the female genital tract. The women are generally elderly, in the sixth or seventh decade of life. Thirty per cent are over the age of 70, and 40% are between the age of 60 and 70 years. Increasing number of lesions are now seen in younger women, and most of them suffer from sexually transmitted diseases like HPV and HIV infection. Smoking is also a risk factor in these young women. However, only 2% are below 30 years of age. Nulliparous and women of low parity are disposed to vulval cancer. Vulval cancer is associated with cervical and ovarian cancer in 20% cases. This may be related to viral infection in the genital tract in the former and low parity and older age group in the ovarian cancer.

Aetiology

The causes are the same as those of in-situ carcinoma. The lesion associated with VIN and atypical dystrophy often progresses to invasive cancer. VIN however does not always precede invasive cancer as is seen in cervical cancer. Squamous cell carcinomas account for 90% of all vulval cancers.

Clinical Features

Eighty per cent women complain of pruritus, vulval swelling, lump or an ulcer. The lump may be papular, raised pigmented area. The ulcer has often an everted margin. The surrounding skin may be fissured, cracked and indurated. Leukoplakic or dystrophied area may be present, and these may be single or multifocal. The lesion is more commonly encountered over the labia majora (70%), but the clitoris and perineal area may be involved. The anterior two-thirds of the vulva is usually involved. The lesion is single in 98% cases, and multiple lesions are seen in only 2% in elderly women.

The ulcerative lesions bleed, and cause offensive vulval discharge. Pain is a late feature of the disease. When the urethra is involved, the woman complains of dysuria and micturition difficulty. When the anal area is affected, rectal symptoms in the form of rectal bleeding and painful defecation develop. The inguinal lymph nodes may or may not be palpable. A woman may be diabetic, hypertensive or obese.

Differential Diagnosis

Tubercular or syphilitic ulcer may be identified by biopsy. Elephantiasis vulva may also be initially mistaken for vulval cancer. Soft sore and lymphogranuloma are identified by biopsy.

Staging

Refer to Table 37.4.

TABLE 37.4 Staging of vulval cancer

Stage I	Tumour confined to the vulva
IA	Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm*, no nodal metastasis
IB	Lesions >2 cm in size or with stromal invasion >1.0 mm*, confined to the vulva or perineum, with negative nodes
Stage II	Tumour of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes
Stage III	Tumour of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino–femoral lymph nodes
IIIA	(i) With 1 lymph node metastasis (≥5 mm), or (ii) 1–2 lymph node metastatis(es) (<5 mm)
IIIB	(i) With 2 or more lymph node metastases (≥5 mm), or (ii) 3 or more lymph node metastases (<5 mm)
IIIC	With positive nodes with extracapsular spread
Stage IV	Tumour invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures.
IVA	Tumour invades any of the following: (i) Upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or (ii) Fixed or ulcerated inguino–femoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

*The depth of invasion is defined as the measurement of the tumour from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

Spread of the Tumour

The tumour proliferates mainly by direct spread to the adjacent organs and by the lymphatics; blood-borne metastases are rare.

Parry Jones was the first to describe the lymphatic spread that occurs in a systematic manner. At first, the superficial inguinal nodes are involved through lymphatic emboli, but later lymphatic channel permeation occurs causing lymphatic blockage and leg oedema. The malignancy spreads to deep nodes and via the gland of Cloquet (uppermost of the femoral or the lowermost of the external iliac gland) to the external iliac glands, obturator and common iliac nodes in the advanced stages.

Laterally placed tumours rarely spread to the contralateral inguinal glands, but centrally located lesion involves the lymph nodes of the opposite side in 25% cases and this is because of crossing of lymphatics in the midline.

Lymph nodes not clinically suspicious may show metastasis in about 25% cases.

Inguinal lymph nodes are involved in 10% in Stage I, 30% in Stage II, 70% in Stage III and 100% cases in Stage IV.

See Figure 37.3 for lymphatic drainage of the vulva.

Lymphatics of the clitoris drain directly into the pelvic lymph nodes. The regional lymph nodes are assessed by

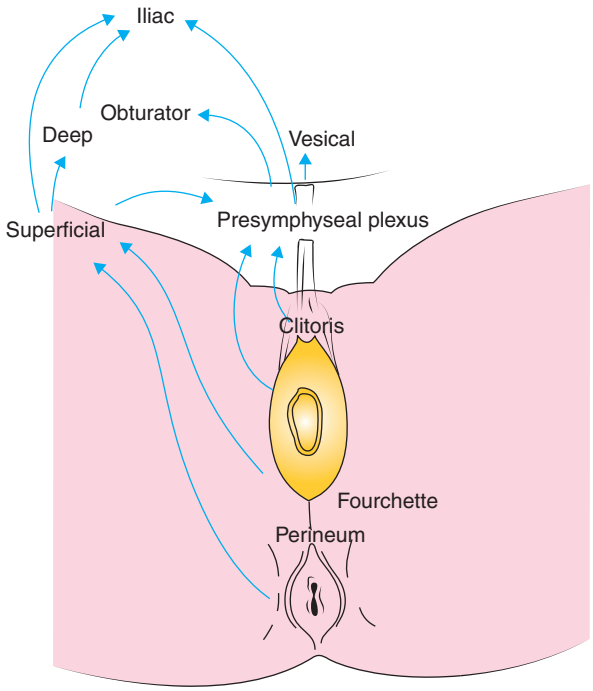

Figure 37.3 Lymphatic drainage of the vulva.

MRI and PET. The involvement of the lymph nodes depends upon the site of the lesion, its size and depth of invasion.

Investigations

Diagnostic investigations include:

- Punch or excision biopsy depending upon the size of the lesion.
- Cystoscopy if urethra is involved.
- Anoscopy and proctoscopy if the perianal area is involved.
- X-ray of chest and bones.
- CT and MRI scans for lymph node metastasis.
- Lymphography is superior to CT scan and can detect metastasis in the lymph nodes 2–5 mm in size, whereas CT can pick up metastasis only if it is more than 1 cm.

Restricting unnecessary lymph node dissection reduces the surgical morbidity in early cancer. However, to do this, determination of the extent of primary lymph node (sentinel) involvement is necessary. Lymphatic mapping and sentinel node biopsy (frozen section) before or during surgery help in carrying out adequate surgical procedure with good prognosis.

Mapping is done by:

- Intraoperative intradermal injection of blue dye around the tumour. A detection rate of 100% is reported.
- Labelling tissues with radioactive tracer and localization with a hand-held detector.
- Lymphoscintigraphy has also 100% detection rate.

Microinvasive vulval cancer Stage IA is applicable only to a single lesion of squamous cell carcinoma up to 2 cm in size and less than 1 mm invasion below the epithelium with

no evidence of vascular space invasion and lymph nodal involvement. Adenocarcinoma and melanoma are not included in this group of tumours because of their high propensity for nodal involvement. Microinvasive tumours can be treated by local excision with a margin of 2 cm beyond the lesion, provided the surrounding skin is not dystrophic. If it is dystrophic, vulvectomy is recommended because of the possible recurrence of cancer in the dystrophic tissue. Multiple foci do not come under this classification and require more radical surgery.

Treatment. The traditional treatment by radical vulvectomy with bilateral lymphadenectomy of inguinal, femoral and pelvic nodes, as described by Way and Taussig in 1935, has undergone radical modification in recent years. This is based on the observation of high primary mortality of radical surgery, a high percentage of negative lymph node involvement and satisfactory 5-year cure rate with conservative approach (Table 29.5). Besides, invasive cancer encountered in young women has also welcomed this conservative surgery.

Radical surgery can cause wound infection, haemorrhage and thrombo-embolism. Late sequelae include scarring and disfigurement, stenosis of vulva, dyspareunia, sexual dysfunction, lymphoma, lymphoedema, genital prolapse and stress incontinence of urine. The factors to be considered before individualizing the surgical treatment are the general condition of the woman, stage and site of the tumour, tumour histology and differentiation. The surgery is now performed with a separate groin incision rather than extensive skin incision over a wide area which is mutilating and difficult to heal. Primary mortality of surgery is 1–5%.

Stage I. Lateral lesions less than 2 cm can be dealt with by partial vulvectomy with a margin of 3 cm beyond the growth, or unilateral vulvectomy, accompanied by ipsilateral inguinal node dissection. If the frozen section reveals absence of involvement of glands, nothing more is required. This is because, in this case, the contralateral lymph nodes are involved in only 0.4% and extensive surgery will not improve survival, but add to morbidity. Ipsilateral lymph node involvement demands contralateral removal of inguinal glands. The pelvic lymph nodes are removed only if the gland of Cloquet (femoral) shows malignant cells. Alternatively, a woman is subjected to postoperative radiation, in place of extensive pelvic node dissection. A central tumour requires bilateral inguinal node dissection.

TABLE 37.5 Results of treatment and 5-year survival rates for cancer of the vulva

FIGO Staging	5-Year Survival Rates
Stage I	90%
Stage II	80%
Stage III	About 50%
Stage IV	About 15%
Total	About 60%

Stage II. The tumour between 2 and 4 cm (Stage II) will require total vulvectomy and bilateral groin lymph node dissection. If these are positive, pelvic node dissection or postoperative radiotherapy is required to the pelvic nodes.

If the tumour is more than 4 cm in size, poorly differentiated or it is a melanoma or adenocarcinoma, nothing less than radical vulvectomy and bilateral lymphadenectomy with pelvic node dissection are required. A separate vulval incision and two groin incisions are employed.

Stage III. Megavoltage radiotherapy 4000–5000 rads over a period of 5 weeks causes shrinkage and at times total disappearance of the tumour. Local excision of the shrunken tumour is then adequate and eliminates the need for exenteration operation. Local recurrence can be dealt with by chemotherapy. Forty per cent survival and 30% recurrence have been reported.

Stage IV. It is treated by chemotherapy or radiotherapy. Anal involvement is satisfactorily treated with infusion of 5-FU and mitomycin-C, followed by radiotherapy 3000 rads, over 3 weeks. Local excision of residual tumour may be required. 5-FU 750 mg/m^2 is given daily 3–5 days, and mitomycin-C 10 mg/m^2 bolus is given on the first day. Cisplatin (10 mg/mL weekly) is also now being tried as a radiation sensitizer with radiation of 500 mg/m^2. Chemotherapy avoids exenteration operation with its associated high mortality and morbidity. Fifteen per cent 5-year survival is reported. Other chemotherapy agents used are:

- Bleomycin 5 mg day 1–5
- Methotrexate 15 mg day 1–4
- To Mustin 40 mg day 5–7

This regime is administered weekly for 6 weeks.

Bartholin's Gland Tumour

Bartholin's gland tumour is a rare unilateral tumour, commonly an adenocarcinoma, and carries a poor prognosis. Radical vulvectomy is the treatment of choice.

Vulval Sarcoma

Vulval sarcoma is a rare tumour which occurs in younger women (Figure 37.4). Treatment is local excision. Metastasis is common. The prognosis is poor.

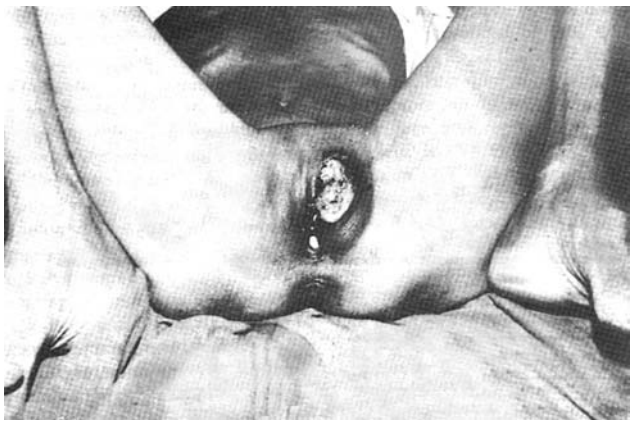

Figure 37.4 Sarcoma of the vulva.

Vulval Melanoma

Malignant melanoma accounts for 3–5% of all vulval tumours. It occurs at all ages, and may develop in a mole or occur de novo. The lesion is pigmented and presents as either nodular or superficial spreading tumour. The edges of the lesion are often irregular, and frequently ulcerate and bleed. The treatment is managed by vulvectomy and bilateral node dissection. Postoperative radiotherapy may be required. Prognosis is poor.

Rodent Ulcer

This uncommon lesion presents as an ulcer which keeps invading the deeper tissues of the vulva. Biopsy shows basal cell carcinoma. It is locally malignant and responds well to wide local excision.

Persistent Cancer (Residual)

Persistent cancer is one which develops within 6 months of primary treatment. Local excision with wide margin is required.

Secondary Growth of the Vulva

Secondary growths of the vulva are metastases from choriocarcinoma, endometrial and ovarian cancer. They are treated by radiotherapy or chemotherapy.

Distal metastatic growths are rare. They are treated with radiotherapy and chemotherapy.

Fifty per cent recurrent growths are seen at the local site within 2 years of primary treatment, and occur with large growths and lymph node involvement. They are treated by exenteration operation, radiotherapy and chemotherapy.

Recurrent growths. Recurrent growths occur in 30% cases within 2 years. Local recurrence is seen in 75% cases. Lymph node and distal metastasis are rare. If the growth is small, local excision with a wide margin over 2 cm is adequate; otherwise, radiotherapy or chemotherapy is employed as palliative treatment.

Exenteration operation with removal of bladder/rectum with vulvectomy is very rarely performed these days.

Prognostic Factors

Prognostic factors are the size of the tumour, grading, histology, lymph node involvement and immune status of the woman. Groin node status is the best prognostic predictor.

When the lymph nodes are not involved, 5-year survival is 90%. Lymph node involvement diminishes the survival rate proportionate to the number of lymph nodes involved.

Vulval Cancer in Young Women

Vulval intraepithelial neoplasia is mostly encountered in young women. Using barrier contraceptives and maintaining hygiene can reduce the transmission of HPV infection which normally causes VIN. Early diagnosis and conservative therapy can cure the disease, avoid mutilating surgery and improve the survival rate. HPV vaccine can prevent malignancy in these cases in future.

For HPV vaccine, refer to Chapter 41 on cancer of the cervix.

Vaginal Cancer

Primary vaginal cancer is a rare cancer accounting for less than 0.2% of all cancers in women. It occurs in elderly women often over 70 years of age when sexual activity has generally ceased. Unfortunately, only about one-third of the patients have regional disease at the time of diagnosis; therefore, late diagnosis is not uncommon (Figure 37.5A and B). An unusual tumour clear cell adenocarcinoma was seen in young women who were themselves exposed to diethylstilboestrol (DES) in utero. However, such cases are fast disappearing with withdrawal of the drug. Cancer of the cervix, bladder and urethra, vulva and lower bowel may

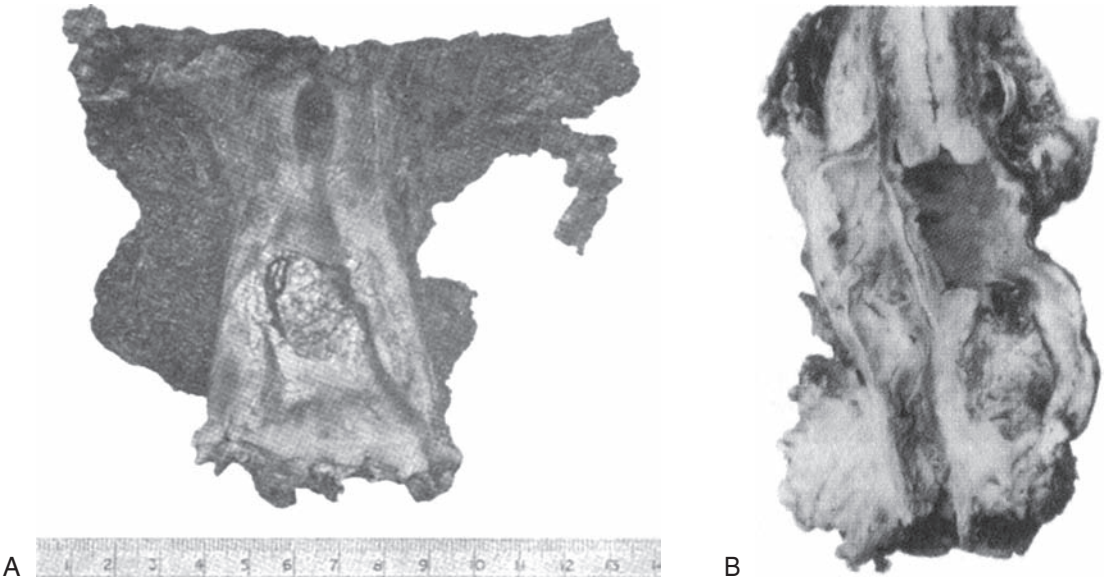

Figure 37.5 **(A)** Carcinoma of the upper-third of the vagina removed by extended hysterocolpectomy. **(B)** Advanced cancer of the lower one-third of vagina. (From: Willson et al. *Textbook of Gynaecology and Obstetrics*, BICL.)

spread to involve the vagina. Metastases from cancer of the uterus, ovary and trophoblastic tumours have been known to occur in the vagina. Cancer over a decubitus ulcer in prolapse is also known to occur (Figures 37.6 and 37.7).

Clinical Features

Vaginal cancer is generally asymptomatic in its earlier stages. The usual complaints are presence of watery discharge, or postcoital bleeding; the lesions may be diffuse, raised velvety patches bleeding on touch, a whitish patch or ulcer. Cytology/Schiller's iodine test/colposcopy and biopsy help settle the diagnosis. The lesions are often multifocal and in the upper-third of the posterior wall. The extent of spread may be determined by combined vaginal and rectal examination. Diffuse spread may involve the urethra and bladder anteriorly and the large bowel posteriorly when urinary and bowel symptoms may occur. Cancers may arise de novo in younger women exposed to DES in utero, when the upper one-third vagina is involved, following trophic ulcers in women with procidentia, following prolonged and neglected use of ring pessary for prolapse, or as spread from other pelvic organs. Virus infection may be a causative factor.

It may also develop years later following radiation for cancer of the cervix.

The lesion is squamous cell carcinoma in 90% cases, rarely adenocarcinoma arising from vaginal adenosis in young girls. The tumour in the upper vagina drains into pelvic lymph nodes and that in the lower part drains into inguinal lymph nodes (Figure 37.5).

Vaginal intraepithelial neoplasia is rare, and always progresses to invasive cancer.

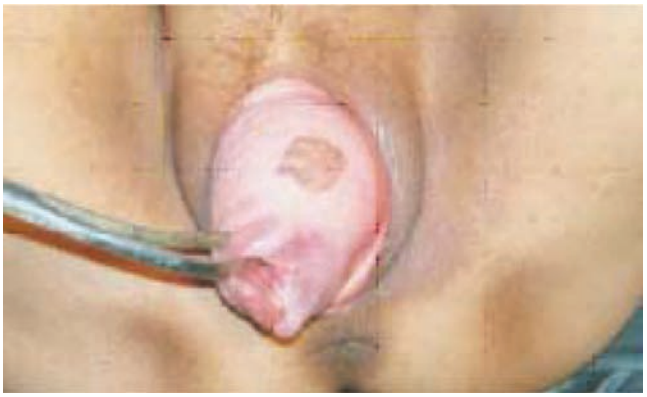

Figure 37.6 Carcinoma in a case of prolapse. (From: Sengupta et al. *Gynaecology for Postgraduates and Practitioners, 2nd ed.* Elsevier, 2007.)

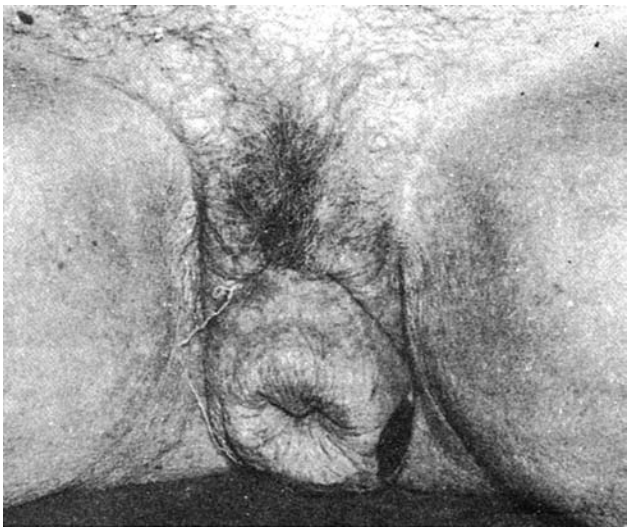

Figure 37.7 Carcinoma of the vagina arising in a procidentia of many years duration. The carcinomatous ulcer lies to the left of the patient's cervix. Malignant change in a procidentia is rare.

Staging

Refer to Table 37.6.

Diagnosis

Suspicious areas of plaque/white patch should be subjected to Schiller's test and colposcopic biopsy. All gross lesions like nodule, papule, ulcer or mole should be biopsied. Local application of oestrogen in old women enhances colposcopic view. Colposcopy is difficult on account of a large vaginal area, multiple lesions and vaginal folds.

Management

Pretreatment Work-Up

Complete history and examination, WBC, urinalysis, blood sugar estimation, liver function test (LFT), renal function test (RFT), chest radiography, ECG, cystoscopy, proctoscopy and barium enema may be required. CT and MRI are done for nodal study.

Treatment

Vaginal intraepithelial neoplasia (VAIN). It is treated with local excision biopsy, CO_2 laser and local application of 5-fluorouracil cream. Electrocautery and cryotherapy are best avoided. Invasive cancer is treated with local radiotherapy, Wertheim hysterectomy with total colpectomy, or exenteration operation for advanced cases involving

TABLE 37.6 Vaginal cancer staging

Stage 0	Vaginal intraepithelial neoplasia (VAIN)
Stage I	Carcinoma limited to the vaginal wall
Stage II	Carcinoma extending beyond the vagina, but not extending to the pelvic side walls
Stage III	Carcinoma extends up to the pelvic walls
Stage IVA	Carcinoma extending beyond the true pelvis/or involving the bladder and/or rectum, or evidence of distal metastasis
Stage IVB	Spread to the distal metastasis

bladder/bowel. Overall survival is 30–40%. Creation of neovagina is required in young women.

Prophylaxis. Treating a decubitus ulcer and proper care of a ring pessary in a prolapse can avoid cancer of vagina.

Sarcoma. Sarcoma botryoides is a rare tumour seen in children.

This tumour arises in the mesenchymal tissues of the vagina and in rare cases, in the cervix before the age of 2 years. It presents as a haemorrhagic grape-like polyp or as a fleshy mass and consists of rhabdomyoblasts with vacuolated cytoplasm, myxoedema and stroma with fusiform cells. The tumour spreads by local infiltration, lymphatics and blood stream.

Examination is done under anaesthesia; biopsy confirms the diagnosis. CT and MRI indicate its spread.

Treatment. Chemotherapy with VAC (vincristine, adriamycin and cyclophosphamides) is the gold standard in treating this tumour. Other drugs used are cisplatin, actinomycin, cyclophosphamide and ifosfamide.

Surgery is limited to the local residual tumour. Interstitial radiation is used in advanced stage.

Key Points

- Pre-invasive cancer of vulva (VIN) is caused by human papilloma virus in young women.
- VIN is usually a multifocal lesion in young women, but a single lesion in older women.
- In young women, 90% regress, 10% progress to invasive cancer within 8 years. Careful follow-up is recommended.
- VIN in older women invariably progresses to invasive cancer and should be treated by vulvectomy.
- Conservative surgery ablative as well as local wide excision is adequate in young women. Simple vulvectomy should be performed in elderly women. Follow-up is necessary.
- Radical vulvectomy is required if the regional lymph nodes are involved.
- Prognosis depends upon the lymph node involvement which in turn depends upon the site, size and depth of the lesion.
- Vaginal cancer is rare and difficult to diagnose in its early stage.
- Radical surgery is usually required. Radiotherapy is palliative in advanced stages.

Self-Assessment

1. A woman, 55-year old, presents with a vulval ulcer. Discuss the differential diagnosis and management.
2. Discuss the management of vulval cancer stage I.
3. Discuss the management of vulval cancer stage II.

Suggested Reading

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Chapter

38

Cervical Intraepithelial Neoplasia, Carcinoma of Cervix

CHAPTER OUTLINE

Carcinoma of the cervix continues to be the most common genital cancer encountered in clinical practice in India (80%). The universal application of Pap smears in Western communities has led to a drastic decline in the number of invasive cancers of the cervix and a higher detection of pre-invasive lesions. However, this has not happened in India and a drive against cancer must continue to keep the disease under control.

Five lakh new cases are reported annually world over. In India alone, 130,000 new cases occur with the death toll of 70,000 cases every year. Cancer of the cervix accounts for 15% of all cancers in women.

Prevalence rate is 2.3 million annually globally. In India, it is 13–24 lakhs per year and 75% are in the advanced stages.

Aetiology, Epidemiology and Predisposing Risk Factors

There are many clinical characteristics that predispose a woman to cervical cancer. These high-risk features are:

- Average age 35–45 years. Pre-cancerous lesions occur 10–15 years earlier (Figure 38.1).
- Coitus before the age of 18 years.
- Multiple sexual partners.
- Delivery of the first baby before the age of 20 years.
- Multiparity with poor birth spacing between pregnancies.
- Poor personal hygiene.
- Carcinoma of the cervix shares similar epidemiological features to those of sexually transmitted diseases and viral infections and these are strongly linked to cancer cervix as causative agents.
- Poor socioeconomic status.
- At one time, exposure to smegma from uncircumcised partners was considered an important factor, accounting for lower incidence of cancer of the cervix amongst Jews and Muslims. Now it is realized that the incidence of human papilloma virus (HPV) is low in circumcised men, and that is the reason for low incidence of cancer in their wives.
- Smoking and drug abuse, including alcohol, are immunosuppressive (13-fold).
- Women with STD, HIV infection, herpes simplex virus 2 infection, HPV infection (16, 18, 31, 33) and condylomata have a high predisposition to cancer. Of these, HPV is now considered the most important oncogenic cause. Most HPV infection 16, 18 are symptomless in young women and clear within 2 years. Persistent infection is the cause of cancer of the cervix in 70–90% cases. Before the age of 30 years, 90% women with intact immune system are able to get rid of HPV infections. 10% with persistent infection after the age of 30 years tend to progress to CIN or invasive cancer.
- Immunosuppressed individuals (following transplant surgery), viral infections and HIV.
- Women with pre-invasive lesions.
- Women who do not come for regular health check-up and Pap tests.
- COC and progestogens use over 8-year periods can cause adenocarcinoma of the endocervix (double the risk).
- Five per cent women exposed to diethylstilboestrol in utero developed carcinoma of vagina and cervix. With withdrawal of this hormone, its incidence has dropped.

Cervical Intraepithelial Neoplasia or Pre-Invasive Cervical Cancer (Stage 0)

Cervical dysplasia is a cytological term used to describe cells resembling cancer cells. Cervical intraepithelial neoplasia

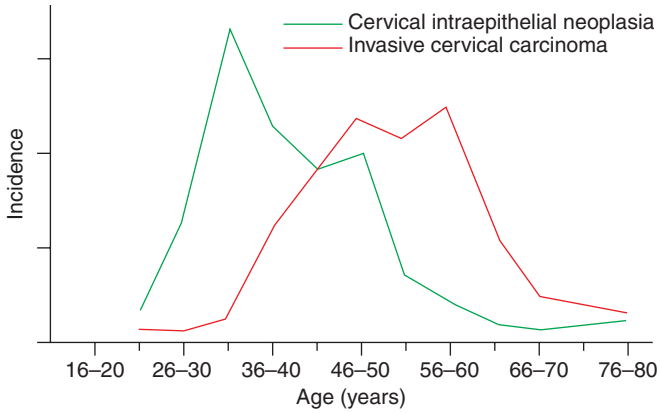

Figure 38.1 General levels of age incidence of cervical carcinoma in situ and invasive cervical carcinoma.

(CIN) refers to the histopathological description in which a part or the full thickness of the stratified squamous epithelium is replaced by cells showing varying degrees of dysplasia; however, the basement membrane is intact. Dysplasia represents a change in which there is an alteration of cell morphology, and disorderly arrangement of the cells of the stratified squamous epithelium. The cells vary in size, shape and polarity. There is an alteration in the nuclear cytoplasmic ratio, and the cells reveal large, irregular hyperchromatic nuclei with marginal condensation of chromatin material and mitotic figures. These lesions progress with time and ultimately end up as frank invasive cancers. *While 4% reach the invasive stage by the end of 1 year and 11% by end of 3 years, as much as 22% become invasive by 5 years and 30% by 10 years* (Table 38.1).

Metaplasia

The squamocolumnar junction represents the transformation zone where endocervical epithelium meets the squamous epithelium of the ectocervix. The reserve cells lying beneath the columnar epithelium at this junction sometimes transform into mature squamous cells—this is known as metaplasia. Metaplastic cells are normal cells without nuclear atypia and do not become malignant. Atypical metaplasia with abnormal nuclear changes is, however, a precursor of dysplasia and malignancy.

pH changes, hormonal effect, infection and certain mutagens cause atypical metaplasia. *Aneuploidy is the hallmark of malignant potential of these cells and diploidy or polyploidy is seen in benign and reparatory cells.*

TABLE 38.1 Course of CIN disease

	Regression	Persistence	Progresses	Age
CIN I	80–90%	10–20%	1–4%	<30 years
CIN II	30–40%	40%	20%	30–35 years
CIN III	20–30%	50–60%	Almost all	35–45 years

Dysplasia (Figures 38.2–38.7)

Dysplasias are graded as:

1. *Mild dysplasia (CIN-I).* The undifferentiated cells are confined to the lower one-third of the epithelium. The cells are more differentiated towards the surface. Mild dysplasia due to infection is often seen in young women indulging in sexual activity. CIN-I is lately described as low-grade squamous intraepithelial lesions (LSIL) according to the Bethesda classification. 'Ascus' is a term described in the Bethesda system as atypical cells of undetermined significance. The intermediate cells mostly display mild dysplasia with enlarged nuclei and irregular outline. One per cent progress to cancer over the years.
2. *Moderate dysplasia (CIN-II).* Undifferentiated cells occupy the lower 50–75% of the epithelial thickness. The cells are mostly intermediate with moderate nuclear enlargement, hyperchromasia, irregular chromatin and multiple nucleation. Thirty per cent of CIN II regress, 40% persist and the rest progress to invasive cancer.
3. *Severe dysplasia and carcinoma in situ (CIN-III).* In this grade of dysplasia, the entire thickness of the epithelium is replaced by abnormal cells. There is no cornification and stratification is lost. The basement membrane, however, is intact and there is no stromal infiltration. Often, an abrupt change in histological appearance from normal to abnormal is apparent (Figures 38.2–38.7). The cytology cells are mostly parabasal with increased nuclear–cytoplasmic ratio. The nuclei are irregular, with coarse chromatin material; mitosis and multinucleation are common. Almost all progress to invasive cancer over 10–15 years.
4. *Tadpole cells are seen in invasive cancer.* CIN-II and CIN-III are described as high-grade squamous intraepithelial lesions (HSIL) according to the latest Bethesda classification. *HSIL have a propensity to progress and become invasive, and therefore need investigations and treatment.*

The term 'cervical intraepithelial neoplasia' denotes a continuum of disorders from mild through moderate to severe dysplasia and carcinoma in situ. Mild dysplasia is often seen with inflammatory conditions like trichomoniasis and HPV, and is reversible following treatment, whereas the severe varieties progress to invasive cancer in about 10–30% of cases in 5–10 years time.

The Indian Council of Medical Research (ICMR) reports the incidence of dysplasia to be 15:1000 women cytologically screened. The incidence of severe dysplasia is reported to be about 5:1000.

Koilocytes. These cells are often seen in young women suffering from HPV infection, and are cells with perinuclear halo in the cytoplasm. Koilocytes disappear as dysplasia advances.

Diagnosis

Diagnosis of cervical dysplasia is mainly based on cytological screening of the population. The peak incidence of occurrence of dysplasias appears to be 10 years earlier than

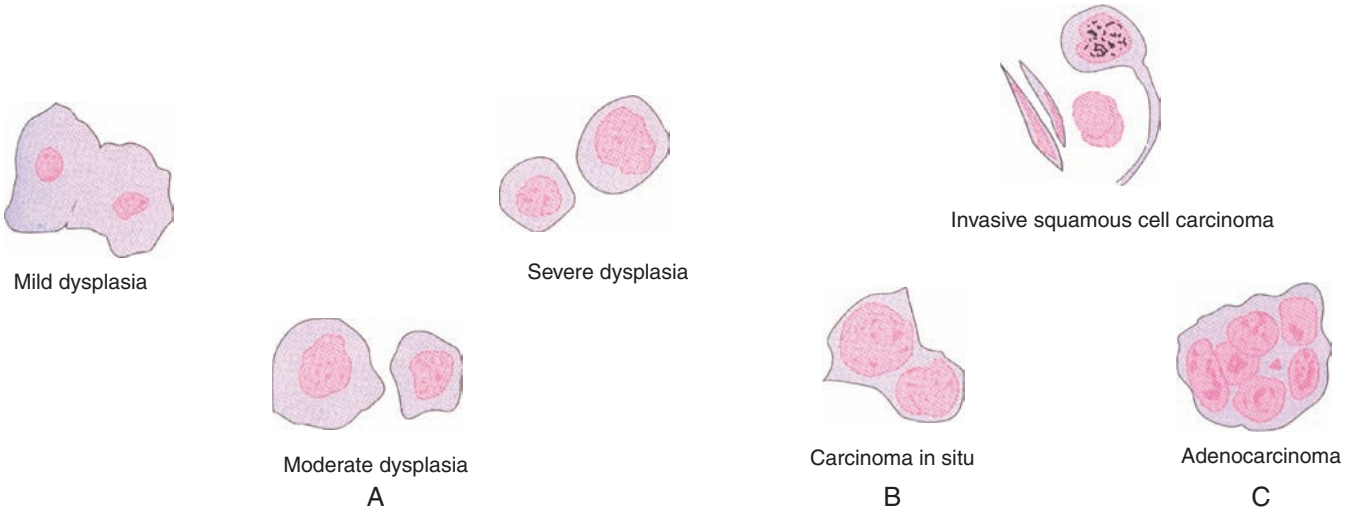

Figure 38.2 Dysplasias: **(A)** Mild and moderate dysplasias. **(B)** Severe dysplasia and carcinoma in situ. **(C)** Invasive cell—carcinoma and adenocarcinoma.

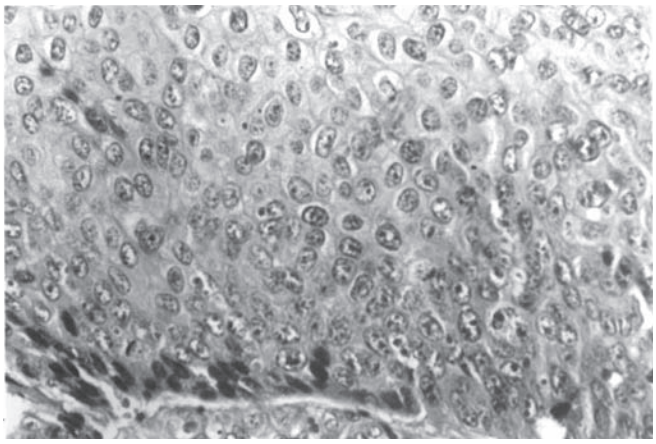

Figure 38.3 Pap smear. Cervix CIN III.

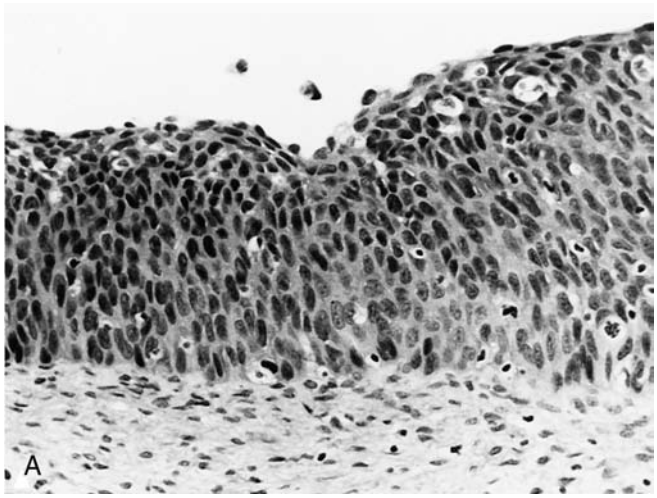

Figure 38.4 Cervical intraepithelial neoplasia 1 (mild dysplasia). Atypical cells are present in the lower one third of the epithelium (H&E stain, ×250). (From Figure 28-5A. Gretchen M Lentz, Roger A Lobo, David M Gershenson, et al: Comprehensive Gynecology, 6th Ed. Mosby: Elsevier, 2012.)

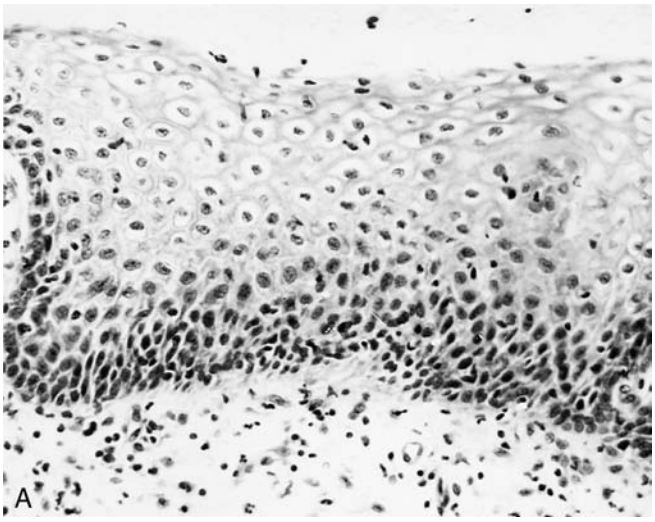

Figure 38.5 Cervical intraepithelial neoplasia 3 (severe dysplasia, carcinoma in situ). There is a lack of squamous maturation throughout the thickness of the epithelium. Almost all the cells have enlarged nuclei with granular chromatin. Note that the basement membrane is intact, showing that this process is confined to the epithelial layer only. (From Figure 28-7A. Gretchen M Lentz, Roger A Lobo, David M Gershenson, et al: Comprehensive Gynecology, 6th Ed. Mosby: Elsevier, 2012.)

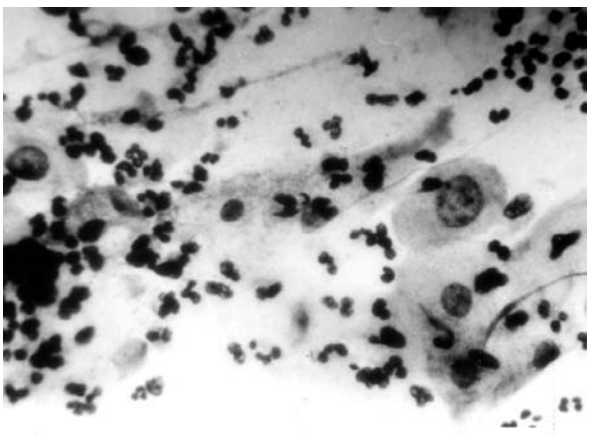

Figure 38.6 Pap smear—mild dysplasia.

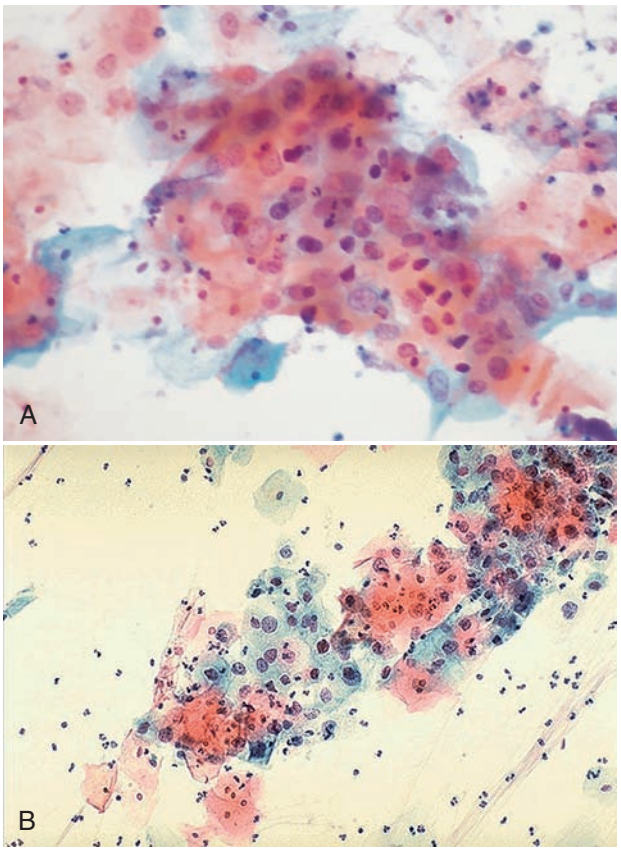

Figure 38.7 (A) Cervical cytology smear in CIN. This cytology preparation shows a clump of cervical epithelial cells demonstrating moderate and severe dyskaryosis. (From Figure 19.10. Alan Stevens, James Lowe and Ian Scott: Core Pathology, 3rd Ed. Elsevier, 2009.) **(B)** Cervical squamous dysplasia, Pap smear (From Figure 13-25. Edward C. Klatt: Robbins and Cotran Atlas of Pathology, 2nd Ed. Saunders: Elsevier, 2010.)

that of frank invasive cancer. Many of these women are asymptomatic. Some women complain of postcoital bleeding or discharge. On inspection, the cervix often appears normal, or there may be cervicitis or an erosion which bleeds on touch. Some women present with postmenopausal bleeding.

Routine cytological screening or Pap smear should be offered to all women above the age of 21 years who are sexually active for at least 3 years. Women at risk for cervical cancer have been detailed earlier in this chapter. In all women with abnormal Pap tests showing mild dysplasias, it is important to treat any accompanying inflammatory pathology and repeat the Pap test. If it persists to be abnormal, colposcopic examination and selective biopsies (Tables 38.2–38.5) (see Chapter 6 for details) are to be considered.

DNA study. Diploid or polyploid nucleus is normal. Aneuploidy is a hallmark of malignant potential and mandates treatment.

Cytology alone does not indicate which abnormal cells will progress to cancer. Further tests are required. Usefulness of Pap smear in the screening programme for cancer cervix is shown by the following:

- Long latent period of 10–15 years between the diagnosis of CIN and invasive cancer allows adequate treatment of CIN and prevention of invasive cancer.
- Screening programme has proved successful in reducing the incidence of invasive cancer by 80% and its mortality by 60% in developed countries.

Because of 15–30% false-negative reporting, it is prudent to repeat Pap smear annually for 3 consecutive years. If it continues to remain negative, the Pap smear is repeated 3–5-yearly up to the age of 50 years. After 50 years, the incidence of CIN drops to 1%. The presence of endocervical cells in the smear indicates a satisfactory smear. A false-negative report is due to improper technique in smear taking (not through 360°), dry vagina and poor shedding of cervical cells or in drawing of squamo-columnar junction as in menopausal women (proper cells not available for cytology).

HSIL. The presence of high-grade squamous intraepithelial neoplastic cells is significant as these have the potential to progress to invasive cancer and need to be treated.

Sensitivity of Pap smear for HSIL is 70–80% and specificity 95–98%. While false-positive smear may be unnecessarily investigated and treated, false-negative reporting is more ominous and cancer lesion may be missed. Pap smear in postmenopausal women is inaccurate and often negative on account of indrawing of squamocolumnar junction, dry vagina and poor exfoliation of cells. This can be improved by administration of oestrogen cream daily for 10 days

TABLE 38.2 Classification of Pap smear

Pap Class System (1954)	Scheme I Reagen (1956) (WHO)	Scheme II Richart (2001)	Scheme III Bethesda (1988)
Class 1	Negative for malignant cells	Negative	Within normal limits
Class 2	• Inflammation • Squamous atypia • Koilocytes		Reactive and reparative changes (ascus)
Class 3	Mild dysplasia	• CIN-I (HPV)	• LSIL (HPV)
Class 4	• Moderate dysplasia • Severe dysplasia • Carcinoma in situ	• CIN-II • CIN-III	• HSIL • HSIL
Class 5	Invasive cancer	Invasive cancer	Invasive cancer

TABLE 38.3 Indications of conization

Diagnostic	• Entire squamocolumnar junction not visible, large lesion • Endocervical CIN • Microinvasion suspected • Discrepancy between cytology and colposcopy
Therapeutic	In CIN II, III
Methods	• Cone biopsy • LLETZ, LEEP (loop electrosurgical excision procedure), NETZ

TABLE 38.4 Bethesda system of cytology reporting

Satisfactory cytology—endocervical cells seen
Unsatisfactory
1. **Squamous cell abnormalities**
   - Atypical squamous cells (ASC)
     - Ascus—atypical cells of undetermined significance
     - ASC- H—cannot rule out high-grade lesion
   - Low-grade squamous intra epithelial lesion (LSIL)—includes CIN I
   - High grade squamous intraepithelial lesion (HSIL)—includes CIN II, III
   - Squamous cell carcinoma
2. **Glandular abnormalities**
   - Atypical glandular cells
   - Adenocarcinoma in situ
   - Adenocarcinoma
3. **Other malignant neoplasms**

TABLE 38.5 Detection of cervical neoplasia

Cytology	Pap smear/Liquid based cytology—automated computerized image processor
Positive cytology • Speculoscopy • Spectroscopy • Cervicography • Magnoscope • AgNOR	HPV testing by PCR
Colposcopically directed biopsy Cone biopsy	

or 400 µg misoprostol. To reduce the incidence of false-negative reporting, the following procedures are added to Pap screening.

- *Endocervical scrape cytology by endocervical brush or curettage*. Endocervical scrape should be obtained first with Pipelle/cotton swab followed by ectocervical smear to avoid the latter from air drying.
- Incorporating HPV testing by hybridization or polymerase chain reaction in young women. This improves the predictive value of Pap smear to 95% and reduces the number of referrals for colposcopic evaluation. A young woman with HPV infection should be followed up with Pap smear. Incidentally, it is observed that the prevalence of HPV-positive cases drops with advancing age (regression) or are transient, but in persistent HPV infection, the incidence of HSIL rises after the age of 30 years. The specificity of Pap smear in HPV-infected cases is therefore low in young women.

Cytology with added HPV testing helps to triage ascus and CIN cells.

- *Liquid-based cytology*: Here the smeared *plastic* (not wooden) *spatula is placed in a liquid fixative* (buffered methanol solution) instead of smearing on a slide. This removes the blood, mucus and inflammatory cells. The suspended cells are then gently sucked onto a filter membrane and the filter is pressed onto a glass slide to form a thin monolayer, and then it is stained. The liquid can also be employed to test HPV infection, making it a cost-effective technique. The cells wash off the plastic device more than the wooden one, and the fixation solution contains haemolytic and mucolytic agents. This improves specificity and sensitivity of the test. Besides HPV testing, the liquid can also be used for genetic study and repeat cytology if required. Disadvantages are increased cost, need of trained personnel and transportation and storage of so many vials.
- Automated computerized image processor eliminates 25% most likely negative smears and 75% are selected for cytotechnician screening.

Since cytology alone does not give a clue to which abnormal cells progress to invasive cancer, and aneuploidy which suggests the risk of progression is not routinely performed, it is necessary to submit all women with HSIL cytology for colposcopic study and biopsy of suspicious lesions.

- *Visual inspection of acetowhite areas (VIA)*. Where the facilities for Pap screening does not exist, VIA is able to select abnormal areas on the cervix by applying 5% acetic acid (down staging)—acetic acid dehydrates the abnormal areas containing increased nuclear material and protein which turn acetowhite. The normal cells containing glycogen remain normal. Though this has low specificity and high false-positive findings, false–negative, which really matters, is seen in only 0.9% cases. The abnormal areas are biopsied. Instead of acetic acid, Schiller's iodine can also be employed (VILI—visual inspection with Lugol's iodine). Normal cells containing glycogen take up iodine and turn mahogany brown, and abnormal area remains unstained. Dull white plaques with faint borders are considered LSIL and those with sharp borders and thick plaques contain HSIL. VIA is a reliable, sensitive and cost-effective alternative to cytology in low-resource settings. 'See and biopsy' in one sitting is possible with VIA and VILI.

Abnormal areas may be cauterized (or cryotherapy) in the same sitting. Though it may prove 'overtreatment', as a considerable number of women may have benign lesions, this is feasible and convenient in rural and peripheral set-ups.

Speculoscopy uses a special disposable low-intensity blue-white magnifying device or loupe. This has not proved effective and more false-positive cases are unnecessarily referred for colposcopic study.

Spectroscopy. Cervical impedance or fluorescence spectroscopy is specific and sensitive, and provides instant results unlike Pap smears. It is a noninvasive technique which probes the tissue morphology and biochemical composition.

Magnoscope has a magnifying lens built in source. It magnifies cells five times and enables visualization of punctuation and mosaics. It is portable and useful in rural areas. Therefore, it is introduced in a few centres in India.

Microspectrophotometry is also able to distinguish between benign and malignant cells.

Colposcopy. The aims of colposcopy are (Figures 38.8–38.11):

- To study the cervix when Pap smear detects abnormal cells.
- To locate abnormal areas and take a biopsy.
- To study the extent of abnormal lesion.
- Conservative surgery under colposcopic guidance.
- Follow-up of conservative therapy cases.

Colposcopy reduces the false-positive findings, but 6–10% ascus cells reveal HSIL (false negative).

Abnormal areas revealed under colposcopy are acetowhite areas, mosaics, punctuation and abnormal vessels (see Chapter 7) (Figure 38.12). While Pap smear detects abnormal cells, colposcopy locates the abnormal lesion.

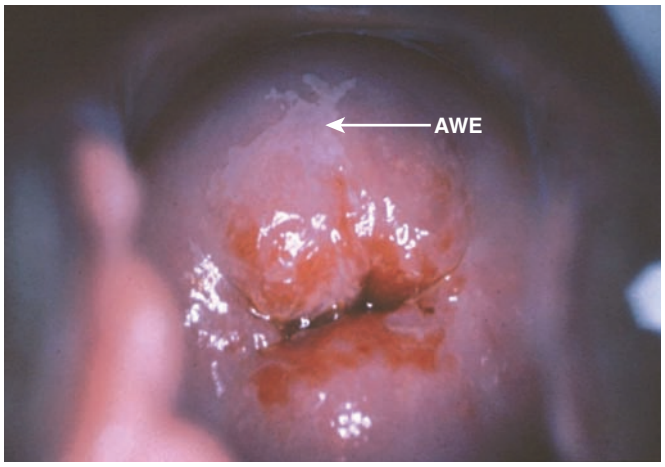

Figure 38.9 Colposcopy showing acetowhite areas. (From Figure 137-4E. John L Pfenninger and Grant C Fowler: Pfenninger and Fowler's Procedures for Primary Care, 3rd Ed. Mosby: Elsevier, 2011.)

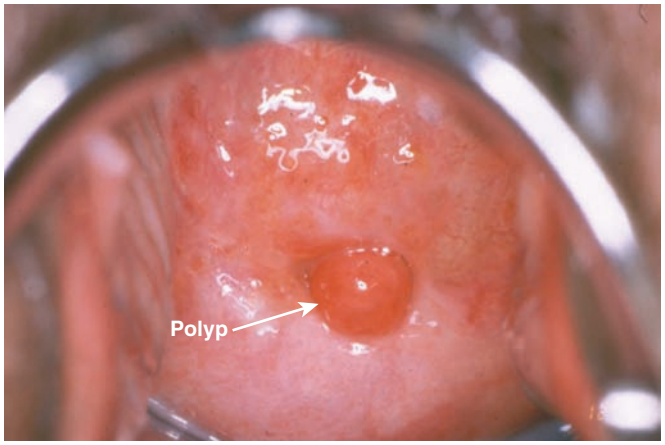

Figure 38.10 Cervical polyp seen. (From Figure 137–40. John L Pfenninger and Grant C Fowler: Pfenninger and Fowler's Procedures for Primary Care, 3rd Ed. Mosby: Elsevier, 2011.)

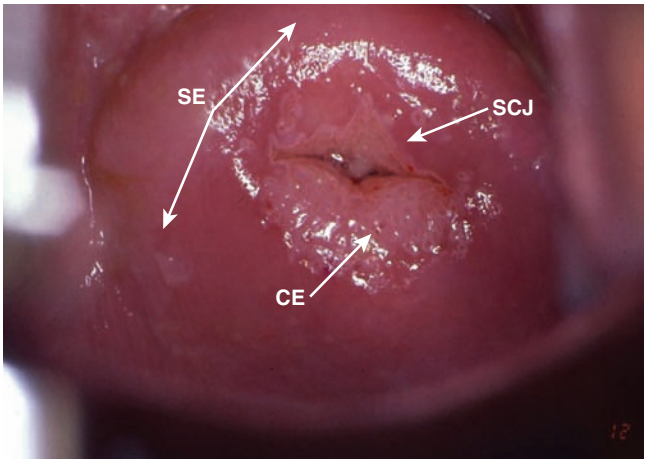

Figure 38.8 Normal colposcopic picture of the transformation zone: squamous epithelium (SE), columnar epithelium (CE) and squamocolumnar junction (SCJ). (From Figure 137-2B. John L Pfenninger and Grant C Fowler: Pfenninger and Fowler's Procedures for Primary Care, 3rd Ed. Mosby: Elsevier, 2011.)

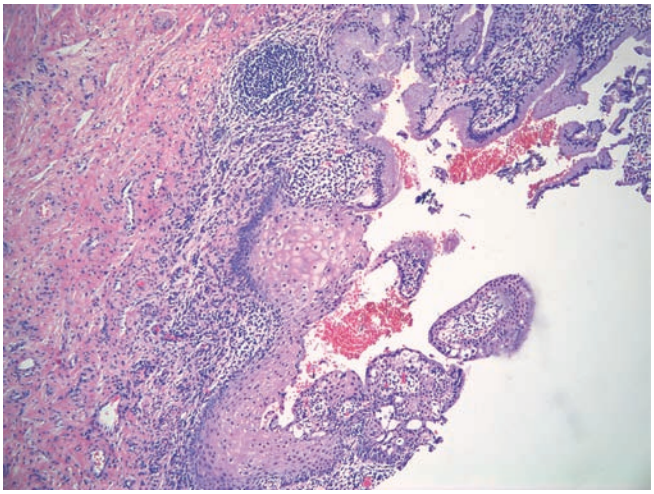

Figure 38.11 Squamous metaplasia of the cervical transformation zone. Microscopic section of uterine cervix with abutting squamous and glandular mucosa (From Figure 13.5. Thomas C. King: Elsevier's Integrated Pathology. Elsevier, 2007.)

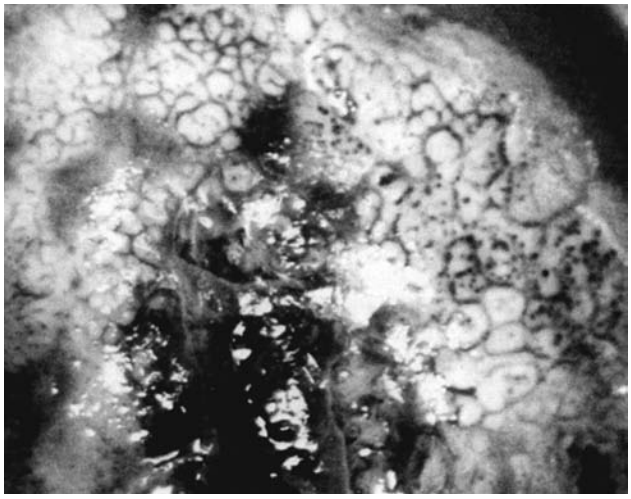

Figure 38.12 Colposcopy view showing punctuations, mosaic pattern and abnormal vascular patterns suggestive of CIN lesions requiring biopsy. (From: *Haines & Taylor's Obstetrical and Gynaecological Pathology*, 3rd ed. Churchill.1987.)

Colposcopic study is challenging in postmenopausal women because of:

- Narrow vagina, senile vaginitis
- Squamocolumnar junction is indrawn and not visible
- Atropic cervix flush with vagina

Oestrogen cream for 7–10 days and 400 μg misoprostol 3–4 h before colposcopy expose the ectocervix better. Colposcopy decides if a small biopsy or cone biopsy is required.

Cervicography. It is useful when a colposcopist is not available for spot evaluation. A photograph of the entire external os is taken with a 35-mm camera after application of 5% acetic acid and sent to the colposcopist for selecting areas for biopsy. Because of 50% specificity and sensitivity, this technique is not cost-effective.

Cone biopsy. It is both diagnostic and therapeutic. Whenever the area of abnormality is large, or its inner margin has receded into the cervical canal, the squamocolumnar junction is not completely visible on colposcopy, or there is discrepancy between cytology and colposcopy, a wide cone excision including the entire outer margin of the lesion and the entire endocervical lining is obtained using cold-knife technique under general anaesthesia/large loop excision of the transformation zone (LLETZ)/or laser excision. Laser excision is associated with less bleeding, infection and faster healing, without scar formation.

Cone biopsy (Table 38.3) can cause bleeding, infection, cervical stenosis and incompetent os. However, it is also required if endocervical or microinvasive lesion is suspected.

AgNOR is a new molecular tumour marker which stands for silver-stained nucleolar organizer regions; DNA is present in dysplastic cells. They appear as black dots which increase in number but decrease in size with advancing dysplasia. The lesions with low counts often regress, whereas those with high counts progress and need treatment.

HPV testing. Eighty per cent ascus and LSIL positive smears are preceded by HPV infection in young women. While 80–90% are transitory and self-limited, and disappear over a period of 18 months or so, only 10–20% persist and form a high-risk group beyond 30 years of age. Incorporating HPV testing in cytology screening improves the predictive value, reduces unnecessary colposcopy referral and overtreatment, but justifies follow-up in persistent cases.

The HPV testing is done either by study of cells in liquid-base cytology, or endocervical secretion and self-obtained vaginal swab. A combined HPV testing and Pap smear yields 96% sensitivity as compared to only 60–70% with Pap smear alone. Polymerase chain reaction, southern blot or hybrid capture detect HPV DNA.

Treatment of dysplasia and CIN (Table 38.6, Figures 38.13–38.18)

Treatment of dysplasia based on cytology or colposcopy alone is not appropriate because of their false findings. A false-positive finding means unnecessary treatment or overtreatment. As mentioned before, more serious is false-negative finding which undermines the treatment and allows invasive growth to occur. As much as 50% of persistent LSIL (CIN-I) show HSIL (CIN-II, CIN-III), mandating colposcopic biopsy for confirmation prior to treatment and also to rule out invasive cancer.

- *Mild dysplasia* (LSIL) is usually due to infection which should be treated and cytology follow-up done every 3–6 months. Indication for colposcopy and treatment of LSIL are:
  - Persistent LSIL (CIN-I) over 1 year
  - Patient shows poor compliance
  - LSIL showing HSIL on colposcopy or LSIL progresses to HSIL during the follow-up.
- *Moderately severe to severe dysplasias (CIN-II and CIN-III).* The treatment options are the following.
- *Local destructive methods:* (i) Cryosurgery, (ii) fulguration/electrocoagulation and (iii) laser ablation.
- *Excision of abnormal tissue:* (i) Cold-knife conization, (ii) laser conization, (iii) LLETZ, (iv) LEEP and (v) NETZ.
- *Surgery:* (i) Therapeutic conization, (ii) hysterectomy and (iii) hysterectomy with removal of vaginal cuff if carcinoma in situ extends to the vaginal vault.

Criteria for conservative methods are as follows:

- The entire lesion should be visible within the squamocolumnar junction.
- No micro- or macroinvasion as proved by histological study through biopsy.
- No evidence of endocervical involvement.
- Cytology and histology must correspond.
- Young woman desirous of childbearing.

Cryosurgery. Introduced by Townsend, it is suited for small lesions. Cryosurgery causes destruction of cells by crystallization of intracellular fluid. Freeze–thaw–freeze

TABLE 38.6 Comparison of different methods of treatment of dysplasia and CIN

Characteristics	Cryotherapy	Coagulation	Laser Ablation	Conization Knife	Laser Conization	LLETZ	Leep
Place	OPD	OT	OPD	OT	OPD or OT	OPD	OPD
Anaesthesia	Nil	GA	Nil analgesia	GA	Local	Local	Local
Instrument's cost and portability	Cheap, portable	Cheap, portable	Expensive	Cheap, not portable	Expensive, not portable	Cheap, portable	Cheap, portable
Risk of equipment	Nil	Nil	Yes	Nil	Yes	Nil	Nil
Complications during surgery	Nil	Bleeding risk	Personnel	Bleeding risk	Personnel	Nil	Nil
Depth of destruction	4–5 mm	8–10 mm	7 mm	–	–	–	–
Pain	Nil	Painful	Slight	–	Slight	Nil	Slight
Bleeding	Nil	+	Nil	++	Slight	Slight	
Sepsis	Discharge	+	Nil	+	Nil	Slight	Slight
Healing	6–8 weeks	6–8 weeks	4 weeks	6–8 weeks	4 weeks	4–6 weeks	4–6 weeks
Tissue for histology	NA	NA	NA	Available with excision methods	Tissue available	Available histology	Available
Cure rate	90%	90–95%	90–97%	90–95%	90–95%	90–95%	90–95%
Pregnancy complications	Nil	Nil	Nil	Stenosis cervix, abortion, premature labour, cervical dystocia with excisional methods		Cervical stenosis	
Postoperative transformation zone	Indrawn	Indrawn	Seen	Visible with zone excisional method			

NA: Not available, GA: General anaesthesia.

Figure 38.13 Cryotherapy probes with various size tips. (From Figure 2. Stephanie Long and Lawrence Leeman: Treatment Options for High-Grade Squamous Intraepithelial Lesions. Obstetrics and Gynecology Clinics, Vol 40(2): 291–316, Elsevier, 2013.)

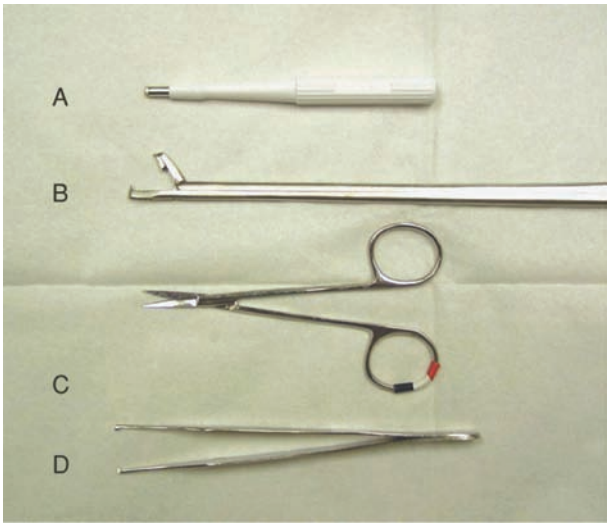

Figure 38.14 (A) Keyes punch biopsy. (B) Cervical punch biopsy forceps. (C) Iris scissors. (D) Tissue forceps. (From Figure 1A. Pre-procedure. Procedure Consult. Vulvar Biopsy. Editors: Michael L Tuggy, Jorge Garcia.)

Figure 38.15 Electrodes (Utah Medical, Midvale, UT) used for a loop electroexcision procedure. The width of the excised tissue specimens can range from 1.0 to 2.0 cm, and the specimen depth can be adjusted by sliding the guard attached to the electrode shaft. Following excision, the base of the cervix is often gently cauterized with a ball electrode. (From Figure 28.15. Gretchen M Lentz, Roger A Lobo, David M Gershenson, et al. Comprehensive Gynecology, 6th Ed. Mosby: Elsevier, 2012.)

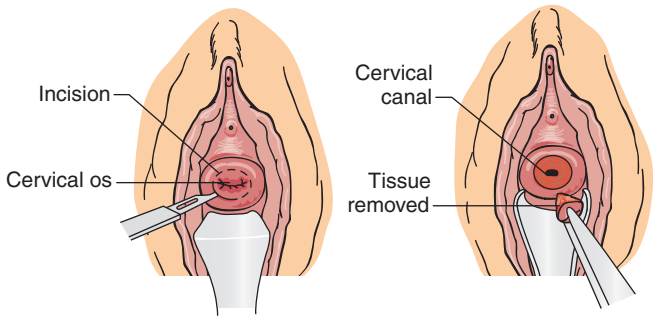

Figure 38.16 Conization technique. (A) Incision. (B) Removal of tissue. (From Figure 134-3. John L Pfenninger and Grant C Fowler: Pfenninger and Fowler's Procedures for Primary Care, 3rd Ed. Mosby: Elsevier, 2011.)

technique over 9 min destroys the tissue up to 4–5 mm deep; it is done as an OPD procedure without analgesia. CO_2 (–60°C), Freon (–60°C) and nitrous oxide (–80°C) are the freezing agents. A small lesion can be dealt with in one stroke applied for 3 min. A large lesion may require segments to be treated piecemeal. Application of acetic acid, Lugol's iodine or preferably colposcopic view helps to eradicate the entire lesion in one sitting. The woman should abstain from intercourse for 4 weeks. Repeat cryosurgery can be done 3 months later if the entire region is not previously treated as seen by cytology or other alternative method chosen. Cryosurgery is the best-tolerated technique, least painful and cheap. The main disadvantage is profuse discharge. Another disadvantage is in drawing of squamocolumnar junction. CO_2 is cheaper, but nitrous oxide has a more cooling effect, hence depth of penetration and destruction are more.

Electrocoagulation uses temperature over 700°C and destroys the tissue up to 8–10 mm deep. Since the procedure is painful, it is done under general anaesthesia. Recurrence, bleeding, sepsis and cervical stenosis are its complications. Squamocolumnar junction gets indrawn within the cervical canal.

Laser ablation boils, steams and explodes the cells. The laser is very expensive and can be harmful to the personnel (burn injury to the skin and eyes). It destroys the tissue up to 5 mm deep.

However, laser ablation is useful when the CIN extends up to the vaginal vault. Laser causes minimal bleeding, no infection, no post-laser scar formation and no deeper excision. It is an OPD procedure done under local anaesthesia and under colposcopic guidance. More importantly, laser does not cause indrawal of squamocolumnar junction and therefore, repeat laser is possible for residual lesion unlike cautery or cryosurgery. Recurrence of 2–8% is reported.

Excisional and cone biopsy provide tissue for histopathological study and can be therapeutic.

Punch biopsy under colposcopic view can remove the entire lesion, if small, and can be performed under sedation or local anaesthesia.

Large loop excision of the transformation zone (LLETZ) uses low-voltage diathermy under local anaesthesia. The loop is advanced into the cervix lateral to the lesion until the required depth is reached. It is then taken across to the opposite side and a cone of tissue removed. A loop size of less than 2 cm gives a better cone than a larger one. The low cost of the equipment and harmless effects on personnel makes LLETZ more popular than laser. Besides, it takes shorter time to perform with similar success and recurrence as that of laser.

Loop electrosurgical excision procedure (LEEP) is even simpler than LLETZ. LEEP is applicable anywhere in the lower genital tract; whereas, LLETZ is applicable only to the cervix.

With the availability of LEEP, a simple and effective method, laser seems to have taken a backseat.

Needle excision of transformation zone (NETZ) removes cervical tissue in one piece.

All the excisional procedures should be done in the immediate postmenstrual phase, most of them under colposcopic view and under local anaesthesia; this reduces incomplete excision to only 2–3%.

Only 0.1–0.5% cases of invasive cancer are detected during the follow-up of these cases.

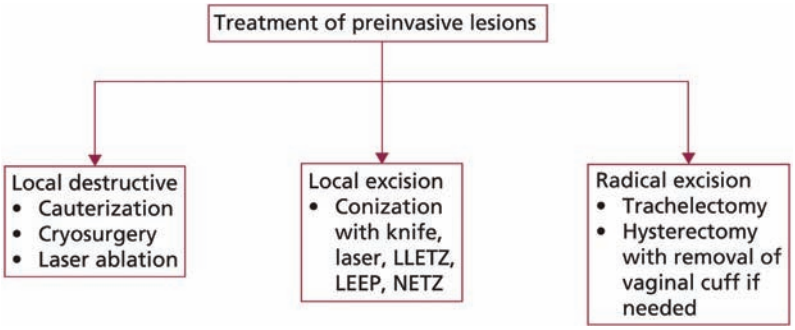

Figure 38.17 Treatment of pre-invasive lesions.

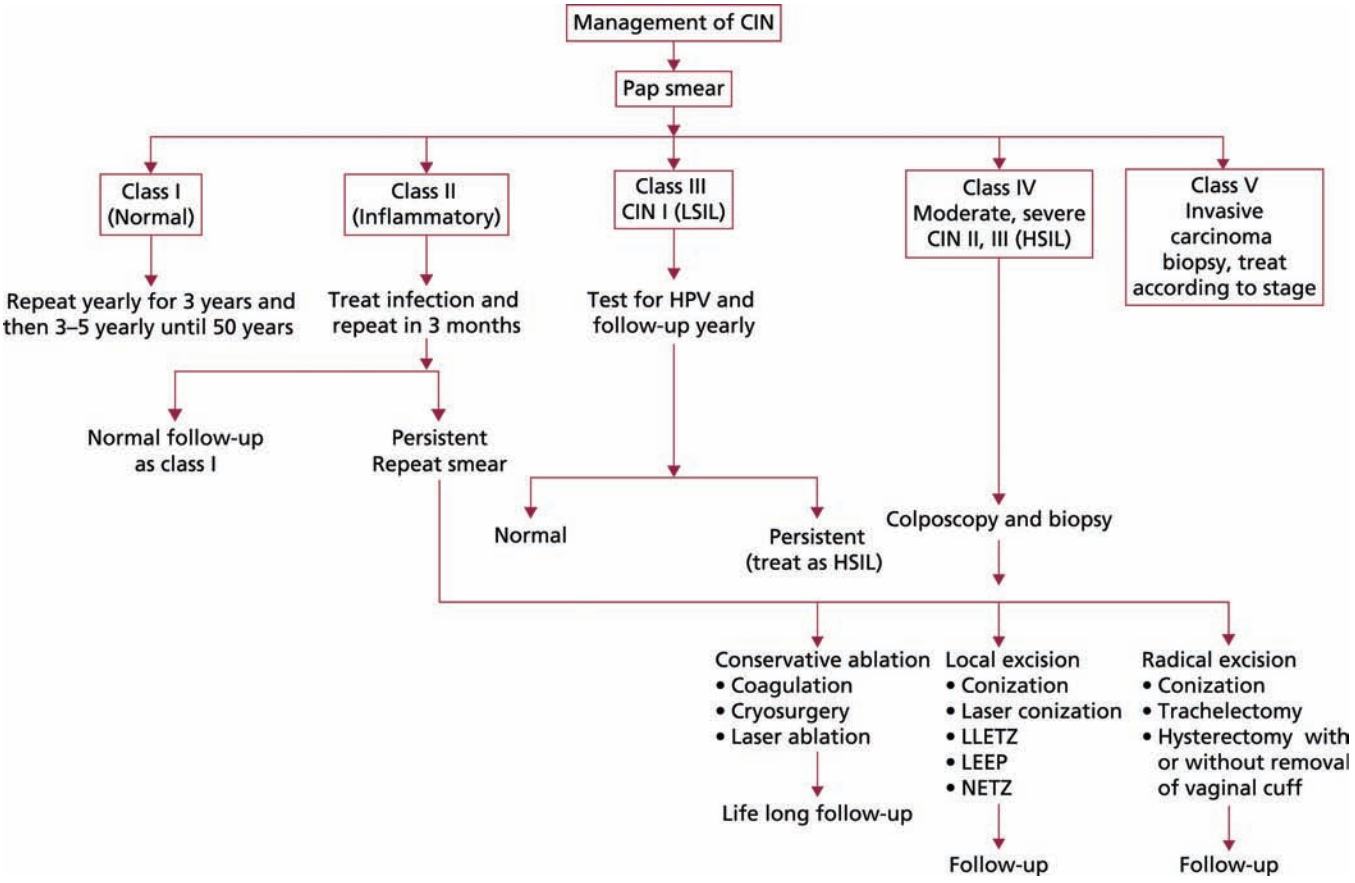

Figure 38.18 Management of CIN.

Since excisional treatment may cause stenosis of the cervix, abortion and preterm labour, ablation therapy may be better suited for young women desiring future childbirth. Recurrence or persistent lesions of 2–8% can be avoided by application of Schiller's iodine during therapy. Repeat cytology and repeat therapy if required should be delayed for 3 months, for the healing of primary treatment.

Conization includes the entire outer margin (Figure 38.19) and endocervical lining short of internal os. A smaller cone is desirable in young women to avoid abortion or preterm labour. Complications are bleeding, sepsis, cervical stenosis, abortion and preterm labour. Conization is required (i) in endocervical dysplasia; (ii) when transformation zone is not completely visualized; (iii) when there is discrepancy in findings between cytology, colposcopy and biopsy; and (iv) microinvasion is suspected.

Hysterectomy is desirable in:

- Older and parous women
- When a woman cannot comply with the follow-up
- If uterus is associated with fibroids, DUB or prolapse
- If microinvasion exists
- If recurrence follows conservative therapy or persistent lesion.
- In-situ adenocarcinoma cervix

Following conservative therapy, cytology is deferred for 3 months for inflammatory and regenerative changes to settle. In some cases, the squamocolumnar junction may

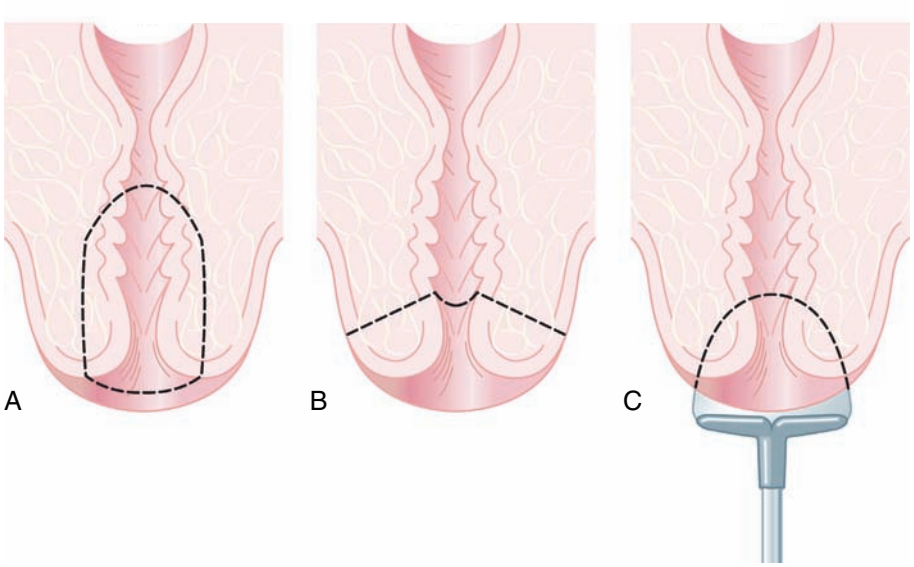

Figure 38.19 Cone biopsy of the cervix. **(A)** Diagnostic conization performed when the squamocolumnar junction is not fully visualized colposcopically. **(B)** Therapeutic conization performed for disease involving the ectocervix and distal endocervical canal. **(C)** Loop electrosurgical excision procedure. The goal of the procedure is to remove the cervical tissue above the squamocolumnar junction, including any visible lesions. (Source: Hacker NF, Gambone JC, Hobel CJ, *Hacker and Moore's Essentials of Obstetrics and Gynecology*, 5th ed. Philadelphia: Elsevier, 2010.)

retract within the os—5% women progress to invasive cancer during follow-up. Life long follow-up is therefore necessary.

Complications of these procedures are charted in Table 38.6.

Choosing between various modalities within the group of conservative treatment is a matter of gynaecologist's preference, the availability of the equipment and its cost.

Prophylaxis

Majority of cancer cervix are HPV related. Fortunately, HPV vaccine is now available, though very expensive as of today. Given to adolescents before exposure to the virus (before sexual activity begins), 70% protection is expected. What is not known is the duration of immunity and if booster doses will be needed during the reproductive period.

Prophylactic HPV Vaccines

Gardasil is a quadrivalent vaccine against HPV 16, 18, 31, 38 to be given to adolescents at 0, 2 and 6 months intramuscularly in the deltoid muscle.

Cervarix is bivalent against HPV 16, 18 to be given (0.5 mL) at 0, 1 and 6 months.

Immunity is expected to last 10 years, and re-immunization may be required.

There is no need to test the young woman for HPV infections if given before the start of sexual activity.

Oral vaccine is under trial.

Side effects of vaccine

- Local pain and swelling
- Dizziness, headache and myalgia
- Anaphylactic reaction
- Lymphadenopathy

The vaccine is also applicable prophylaxis for male adolescents.

Other prophylaxis is the use of barrier contraceptives to prevent transmission of viral infections and other sexually transmitted infections from man to woman.

If a patient is in the middle of a vaccination course, when she gets pregnant, all further vaccinations should be stopped until after the delivery. Medical termination of pregnancy is however not required. The woman can continue remaining on vaccination during lactation.

Other vaccines if required can be given simultaneously, but at different sites.

Invasive Cancer of the Cervix

About 100,000 women develop invasive cancer every year in India. In India, the incidence is 20–35 per lakh in women between 35 and 65 years, whereas in developed countries, where screening programme is on, the incidence has fallen to 8 per lakh.

Pathology

Pap smear in invasive cancer shows tadpole cells, fibres and malignant cells and haemorrhage, and necrosis in the background. It is customary to identify two types of cancers of the cervix. The first and more common variety is the epidermoid carcinoma. It arises from the stratified squamous epithelium of the cervix, and accounts for almost 80% of all cancers in the cervix. The second variety, endocervical carcinoma, arises from the mucous membrane of the endocervical canal, and accounts for 20% of all cervical cancers. Histologically, 95% of cervical cancers are squamous carcinomas and only 5% are adenocarcinomas. This is because the columnar epithelium of the endocervix

often undergoes squamous metaplasia (Figures 38.20–38.23), before undergoing malignancy.

Endocervical cancers of the cervix have recently increased in incidence because of prolonged use of oral combined contraceptive pills and progestogens pills which have profound effect on glandular epithelium (Figure 38.21).

The malignant cells are endometrioid, adenocarcinoma, clear cells and adenosquamous, squamous cells.

Squamous cell cancers of the ectocervix appear as proliferative growths, ulcers or as flat indurated areas. The common proliferative or cauliflower-like growth is vascular, friable and bleeds on touch. It undergoes ulceration and necrosis, which is associated with an offensive foul-smelling vaginal discharge. The leucorrhoeal discharge is often blood-stained. Histologically, the tumour is graded as well-differentiated (showing epithelial pearl formation—see Figure 38.20) or ill-differentiated. The endocervical growth remains confined to the cervical canal for a long time causing a barrel-shaped enlargement of the cervix, and only at a late stage does it protrude beyond the external cervical os and become visible.

The mode of spread of the cancer is by continuity (involves the vagina, parametrium and uterine body) or by contiguity (urinary bladder, bowel), by lymphatic spread (lymph nodes of the pelvis—parametrial nodes, obturator, hypogastric and rarely distant nodes) or through vascular embolization to distant sites like lungs, liver, bones, kidneys and brain. Ovarian metastasis occurs in only 1% in squamous cell cancer but occurs in 10% in adenocarcinoma of endocervix.

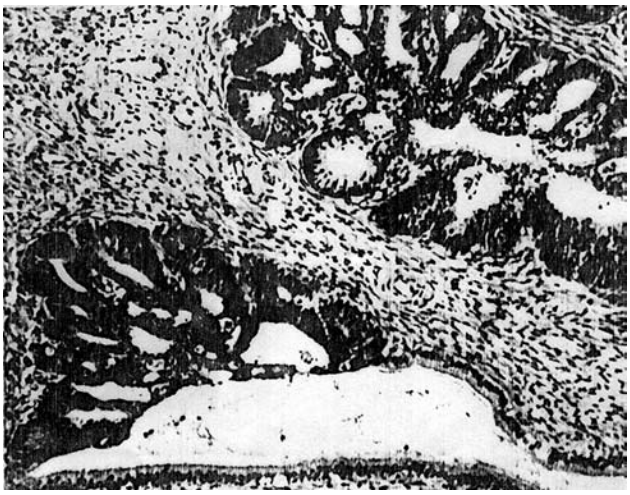

Figure 38.21 Adenocarcinoma in the endocervical glands.

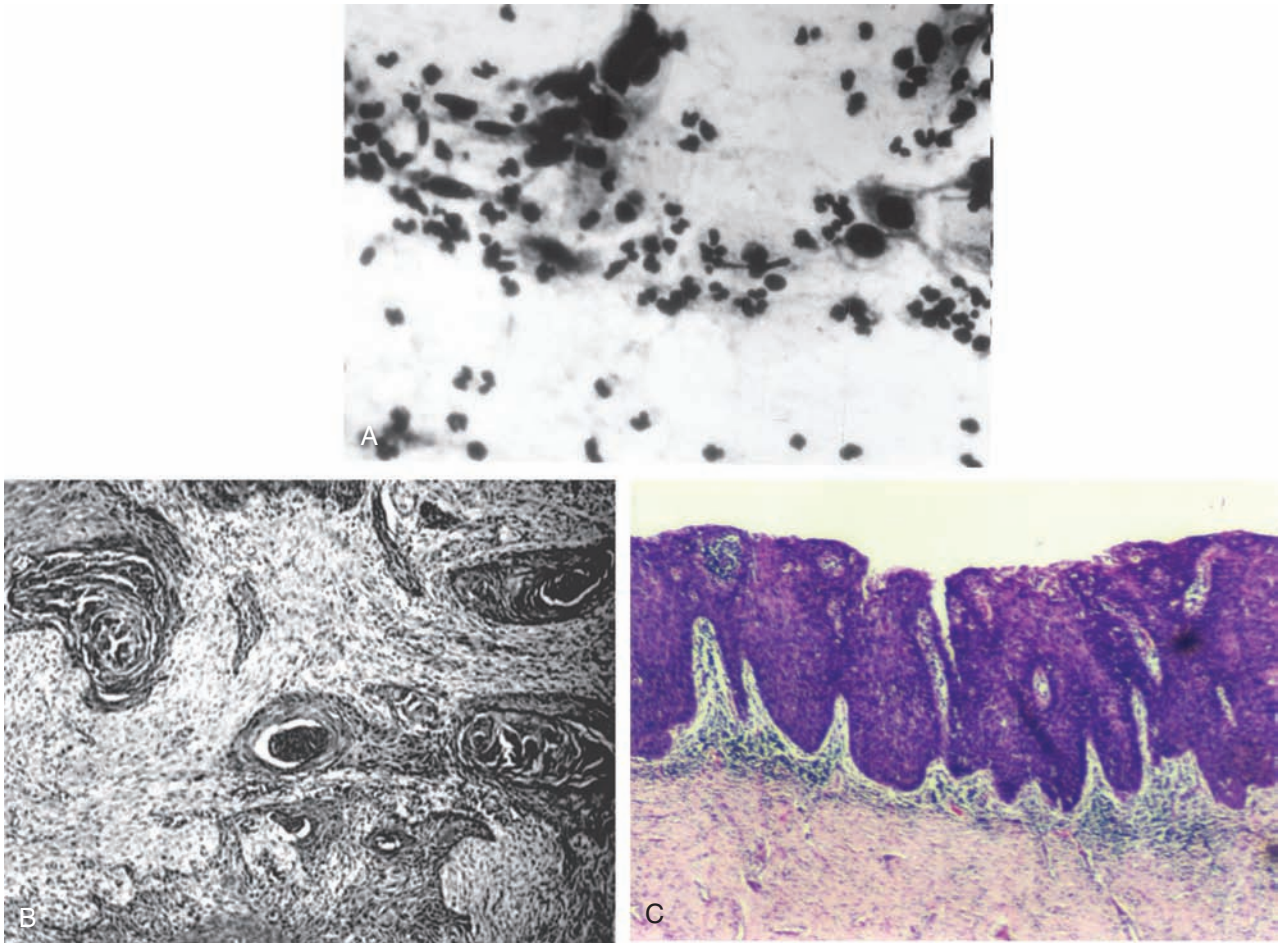

Figure 38.20 **(A)** Squamous cell carcinoma. **(B)** Squamous carcinoma of the cervix showing epithelial pearls (×52). **(C)** Cervical dysplasia CIN III.

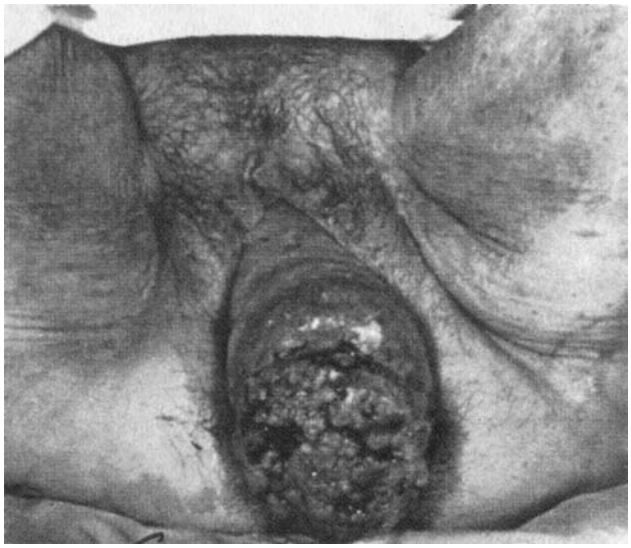

Figure 38.22 Large fungating carcinoma of the cervix in a case of procidentia. (From: Wilson et al. *Textbook of Gynaecology and Obstetrics*. BICL.)

Figure 38.23 Ulcerative carcinoma of the cervix. The specimen was removed by synchronous hysterocolpectomy. Note that the cervix has been almost entirely eroded by the growth. Note also the extent of the parametrium and paracolpos by this method.

Clinical Features

Cancer of the cervix occurs in young women (35–45 years) in the childbearing period of life. The patient presents with the complaints of irregular menses, menometrorrhagia, continuous bleeding, postcoital bleeding, leucorrhoea and blood-stained or offensive discharge.

The cervix reveals a growth, which bleeds on touch or an ulcer with edges that bleed on touch. The uterus is bulky due to pyometra in the advanced stage when the cervix gets blocked by growth. The induration is felt, and rectal examination reveals thickened induration of uterosacral ligaments.

In all suspected cases, a Pap test, Schiller's iodine test and a definite biopsy are recommended.

Tissue biopsy in a case of frank invasive cancer reveals that there is a loss of stratification and cellular polarity, the cells show alteration of morphology, the nuclear: cytoplasmic ratio is increased and the tumour cells show hyperchromatism. Thickening of the nuclear membrane, clumping of the chromatin material, penetration of the underlying basement membrane and leakage of the cancer cells into the underlying stroma, which reveals cellular infiltration, are evident (Figures 38.24 and 38.25).

Differential Diagnosis

The cervical growth and ulcer may be mistaken for tubercular and syphilitic ulcer, mucus and fibroid polypus and a rare sarcoma of the cervix. Biopsy settles the diagnosis.

Staging of Cancer of the Cervix (Figures 38.26–38.38, Table 38.7)

Pre-invasive cancer is diagnosed by histological examination of biopsy depending upon the depth and horizontal extent of the diseases.

The invasive staging is essentially based on clinical findings (chest radiograph, IVP, cystoscopy and proctoscopy are permitted). Lately, CT and MRI are also included in pretreatment strategy, but FDG-PET is considered the gold standard in the investigation (see later). MRI is more sensitive than clinical examination in detecting parametrial involvement and regional lymph nodes.

Pelvic lymph nodes are involved in 5% in Stage I, 15% in Stage II and 25% in Stage III. Para-aortic nodes are infiltrated in advanced cases (20% in Stage II, 30% in Stage III). Ureteric obstruction occurs in 30% in Stage III and 50% in Stage IV. Hypercalcaemia indicates bone metastasis.

Diagnosis

Biopsy and histopathologic evidence of invasive malignancy should precede any treatment modality. This may be from a suspicious growth, edge of an ulcer or colposcopy-directed biopsy from suspicious areas.

Investigations

Basic investigations include a haemogram, urinalysis, test of blood sugar levels—both fasting and postprandial—liver function tests, renal function tests, serum electrolytes, blood ABO and Rh group, descending pyelography, cystoscopy, radiography of chest, ECG and proctoscopy.

A cystoscopy and proctoscopy may be required to assess the involvement of the bladder and rectum prior to finally assigning the stage of the disease.

- *CT and MRI* are now employed in routine investigations of invasive cancer of the cervix. While they detect lymph node enlargement more than 1 cm, multiplanar MRI offers improved imaging in staging and in pretreatment assessment of the growth and its spread as compared to CT. MRI can identify parametrial infiltration, but cannot always differentiate between

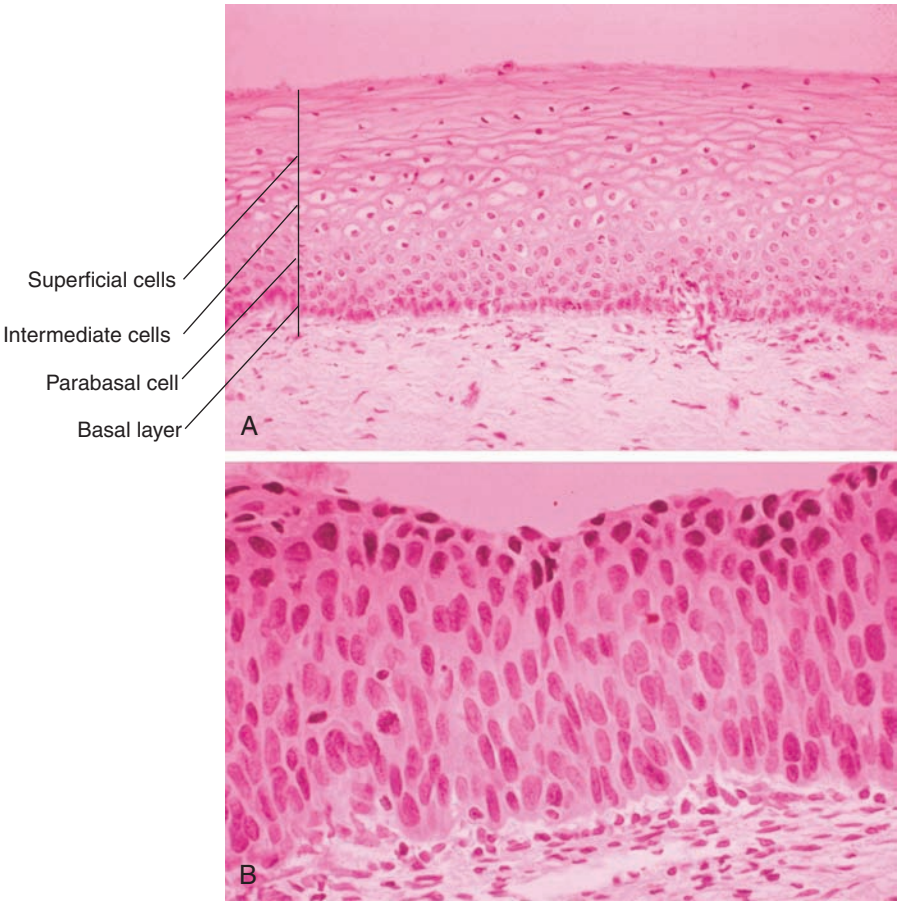

Figure 38.24 Histologic appearance of **(A)** normal cervical squamous epithelium and **(B)** carcinoma in situ of the cervix. In the normal epithelium, note the orderly maturation from the basal layer to the parabasal cells, glycogenated intermediate cells and flattened superficial cells. In the carcinoma in situ, the entire thickness of the epithelium is replaced by immature cells that are variable in size and shape and have irregular nuclei. Mitotic figures are seen in the lower two-thirds of the epithelium. (Source: Hacker NF, Gambone JC, Hobel CJ, *Hacker and Moore's Essentials of Obstetrics and Gynecology*, 5th ed. Philadelphia: Elsevier, 2010.)

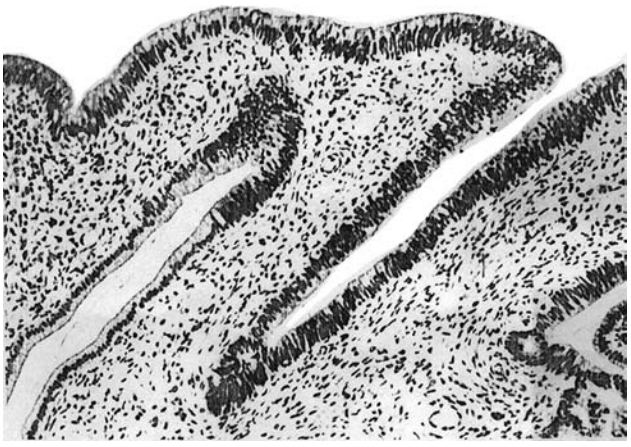

Figure 38.25 Adenocarcinoma in situ. The superficial parts of the crypts are lined by epithelium which shows loss of polarity and nuclear atypia (×155). (From: *Haines & Taylor's Obstetrical and Gynaecological Pathology*, 3rd ed. *Churchill,* 1987.)

inflammatory fibrotic and malignant infiltration. Because of intestinal peristalsis, para-aortic lymph nodes are not clearly visible on MRI. MRI is safe during pregnancy, but CT is not so because of radiation. A small lymph node less than 1 cm cannot be picked up by CT or MRI. It is important to emphasize that CT and MRI findings should not alter the clinical staging.

- *Positron emission tomography (PET)*, a noninvasive scan, detects tissue biochemical changes and para-aortic node involvement, and maps the area of concern.
- *FDG-PET using F-18 fluoro-2-deoxy-D-glucose* is useful in the determination of primary treatment, lymph node detection and local recurrence detection. The test is based on the fact that malignant tissue exhibits greater glycolysis than normal tissue, and FDG accumulates in the malignant tissue resulting in increased tumour contrast. While CT and MRI show anatomical changes, PET shows biochemical changes in the tissues. A combination of PET and CT would predict the presence of malignant tumour and its anatomy better than either singly. *FDG-PET is now considered a gold standard in the investigation of cancer cervix.*

Pre-Invasive Cancer in Pregnancy

A woman presents with bleeding during pregnancy. Postcoital bleeding may be another symptom.

The cervix may appear normal or show chronic cervicitis or erosion. Pap smear and colposcopy-directed biopsy confirm the diagnosis. Cone biopsy should be avoided whenever possible, because of postbiopsy bleeding and abortion. Besides, transformation zone is usually clearly visible during pregnancy for biopsy. The woman is allowed a vaginal delivery, provided invasive lesion is excluded. Six weeks

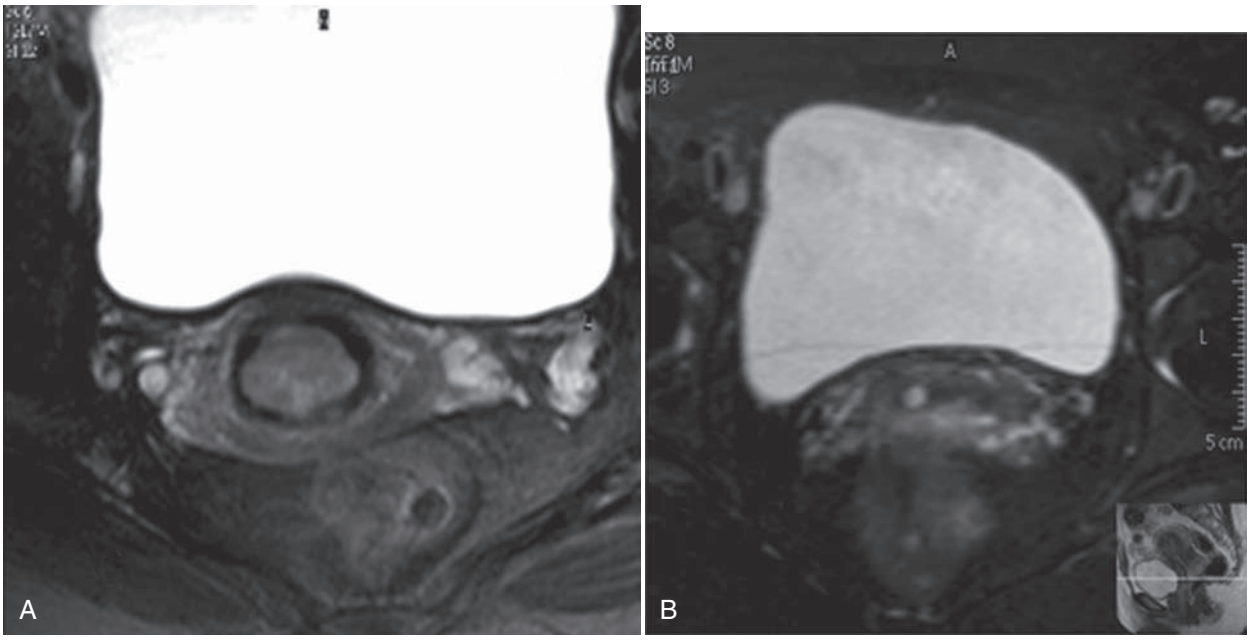

Figure 38.26 **(A)** MRI showing noninvasive cervical carcinoma with no parametrial invasion. (Courtesy: Dr Parveen Gulati, New Delhi.) **(B)** MRI showing carcinoma cervix with parametrial invasion. (Courtesy: Dr Parveen Gulati, New Delhi.)

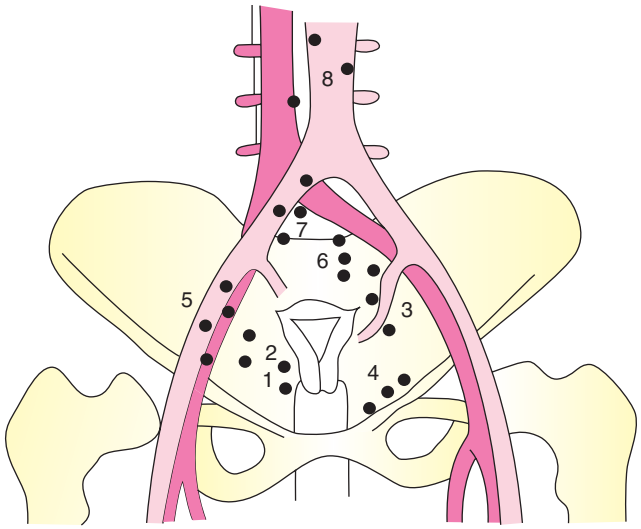

Figure 38.27 The distribution of pelvic nodes draining lymphatics from the cervix. Lymph node of drainage of the cervix: (1) paracervical, (2) parametrial, (3) internal iliac, (4) obturator, (5) external iliac, (6) presacral, (7) common iliac and (8) para-aortic.

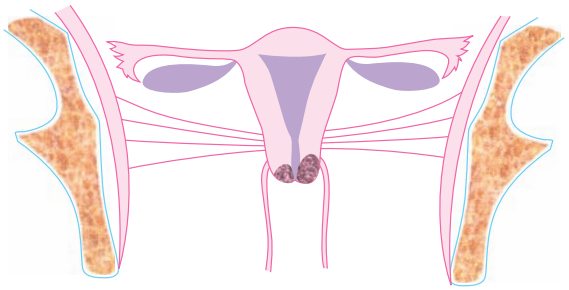

Figure 38.29 Carcinoma of the cervix. Stage I: Infiltrating type.

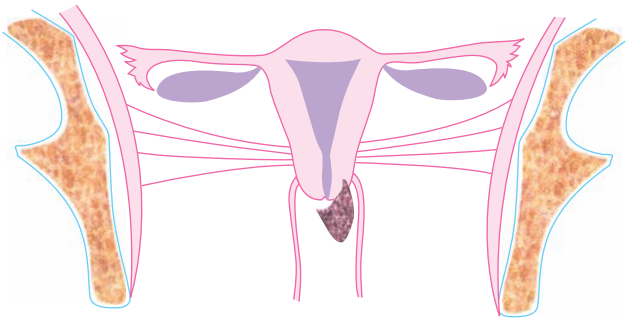

Figure 38.30 Stage I: Cauliflower type.

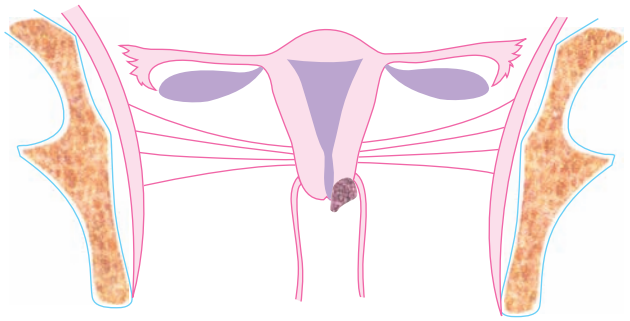

Figure 38.28 Carcinoma of the cervix. Stage I: Ulcerative type.

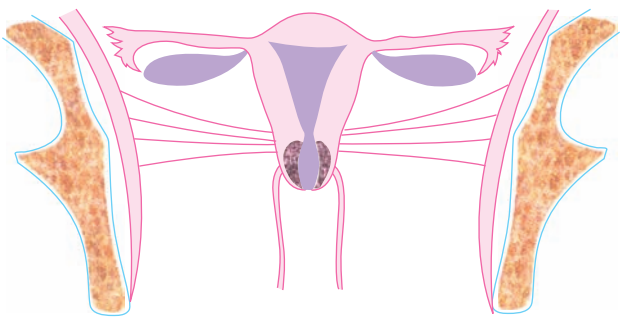

Figure 38.31 Stage I: Endocervical type.

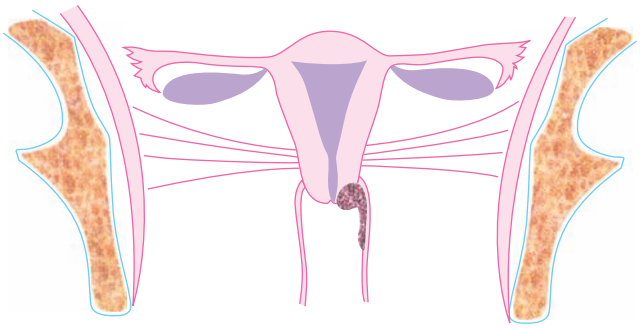

Figure 38.32 Stage II: Infiltration of the vagina.

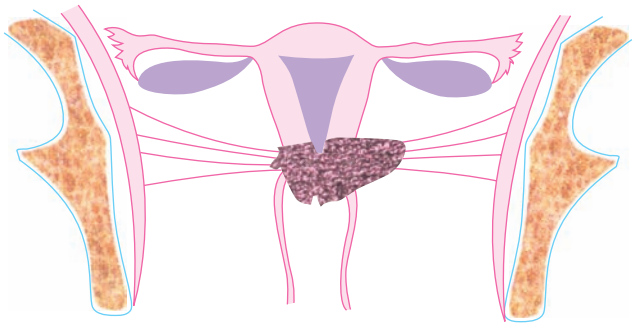

Figure 38.33 Stage II: Infiltration of the parametrium.

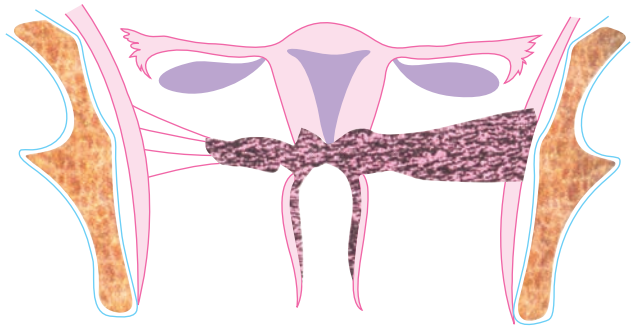

Figure 38.34 Stage III: Infiltration of the parametrium together with the whole of the vagina. Fixity of the parametrium by malignant invasion into the pelvic wall.

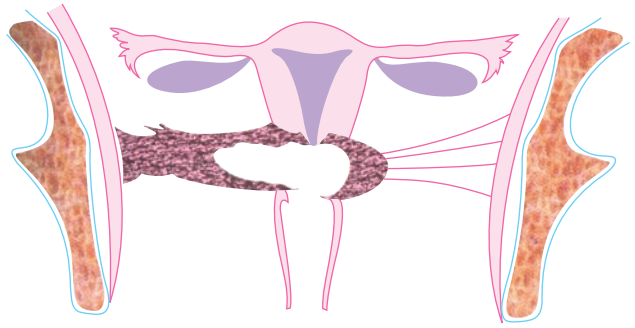

Figure 38.35 Stage III: Infiltration of the parametrium. The vagina is not involved.

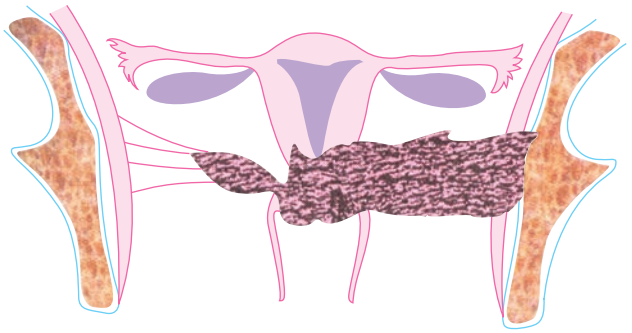

Figure 38.36 Carcinoma of the cervix. Stage III: Infiltration of the parametrium as far as the periosteum, but not through it.

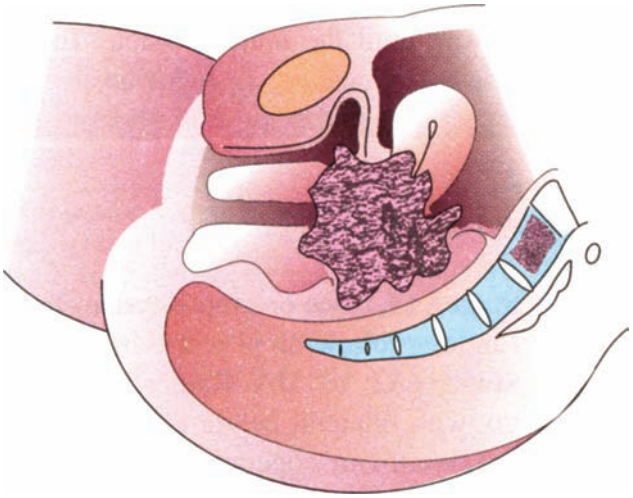

Figure 38.37 Carcinoma of the cervix. Stage IV: Infiltration into the rectum and bladder, together with bone metastases.

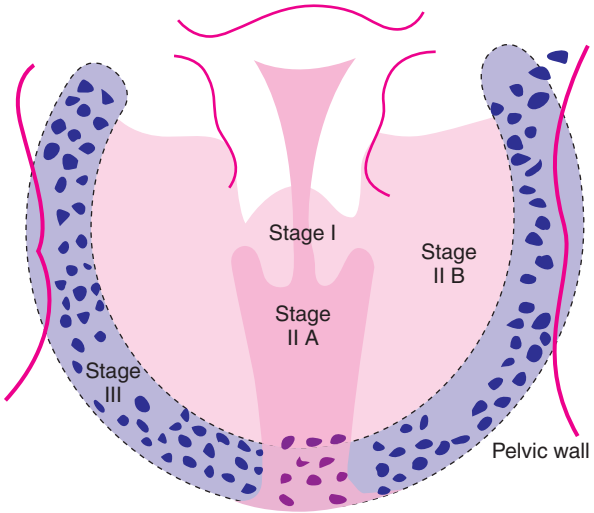

Figure 38.38 Staging of cancer cervix. (From: Wilson et al. *Textbook of Gynaecology and Obstetrics*. BICL.)

TABLE 38.7 Carcinoma of the cervix uteri—staging

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥7 mm
IA1	Measured stromal invasion of ≤30 mm in depth and extension of ≤70 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >70 mm
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancer greater than Stage IA*
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4 cm in greatest dimension
IIB	With obvious parametrial invasion
Stage III	The tumour extends to the pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctioning kidney**
IIIA	Tumour involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

*All macroscopically visible lesions—even with superficial invasion—are allotted to Stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with 'early (minimal) stromal invasion' (−1 mm).

**On rectal examination, there is no cancer-red space between the tumour and the pelvic wall. All case with hydronephrosis or nonfunctioning kidney are included, unless they are known to be due to another cause.

Source: FIGO guidelines.

postpartum, another Pap smear followed by colposcopy will refute or confirm the diagnosis of carcinoma in situ, and managed as in nonpregnant state (Figure 38.39).

Invasive Cancer of the Cervix and Pregnancy

The incidence of cancer of the cervix is reported in 1:2500 pregnancies.

The woman presents with antepartum bleeding. The cervix presents a similar picture as in the nonpregnant condition.

Cone biopsy can cause profuse bleeding; therefore, the diagnosis is confirmed on multiple biopsies or colposcopy-directed biopsies. MRI is permissible as it does not cause radiation. CT is contraindicated.

Management

The pregnancy does not appear to alter the biological behaviour of the tumour, and treatment management is related to duration of pregnancy.

If cancer of the cervix is detected remote from term, Wertheim's hysterectomy with or without follow-up radiotherapy is desirable. Alternately, primary radiotherapy is also feasible.

If pregnancy is approaching term, it may be prudent to wait until the fetus is viable. Elective classical caesarean delivery is followed 4 weeks later by surgery or radiotherapy as in a nonpregnant state. Breast feeding is contraindicated in radiotherapy or chemotherapy.

Treatment of Invasive Cancer

Treatment depends upon the age, need to preserve fertility, size of the lesion, stage and general condition of the woman.

Better understanding of early lesions have permitted a more conservative surgical treatment without compromising the success, at the same time reducing the morbidity and retaining the fertility potential in younger women.

Stage IA1. The diagnosis is by cone biopsy. The lymph node involvement in this stage is only 0.5%. Therefore, conization with a clear margin is considered adequate and is diagnostic as well as therapeutic. Hysterectomy in a young woman is considered a radical surgical approach with increased morbidity but without improved survival. Hysterectomy is appropriate in elderly and parous women, or those having a diseased uterus. Lymphadenectomy is not required, but life long follow-up is necessary. Lymphatic or vascular channel infiltration however mandates treatment as in Stage IB.

Stage IA2. Lymph node involvement and recurrence rate is not more than 5%, provided vascular and lymphatic channels are not involved. Extended hysterectomy and lymph node sampling are recommended, provided the growth is less than 2 cm. Nodal involvement requires postoperative radiotherapy. In a young woman desirous of childbearing, conservative treatment comprising laparoscopic lymphadenectomy followed by vaginal trachelectomy introduced by Dargent (1987) is appropriate and does not compromise on its success. Fertility-conserving trachelectomy consists of whole or at least 80% removal of the cervix, upper vagina and cutting Mackenrodt's ligament on either side. Involvement of lymphatic or vascular channel needs similar treatment as in Stage IB. Before conservative surgery, MRI mapping for local extension and lymph node involvement is needed. Obturator gland is the sentinel node—if negative, no further lymphadenectomy is required. Injection of blue dye into the cervical tissue before surgery identifies lymph nodes. Conception rate of 30–40% at the end of 1 year, with miscarriage (20–30%), preterm labour (18%) and

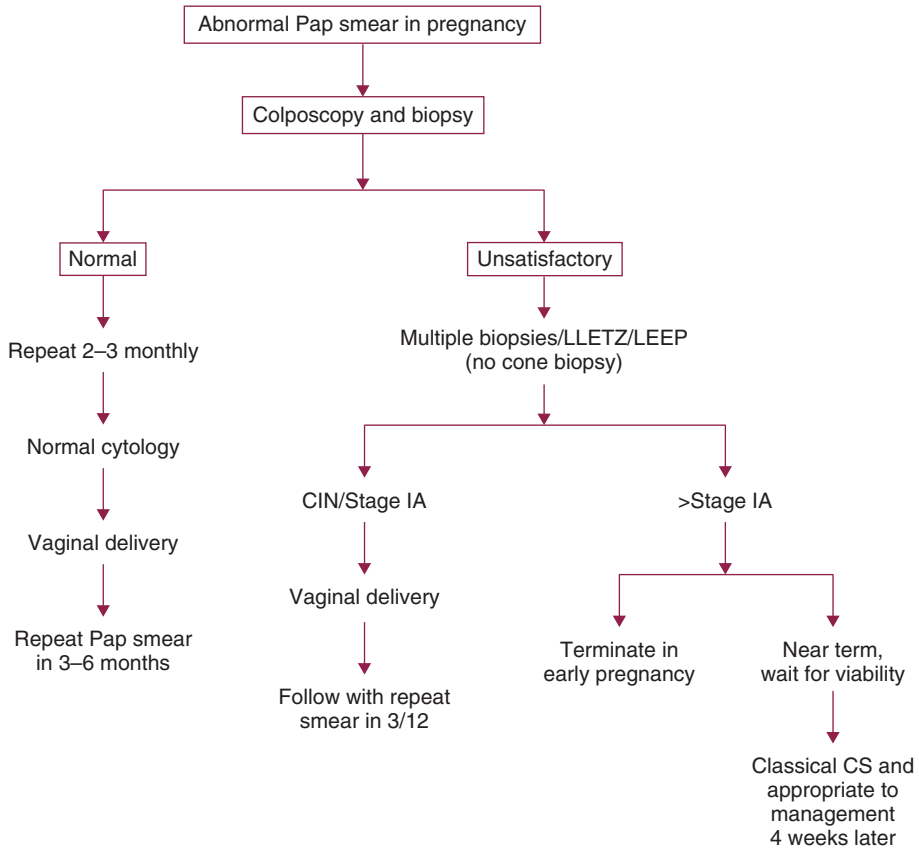

Figure 38.39 Abnormal Pap smear in pregnancy.

chorioamnionitis is reported. Recurrence rate of 5% is also reported. *Contraindication to fertility-preserving operation is a lesion more than 2 cm.* Cervical cerclage at the time of primary surgery may reduce the pregnancy complications of abortion and pre-term labour (Figure 38.40).

Stages IB and IIA. The treatment options are as follows:

- Wertheim's hysterectomy.
- Schauta's vaginal hysterectomy (known as Mitra operation in India) and Taussig's or laparoscopic lymphadenectomy.
- Primary radiotherapy.
- Combined surgery and radiotherapy. Injection of blue dye into the cervical tissue before surgery identifies lymph nodes. *Negative sentinel lymph node (obturator gland) avoids pelvic lymphadenectomy.*

Wertheim's hysterectomy, also known as Meigs–Obayashi hysterectomy, *is the surgical treatment in Stage IA, with lymphovascular invasion and tumour size of 2 cm, and also in Stages IB and IIA.* It comprises exploratory laparotomy, removal of the entire uterus, both adnexa, pelvic lymph nodes, medial one-third of the parametrium on either side and upper one-third of the vagina, sparing sacral glands. Since the ovaries are involved in only 1%, they may be retained if healthy in a young woman. The ovaries maybe extrapolated outside the pelvis to avoid damage in case radiotherapy is required later. Lately, Wertheim's hysterectomy is performed laparoscopically by experts, and also by a robot.

Schauta's operation is an extended vaginal hysterectomy consisting of removal of the entire uterus, adnexa, most of the vagina and medial portion of the parametrium. This is preceded by laparoscopic pelvic lymphadenectomy or followed later by extraperitoneal (Taussig's) lymphadenectomy. Alternatively, postoperative pelvic radiotherapy may be employed. With the possibility of laparoscopic lymphadenectomy and lesser morbidity of vaginal approach, Schauta's operation is gaining popularity among many oncologists.

Complications of Wertheim's hysterectomy are as follows:

- Primary mortality—1% anaesthesia risks.
- Haemorrhage during surgery.
- Trauma to the bladder, ureter (1–2%) causing fistula.
- Dysfunction of bladder due to nerve damage. Damage to the obturator and genitofemoral nerve.
- Sepsis.
- Thrombo-embolism, pulmonary and urinary tract infection.
- Paralytic ileus, peritonitis, wound sepsis, burst abdomen, scar hernia.
- Lymphocyst formation in the broad ligament.
- Lymphoedema (10–20%).
- Dyspareunia due to shallow vagina.
- Psychological problems.

Radiotherapy. Primary radiotherapy, consisting of brachytherapy followed by external radiation, yields the same

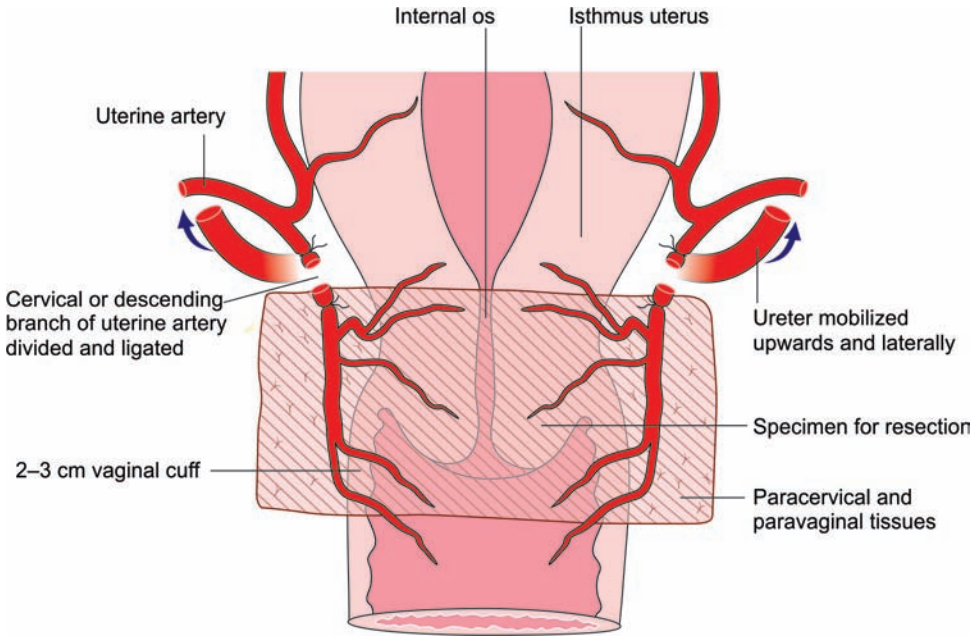

Figure 38.40 The technique used for radical trachelectomy. Area of tissue for resection (shaded) including cervix and upper vagina with paracervical and paravaginal tissues up to the level of the uterine isthmus.

5-year cure rate as that of surgery, i.e. 80–90%. It is, however, observed that many surgical cases show positive lymph node metastasis which require additional postoperative radiotherapy anyway, and this combined therapy increases the morbidity in the woman. Therefore, some oncologists prefer to avoid surgical complications and employ primary radiotherapy (see Chapter 41).

Chemoradiation with cisplatin 40 mg[2] weekly with radiotherapy improves the radiation effect, as cisplatin acts as a radiosensitizer agent. Lately, many prefer carboplastin to cisplatin, as it is less toxic.

Young women in this group warrant special consideration regarding the destruction of ovaries, stenosis of vagina and occurrence of pyometra following radiotherapy, which are not desirable. *Primary surgery therefore is the treatment of choice in young physically fit women.* Brachytherapy is first applied if the lesion is small, followed 5–6 weeks later by external radiotherapy. In case of a large lesion, external radiotherapy is used first, followed by two applications of brachytherapy 2 weeks apart. This shrinks the tumour, and allows insertion of internal applicator.

The advantages and disadvantages of surgery and radiotherapy are mentioned in Table 38.8.

Combined therapy may be required in the following:

- Postoperative radiotherapy if the lymph nodes show metastasis.
- Preoperative chemoradiotherapy in endocervical carcinoma as follows:
  - Neoadjuvant paclitaxel 90 mg and injection ifosfamide 2000 mg plus mesna 400 mg weekly for 3 cycles.
  - Cisplatin 50 mg weekly followed by surgery yields 94% success in early stages.
- Recurrence of cancer.

Stages IIB, III and IV. Chemoradiotherapy can improve the survival and allow the woman to spend a comfortable life or increase the duration of remission. A centrally placed growth, a bladder and rectal fistula may be subjected to exenteration operation (see later).

Recent trend is to treat Stage IIB with chemoradiation or chemotherapy for the first 3 months followed by surgery.

Recurrent growth. Twenty to twenty-five per cent of early lesions recur within 2 years of primary treatment. This may be centrally located or on the lateral pelvic wall with lymph node involvement or distal in the para-aortic nodes, lungs, liver or bones. Most recurrences are related to the size of the primary growth of more than 2 cm, stage of cancer, lymph node involvement and tissue differentiation.

The symptoms appear late, but are similar to those of early cancer. The development of sciatic pain, lymphoedema of the leg and fistula are sure signs of recurrence. It is important to differentiate inflammatory from malignant, parametrial thickening. On pelvic examination, inflammatory infiltration is smooth whereas malignant infiltration is nodular.

Pap smear is difficult to interpret. The cells appear large with cytoplasmic vacuolation, multinucleation and nuclear shrinking with inflammatory cells in the first few months of radiotherapy. Fine-needle aspiration cytology (FNAC) and tricot needle biopsy confirm the recurrence. Cystoscopy, sigmoidoscopy, CT, MRI and PET are required to study the extent of the growth.

MRI is superior to CT in identifying malignant infiltration in the parametrium, but in case of difficulty, MRI is repeated 3 months later; PET also helps. CT is specific in 60–70% cases,

TABLE 38.8 Advantages and disadvantages of surgery compared with radiotherapy

Surgery	Radiotherapy
Advantages	
• Accurate surgical staging possible • Pelvic lymphatic glands can be removed • Conservation of ovaries–transposition of ovaries in case postoperative chemotherapy is required • A more pliable, but short vagina retained • Applicable if fibroids, adnexal masses present • Failed surgery can be treated with radiotherapy	• Survival rates for surgery and radiotherapy are similar • Applicable to all stages between Stages IB and IV • OPD procedure
Disadvantages	
• Surgical mortality—1% • Anaesthesia complications • Haemorrhage, trauma during surgery • Sepsis—wound, pelvic, chest, urinary tract, burst abdomen • Bladder atonicity, fistula, ureteric injury, bladder dysfunction due to denervation • Paralytic ileus, thrombophlebitis, embolism • Lymphocyst formation • Many require radiotherapy postoperatively • Scar hernia, pelvic adhesions • Obturator nerve damage	• Anaemia • Ovarian destruction • Pyometra—decreased libido due to ovarian failure • Vaginal stenosis • Bladder—cystitis, fistula, ureteric stenosis • Bowel—chronic diarrhoea, proctitis, rectal stricture, fistula—skin burn • Avascular necrosis of femoral head • Not applicable in the presence of ovarian tumour, adnexal mass, fibroids, prolapse • Risk of sarcoma a few years later

but MRI is specific in 70–90%. PET–CT is more specific than the two.

Management. Recurrent growth following radiotherapy can be treated by hysterectomy in a small central growth or exenteration operation. Most recurrences are centrally placed and 30% are fit to be managed by pelvic exenteration operation. Anterior exenteration comprises hysterectomy and removal of the bladder with ureteric implantation in the ileal conduit. Posterior exenteration removes the uterus and the rectum with low rectal anastomosis, avoiding permanent colostomy. In total exenteration, both bladder and rectum are removed in addition to the uterus. Vaginoplasty may be required in young women. *Exenteration operation is indicated in recurrent and residual tumours centrally located.*

Exenteration surgery makes the life of the woman comfortable, with 5% surgical mortality but 60% 5-year cure rate. The following are the contraindications to this operation:

- Age over 80 years.
- Woman does not accept mutilation.
- Presence of lymph node or distal metastasis.
- Fixed tumours.

Lateral recurrence is managed by radiotherapy in a previous surgical case, but repeat radiotherapy can cause fistula unless radiotherapy was applied more than 1 year ago.

Distal metastasis has only 5% 5-year survival rate, but chemotherapy has recently shown considerable improvement in short-term remission in 20–40% cases. Of all drugs, cisplatin proves most promising, singly or in combination.

The details of radiotherapy chemotherapy are given in Chapter 41.

Pre-invasive glandular endocervical lesion also known as carcinoma—in situ endocervix, or as cervical intraepithelial glandular neoplasm (CIGN)– is now proved to exist, though very rare. Many endocervical cancers arise de novo without passing through the in situ stage. It exists as low- or high-grade lesions. It may appear anywhere along the endocervix, but is mostly seen near the squamocolumnar junction.

If the woman is young, nulliparous or of low parity, HPV infection and oral combined pills are probable causes of this lesion.

It is difficult to pick up the cells in routine cytology and difficult to interpret. Similarly, colposcopy may miss the lesion if located within the cervical canal. Endocervical brush or endocervical curette is required to detect this lesion. In a suspected case, when cervical cytology shows abnormal glandular cells, cone biopsy is required.

The lesion is best treated with either cold-knife conization or hysterectomy. LLETZ can leave a residual tumour if the lesion is located high up in the cervical canal. Follow-up is necessary, as residual tumour can grow into endocervical cancer. Conization is applicable only in young women after counselling regarding recurrence. Hysterectomy is ideal otherwise.

Conservative surgery in a young woman.

In a young woman wishing to conserve fertility potential, the following measures are recently being tried:

1. Trachelectomy with lymphadenectomy and cervical cerclage.
2. Transposition of the ovaries outside the pelvis in case radiotherapy is required.
3. Oocyte and embryo cryopreservation prior to chemoradiation.

Endocervical Cancer

Endocervical cancer usually occurs in a young woman around 35 years, nulliparous or of low parity. Viral infections

and combined oral pills probably cause this cancer. The symptoms, similar to those of squamous cancer, appear late. The cervix appears barrel-shaped with the growth pouting through the external os in the advanced stage. The parametrial infiltrations occur early, so also the spread to the uterus.

Pap smear has low sensitivity, but endocervical cytology, curettage or cone biopsy improves the detection rate.

In invasive cancer, chemoradiation for 6 weeks should be followed by Wertheim's hysterectomy. The ovaries should be removed because of the advanced growth at diagnosis and distal spread. Ovaries are involved in 10% cases.

HRT can be prescribed following oophorectomy in cancer cervix.

Results

Refer to Table 38.9.

Prognosis

Prognosis is related to tumour volume, staging, lymph node involvement and grading of the tissue. It is worse than that of squamous cell carcinoma. Raised carcinoembryogenic antigen (CEA) level indicates bad prognosis.

Stump cancer cervix occurs in 1–2% following subtotal hysterectomy performed for benign lesions. If it occurs within 2 years of surgery, it is likely that it was present at the time of hysterectomy. Pap smear prior to hysterectomy reduces its risk. Management is difficult, involving both surgery as well as radiotherapy. Conization with external radiotherapy is recommended.

Palliative Treatment in Terminal Stage

- Pain relief with morphia and tramadol. Oral morphia 5–60 mg.
- Vomiting: Correct dehydration and electrolyte imbalance. Neutropenia, uraemia and chemoradiation are the causes of vomiting.
  - Haloperidol 1.5–3 mg (dopaminergic antagonist).
  - Metoclopramide, domperidone and corticosteroids for bowel oedema improve appetite (60–100 mg daily prednisone). Dexamethasone 4–8 mg daily 3–5 days.
- Lymphatic leg oedema stockings, garments, massage.
- Diuretics and spironolactone for ascites.

TABLE 38.9 Comparison of FIGO staging and 5-year survival rate

FIGO Staging	5-Year Survival Rates
Stage I	>90%
Stage IIA	>80%
Stage IIB	>65%
Stage IIIA	About 45%
Stage IIIB	About 35%
Stage IV	<15%

- Vaginal discharge—Betadine douche or metronidazole irrigation.
- Ondansetron 4 mg t.i.d. for radiation vomiting.
- Ascites tapping

Profuse vaginal bleeding – packing, administration of tranexamic acid 500 mg IV 6–8 hourly. As a last resort, ligation of internal iliac arteries.

Future Development

Gene therapy may have a role in locally advanced disease. It is possible for the direct injection of DNA–liposomal complexes and human leucocyte antigen, which may promote a favourable cytotoxic immune response. This may have a role in reducing local recurrence.

Key Points

- Carcinoma of the cervix is the most common genital tract cancer and ranks next to breast cancer. It is a disease of young women between the age of 35 and 50 years.
- Human papilloma virus (HPV) infection is now proved to be the most important cause of pre-invasive and invasive cervical cancer. It is sexually transmitted. Other contributory factors are early age of sexual activity, multiple partners, poor hygiene, multiparity and immunosuppressive conditions, such as HIV.
- Use of barrier contraceptives prevents transmission of viral infection to a woman and prevents pre-invasive and invasive cervical cancer. Prolonged use of oral combined pills and progestogen-only pills increases the risk of endocervical cancer.
- Ninety per cent of young women with HPV infection show spontaneous resolution within 2 years and do not develop cancer. Only those with persistent infection after the age of 30 years are at high risk for pre-invasive and invasive cancer.
- Step-wise development of cancer cervix from HPV infection, and its persistence leading to pre-invasive and invasive cancer takes 10–15 years. This long period allows routine screening and treatment of pre-invasive cancer, so that invasive cancer does not develop.
- Routine Pap smear and colposcopic study and biopsy pick up pre-invasive lesions (CIN) effectively in 90% cases. Adding HPV testing further improves the pick-up rate.
- Ablative therapy is a successful fertility-conserving therapy in young women, but life long follow-up is necessary to detect recurrence. Hysterectomy is reserved for elderly and multiparous women. Follow-up is necessary irrespective of treatment for pre-invasive cancer.
- Treatment of cervical dysplasia by conservative treatment reduces the incidence of cancer of the cervix without increased surgical morbidity.

- Endocervical cancer is difficult to diagnose in its early stage, as the tissue is not available for cytology and colposcopy. Endocervical scrape and cone biopsy are required for diagnosis. Treatment is chemoradiation followed by Wertheim's hysterectomy.
- Radiotherapy is applicable in all invasive cancers. Because of ovarian atrophy, vaginal stenosis and pyometra, primary surgery is preferred in young women.
- Prognosis in invasive cancer depends upon the size of the lesion, stage, involvement of lymph nodes and cell differentiation.
- Prophylactic vaccine against HPV is now available. Given before the start of sexual activity, the vaccine is expected to reduce the incidence of cervical cancer.

Self-Assessment

1. Discuss the causes of carcinoma of the cervix.
2. Discuss the clinical features and management of pre-invasive cancer of the cervix.
3. Describe the clinical features of invasive cervical cancer and the differential diagnosis.
4. How will you investigate a case for cancer of the cervix.
5. Discuss the management of Stage IB cancer of the cervix.
6. Describe the various stages of cancer of the cervix.
7. Discuss the diagnosis and management of endocervical cancer.

Suggested Reading

Duncan J, Shulman P:. Yearbook of Obstetrics, Gynaecology and Women's Health; 40: 423, 2010.
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Chapter

39

Cancers of Endometrium, Uterus and Fallopian Tube

CHAPTER OUTLINE

Endometrial Cancer

Endometrial cancer has recently emerged as the more frequently encountered gynaecological cancer accounting for 20–25% of all genital cancers in the developed countries, not only because of the longer survival of women, but mainly because of the marked decline in cervical cancer by screening programme (Figures 39.1–39.5). In developing countries including India, the incidence has remained low at 5–7% of all genital cancers; cervical cancer continues to predominate and is seen in 1.8 per 100,000 population.

The peak incidence of endometrial cancer is 55–70 years, 20–25% occur in perimenopausal women and only 5% develop in women below the age of 45 years when they are well-differentiated with good survival. Women are either nulliparous or of low parity. An early menarche and late menopause is characteristic of women suffering from this cancer, indicating the prolonged exposure to oestrogen hormone. Seventy-five per cent of the tumours are localized in the uterus when diagnosed and surgery is the cornerstone in its management. It is surprising that oestrogen-dependent endometrial cancer can develop in atropic endometrium in a postmenopausal woman when the level of the hormone is lowest. However, the behavioural pattern differs; endometrial cancer is poorly differentiated in postmenopausal women, whereas in young women, it is well-differentiated and curable. After the age of 80 years, the incidence drops.

Predisposing Factors (Table 39.1)

Any factor that increases the exposure of endometrium to unopposed or high oestrogen level, both endogenous and exogenous, increases the risk of endometrial cancer. This is also linked to dose and duration of exposure; the risk persists for 10 years after the hormone exposure. The endometrial cancer therefore is encountered in the following conditions:

- Unopposed and unsupervised administration of hormone replacement therapy after menopause predisposes the woman to endometrial hyperplasia and cancer. Fortunately, the malignancy is well-differentiated with good prognosis.
- Chronic nonovulatory cycles as seen in abnormal uterine bleeding.
- In some families, a strong familial predisposition is noticed. This may be due to genetic or dietetic habits such as animal protein and fat. The oestrone is derived by peripheral aromatization in the fat tissue from androstenedione and contributes to a high level of oestrogen. Women with familial Lynch II syndrome suffering from anorectal and breast cancer are also likely to suffer from endometrial cancer.
- Tamoxifen given to women with breast cancer increases the risk of endometrial hyperplasia and cancer to two- to

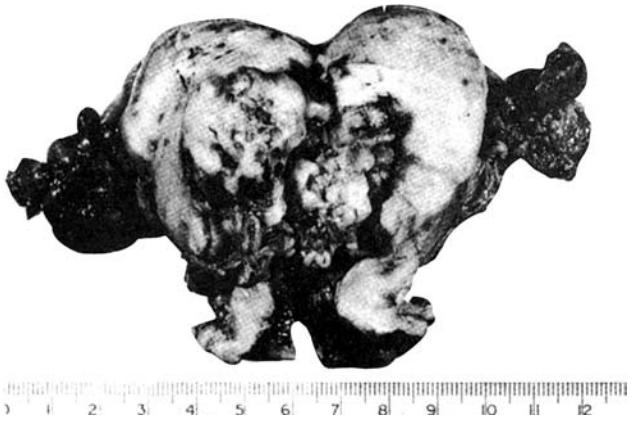

Figure 39.1 An adenocarcinoma of the endometrium. The growth forms a large tumour projecting into the cavity of the body of the uterus.

Figure 39.2 Stage II carcinoma of the endometrium. The muscle is deeply and extensively infiltrated but has not yet reached the serosa.

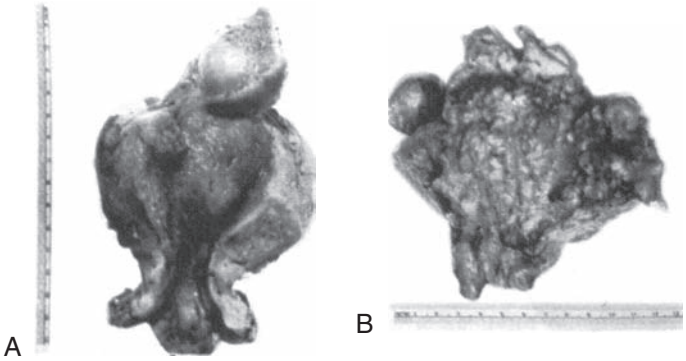

Figure 39.3 **(A), (B)** Invasive cancer of endometrium—localized and diffuse varieties. (From: Wilson et al. *Textbook of Gynaecology and Obstetrics.* BICL.)

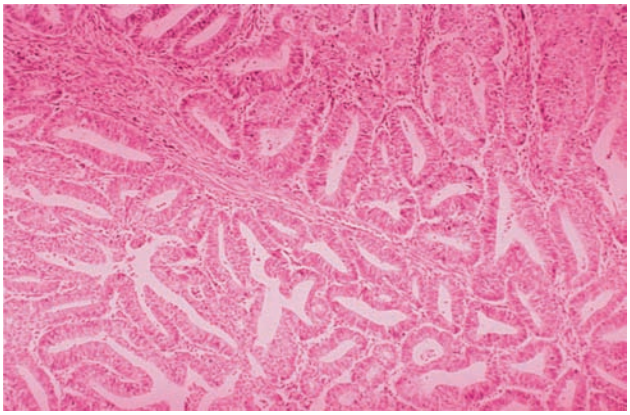

Figure 39.4 Well-differentiated endometrial adenocarcinoma (histologic study). Note the back-to-back glands with minimal intervening stroma and the gland-within-gland pattern. (Source: Hacker NF, Gambone JC, Hobel CJ, *Hacker and Moore's Essentials of Obstetrics and Gynecology*, 5th ed. Philadelphia: Elsevier, 2010.)

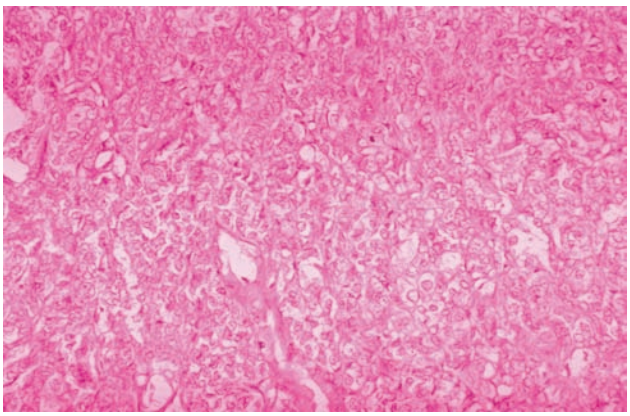

Figure 39.5 Poorly differentiated endometrial adenocarcinoma (histologic study). Note the predominantly solid nature of the tumour with minimal gland formation. (Source: Hacker NF, Gambone JC, Hobel CJ, *Hacker and Moore's Essentials of Obstetrics and Gynecology*, 5th ed. Philadelphia: Elsevier, 2010.)

TABLE 39.1 Endometrial cancer: Aetiology and high risk

- Unopposed oestrogen or high level of oestrogen
- Chronic anovulation, PCOD
- Familial predisposition
- Tamoxifen
- Obesity, hypertension, diabetes
- Feminizing ovarian tumour
- Low parity
- Late menopause

threefolds. Raloxifen has no adverse effect on the endometrium.

- Combined oral hormonal pills have a protective effect and reduce its risk by 40–50%; adding progestogens for 12 days each cycle to oestrogen in hormone replacement therapy (HRT) reduces its risks to 2%.
- Obesity, hypertension and diabetes characterize this cancer in 30%. Obesity reduces the level of serum sex hormone–binding protein and allows free oestrogen to circulate in the body. Moreover, peripheral conversion of epi-androstenedione is aromatized to oestrone in the peripheral fat.
- Infertile women and women with polycystic ovarian syndrome on account of nonovulation have high oestrogen. There is more chance for them to develop endometrial hyperplasia and endometrial cancer than normal women.

The uterine fibroid is associated with endometrial cancer in 3% after the age of 40 years.

- Fifteen per cent women with endometrial cancer have feminizing ovarian tumour at the time of diagnosis.

Risk Factors for Endometrial Cancer

- Endogenous oestrogen dependent
  - Nulliparity, low parity
  - Polycystic ovary syndrome (PCOS)
  - Early menarche, late menopause
  - Functioning ovarian tumours
  - Obesity, hypertension, diabetes, hyperlipidaemia
- Exogenous oestrogen
  - Unopposed oestrogen therapy
  - Tamoxifen
- Other risk factors
- Hereditary

Pathology (Figure 39.6)

Endometrial cancer may be localized or diffuse. It may appear as a nodule, a polyp or as a diffuse lesion involving the entire uterine cavity. It extends to the endocervix in the advanced stage, and invades the myometrium to a varying degree. Later, it involves the vault by direct spread, or suburethral metastasis occurs through a retrograde lymphatic or vascular channel. It spreads to the adnexa, ovaries as well as to the pelvic and para-aortic nodes. The fundal growth spreads to para-aortic lymph nodes via ovarian lymphatics and also to superficial inguinal lymph nodes via the round ligament. Distal metastasis occurs in the lungs, liver, brain and bones.

To the naked eye, the endometrial curettings appear plentiful, pale and friable. Histologically, endometrial cancers are adenocarcinoma in 75%. The rest are clear cells, squamous and serous variety, which are more malignant than adenocarcinoma. The grading of these tumours is based on differentiation, glandular architecture and anaplasia of the cells. Adenoacanthoma is least malignant (Figures 39.4–39.6). Necrosis in the tumour has an adverse effect on women's survival.

Grade 1: The glandular pattern is maintained, but cells show atypia.
Grade 2: Some glands show papillary pattern and are solid.
Grade 3: The glands are solid with cellular proliferation, and glandular architecture is lost. The endometrium is packed with glands and little stroma.

Types

There are two varieties of endometrial cancer.

Type I are oestrogen-dependent and account for 90% growths. The source of oestrogen may be endogenous or exogenous. They are well-differentiated with good prognosis.

Type II are oestrogen-independent and develop in atropic endometrium. They are mostly undifferentiated with poor prognosis. P_3 mutations are recognized in type II tumours.

As mentioned before, oestrogen-stimulated endometrial cancers are well-differentiated, whereas cancers developing in atropic endometrium in menopausal women are poorly differentiated.

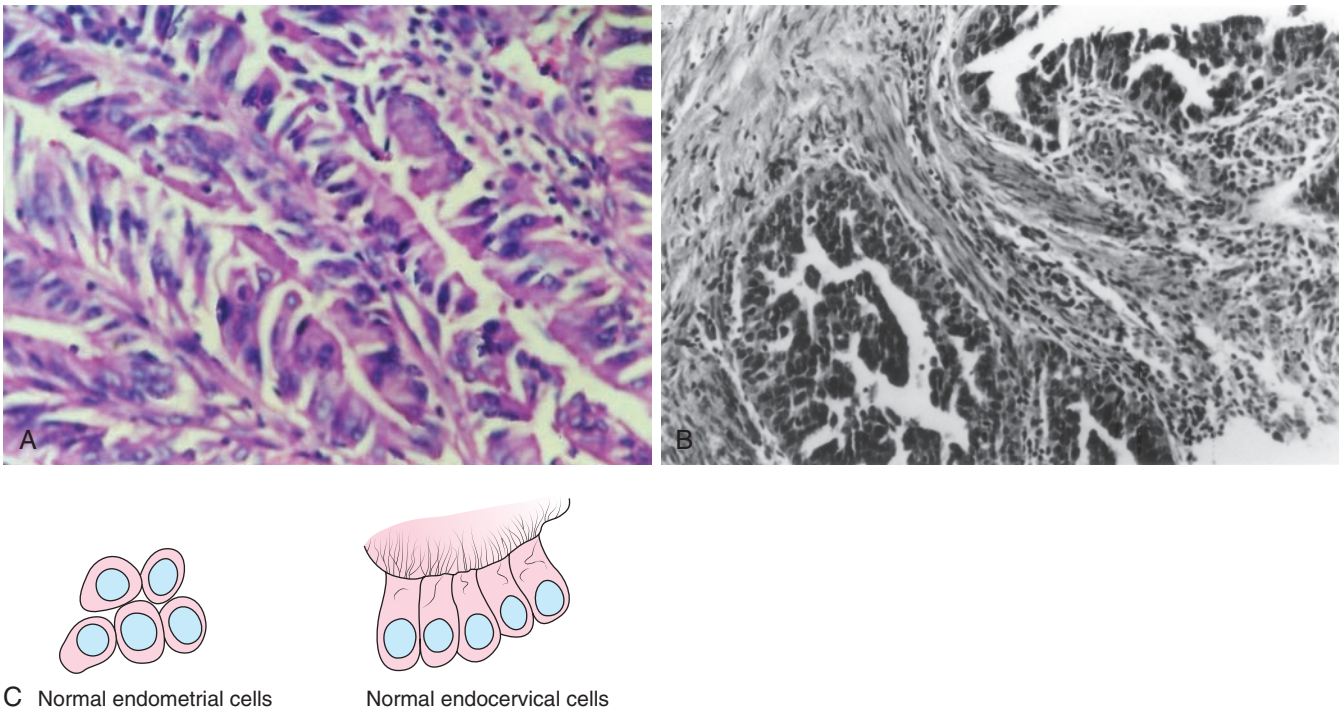

Figure 39.6 **(A)** Endometrial cancer. **(B)** Well-differentiated endometrial cancer infiltrating the myometrium. **(C)** Normal endometrial and endocervical cells.

While simple hyperplasia progresses to cancer in 10–20%, atypical hyperplasia is a precursor of cancer in 60–70% cases. Higher-grade cancers have poor prognosis, as they spread earlier and faster to lymph nodes and distal organs.

Clinical Features

Endometrial cancer may be asymptomatic in 7–10% to begin with. It manifests as menorrhagia or irregular periods in perimenopausal women. A menopausal woman presents with postmenopausal bleeding. History of PCOS or HRT may be elicited. The woman may be obese, hypertensive or diabetic. Pain and lumps appear late in advanced stages.

The clinical features of a bulky uterus may not always be present. A bulky uterus is due to growth itself or due to associated fibroid or pyometra. An adnexal tumour is often a feminizing tumour if present. In the advanced stage, the cervix is bulky and the os is patulous with the growth protruding through the os. A metastatic vaginal growth is visible near the urethra. A benign poly can undergo secondary malignant change.

Discovering lower genital tract lesion in a postmenopausal woman does not rule out endometrial cancer. Both may exist and investigations are required to rule out endometrial cancer.

Investigations

Various investigations confirm the diagnosis and assess its stage and extent of the disease, so that appropriate and optimal treatment may be planned.

A cost-effective screening programme is not available for endometrial cancer but high-risk cases should be observed from time to time.

- *Pap smear* is only 50% sensitive and not reliable. The cytological endometrial cells reveal large round cells with dark nuclei filling most of the cells.
- *Aspiration cytology* from the uterine cavity 6-monthly is effective in screening high-risk cases, and those on tamoxifen and HRT. The aspiration is done with a Pipelle curette, Isaac aspirator, Vibra aspirator Gravely jet wash and Novak curette as an OPD procedure (Figure 39.7).
- *Fractional curettage* comprises histological study of endocervical scraping before dilating the cervix, followed by cervical dilatation and curettage from the isthmus, body of the uterus and fundus separately, so that the extent of the lesion can be evaluated.

Figure 39.7 Vibra aspirator for suction curettage.

- *Hysteroscopy and biopsy* visualizes the entire uterine lining and select biopsy from suspicious areas; both reduce the chances of missing the lesion. Even then, this is not 100% predictive, as an early lesion can be missed. Recently, the concern regarding spilling of cancer cells into the peritoneal cavity during hysteroscopy is expressed.
- *Ultrasound* is useful in studying the endometrial thickness, irregular line, detecting polypi and associated ovarian tumour or ovarian metastasis. The extension to the cervix can also be recognized. In a postmenopausal woman, the normal endometrium should not exceed 4 mm in thickness and 10 mm in a perimenopausal woman. In a menopausal woman with vaginal bleeding, even an endometrial thickness of less than 4 mm runs the risk of cancer and the entire endometrium should be subjected to histopathology study.
- *Doppler ultrasound* revealing a low resistance index of 0.37–0.7 or below is seen in endometrial malignant lesions.
- *Sonosalpingography* is very useful in detecting endometrial polypi which could be malignant.
- *CA-125* tumour marker is raised above 35 IU/mL in some cases, but not in all, and is not specific for endometrial cancer.
- *CT* has a predictable rate of 85% in studying the extent of spread of the lesion. Hypodensity in the myometrium suggests myometrial infiltration. The pelvic and aortic nodes are defined if enlarged to more than 1 cm. CT is superior to MRI in detecting ascites, bowel and omental metastasis, but radiation exposure is the disadvantage.
- *MRI* is superior to CT in detecting myometrial involvement and nodal enlargement with 90% detection rate and without radiation hazard. Normally, between the endometrial and myometrial junction, a low-intensity zone exists and if this zone is intact, myometrial invasion can be ruled out, and the tumour is staged as Stage I. MRI is more expensive and time-consuming but accurate staging is possible in 80–90% (sensitivity 72% and specificity 96%) (Figure 39.8).
- X-ray of lungs and bone and liver scanning by ultrasound are useful in advanced stage.
- PET–CT reveals metabolic activity in the tissue and is a gold standard for staging.

Differential Diagnosis

Endometrial cancer can be mistaken for senile endometritis, tubercular endometritis, atypical hyperplasia and polypi. The lesions in the lower genital tract also cause postmenopausal bleeding, but can be easily visualized on speculum examination.

Staging (Table 39.2)

Surgical staging is now recommended but clinical staging is applicable in inoperable cases. A staging laparotomy is recommended through a midline lower abdominal incision and any peritoneal ascitic fluid or washing is collected for cytology. Complete abdominal exploration followed by total abdominal hysterectomy (TAH) along with bilateral

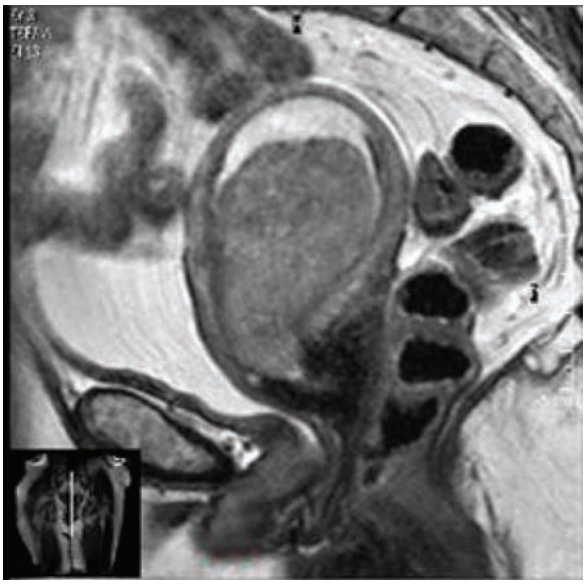

Figure 39.8 MRI showing extension of endometrial cancer into the cervix. (Courtesy: Dr Parveen Gulati, New Delhi.)

TABLE 39.2 Carcinoma of the endometrium staging

Stage I*	Tumour confined to the corpus uteri
IA*	No or less than half myometrial invasion
IB*	Invasion equal to or more than half of the myometrium
Stage II*	Tumour invades cervical stoma, but does not extend beyond the uterus**
Stage III*	Local and/or regional spread of the tumour
IIIA*	Tumour invades the serosa of the corpus uteri and/or adnexae#
IIIB*	Vaginal and/or parametrial involvement#
IIIC*	Metastases to pelvic and/or para-aortic lymph nodes#
IIIC1*	Positive pelvic nodes
IIIC2*	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV*	Tumour invades bladder and/or bowel mucosa, and/or distant metastases
IVA*	Tumour invasion of bladder and/or bowel mucosa
IVB*	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

*Either G1, G2 or G3.
**Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.
#Positive cytology has to be reported separately without changing the stage.
Source: FIGO guidelines.

salpingo-oophorectomy (BSO) omentectomy and pelvic and para-aortic lymph node sampling remains the cornerstone in the management of early endometrial cancer.

Treatment

Stage 0 (endometrial hyperplasia). Simple endometrial hyperplasia develops malignancy in 10–20% but atypical hyperplasia develops malignancy in 60–70%. Total hysterectomy with removal of ovaries is the treatment in elderly women. In a younger woman, progestogen therapy, medroxyprogesterone acetate (30–40 mg) daily, is offered for 6–12 months with life-long follow-up. Mirena IUCD is also applicable. Norethisterone 10 mg daily is considered superior to medroxyprogesterone (MDPA) by many in its action on the endometrium. Besides, MDPA causes osteoporosis on prolonged therapy. *Transcervical resection of endometrium is contraindicated;* malignancy developing later cannot be detected following this therapy.

Periodical curettage and histopathological study is desirable in the follow-up with hormonal therapy.

Surgery

Surgical staging, abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic as well as para-aortic lymph node sampling remains the cornerstone in the management of early endometrial cancers.

The abdomen is opened by a vertical incision that allows a thorough intra-abdominal exploration. Peritoneal washings are obtained from sub-diaphragmatic areas, paracolic gutters and the pelvis, and sent for cytology. Following hysterectomy and BSO, omentectomy, the uterus is opened away from the operation area by an assistant and the tumour size, myometrial invasion and cervical extension assessed. The frozen section is preferred. Lymph node sampling or lymphadenectomy is dictated by the pre-operative grading of the tumour, histopathology report and myometrial invasion.

All grades 2 and 3 in Stage I, clear cell, serous and adenosquamous cancer, and myometrial invasion require pelvic lymphadenectomy and para-aortic lymph node sampling. There is no need to remove the vaginal cuff. However, omentectomy is advisable in advanced stages.

Although abdominal route is conventionally used, vaginal route is now preferred in obese diabetic women and women with prolapse because of its lesser morbidity. This is combined with laparoscopic lymphadenectomy or post-operative radiotherapy.

Stage IA myometrium is infiltrated in 4% and pelvic lymph nodes in 2%.

Stages IB. Since lymph nodes are involved in 10–40%, post-operative pelvic radiotherapy 4000–5000 cGy is recommended over 5–6 weeks, as well as vaginal vault radiotherapy.

Stage II. Brachytherapy is followed either 1 week or 6 weeks later by surgery and external radiotherapy as dictated by histological findings. Alternately, Wertheim's hysterectomy can be chosen.

Lately, laparoscopic staging with lymph node sampling and laparoscopic assisted vaginal hysterectomy show a lesser morbidity in early stages. The only risk of laparoscopic surgery is portal site metastasis.

Stage III is inoperable. Doxorubicin 60 mg/m^2 with cisplatin and paclitaxel is employed. Medroxyprogesterone acetate 1 g weekly IM is adjuvant to chemotherapy. Thirty per cent response is reported in lung metastasis. Debulking surgery is now attempted.

Stage IV. Palliative radiotherapy, chemotherapy and progestogen may prolong life.

The study of lymph nodes will determine the need for postoperative pelvic radiotherapy.

Postoperative Radiotherapy

Application of postoperative radiotherapy depends upon the surgicopathological findings and staging.

The commonest local metastasis occurs in the vaginal vault in 15% cases. The incidence now has been reduced to 1–2% by delivering radiation to the vaginal vault with the help of the colpostat 4 weeks after the surgery (brachytherapy). Dose of 6000–7000 cGy is delivered over a period of 6 weeks. Vaginal stenosis and dyspareunia are the complications.

Pelvic postoperative radiotherapy (external) in a dose of 6000 cGy over a 6-week period is also recommended in high-risk cases such as undifferentiated tumour, myometrial infiltration, pelvic node involvement, and in serous, clear cell and adenosquamous carcinoma. The postoperative radiotherapy is required in Stages IA (Grade 3), IA2, IB and II. Chemo-radiation yields a better effect.

Whole-abdomen radiation is required when para-aortic lymph nodes are involved, while protecting the liver and kidneys.

It is observed that women who receive pelvic radiotherapy often develop distal metastasis. Therefore, some advocate pelvic as well as abdominal radiotherapy to improve their survival.

The most important factors in considering the need for postsurgical radiotherapy are (1) histology; (2) grading as studied by biopsy and (3) depth of myometrial invasion as seen by ultrasound, MRI and at the time of surgery.

Primary Radiotherapy

Stages III and IV are not operable. They are treated with brachytherapy followed by external radiation. The uterine cavity can be packed with Heyman capsules. Adjuvant chemotherapy and progestogen therapy prolong remission and improve quality of life. Hormonal therapy is nontoxic and does not need hospitalization.

Progestogens

- Medroxyprogesterone acetate (MDPA) 1 g weekly or 200 mg orally daily.
- 17-α progesterone or norethisterone 1 g IM weekly. Norethisterone is stronger than MDPA and suppresses oestrogen receptors. Thirty per cent response with hormone is reported, especially with lung metastasis. Tamoxifen 10 mg twice daily is also useful in reducing oestrogen receptors (for chemotherapy refer to Chapter 41).

  Doxorubicin, platinum and taxane carboplastin are under trial.

Recurrent Growths

It occurs within 2 years in 50% and in 3 years in 75%.

The metastasis occurs in the vaginal vault, lateral pelvic wall, lymph nodes, lungs, liver, brain and bones. Distal metastasis occurs mostly in women who have undergone surgery and postoperative pelvic radiotherapy.

Postoperative vaginal vault radiotherapy reduces the recurrence in the vaginal vault.

Tamoxifen 20–40 mg daily produces good response in 20%.

Prognosis: Depends upon histology of the tumour, grading, myometrial infiltration, pelvic node involvement and staging. While Stage I 5-year survival is 75%, it reduces to 10–20% in Stage IV. Stage II survival rate of 55% and Stage III survival of 30% is reported.

It is important that a woman who has been treated for uterine malignancy should not be offered hormonal replacement therapy for menopausal symptoms.

Prophylaxis

- Adding progestogen for 12 days in hormone replacement therapy reduces the risk of endometrial hyperplasia and cancer to 2%.
- A woman on tamoxifen needs periodical ultrasound scanning to study the endometrial thickness. Raloxifen has no adverse effect on the endometrium
- Mirena IUCD is effective against simple endometrial hyperplasia.
- Oral combined pills reduces cancer risk by 40–50%.

Sarcoma of the Uterus

Uterine sarcomas are rare tumours comprising 4.5% of all malignant growths of the uterus and 1–3% of all genital tract cancers. About 0.5% of all myomas undergo sarcomatous change (Figure 39.9). The tumours arise most frequently in women between the ages of 40 and 50, and are rare before 30. The incidence of pre menopausal and postmenopausal sarcoma is almost equally divided. Twenty-five per cent patients are nulliparous, but parity is unrelated in the aetiology. About 8% sarcoma occurs in women who received radiation for carcinoma cervix 8–10 years earlier.

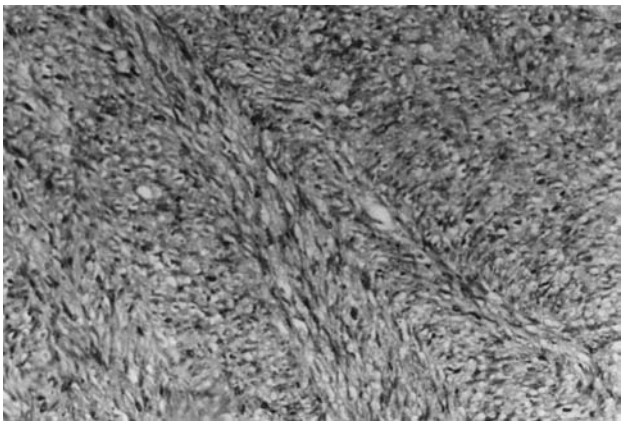

Figure 39.9 Histopathology showing fibrosarcoma.

Four types of uterine sarcomas are described: (i) in the intramural, the tumours arise in the myometrium; (ii) in the mucosal, the tumour develops from the endometrium of the uterus; (iii) the tumour arises in a pre-existing myoma (25–40%) and (iv) a rare but interesting tumour known as the grape-like sarcoma of the cervix. The most common form of sarcoma of the uterus is the intramural type. Histologically, the tumour may be round-, spindle-, mixed- or giant-celled. The most common form is the spindle-celled tumour which is termed as leiomyosarcoma. To the naked eye, the cut surface of the tumour is haemorrhagic and irregular, without the whorled appearance of a myoma. The consistency is friable and soft. The outline is irregular with invasion into the surrounding structures without a demonstrable capsule. The mucosal form sometimes tends to project in the form of a polypus into the cavity of the uterus, while in other cases, it spreads around the cavity of the uterus to produce a uniform enlargement. Two-thirds are intramural, one-fifth are submucous and one-tenth are subserously located.

Metastasis forms relatively early; the spread occurs by the blood stream, by lymphatics, by direct spread and by implantation. As a result of blood stream dissemination, metastases form in the lungs and kidneys. Lymphatic spread involves pelvic lymph nodes in 35% cases in Stages I and II, and para-aortic glands in 15% cases. Direct spread into the peritoneal cavity leads to multiple metastases over the peritoneum with accompanying ascites and large deposits in the omentum. By implantation, metastases form at the vulva. It has been computed that the average duration of life from the commencement of symptoms is about 2 years.

Sarcoma is diagnosed before the removal of the uterus only very exceptionally. Failure to respond and shrink in size following GnRH administration strongly suggests the possibility of malignancy. Positron emission tomography (PET), Doppler ultrasound and MRI may help in the diagnosis. With mucosal tumours which produce continuous bleeding, a histological examination of curettings may enable a diagnosis to be made. Again, rapid enlargement of a quiescent myoma in a woman of postmenopausal age is almost pathognomonic of sarcomatous change. Sarcoma of the uterus usually causes rapid enlargement of the uterus with profuse and irregular vaginal bleeding. Pain is present in 60% of cases and fever due to degeneration or infection may also occur in about one-third of the patients. If the tumour has encroached upon the cavity of the uterus and caused postmenopausal bleeding, diagnosis may be made by curettage. The interpretation of the histology is very difficult because of the presence of degenerative and infective changes. However, mitotic count more than 10 per 10 high-powered field and an atypical cell would be the warning signs.

Treatment

The treatment of sarcoma of the uterus consists of total hysterectomy with bilateral salpingo-oophorectomy, followed by a full course of radiation therapy. If the growth is in the region of the isthmus or cervix, a radical hysterectomy of the Wertheim type with bilateral lymph node excision probably offers the best chance of cure, since in many cases, the glands may be involved. This is followed by radiation therapy. The 5-year cure rate is under 30% and largely depends on the type of growth, being worst in the round cell variety where the growth originates in the endometrium. The presence of distant metastases is a contraindication to surgery unless of a palliative nature, e.g. to stop uterine haemorrhage.

Radiotherapy is ineffective in distal metastasis. Chemotherapy is the only hope and comprises a combination of cyclophosphamide, vincristine, doxorubicin, and dacarbazine or vincristine, actinomycin and cyclophosphamide (VAC). It reduces the recurrence rate. The conservation of ovaries does not adversely influence the prognosis, and it is a wise decision to leave them behind during hysterectomy in a young woman. Since breast cancer is seen associated with leiomyosarcoma, it is prudent to screen the woman's breasts. Rhabdomyosarcoma is a rare, highly malignant tumour in children. It is now managed by chemoradiotherapy. The prognosis is poor with 40% 5-year survival. A 50% response is reported with docetaxel and gemcitabine. Progestogen and aromatase inhibitor hold future promise.

Mesodermal Mixed Tumour (Including Botryoid and Grape-Like Sarcoma)

Uterine sarcoma arises typically in the body of the uterus, while sarcoma of the cervix is very rare. Eight per cent follow pelvic radiotherapy. Pathologically, the tumours should be regarded as mesodermal mixed tumours as they often contain cartilage, striated muscle fibres, glands and fat. The stroma is embryonic in type, similar to the embryonal mesenchyme. Grape-like sarcoma of the cervix arises typically in adult women, metastases develop rapidly, and local recurrence follows their removal.

Somewhat similar tumours are known to develop in the vagina in children at a very early age, and such tumours contain striated muscle fibres and an embryonic stroma. Rather similar tumours sometimes develop in the body of the uterus in old women, and in this way three types of mixed tumours, namely the vaginal tumours of children, the grape-like sarcoma of the cervix, and the mixed tumours of the body of the uterus of old women can be distinguished. In all cases, the prognosis is bad and rapid recurrence follows their removal.

Choriocarcinoma

Choriocarcinoma is rare, but it is one of the most malignant growths arising in the body of the uterus. The nongestational choriocarcinoma appears as part of a germ cell gonadal neoplasm, both in males and in females. The nature of choriocarcinoma can be identified by DNA study of the tumour. In nongestational choriocarcinoma, DNA is of maternal origin, whereas in molar pregnancy choriocarcinoma, DNA is of paternal origin.

In a woman, this neoplasm follows a pregnancy, and the recognized data of the incidence shows that 50% of cases follow evacuation of a hydatidiform mole, 25% follow an abortion and 20% follow full-term pregnancy, while 5% follow extrauterine pregnancy. The malignancy may appear many years after a full-term pregnancy or an abortion. However, it develops within 2 years of a molar pregnancy. The long period that elapses between the pregnancy and the development of choriocarcinoma makes the clinical suspicion of malignancy rather difficult. A primary choriocarcinoma arising in the placenta during pregnancy that led to fetal metastasis in the liver has been documented.

About 4–10% molar pregnancy develops choriocarcinoma, within 2 years. Postmolar gestational trophoblastic disease may be an invasive mole or choriocarcinoma, but non-molar gestational trophoblastic disease is always a choriocarcinoma.

Incidence

Choriocarcinoma exhibits a geographical distribution very similar to that of a hydatidiform mole. The incidence in the UK and the USA is of the order of 1:50,000 to 1:70,000 pregnancies, and it is 10 times more common in Southeast Asia. An older woman with high parity and belonging to a low socioeconomic group runs a high risk of developing this malignancy.

Morbid Anatomy

To the naked eye, the growth appears as a solid purple friable mass. The majority of primary growth arises in the body of the uterus and develops first within the endometrial cavity (Figure 39.10). In such cases, the growth projects into the cavity of the uterus, quickly ulcerates and causes a blood-stained discharge, which later becomes offensive and purulent as the growth becomes infected and necrotic. There may be periodic episodes of fresh haemorrhage. Growths of this kind superficially resemble placental polypi, but choriocarcinoma always infiltrates the wall of the uterus, while a placental polypus is clearly demarcated from the myometrium and can be easily detached. Choriocarcinoma does not necessarily develop primarily in the endometrium, and it is not uncommon for the growth to start in the myometrium in the deeper tissues of the uterine wall. Primary choriocarcinoma of the uterus may erode through into the broad ligament or peritoneal cavity and cause profuse bleeding, or it may cause enlargement of the uterus to such a degree that the fundus of the uterus reaches upwards to the level of the umbilicus. Metastases form early and dissemination usually occurs by way of the blood stream. Ones which can be detected easily are those found in the lower third of the vagina and at the vulva. Such metastases form purple haemorrhagic projections either into the vagina or around the vaginal orifice. Their appearance is characteristic and pathognomonic of choriocarcinoma. These metastases are interesting pathologically, for they are comparable to the vaginal metastases

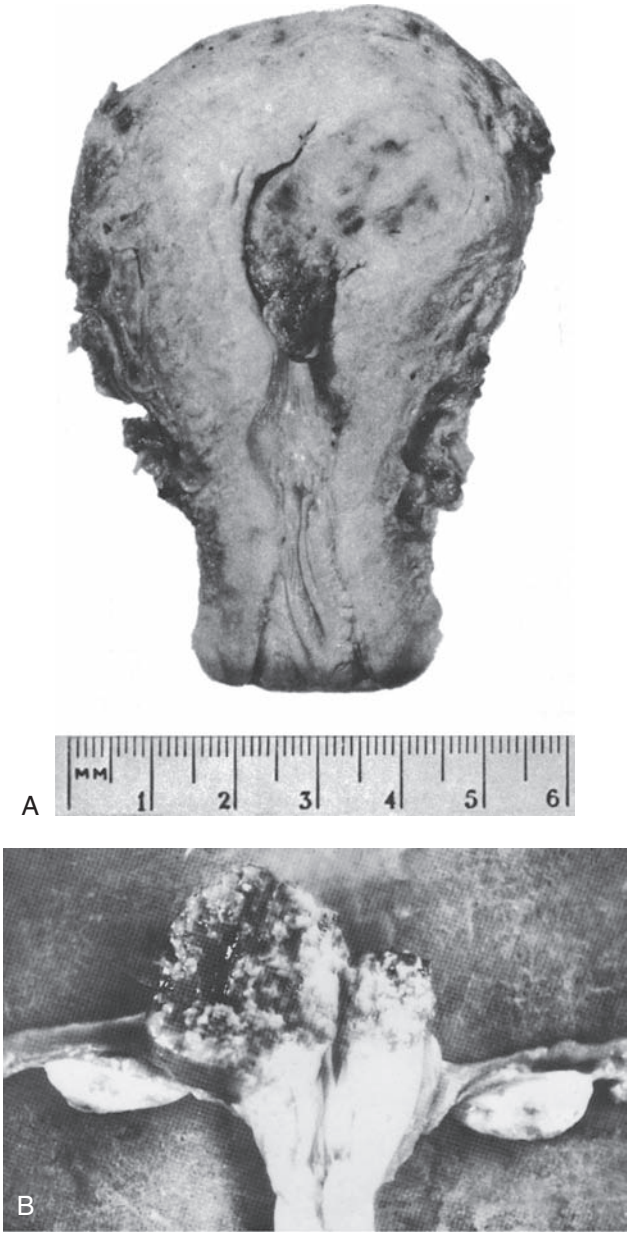

Figure 39.10 Choriocarcinoma of the uterus. **(A)** The tumour has infiltrated the myometrium and presents as a polypoid excrescence into the cavity of the uterus. It is therefore, readily diagnosed on exploratory curettage. **(B)** Patient came with massive intraperitoneal haemorrhage. (Courtesy: Dr Narayan M Patel, Ahmedabad.)

sometimes found with carcinoma of the body of the uterus and malignant ovarian tumours. Such metastases are produced by retrograde spread along the venous channels of the vaginal plexuses of veins. The general metastases probably develop early, the growth disseminating by way of the blood stream. Multiple metastases may form in the lungs and cause haemoptysis (Figure 39.11). Vaginal metastasis forms in 30% cases. Deposits are frequently found in the kidneys, brain, spleen and liver, but when the dissemination is widespread, almost any organ may be affected and large emboli may get held up in the large arteries of the systemic circulation. The most common metastases are seen in the lungs (80%), brain and liver (10% each).

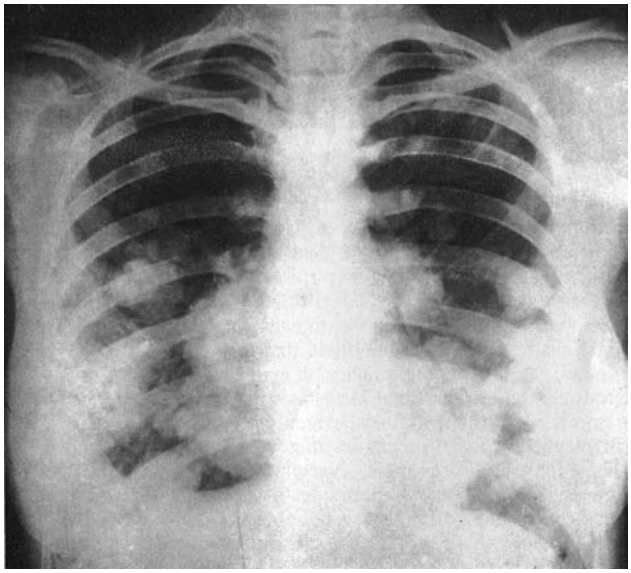

Figure 39.11 Multiple 'cannon ball' metastases in lungs from choriocarcinoma.

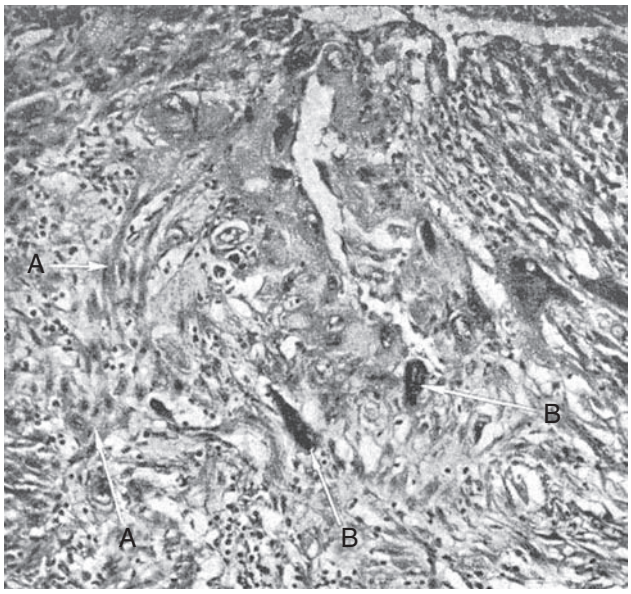

Figure 39.12 Invasion of the myometrium by trophoblast in choriocarcinoma. The section lay deep in the myometrium. Note the **(A)** cytotrophoblast and **(B)** dark syncytial cells (×145).

Less common sites are gastrointestinal tract (GIT), kidney, spleen, genital tract and the lymph nodes (10%). In advanced cases, the parametrium may be extensively infiltrated with growth. Invasion of the ovaries is usually by way of the blood stream. Ovarian cysts of the granulosa lutein type are found in about 9% cases (Table 39.3).

The histological appearance is very typical. Syncytium, cytotrophoblast and degenerated red blood cells constitute the growth. The cells are actively growing and show such malignant characters as typical mitotic division and anaplastic changes. In some areas, the cells are translucent or vacuolated and may resemble decidual cells. No relics of chorionic villi can be detected, the growth consisting solely of embryonic syncytium, cytotrophoblast and degenerated blood cells. *The absence of villi must be stressed as a differential diagnostic* feature which separates the malignant choriocarcinoma from the benign and invasive mole in which villi are demonstrable. This is because the trophoblast grows in such extensive columns as to completely obliterate the villous pattern. The other distinguishing feature of malignancy is invasion of the uterine wall by trophoblastic cells, with destruction of muscle tissues accompanied by necrosis and haemorrhage (Figure 39.12). The primitive infiltrating properties of the embryonic cytotrophoblast are retained in choriocarcinoma so that vessels are eroded and local haemorrhages are produced, which cause the typical macroscopical appearances. As a result of erosion of vessels, the growth penetrates into the systemic blood stream, and generalized metastases are apt to develop early.

There is clinical evidence that metastases may regress after the removal of the primary growth but this is rare. The radiograph of lungs presents the haemorrhagic metastasis as a 'cannon ball' (see Figure 39.11), while, in reality, they may be only zones of haemorrhage. It may also present a woolly appearance due to diffuse haemorrhage. It must be remembered that vaginal nodules resembling the metastases of choriocarcinoma can occur with benign hydatidiform mole and even normal pregnancy, according to Magnus Haines. This concept of benign trophoblastic embolism must considerably influence our thinking on the question of spontaneous regression of the so-called malignant metastases in choriocarcinoma. Choriocarcinoma, as with hydatidiform moles, show high levels of β-hCG, in the urine and serum.

TABLE 39.3 Spread of choriocarcinoma

Lungs	80%	X-ray chest, CT
Vaginal metastasis	30%	Speculum examination, βhCG
Pelvis	20%	Pelvic examination, ultrasound, CT
Liver	10%	Ultrasound, CT
Brain	10%	CT, βhCG
Gastrointestinal kidney, spleen	rare	Ultrasound, βhCG

Symptoms and Signs

These are dependent upon the site of growth. Persistent or irregular uterine haemorrhage following an abortion, a molar pregnancy or a normal delivery should always raise the suspicion of choriocarcinoma. The bleeding is usually profuse, but sometimes there may be only blood stains. An offensive vaginal discharge develops when secondary infection supervenes; pyrexia and cachexia will be the accompanying symptoms. *When amenorrhoea occurs, it is due to a very high level of hCG secreted by the metastatic growth outside the uterus.* The rupture of the uterus with intraperitoneal haemorrhage simulates an ectopic pregnancy. The disease may present by way of its metastasis. Dyspnoea and

haemoptysis are noticed with lung metastasis. The appearance of neurological symptoms like haemiplegia, epilepsy, headache and visual disturbances suggests brain metastasis.

On examination, a vaginal metastasis appears as a bluish red vascular tumour which bleeds easily on touch. The uterus may be enlarged. The granulosa lutein cysts are palpable in some cases. The liver and brain metastasis are often associated with lung and pelvic metastasis.

Differential Diagnosis

- Postdelivery and postabortal retained placental tissue or placental polyp; both the conditions cause secondary postpartum haemorrhage (PPH). Curettage will help to diagnose choriocarcinoma. However, the diagnosis can be missed if the growth is in the myometrium. β-hCG level in serum and the urine will establish the correct diagnosis. Ultrasound and CT scans confirm the diagnosis.
- When choriocarcinoma develops many years following a pregnancy, its clinical diagnosis is difficult to make. Irregular bleeding mandates curettage which will reveal the cause of bleeding. Ultrasound will reveal the uterine growth.
- Intraperitoneal haemorrhage following spontaneous uterine perforation by the tumour growth may simulate ectopic pregnancy. The treatment is laparotomy in both these conditions when the true nature of the lesion becomes obvious.
- *Pulmonary metastases*. The pulmonary symptoms may resemble pulmonary tuberculosis. The 'cannon ball' metastasis is typical of a malignant lesion.
- *Brain metastases.* The neurological symptoms point towards a brain lesion. The elevated hCG level in the serum or preferably in cerebrospinal fluid (CSF) and CT scan will establish the diagnosis.

When the metastasis develops more than 1 year following abortion, diagnosis of choriocarcinoma becomes difficult. *Think of choriocarcinoma if the young woman develops neurological symptoms with a history of past abortion, or pregnancy and estimate β-hCG level in CSF*.

Staging

Refer to Tables 39.4 and 39.5, and Figure 39.13.

TABLE 39.4 FIGO classification of gestational trophoblastic diseases

Stage I	Disease confined to the uterus
Stage II	GTD extends outside of the uterus but is limited to the genital structure
Stage III	Lung metastasis with or without genital tract involvement
Stage IV	Other metastasis
IVA	No risk factor
IVB	One risk factor
IVC	Two risk factors
Risk factors	
1.	Serum β-hCG level >100,000 mIU/mL
2.	Duration of disease >6 months

Diagnosis

The diagnosis is based on clinical features and histological evidence when available. Serum β-hCG level, X-ray of lungs as well as CT scan of lungs and brain, and ultrasound scan of liver and pelvis help in establishing the correct diagnosis. PET is employed in difficult cases with unusual symptoms and signs.

Treatment

Chemotherapy

One of the biggest triumphs of medical science is effective chemotherapy in choriocarcinoma. Histopathological evidence may not be available in every case, especially in invasive and metastatic tumours. Since β-hCG is a very specific marker, the chemotherapy can be administered based on this alone.

Unlike other malignant lesions, the treatment of choriocarcinoma is mainly chemotherapy, both for local and distal metastases.

The most effective chemotherapeutic agent is the folic acid inhibitor methotrexate, a mixture of 4-amino-10-methyl folic acid and related compounds. This drug interferes with the formation of nucleic acid and mitosis in the malignant cells and thereby arrests the growth. The staging decides whether single or multiple drug therapy is required.

Methotrexate is given orally 5 mg five times a day for 5 days. It is also given by intramuscular injection. Bagshaw has advocated intra-arterial (femoral) perfusion of 25 mg methotrexate in a local pelvic growth. The course of chemotherapy is repeated at intervals of 10–20 days depending on the blood picture and side effects of the drug. The patient should completely recover from any toxic side effect before the second course is started. These courses are continued until complete regression of the primary tumour and all metastases are achieved—indicated when three consecutive weekly radioimmunoassays for hCG in serum are negative. Thereafter, one more course is administered. This is done because even radioimmunoassay cannot detect β-hCG level below 1 μ/mL, and the last course hopefully destroys any minute trophoblastic tissue that might have been left untouched. Methotrexate has the following side effects: (i) ulcerative stomatitis, gastric haemorrhage; (ii) skin reaction; (iii) alopecia; (iv) bone marrow depression, leading to anaemia, leucopenia and agranulocytosis and (v) liver and kidney damage.

It is advisable to check on haemoglobin, white cell count and platelet count and carry out liver function tests, kidney function tests and radiograph of chest before instituting this chemotherapy. Methotrexate is contraindicated in liver disease. To avoid or to reduce toxicity, 'folic acid rescue regime' is recommended. This regime consists of citrovorum (folinic acid) 6 mg intramuscularly and methotrexate

TABLE 39.5 WHO prognosis scoring system for GTD

Prognostic Factors	0	1	2	4
• Age (years)	<39	>39	—	—
• Antecedent pregnancy	Mole	Abortion	Term pregnancy	
• Interval (months)	<4	4–6	7–12	>12
• Pretreatment hCG (mIU/mL)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
• ABO group	A	B	—	—
• Size of tumour (cm)	<3 cm	3–5 cm	>5 cm	
• Site of metastasis	Lung	Spleen kidney	GI liver	Brain
• Number of metastasis	—	1–4	5–8	>8
• Previous failed chemotherapy			Single drug	2 or more
<4—Low risk; 5–8—Middle risk; >8—High risk				
FIGO scoring system 2008				
• Age (years)	<40	>40	—	—
• Prior pregnancy	Molar	Abortion	Term pregnancy	—
• Interval from previous pregnancy (months)	<4	4–6	7–12	>12
• Pretreatment (β-hCG)	<1000 IU	1000–10,000	10,000–100,000	>10,000,000
• Size of tumour	<3 cm	3–5 cm	>5 cm	
• Site of metastasis	Lungs	Spleen kidney	GI	Brain liver
• Number of metastases	—	1	4–8	>8
• Prior chemotherapy			Single	Multiple

Up to 6 score—low risk.
More than 6 score—high risk.

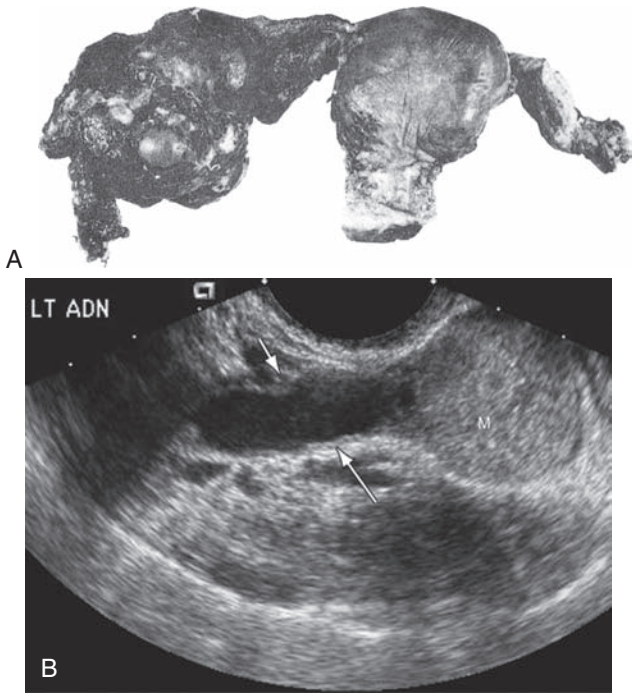

Figure 39.13 **(A)** Carcinoma of the fallopian tube. One fallopian tube containing papillary growth lies to the left. Between it and the uterus lies the corresponding ovary, while the opposite tube and ovary lie to the right. **(B)** Fallopian tube carcinoma in a 49-year-old woman with vaginal discharge. Transvaginal ultrasound in the transverse plane of a fallopian tube carcinoma appearing as a solid mass (M) within a dilated fallopian tube (arrows). (Figure (B) From Figure 28-3. Julia Fielding, Douglas Brown and Amy Thurmond. Gynecologic Imaging: Expert Radiology Series. 427-436, Saunders: Elsevier, 2011.)

administered on alternate days, so that one course of treatment lasts for a total of 10 days.

Combined chemotherapy is recommended in high-risk cases. A variety of combinations of chemotherapeutic agents are being used, such as (i) methotrexate, actinomycin-D and cyclophosphamide (MAC) and (ii) methotrexate, actinomycin-D and adriamycin (MAA). The number of courses depends on the severity of the disease and response of the patient.

Bagshaw treated cases with a combination of etoposide, methotrexate and actinomycin-D and claimed equally good results with less side effects. All authors agree that it is more effective to treat the high-risk cases with combined therapy ab initio than to treat them with combined therapy only after a failed attempt with a single agent.

The course is repeated every 2 weeks depending upon recovery from toxicity.

MAC treatment comprises the combination of methotrexate 50 mg IV, actinomycin-D 0.5 mg IV and cytoxan 250 mg IV daily for 5 days and repeat every 3 weeks (Table 39.6).

Alternative course is that of EMA-CO regime.

Course 1—(EMA)

Day 1. Etoposide 100 mg/m^2 IV
Infusion in 200 mL saline over 30 min.
Actinomycin-D 0.5 mg IV stat.
Methotrexate 100 mg/m^2 IV infusion over 12 h.
Day 2. Etoposide 100 mg/m^2 IV infusion in 200 mL saline over 30 min
Actinomycin-D 0.5 mg IV stat.

TABLE 39.6 Triple therapy (MAC)

Day	Drug	Dose
1	Methotrexate	1 mg/kg IV
	Actinomycin-D Methotrexate	12 μg/kg IV (maximum 1 mg) 1mg/kg IV
	Cyclophosphamide	3 mg/kg IV
2	Folinic acid	0.1 mg/kg IM
	Actinomycin-D	12 μg/kg IM
	Cyclophosphamide	3 mg/kg IV
3	Same as day 1	
4	Same as day 2	
5	Same as day 1	
6	Folinic acid	0.1 mg/kg IV
7	Methotrexate	1 mg/kg IM
8	Folinic acid	0.1 mg/kg IM

Folinic acid 15 mg IM every 12 h for four doses, starting 24 h after methotrexate.

Methotrexate.

Course 2—(CO)

Day 8. Vincristine (Oncovin) 10 mg/IV stat

Cyclophosphamide 600 mg IV in saline.

The course is repeated every 3 weeks.

The placental site trophoblastic disease is often resistant to chemotherapy, and hysterectomy is recommended.

In brain and lung metastases, previous treatment with radiotherapy is now replaced by chemotherapy, because the results are good and radiotherapy causes extensive fibrosis.

Methotrexate 12.5 mg is injected intrathecally every 2–4 weeks' interval until hCG level becomes negative.

New drugs such as taxol, topotaxol and gemcitabine (antimetabolite) have been used in resistant cases. Gemcitabine—1250 mg/m^2 days 1–8 with cisplatin.

A rare case of leukaemia has been recently reported following repeated courses of chemotherapy. Therefore, chemotherapy is now restricted to a maximum of six courses.

Surgery

Hysterectomy is indicated in the following conditions:

- High-risk cases over the age of 40 years, multiparous.
- Chemotherapy ineffective.
- Haemorrhage due to uterine perforation.
- Large-sized growth in the uterus.
- Placental site trophoblastic disease does not respond to chemotherapy, and hysterectomy is the only solution.

Hysterectomy is preceded and followed by chemotherapy. Methotrexate 10 mg is administered on the day of the operation and continued postoperatively for 4–5 days to prevent the risk of dissemination and development of distal metastasis (Lewis 1966). There is no need to remove the ovaries as ovarian metastasis is rare and can be effectively treated by chemotherapy. Hysterectomy reduces the number of chemotherapy courses.

TABLE 39.7 Management of metastasis

Vagina	Vaginal pack for bleeding, wide excision, chemotherapy
Lungs	Chemotherapy lobectomy if the growth is localized or resistant to chemotherapy
Liver	Chemotherapy radiation
Brain	• Chemotherapy • Intrathecal chemotherapy • Surgery • Radiation

Role of radiotherapy is limited due to acute bleeding from vaginal metastasis and brain and liver metastases. The postradiotherapy fibrosis is the disadvantage.

A solitary lung metastasis can be dealt with by thoracotomy and lobectomy. Craniotomy is rarely resorted to in a solitary brain tumour.

The role of stem cell support and autologous bone marrow needs to be explored in the future.

Cerebral Metastasis (*Table 39.7*)

A focal lesion detected by CT/MRI can be excised to prevent haemorrhage in the tumour and death. A large lesion is treated with radiation given in a dose of 30 Gy in 10 fractions 5 days a week for 2 weeks along with EMA/CO and this yields 80% response. Liver metastasis should receive whole-organ radiation over 10 days in a dose of 20 Gy.

Lobectomy is required in a chemotherapy resistant case.

Follow-up:

Serum βHCG is done every week. Once negative, it is repeated every 2 weeks for 3 months. Thereafter, every month for one year, then 6 monthly long life.

Prognosis

Overall cure rate in recent years has been excellent with chemotherapy alone, and surgery is undertaken only in selective cases described above. With chemotherapy, 100% success has been claimed in low-risk group (Lewis 1980) and 90% success in high-risk group. A successful pregnancy has followed treatment with chemotherapy. However, it is advisable for the patient not to conceive for a year after the drug has been stopped, because the chemotherapeutic drugs have an adverse effect on chromosomes and an abnormal embryo may be produced. The follow-up of the woman, however, should be maintained for life.

Fallopian Tube Cancer

Primary carcinoma of the fallopian tube is uncommon and accounts for only 0.3% of all cancers of the female genital

tract, though metastatic growths from the uterus, ovaries and gastrointestinal tract are common.

The tumour is bilateral in one-third of cases when it resembles pyosalpinx or tubercular lesion. The tumour is often an adenocarcinoma though choriocarcinoma may develop in a tubal ectopic pregnancy or in a tubal mole. The tumour is highly malignant and spreads rapidly to the surrounding areas, and via lymphatics to the pelvic organs. Very often, the tumour is in the advanced stage when diagnosed and mostly it is diagnosed only on histological study after the surgery.

The distal portion of the tube is the common site of cancer.

Staging

Staging. Though FIGO classification does not exist, Erez classification is as follows:

Stage I: The tumour is limited to the mucosa and muscle.
Stage IIA: The serosa is breached but the tumour has not spread to other organs.
Stage IIB: The tumour invades the pelvic organs.
Stage III: Metastasis outside the pelvis but within the abdominal cavity.
Stage IV: Extra-abdominal metastasis is present. Paraaortic lymph nodes are involved in the advanced stages.

Clinical Features

The tumour occurs in menopausal women, 50% of them are nulliparous. The early symptom is a watery discharge per vaginum, which may at times be amber-coloured. Sooner or later, postmenopausal bleeding develops. A lump may be too small to be felt on clinical examination. Pain is a late symptom (Figure 39.12).

Differential Diagnosis

The condition is often mistaken for uterine or ovarian malignancy, and tubercular adnexal mass.

Investigations

The clinical diagnosis is difficult and often missed.

- Pap smear: The adenomatous cancer cells are very rarely seen and Pap smear screening is unreliable.
- Uterine curettings are negative in postmenopausal bleeding so also hysteroscopic examination. Negative curettings in postmenopausal bleeding should arouse the suspicion of fallopian tube malignancy.
- Laparoscopy shows adnexal mass.
- Ultrasound showing an adnexal mass in a postmenopausal woman with postmenopausal bleeding suggests tubal cancer.
- Doppler flow velocity shows low-resistance blood flow.
- Sometimes serum level of CA-125 is raised in adenocarcinoma.

Management

Surgical staging is important. In operable cases, surgery is similar to that of ovarian malignancy and consists of hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node sampling and omentectomy.

Postoperative radiotherapy, chemotherapy and progestogen hormonal therapy are often required.

Choriocarcinoma if diagnosed is treated either by surgery or by chemotherapy.

Prognosis

Prognosis is poor and overall 5-year cure rate is 25%.

- Stage I survival is 60%.
- Stage II survival is 40%.
- In advanced stage, survival is 10%.

Key Points

- Endometrial cancer accounts for 20–25% of all genital cancers.
- The risk factors are older age group, unopposed oestrogen therapy, tamoxifen, obese hypertensive, diabetic women as well as chronic anovulation seen in PCOS.
- While simple hyperplasia leads to endometrial cancer in 10–20%, atypical hyperplasia has 60–70% risk of endometrial cancer.
- Early stage of endometrial cancer is treated by hysterectomy, bilateral salpingo-oophorectomy and omentectomy. Lymphadenectomy is required in the advanced stages.
- CT, MRI are helpful in mapping the myometrial invasion and lymph node involvement.
- Postoperative radiotherapy is required in advanced stages, and for reducing the recurrence in the vaginal vault.
- Progestogen and Mirena can prevent endometrial hyperplasia. Progestogens are effective in 30% cases with lung metastasis.
- Primary fallopian tube cancer is very rare and is difficult to differentiate from ovarian and endometrial cancers clinically. Prognosis is poor.
- Choriocarcinoma is rare, but highly malignant.
- Choriocarcinoma follows a molar pregnancy, abortion, team pregnancy and ectopic pregnancy.
- Fifty per cent cases account for postmolar pregnancy and occur within 2 years.
- The long interval of years between pregnancy and choriocarcinoma makes the diagnosis difficult.
- Primary treatment of choriocarcinoma is chemotherapy and is effective in 90–100% cases.
- Surgery is reserved for selective cases.
- Pregnancy is possible following treatment with chemotherapy. However, conception should be delayed for 1 year to avoid teratogenic effect on the fetus.

Self-Assessment

1. Describe the clinical features of endometrial cancer. How will you investigate the case?
2. What are the high-risk cases for endometrial cancer?
3. Discuss the management of endometrial cancer.
4. Write short notes on:
   - Endometrial hyperplasia
   - Mixed mesodermal tumours
   - Sarcoma of the uterus
5. Describe the clinical features of choriocarcinoma.
6. Discuss the management of choriocarcinoma.

Suggested Reading

Duncan J, Shulman P. Yearbook of Obstetrics, Gynaecology and Women's Health 41: 437, 2010.
Studd J. Progress in Obstetrics and Gynaecology 14: 2000.
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Chapter 40 Ovarian Cancer

CHAPTER OUTLINE

Ovarian cancer is the second most common of all genital cancers and accounts for 10–15% of all gynaecological cancers in developing countries including India. Over the past two decades, there has been an increase in the incidence as well as survival rate amongst women with ovarian cancer. The risk of a woman developing cancer of the ovary in her lifetime is around 1:70 to 1:100. Women of low parity, decreased fertility and delayed childbearing appear to be more predisposed. There appears to be a familial predisposition to the disease. Association between ovarian cancer, colon, breast cancer and endometrial adenocarcinoma has also been recognized. In such families, cancers tend to occur at a younger age (less than 40 years). Five to ten per cent malignant ovarian tumours are genetic, and BRCA-1 and BRCA-2 gene mutations are implicated. BRCA-1 gene mutation on chromosome-17 and BRCA-2 gene mutation on chromosome 13 are noted. BRCA-1 is more carcinogenic than BRCA-2, it occurs earlier in life. With one family member affected, the lifelong risk is 2.7%, but it goes up to 13% with two or more relations. The risk increases with age up to 70 years. Pattern of inheritance is autosomal dominant, and ovarian tumour occurs at a younger age below 50 years, associated with a risk of breast and colonic cancer. Occurrence of mumps prior to menarche and multiple ovulation in IVF (in vitro fertilization) programme appear to increase the risk of ovarian malignancy in later life. Geographical variations are suggestive of the fact that high dietary fat intake, the use of talc on the perineum and industrial pollution are environmental factors implicated in the high incidence in the West. Protective factors include multiparity, breastfeeding, anovulation and use of oral contraceptive pills. These contraceptive pills reduce the incidence of ovarian cancer by 40–50% and the beneficial effect extends for about 10 years after stoppage of pills. The effect is also dose dependent. Repeated ovulation as seen in induction of ovulation, IVF low parity suggests ovulation trauma to the epithelial lining to be carcinogenic. Late diagnosis and early metastasis are responsible for the poor survival rates. Since no satisfactory method of mass screening has as yet been developed, only 20% of cases are confined to the ovaries at the time of diagnosis. Eighty per cent of ovarian malignancies are of epithelial origin and almost 80% are in Stage III or IV at the time of diagnosis. In younger patients, germ cell tumours are more frequently encountered when tumour markers like alpha-fetoproteins, CEA and hCG are useful. Eighty per cent are primary tumours and 20% are secondary from the breast, colon, stomach and uterus. Before menarche, 10% are malignant, during reproductive years, 15% are malignant but after menopause, it rises to 50%. Bilateral tubectomy or hysterectomy reduces the risk of ovarian cancer if the theory of mutagen ascending the genital tract is correct (Table 40.1).

Pathology

Histology of ovarian tumours presents wide variations and poses the greatest clinical challenge. These may be grouped as follows:

- Epithelial ovarian cancers account for 80–90% of ovarian cancers.
- Nonepithelial cancers account for 10–20%.

These include malignancies of: (i) germ cell origin, (ii) sex cord stromal cell origin, (iii) metastatic cancers and (iv) rare malignancies like lipoid cell tumours, sarcomas.

Epithelial Cancers of the Ovary

Seventy-five per cent of epithelial cancers are of the serous histologic type, about 20% are mucinous and 2% are endometrioid. Brenner tumour, clear cell carcinomas and

TABLE 40.1 Risk factors for ovarian cancer

- Age—between 45 and 60 years
- Nulliparous or of low parity
- Woman with previous PCOS, or on tamoxifen
- High-calorie, high-fat diet
- Genetic predisposition BRCA-1 and BRCA-2 genes
- Late menopause
- Breast and gastrointestinal cancer
- Prolonged HRT in menopausal woman

undifferentiated cancers account for 1% or less each. Each tumour type has a histologic pattern similar to a part of the upper genital tract, e.g. serous or papillary (Figures 40.1 and 40.2) pattern resembles the lining of the fallopian tube, mucinous tumours have lining resembling the endocervical glands and the endometrioid tumours have a pattern resembling the endometrium.

As much as 50% of benign serous epithelial tumours undergo secondary malignant change, but only 5% mucinous cysts undergo malignant transformation.

Ten to twenty per cent of these tumours are of low malignant potential (LMP) and are labelled as borderline tumours (Grade 0). They tend to remain confined to the ovaries for long and predominantly occur in the pre-menopausal age groups (30–50 years). They are associated with a good prognosis. Five-year survival is 90%. In contrast, invasive cancers are often seen in women aged 50 to 70 years, and they spread rapidly.

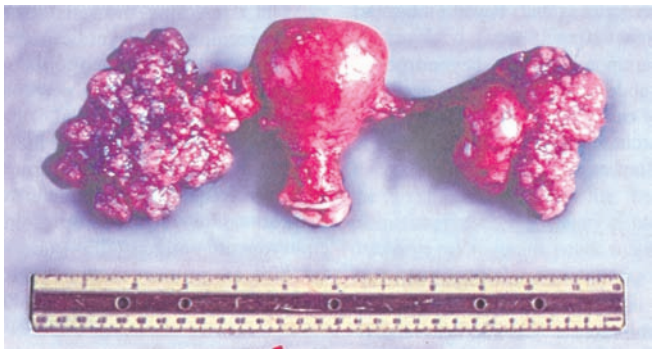

Figure 40.1 Bilateral papillary ovarian carcinoma.

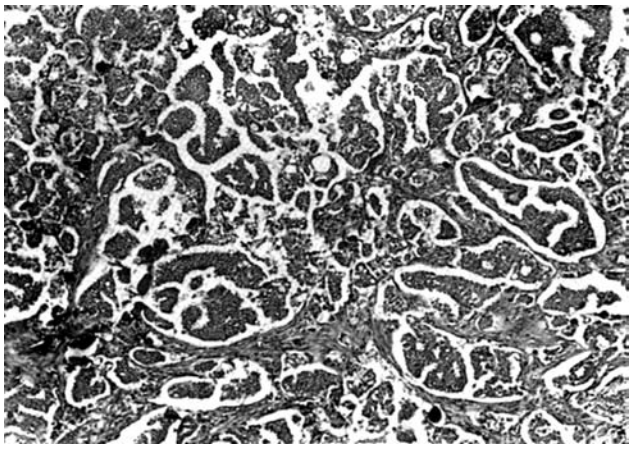

Figure 40.2 Well-differentiated serous papillary carcinoma. (From: Sengupta et al. *Gynaecology for Postgraduates and Practitioners.* BICL.)

Criteria for Diagnosis of Borderline Tumours (See also Chapter on Benign Ovarian Tumours)

- Epithelial proliferation with papillary formations and pseudostratification.
- Nuclear atypia and increased mitotic activity.
- Absence of true stromal invasion.
- Borderline tumours can be either epithelial or mucinous variety.
- Endometrioid carcinoma is associated with endometrial cancer in 20% cases.

These tumours are described in the chapter on ovarian tumours. Only serous and mucinous epithelial tumours fall into this group of borderline ovarian tumours.

Nonepithelial Malignancies of the Ovary

Non-epithelial malignancies of the ovary account for 10–20% of all malignancies of the ovary. The details of these types are as follows:

Germ cell malignancies are derived from the primordial germ cells of the ovary. These include:

- dysgerminoma (refer to Chapter 33);
- teratoma; (a) mature, dermoid cyst, (b) immature—solid/cystic and (c) monodermal teratomas like struma ovarii, carcinoid, mixed and others (Figures 40.3 and 40.4);
- endodermal sinus tumour (Figure 40.4);
- embryonal carcinoma;
- polyembryoma;
- choriocarcinomas; and
- mixed forms.

Endodermal Sinus (Yolk Sac) Tumour

Endodermal sinus (yolk sac) tumour is a rare tumour but the second most common of germ cell origin (Figure 40.5).

Figure 40.3 Immature teratoma. (From: Sengupta et al. *Gynaecology for Postgraduates and Practitioners.* BICL.)

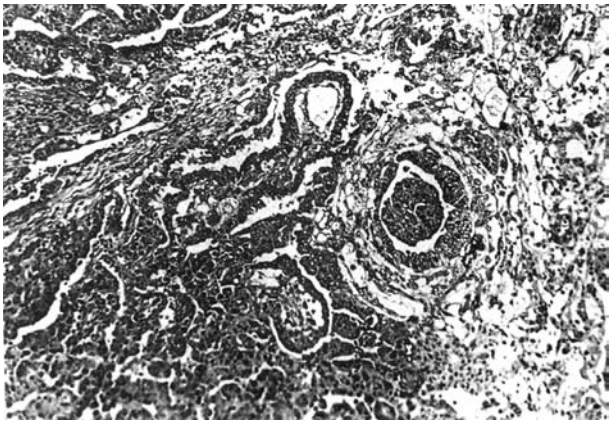

Figure 40.4 Endodermal sinus tumour of the testis. (From: Sengupta et al. *Gynaecology for Postgraduates and Practitioners.* BICL.)

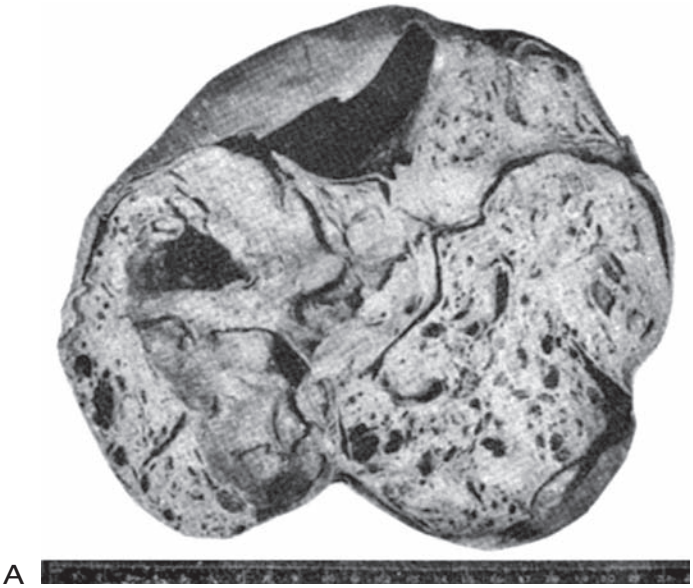

Figure 40.5 **(A)** Solid teratoma of the ovary. **(B)** Teratoma of ovary cartilage and mucous glands.

It is thought to originate from a multipotential embryonal tissue as a result of selective differentiation of yolk sac structures. This explains why the tumour is rich in alpha-fetoproteins and alpha-l-antitrypsin. Histologically, the tumour characteristically presents with papillary projections composed of a central core of blood vessels enveloped by immature epithelium. Intracellular and extracellular hyaline droplets are present in all tumours. The alpha-fetoprotein content can be stained by immunoperoxidase techniques. Most of these patients are children or young women, presenting with abdominal pain and a pelvic mass. The tumours are known to grow rapidly. Although considered to be highly malignant, they respond to chemotherapy with good survival rate.

Choriocarcinoma

Rarely seen in a pure form, generally choriocarcinoma is a part of a mixed germ cell tumour. Its origin as a teratoma can be confirmed in prepubertal girls, when the possibility of its gestational origin can be definitely excluded. The tumours are very vascular.

Histologically, the tumour shows a dimorphic population of syncytiotrophoblasts and cytotrophoblasts. It secretes large quantities of human chorionic gonadotropin (hCG) hormone, which forms an ideal tumour marker in the diagnosis and management of the tumour. The tumour is highly malignant, and metastasizes by blood stream to the lungs, brain, bones and other viscera.

Embryonal Cell Carcinoma

Embryonal cell carcinoma is a rare tumour accounting for about 5% of all germ cell tumours, and occurs in prepubertal girls. It elaborates both alpha-fetoproteins and chorionic gonadotropins. It is associated with the symptoms of precocious puberty and menstrual irregularities. It is highly malignant. The condition may be associated with fever due to torsion, rupture and haemorrhage.

Although 20–25% of all ovarian neoplasms are germ cell tumours, only 3–5% of these are malignant. The incidence of malignant germ cell tumours is lower in Caucasian whites, but threefold higher in Asians and Afro-Americans. Many of these secrete biochemical substances which are used as tumour markers; for example, embryonal carcinomas (AFP, hCG), endodermal sinus tumour (AFP) and choriocarcinoma (hCG). Dysgerminoma and pure germinomas do not secrete these markers, but secrete lactose dehydrogenase.

Dysgerminomas are highly radiosensitive (although, radiotherapy leads to future infertility). They also respond well to chemotherapy without interfering with future fertility and therefore chemotherapy is preferred. The details of dysgerminoma have been described in Chapter 36.

Sex Cord Stromal Tumours

Sex cord stromal tumours are either benign or malignant. The benign tumours are described in Chapter 36. These account for about 5–8% of all ovarian malignancies. This

group of ovarian neoplasms is derived from the sex cords and the ovarian stroma or mesenchyme. These tumours are composed of various combinations of cells consisting of 'female cells' (granulosa, theca cells) and 'male cells' (Sertoli, Leydig cells) as well as morphologically indifferent cells. They are also called mesenchymomas. The tumours of clinical interest are the following.

Granulosa Cell Tumours

Granulosa cell tumours secrete oestrogens. Depending on the age of their appearance, they may cause precocious puberty. Menometrorrhagia and episodes of abnormal uterine bleeding (AUB) are not uncommon in women of childbearing age and postmenopausal bleeding in elderly women. Endometrial hyperplasia occurs in 25–50% of patients, and endometrial carcinoma occurs in about 5% of cases. Theca cell tumour is more oestrogenic and more likely to cause endometrial cancer. A granulosa cell tumour secretes inhibin, a marker for this tumour.

Androblastomas or Arrhenoblastomas (Sertoli–Leydig Cell Tumours)

Androblastomas or arrhenoblastomas occur commonly in the third and fourth decades of life. These tumours are very rare and account for 0.2% of all ovarian neoplasms. They secrete androgens and cause defeminization followed by masculinization. The women experience oligomenorrhoea followed by amenorrhoea, flattening of the breasts, acne, hirsutism, enlargement of the clitoris and finally a change in voice. On removal of the tumour, all the above changes reverse except voice change.

Uncommon Ovarian Cancers

Uncommon ovarian cancers comprise only 0.1% of all ovarian malignancies. The chief representative types in this subgroup are lipid or lipoid cell tumour, sarcoma of the ovary and chorioepithelioma. The lipid cell variety arises from the adrenal cortical cell rests that reside in the vicinity of the ovary. These tumours are often benign or of low grade malignancy. They may be associated with virilization, obesity, hypertension and glucose intolerance.

Malignant mixed mesodermal sarcomas are rare tumours of the ovary. They occur in postmenopausal women. The tumours are very aggressive and metastasize early. Chemotherapy offers the best hope.

Sarcoma

Ovarian sarcomas are rare. Many tumours labelled as sarcomas have been misdiagnosed histologically and are in reality, granulosa cell tumours or anaplastic carcinomas. Sarcomas arise most frequently after menopause, particularly in multiparae. They give rise to multiple metastases. Rhabdomyosarcoma of the ovary has also been described.

Metastatic Carcinomas

Ovarian metastases are commonly from the primary growth in the gastrointestinal tract, notably the pylorus, colon and, rarely, the small bowel; they occasionally occur from the gall bladder and pancreas. They may also occur in late carcinoma of the breast, as seen in 30% of all autopsy material from breast cancer. Carcinomas of the corpus (10%) and cervix (1%) also metastasize to the ovary owing to the close relationship of their lymphatic drainage. Carcinoma of the corpus is 10 times more likely to metastasize to the ovary than the cervix. The reason for this is that the ovarian lymphatics drain the corpus directly whereas the cervical metastases tend to bypass the ovarian lymphatics and travel by way of the hypogastric and aortic glands. About 20% of clinically malignant ovarian tumours are secondary deposits from primary growths elsewhere. Two forms of secondary carcinoma of the ovary are recognized. In the first, the growth corresponds in its histology with the primary growth. Dissemination to the ovaries takes place either by implantation from metastases within the peritoneal cavity or by retrograde lymphatic spread. Both ovaries are replaced by solid carcinomas and multiple secondary deposits are usually disseminated over the peritoneum. A curious feature is that the ovarian tumours are much larger than the other secondary deposits, which is explained by assuming that the ovaries offer a much better environment for the growth of malignant cells than the other intraperitoneal viscera.

These secondary ovarian cancers have the following features. They are solid with irregular surface, and nearly always bilateral. Ascites is common and other obvious peritoneal metastases are present, notably in the omentum which is often replaced by an enormous solid malignant plaque. The method of ovarian infiltration is either by surface implantation or by retrograde lymphatic permeation. Both methods are probably operative and histological examination is rarely able to reveal the route through which the metastases occurred.

The second type of secondary ovarian carcinoma is the Krukenberg tumour.

Krukenberg Tumour

This type of tumour should be diagnosed only if it conforms to the following pattern. Krukenberg tumours are almost bilateral. They have smooth surfaces which may be slightly bossed; they are freely movable in the pelvis (Figure 40.6). There is no tendency to form adhesions with neighbouring viscera and there is no infiltration through the capsule. The tumour retains the shape of the normal ovary and has a peculiar solid waxy consistency although cystic spaces due to degeneration of the growth are common. Histologically, the tumour has a cellular or myxomatous stroma amongst which are scattered large signet-ring cells. These cells are ovoid in shape with a granular cytoplasm and the nucleus is compressed against one pole of the cell so that the outline of the cell resembles a signet ring (Figure 40.7). The tumours are secondary growth in the ovary and most often arise from a primary carcinoma of the stomach (70%), large bowel (15%) and breast (6%). The Krukenberg tumour outstrips the primary growth in size, and unless the histology of the tumour is known, the case may be regarded as one of primary malignant ovarian carcinoma, particularly as the tumours are usually freely movable

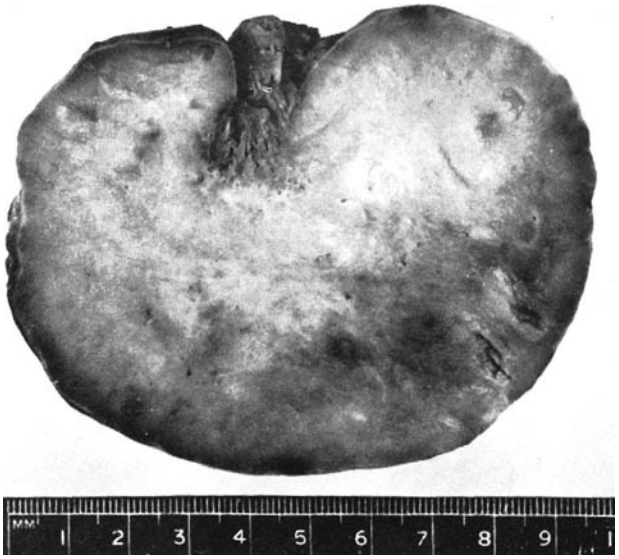

Figure 40.6 Krukenberg tumour of the ovary. The tumour has a solid waxy appearance with an intact capsule free of all adhesions. The cut surface is uniform and preserves the shape of the ovary.

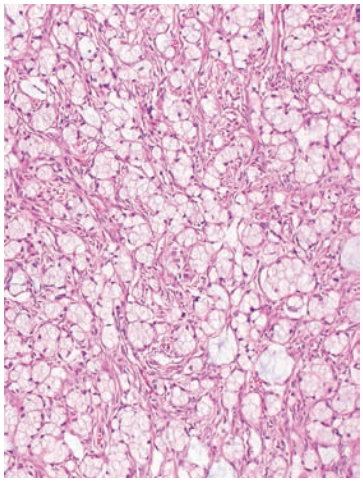

Figure 40.7 Krukenberg tumour. (From Figure 34. *Diagnostic Histopathology*. In: Mucinous tumours of the ovary, 2008.)

without obvious intraperitoneal metastases. The tumours almost certainly arise by retrograde lymphatic spread; the carcinoma cells pass from the stomach to the superior gastric lymphatic glands which also receive the lymphatics from the ovary. Retrograde lymphatic spread can be demonstrated in early cases when carcinoma cells are found infiltrating the ovary by way of the lymphatics in the medulla.

Coincident Carcinoma of the Ovaries and the Body of the Uterus

Cases of coincident carcinoma of the ovaries and the body of the uterus are known. In some cases, the growth is primary in the body of the uterus and forms secondary deposits in the ovaries. In other cases, the primary growth is in the ovaries and secondary deposits reach the cavity of the uterus either by lymphatic permeation or by implantation via the fallopian tube. Another group of cases is well-recognized in which the ovarian carcinomas are histologically different from the carcinoma of the body of the uterus. Any postmenopausal bleeding associated with an ovarian tumour should suggest the possibility of a coincident endometrial carcinoma, and this possibility always demands the removal of the uterus as well as the ovarian tumours.

Metastases in the Uterus

Advanced carcinoma of the ovaries becomes adherent to the surrounding structures so that the uterus is directly infiltrated by the growth. The peritoneal surface of the uterus is also infiltrated in some cases by carcinoma cells disseminated over the peritoneum. In rare cases, metastases form in the endometrium of the uterus as the result of carcinoma cells passing along the fallopian tube into the cavity of the uterus. In some cases of carcinoma of the ovaries, secondary deposits are formed in the vaginal walls, and such metastases correspond to those found in cases of chorioepithelioma and of carcinoma of the body of the uterus, when metastases form by retrograde lymphatic spread.

Direct spread of the tumours occurs in the pouch of Douglas, paracolic gutter, sub-diaphragm on the right side, liver and peritoneal lining.

Metastases in Operation Scars

It is not uncommon after the removal of malignant ovarian tumours for metastases to form in the operation scar and to spread to the adjacent skin.

Spread by Way of Blood Stream

It is rare for carcinoma of the ovaries to spread by way of the blood stream, but with very malignant tumours, metastases may be disseminated in this way. It is therefore important to obtain chest radiograph in all cases with malignant ovarian tumours.

Lymphatic Spread

The regional lymphatic glands of the ovaries are the paraaortic and the superior gastric which are impalpable clinically. Sometimes, the malignant cells permeate to the mediastinal glands when they may ulcerate into the pleural cavity and cause pleural effusion. Sometimes, secondary deposits may be found above the left clavicle in the posterior triangle of the neck, where they have arrived via the main lymphatic ducts in the mediastinum. Once the peritoneum is involved, pelvic lymph nodes will be infiltrated with metastases.

Bilateral Character of Ovarian Tumours

Seventy per cent of primary ovarian cancers are bilateral, whereas nearly all secondary growths are bilateral. Both ovaries may be involved in 16% benign tumours. Even with malignant ovarian tumours, the two ovaries are attacked simultaneously by the disease and the involvement of one by secondary deposits from the other is exceptional. With secondary ovarian carcinomas, if the involvement is by retrograde lymphatic spread, one would expect both ovaries to be involved simultaneously. Similar remarks apply when implantation of carcinoma cells is the cause of development of secondary deposits in the ovaries.

The most important metastases of malignant ovarian tumours are those which form on the peritoneum and lead to the development of large tumours in the omentum. The secondary deposits of carcinoma of the ovaries rarely involve the liver, because the ovarian vessels belong to the systemic system and not to the portal system like those of the intestine and stomach.

Clinical Features

The clinical features are not specific in early stages, resulting in late diagnosis in 70% cases. A woman with a malignant ovarian tumour is either an adolescent or of menopausal or postmenopausal age of low parity. A family history of breast or ovarian tumour may be relevant.

Initially, the woman is asymptomatic. The tumour however grows rapidly and develops symptoms. Abdominal discomfort and pain, abnormal or postmenopausal bleeding and an abdominal lump are the characteristic features. Weight loss, cachexia and anaemia are the symptoms and signs of advanced stage of cancer.

The malignant ovarian tumours are often bilateral, solid and present with ascites. The only benign tumours that cause ascites (Meigs' syndrome) are ovarian fibroma, Brenner tumour and rarely granulosa cell tumour. The tumours are often fixed in the late stage and intraperitoneal metastasis may be palpable abdominally.

The vaginal examination may reveal fixed nodules in the pouch of Douglas, apart from adnexal masses felt separate from the uterus.

Unilateral nonpitting oedema of the leg, pleural effusion and enlarged liver are suggestive of advanced stage of the disease. *Peritoneal tuberculosis mimics ovarian cancer with raised CA-125.*

Screening

There is no satisfactory screening for ovarian malignant tumour. CA-125 and ultrasound have low detection rates in picking up the tumour (Table 40.2). However, a high-risk woman should be under observation. A palpable ovary in a menopausal woman is likely to be malignant and should be investigated.

Investigations

The investigations to confirm the diagnosis and nature of the tumour are described in the chapter dealing with benign ovarian tumours. Further, to confirm or refute malignancy:

- CT and MRI indicate the extent of the tumour spread.
- Tissue markers mentioned earlier suggest the histological nature of the tumour, as well as decide the duration of postoperative chemotherapy or need for radiotherapy. CA-125 is raised in epithelial tumours.

TABLE 40.2 FIGO staging of ovarian carcinoma

STAGE 1: Tumour is confined to the ovary/ovaries.	
1A	Only one ovary is affected by the tumour, the ovary capsule is intact No tumour is detected on the surface of the ovary Malignant cells are not detected in ascites or peritoneal washings
1B	Both ovaries are affected by the tumour, the ovary capsule is intact No tumour is detected on the surface of the ovaries Malignant cells are not detected in ascites or peritoneal washings
1C	The tumour is limited to one or both ovaries, with any of the following: The ovary capsule is ruptured The tumour is detected on the ovary surface Positive malignant cells are detected in the ascites or peritoneal washings
STAGE 2: Tumour involves one or both ovaries and has extended into the pelvis.	
2A	The tumour has extended and/or implanted into the uterus and/or the fallopian tubes Malignant cells are not detected in ascites or peritoneal washings
2B	The tumour has extended to another organ in the pelvis Malignant cells are not detected in ascites or peritoneal washings
2C	Tumours are as defined in 2A/B, and malignant cells are detected in the ascites or peritoneal washings
STAGE 3: The tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis. Includes liver capsule metastasis.	
3A	Microscopic peritoneal metastasis beyond the pelvis
3B	Microscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension
3C	Microscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension and/or regional lymph nodes metastasis
STAGE 4: Distant metastasis beyond the peritoneal cavity. Liver parenchymal metastasis.	

Source: FIGO guidelines.

- Barium meal, barium enema and breast examination are required when metastatic tumour is suspected. X-ray of chest and liver scan are required to detect metastatic growth.
- Ultrasound shows a solid tumour with echogenic or cystic areas, a thick capsule with papillary projectors and a thick septum measuring more than 5 mm in a malignant tumour. The other ovary may be enlarged or bilateral tumours seen. An endometrial lining more than 4 mm in thickness with papillary projections in a perimenopausal woman is seen in a feminizing tumour and if endometrial secondaries are present. Except in Meigs' syndrome, ascites is characteristic of a malignant tumour. Three-dimensional ultrasound is useful.
- Doppler ultrasound showing low pulsatile index less than 1 and resistance index less than 0.4 suggest malignancy.

In a benign tumour, blood flow and vascularity is from the periphery to the centre. In a malignant tumour, neovascularity is initiated in the centre of the tumour.

- D&C is required if the woman develops postmenopausal bleeding.
- Tissue markers.
  - CEA more than 5 ng/mL (normal 2.5–5 ng/mL) is reported in endometrioid, Brenner tumour, mucinous tumour, colonic, liver, breast and lung metastasis.
  - CA-125 is a glycoprotein surface antigen raised in 80% epithelial tumours, but is not very specific, as it is also raised in abdominal tuberculosis and endometriosis as well. It is normal in 50% Stage I epithelial carcinoma. Some have observed raised CA-125 18 months to 3 years prior to clinical detection of malignant ovarian tumours.
- Alpha-fetoprotein, hCG, NB/70K, placental alkaline phosphatase and lactase dehydrogenase (1000 U/L) are the tissue markers for germ cell tumours. Inhibin is raised in granulosa cell tumour. NB/70K is a glycoprotein raised in 60% epithelial tumours (above 11 kU/mL), but also seen in liver and renal failure. The tissue markers are useful during chemotherapy to decide the response and the duration of therapy in postoperative follow-up.
- Fine-needle aspiration cytology (FNAC) and ascetic fluid cytology yield a high false-negative report.
- CT and MRI diagnose dermoid, endometriosis and extent of spread of ovarian malignancy as well as assess lymph node involvement. Since these only pick up lymph nodes enlarged more than 1 cm, some employ lymphography if CT and MRI give negative lymph node involvement, because lymphography can pick up nodes as small as 5 mm.
- Since debulking surgery is undertaken even in advanced stages, diagnostic laparoscopy has lost its importance.

Management

Laparotomy and maximal reduction is the primary and gold standard treatment in all ovarian malignant tumours. Surgical staging is followed by definitive surgery or debulking followed by chemotherapy or radiotherapy.

Surgical staging involves systemic exploration of the undersurface of the diaphragm, liver, stomach, bowel and omentum. The para-aortic lymph nodes should be palpated. Ascitic fluid or peritoneal wash should be collected in heparinized bottles for cytology. The ovaries and uterus should be studied and definitive surgery planned.

Debulking. Optimal debulking surgery is now considered the standard treatment for all *stages of ovarian cancer. The reasons for this recommendation are as follows*:

- Despite well-developed chemotherapy available, recurrence is common. Debulking reduces the amount of chemotherapeutic drugs, reduces resistance to the drugs and improves the blood flow to the residual tumour, thus allowing the chemotherapeutic drugs to reach the tumour tissue. The incidence of recurrence is therefore less and disease-free interval prolonged.
- Reduces ascites and symptoms.

Borderline malignancy. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO) should be done in older women, and conservative ovariotomy in young women, provided peritoneal wash is negative. Frozen section may give false-negative report due to freezing. Instead, lately, imprint cytology of the specimen gives 90% sensitivity and 80% specificity, takes 20 min, is simple and less expensive. No postoperative chemotherapy is required, but follow-up is mandatory in young women. In a young woman, conservation of uterus allows IVF and donor egg use.

Stages I and II. The operable cases (Stages I and II) should undergo total hysterectomy and bilateral salpingo-oophorectomy with omentectomy.

Advanced and inoperable case (Stages III and IV) will benefit from debulking surgery and removal of the tumour. Postoperative chemotherapy and radiotherapy improve the survival and quality of life. The purpose of maximal debulking surgery is to reduce the amount of malignant tissue to be subjected to chemotherapy and relieve the woman of her symptoms. The response to chemotherapy improves with smaller residual tissue and thus remission period and survival is enhanced. Pre-operative cisplatin followed by surgery is lately employed.

Lymphadenectomy. Lately some oncologists believe additional lymphadenectomy improves the survival. The lymph nodes mainly involved are para-aortic lymph nodes.

Postoperative chemotherapy and radiotherapy depend upon the staging and the type of tumour. The duration of chemotherapy is judged by the level of tissue markers.

Interval Surgery

Some advanced and bulky tumours are initially treated by chemotherapy for three cycles. This is followed by debulking surgery and postoperative chemotherapy as dictated by tissue marker.

Laparoscopic surgery is lately undertaken by expert laparoscopists. The disadvantages of laparoscopy are as follows:

- Possibility of spillage during surgery with recurrence.
- Port-site metastasis in 1–1.5% cases. Use of endospecimen bag, lavage and use of intraperitoneal chemotherapy may reduce the risk.

Second-Look Surgery

The following is the role of second-look surgery:

- To detect the presence of any residual tumour following a planned course of chemotherapy and decide if further chemotherapy is required. With the availability of tissue markers for vast majority of ovarian tumours in the follow-up, the importance of second-look surgery is losing ground and surgical morbidity is also eliminated. Besides, microscopic residual tumours may not be detected (false-negative findings) at laparoscopy.

- Following a 3–6 month course of chemotherapy in an inoperable case, second-look surgery may enable TAH and BSO or debulking procedure.
- In a recurrent tumour.
- Instead of laparotomy, second-look laparoscopy is another alternative.

Combination of surgery, radiotherapy and chemotherapy has improved the salvage rate and quality of life considerably.

The terminal stages require analgesics and sedation.

Recurrent tumour. If the tumour recurs following treatment, the following options are applicable depending upon the type of tumour, size and its histology.

- Second-look surgery and removal of the lesion—for a single-site recurrence.
- Chemotherapy—for visceral metastasis.
- Radiotherapy—preferably for nodal metastasis.

Chemotherapy and radiotherapy are described in Chapter 41.

Intraperitoneal chemotherapeutic drug may be instilled in a small residual tumour, at the end of surgery. The trial with chemotherapeutic drugs intraperitoneally is on.

Stem cell therapy may have a role in future. Dysgerminoma and granulosa cell tumour respond well to both chemotherapy and radiotherapy. In a young woman, fertility-retaining surgery of unilateral ovariotomy (if unilateral) is followed by chemotherapy rather than radiotherapy which destroys the other ovary. In the older woman, hysterectomy and bilateral removal of ovaries may be followed by radiotherapy.

Results

Refer to Table 40.3.

Strategies to Reduce the Incidence of Genital Tract Malignancies (Prophylaxis)

There have been advances in strategies evolved to reduce the incidence of genital cancers. The following are notable amongst these:

1. The role and value of periodic 'Pap smear' tests is well-established in reducing the incidence of invasive carcinoma of the cervix.
2. Evaluation of abnormal Pap tests with colposcopy-directed biopsies enables the diagnosis of intraepithelial cancers and diagnosis of early invasive cancer of the cervix. (secondary prevention)
3. The practice of preferring total over subtotal hysterectomy for benign diseases (fibroids, adenomyosis, abnormal uterine bleeding—AUB) protects against risk of future cervical stump carcinoma estimated to occur in 1–2% of cases.
4. Early diagnosis of sexually transmitted diseases (STDs) and their eradication. Herpes and HPV infections render an individual prone to cancer of vulva and the cervix. Barrier contraceptives protect against STD as well as cervical cancer. (primary prevention)
5. HPV vaccine is now available which may eradicate lower genital tract malignancies in young women. The available vaccine is type specific and therefore, protective in only 60–70%.
6. The treatment of cervical dysplasia by CO_2 laser/conization for CIN lesions will reduce the incidence of cancer cervix.
7. Addition of progestogens to oestrogens in hormone replacement therapy (HRT) reduces the risks of uterine endometrial cancer.
8. Thorough investigation of a woman with postmenopausal bleeding often brings to light early unsuspected endometrial/ovarian/tubal cancers.
9. The practice of routine removal of both ovaries when performing hysterectomy for benign conditions after the age of 50 years is a prophylaxis against risk of future ovarian cancer. Prophylactic oophorectomy in a genetically predisposed woman is recommended, though premature menopause remains the risk. This also reduces breast cancer by 50%.
10. Early diagnosis of ovarian cancer is the primary objective for long-term survival, though this is not obtained as of today. Seventy-five per cent tumours are advanced when diagnosed.
11. Oral combined pills reduce the incidence of uterine and ovarian cancer by 40–50%. The effects last for 10 years after stoppage of oral pills. Barrier contraceptives prevent cervical cancer.
12. Gene study can select women at high risk for cancer.
13. Evaluation of adnexal masses with scans, Doppler velocimetric studies and CA-125 tumour marker to diagnose ovarian cancer.
14. Hysteroscopy/laparoscopy/selective biopsies of suspicious lesions.
15. Routine mammography for all women over the age of 40 years, earlier whenever clinical examination reveals a doubtful lump, or in women with strong family history of breast cancer.

TABLE 40.3 Comparison of FIGO staging and Five-year survival rate

FIGO Staging	Five-Year Survival Rates
Stage 0	90–100%
Stage I	70%
Stage II	25–30%
Stage III	10%
Stage IV	0–5%

For many women, the obstetrician-gynaecologist is likely to be the only physician to provide them health care. Hence, the importance of developing skills for evaluation and counselling for genital cancers and adopting clinical practices which reduce the future risks of genital cancers lies with the gynaecologists.

Palliative and Adjuvant Therapy

It is not enough to treat cancer disease per se. Apart from palliative radiotherapy and chemotherapy in the advanced stage of the disease, other adjuvants are necessary in the management of cancers. These are:

- Nutrition
- Relief of pain
- Relief of symptoms
- Psychological support

Nutrition

It is necessary to maintain the woman's nutrition before, during and after surgery, radiotherapy and chemotherapy to obtain a good response and successful cure, longer remission and survival as well as a feeling of well-being. The nutritional problem arises in the advanced stage when cachexia sets in, or following radiotherapy and chemotherapy. The optimal nutritional status is a prerequisite to cancer treatment.

Assessment of Nutritional Status

- Weight of the woman: Weight loss more than 10% of previous weight is considered malnutrition.
- Haemoglobin should be more than 10 g%, ideally 12 g%. Low haemoglobin before surgery can cause sepsis, thromboembolism and poor wound healing. Non-response to radiotherapy and chemotherapy is seen in anoxic tissues.
- Protein: Normal serum albumin is 3.0–3.5 mg/L and hypoproteinaemia is a sign of malnutrition.

Management. The woman should receive adequate calories of 2000–2400 daily along with adequate protein and micronutrients. Anaemia is treated with blood transfusion prior to any treatment. Daily fluid intake should be at least 1500–2000 mL. If the woman cannot tolerate oral diet, intravenous amino acids, glucose and vitamins should be provided. Tube feeding is not always tolerable and comfortable. Initially 50 mL/h, it is increased gradually to the required amount. Hydration is especially important in chemotherapy with cisplatin.

Apart from the above, neutropenia resulting from radiotherapy and certain chemotherapy drugs require blood transfusion.

Relief of Pain

It is important to detect the cause and pathology of pain to deliver appropriate pain killers. Even when cure is not possible, painless days reduce the suffering of the woman and allow her to meet her end in peace and serenity. This palliative treatment should be instituted along with the definitive or other palliative therapy including nutrition mentioned earlier, and not resorted to only in the terminal stage.

Pain may be due to local infiltration, nerve or bone involvement, or psoas muscle spasm. Muscle spasm is relieved with diazepam. Mild pain can be relieved with paracetamol 1 g qid. It provides mild sedation, but may cause constipation in long-term therapy.

Opiates. Morphia one-fourth grain or diamorphine (heroin) 1 mg orally are effective when given 4-hourly. Diamorphine is stronger than morphine; 1 mg of diamorphine is equivalent to 3 mg oral morphine. Subcutaneous injection of heroin (2 mg) can also be given and repeated as required in severe pain. Spinal injection of opiates has also been employed.

Synthetic opiate syrup (methadone) is useful for cough in pulmonary metastasis. The side effects of opiates are vomiting, sedation and constipation which should be managed by haloperidol (3–5 mg) for vomiting at night or metoclopramide. Overdose of opiates include visual hallucinations, myoclonic jerks, respiratory distress, pinpoint pupils and addiction which is not a problem in the terminal ill women. Laxatives will relieve constipation.

Bony Pain. Morphine is not effective against bone metastasis. It requires a nonsteroidal anti-inflammatory drug (NSAID) such as naproxen 500 mg bd and diclofenac 50 mg tid orally or rectally if gastritis occurs. Subcutaneous injection can also be given.

Bisphosphonate, 4-hourly infusion every 3–4 weeks, protects against osteoporosis. Hypocalcaemia should be watched for during this therapy.

When NSAIDs fail to relieve pain, steroids are recommended. Steroids promote feeling of well-being and improve appetite. Prednisone 20 mg daily in divided doses should be administered not too late in the evening, as it can disturb the sleep pattern. High-dose dexamethasone 16–24 mg daily is useful in liver and brain metastasis—it relieves the pressure of the metastasis in these organs. They are also effective in bladder and bowel pain. A single morning dose is adequate because of its long half-life. Diabetes, hypertension, obesity and osteoporosis are its side effects.

Bowel and Bladder Pain. Anticholinergic drugs such as Buscopan 20 mg qid, oxybutynin 5 mg qid/or chlorpromazine 25–50 mg are effective against bladder and rectal pain.

Nerve Pain. Sodium valproate 200–300 mg tid and carbamazepine 100–200 mg tid cure nerve pain. Antidepressants such as amitriptyline 10 mg at night are effective too, but renal function needs observing. In nonresponders, epidural, sacral or pudendal blocks are required. Sympathectomy may be the last resort. Ketamine is effective as an analgesic.

Relief of Symptoms

Vomiting. Vomiting is due to drugs, chemotherapy or radiotherapy, or may be due to cachexia in the terminal stage. Haloperidol 3–5 mg at night or metoclopramide 10 mg tid control vomiting. Cerebral vomiting is treated with cyclizine 50 mg tid or domperidone 20 mg tid. Octreotide reduces intestinal secretion and promotes absorption with the effect that gastric volume is reduced and vomiting stops. It is also effective in diarrhoea. Subcutaneously

300–1200 mg bd is given but the drug is very expensive. Thrush infection is not uncommon and can be treated with fluconazole. Ondansetron 4 mg TID is effective against radiation vomiting.

Psychological Impact

Psychological impact may be considerable. More time involvement, sharing emotions and compassion form the holistic care in the management of a woman suffering from cancer.

Other problems are as follows:

- Decreased sex libido due to vaginal discharge, bleeding and fear of cancer dissemination.
- Dyspareunia following surgery and radiotherapy (short vagina and vaginal stenosis).
- Ovarian removal with menopausal symptoms requires hormone replacement therapy.
- Mental depression due to oestrogen deficiency.
- Ascites requires tapping.
- Hormone therapy in tumours possessing oestrogen and progesterone receptors does well with progestogens and tamoxifen. Well-differentiated tumours possess oestrogen and progesterone receptors than poorly differentiated tumours, so response is good.

Role of Hospitals. Temporary hospitalization gives respite to relatives and provides change of environment for the patient.

The ultimate goal of palliative treatment is to allow the woman to meet her end gracefully and with serenity.

Key Points

- Epithelial tumours are the commonest tumours, and account for 80% of all ovarian malignant tumours.
- Borderline epithelial tumours with low malignancy occur in younger women, and respond well to conservative surgery. The common malignant tumours in adolescents are dysgerminoma, teratoma, embryonal tumours and granulose cell tumour. Conservative surgery followed by chemotherapy yields good results and retains the fertility potential. Radiotherapy is not advocated but recurrence is possible and long-life follow-up is necessary.
- Conservative surgery followed by chemotherapy yields good results and retains fertility potential in young women.
- Primary surgery followed if required by postoperative chemotherapy is the cornerstone in the management of ovarian malignant tumour. Hysterectomy, bilateral salpingo-oophorectomy and omentectomy is the standard surgical procedure. Some include lymphadectomy as well.
- In an advanced stage, a 3-month course of chemotherapy followed by debulking surgery has improved the outcome and survival rate.
- A woman with genital cancer also needs guidance in nutrition, pain relievers and psychological support.
- In case of bilateral ovarian malignant tumours in young women, conservation of the uterus will enable pregnancy by oocyte donor.
- PET, CT improves the early diagnosis in detecting location and recurrence of the tumour, and assesses the response to chemotherapy.
- Ovarian cancer is the second most common genital cancer. It remains asymptomatic for a long time. Many cases are already far advanced at the time of diagnosis.
- The gold standard is abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy in the early and operative cases of ovarian cancer. Debulking, radiotherapy and chemotherapy prolong life and duration of remission.

Self-Assessment

1. Describe the clinical features of malignant ovarian tumour.
2. Discuss the management of malignant ovarian tumour.
3. A woman, 50-year-old, presents with postmenopausal bleeding, abdominal pain and a lump in the lower abdomen. Discuss the differential diagnosis and management.
4. A girl, 10-year-old, is brought with abdominal pain and a lump felt during the last one month. Discuss the differential diagnosis and management.
5. Short notes on:
   - Arrhenoblastoma
   - Krukenberg tumour
   - Borderline ovarian tumour

Suggested Reading

Bonnar J (ed). Recent Advances in Obstetrics and Gnaecology, Paul Donnellan and David Fennelly. In: Recent advances in ovarian cancer. 20: 179, 1999.

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Chapter

41

Radiation Therapy and Chemotherapy for Gynaecologic Cancer

CHAPTER OUTLINE

Radiation Therapy

Radiation therapy plays an important role in the management of gynaecologic malignancies. Its specific curative role has been established beyond doubt in the management of cervical cancer, the most commonly seen cancer in clinical practice. Radiation treatment may also be curative for localized endometrial cancer and when surgery is not possible. It improves prognosis if used as adjuvant postoperative therapy in advanced cervical and endometrial cancer. The scope of radiation therapy has been enhanced in the management of cancers of the vulva and vagina. In selected cases of cancer of the ovary, postoperative adjuvant radiotherapy may be beneficial in controlling the disease. In many cases, a judicious combination of radiotherapy and cancer chemotherapy has contributed significantly in improving the patient's prognosis and survival period.

Cell death in terms of radiation biology is defined as the loss of clonogenic capacity or 'cell reproductive potential'. Ionizing radiation produces free radicals which disrupt the reproductive integrity of DNA-producing cells and thus control cell division and neoplastic growth. Radiation affects both normal cells and tumour cells. However, the dividing mitotic cells are most vulnerable. Hence, by grading the dose of irradiation, a differential effect can be attained by forcing the cancer cells to differentiate and thus lose their malignant potential, stimulate angioblasts and fibroblasts to grow into the tumour cell mass, dividing them into smaller nests of neoplastic cells, and finally as the connective tissue fibroblasts constrict, they cut off the tumour cell blood supply causing tumour necrosis. Anaplastic tumours therefore respond better compared to well-differentiated squamous cell tumours. Adenocarcinoma and sarcoma are poor responders.

Physical Principles of Radiation Therapy

Basic Physics

Radiation physics deals with the measurement of energy that is transferred from the radiation source to the tissue under irradiation.

The therapeutic activity of radiation is mainly related to the process of ionization. There are two forms of *photons* (quanta of radiation whose energy is proportional to their frequency and inversely proportional to their wavelength). One form of ionizing radiation is electromagnetic, which refers to X-rays. These sources of energy have no mass and no electrical charge. They are produced in discrete quanta or photons. A second source of photon radiation comes from the production of gamma rays (similar to X-rays) which result from the decay of radioactive isotopes.

Electromagnetic radiation with shorter wavelengths has a higher frequency, hence higher energy. The energy produced is measured in electron volts (eV), 1 eV = 1.6×10^{-12} ergs. The X-ray radiotherapy units can range from 50,000 eV (50 kV) to over 30 million eV.

Photon radiation is measured in curies (Ci). One curie is defined as 3.7×10^{10} disintegrations per second, which is equivalent to the disintegration of 1 g of radium.

Irrespective of the source of electromagnetic or photon radiation, the transmitted energy diverges from the source of origin and diminishes inversely as the square of the distance traversed ($1/d^2$).

X-rays and photons can be generated as a result of rapidly accelerated electrons in vacuum striking a target. Modern generators that accelerate these electrons to a high speed may do so in a circular fashion (betatron) or linearly (linear accelerator).

Another type of radiation energy, known as particulate radiation, is produced by subatomic particles having a discrete mass. These particles are derived as a result of disintegration of radionuclides. Four different types, namely alpha particles, neutrons, protons and electrons, are produced. *Neutrons* are highly penetrative and have no charge but have a large mass. They cause high-energy collisions with atomic nuclei, principally hydrogen in the tissues. The resultant recoil proton loses energy to the surrounding tissue by ionization, causing cell death.

Photons are positively charged particles and can be produced directly by generators. The high-energy beams produced are used for special applications like the treatment of pituitary tumours.

Alpha particles (helium nucleus) have very little penetrating power and therefore are not of much practical use.

Electrons, also referred to as beta rays, can be produced at different energies by machines for various therapeutic uses.

Radiation Biology

Photons (gamma rays or X-rays) act by dislodging orbital electrons of the tissue through which they pass. This collision produces a fast electron (Compton effect) which then ionizes molecules along its path producing secondary electrons and free hydroxyl (OH) radicals. This process continues until the photon loses all of its energy. Since 80% of the cell contains water, cellular radiation damage is mediated by the ionization of water and production of free radicals, hydrogen (H) and hydroxide (OH).

The free OH radical causes DNA cell damage. The effect may be lethal and kill the cell or it may be sub-lethal, in which case, the cellular DNA may undergo repair and the cell recovers.

The free molecular OH radicals react with molecular oxygen to form peroxides, which in turn further damage the tissues. *Oxygen is therefore important to enhance photon effects*. Large tumours with poor blood supply have poor photon effect in hypoxic areas and are radio-resistant. *Radiation in presence of anaemia, infection and scarred tissue produces poor results.*

The rate of loss of energy of an ionizing particle as it traverses a unit length of medium is known as linear energy transfer (LET). In case of photons, energy transfer from an X-ray or electromagnetic source, the LET is low; hence, multiple tissue bombardments are required to achieve a lethal dose. In case of particulate irradiation with large particles (neutrons), the ionization achieved is high, leading to high LET, more intense ionization and production of more toxic hydroxyl radicals, achieving greater lethal tissue effect independent of tissue oxygenation.

Successful radiotherapy requires a good balance between the dosage to the tumour and to that of the surrounding structure (radiation tolerance) so that least damage is inflicted to the normal tissues, while maximal radio-effect reaches the tumour cells. The aim is to deliver a high dose to the tumour and minimal dose to the normal tissues. Radiosensitizers, cisplatin and 5-fluorouracil, enhance the lethal effect of radiation when given concomitantly. *This combination is called chemoradiation*.

An important principle to remember is that a given dose of radiation kills a constant fraction of tumour cells; hence, each repetitive sitting achieves a similar reduction of tumour cell activity.

There are four phases of a cell cycle: resting phase, RNA and protein synthesis, DNA synthesis and cell division or mitosis. Rapidly dividing cells are the most radiosensitive. This explains the higher response of anaplastic tumours compared to a well-differentiated one.

Fractionation of radiation treatment permits effective treatment of the tumour, and minimizes complications which could result from exposure of normal tissues (bone marrow, normal intestine) to a single large dose. The more effective repair of normal tissue occurring between treatment fractions allows recovery of normal cells which is a therapeutic advantage.

The clinician must be familiar with the unit of measurement of amount of energy absorbed by the tissue, called the rad. Rad is defined as 100 ergs of energy absorbed per gram of tissue.

Lately the term *gray* (1 joule per kg) has been introduced. One gray (Gy) is equivalent to 100 rads.

Summary. Radiation biology produces the following effects:

- Radiation (photons or gamma rays) is transferred from the radiation source to the tissues undergoing irradiation. The process of ionization occurs (Compton effect) along the path of radiation. The free radicals liberated produce tissue damage. Mitotic cells are killed (lethal effect) or undergo differentiation (rendered non-lethal). Proliferation of angioblasts and fibroblasts break up the mass into smaller islands of tissue tumours. Finally, the fibroblasts constrict and cause necrosis of tissue by way of vascularity.
- The effect of transmitted energy, irrespective of the source of irradiation as it diverges from the source of origin, rapidly diminishes inversely as the square of the distance travelled.
- Success of radiotherapy requires a good balance of dosage between the tumour tissue and healthy surrounding tissue.

Radiation Sources: External and Internal Therapy

In general, two techniques are utilized in radiation treatment, brachytherapy (internal) and teletherapy (external).

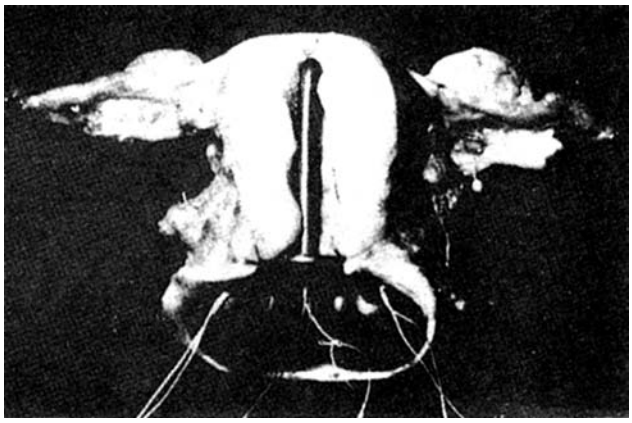

Figure 41.1 Cross-section of an operative specimen demonstrating the correct positioning of the radium in a Manchester insertion. (From: *Shaw's Textbook of Operative Gynaecology*, 3rd ed. BICL. 1968.)

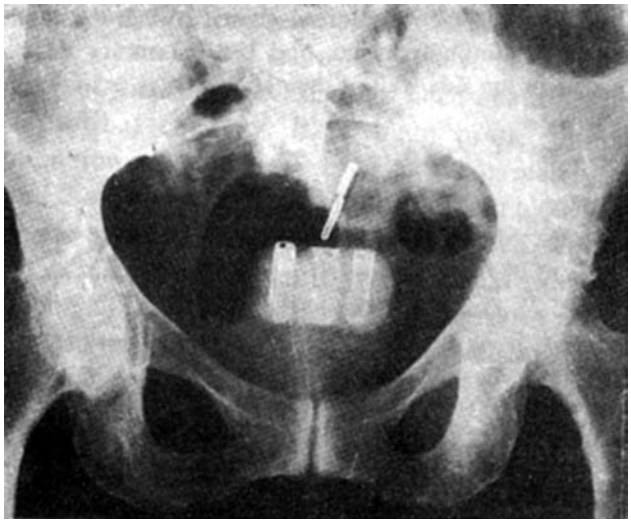

Figure 41.2 X-ray of pelvis, showing positioning of radium in a Manchester insertion. Note that the central opacity between the two ovoids is, in fact, a space and not a third radium-containing ovoid. (From: Macleod and Read, *Gynaecology*. 5th ed. Churchill, 1955.)

Brachytherapy

Brachytherapy is a form of radiation therapy in which the source is placed close to the tumour. The application may be in the form of needles implanted into the tumour (interstitial) or placed in the vagina, cervical canal or uterine cavity (intracavitary) in tandem with vaginal ovoids or use of colpostat.

In the case of cervical and uterine cancer, brachytherapy comprises a central uterine and two ovoids in the vaginal vault. This positioning irradiates the primary growth as well as the parametrium and the obturator lymph nodes (Figure 41.1).

Pre-radiation preparation includes:

- Checking haemoglobin and WCC
- Rectal enema or suppository
- Antibiotic cover

Method. Under general anaesthesia, a self-retaining catheter is inserted into the bladder. The cervix is dilated to allow the insertion of the uterine tube. After inserting the long empty device, two rubber ovoids or platinum boxes are placed in the vaginal fornices. The vagina is then packed with sterile gauze in such a way that the bladder and the rectum are displaced away from the radiation source. Anteroposterior and lateral X-rays of the pelvis are taken to check the correct position of the devices (Figure 41.2). The radioactive substance is then loaded into the device by remote control of 'afterloading technique'. It is unloaded when nursing medical staff enters the patient's room. This reduces the radiation exposure to nurses and doctors (safety method).

Three methods are in vogue (Table 41.1). In the *Paris method*, the radium (which is removed daily for cleaning) is applied continuously for 5 days. In the *Stockholm method*, the radium is inserted on three occasions, with intervals of 7 days between the first two insertions and 2 weeks after the last insertion, each insertion lasting 48 h (Figure 41.3). In the *Manchester technique*, two insertions 72 h each are applied at a week's interval (Figure 41.4).

In brachytherapy, various radioisotopes are used depending on their half-life (Table 41.2). In general, those with a short half-life may be placed in the patient and left permanently (e.g. radioactive gold-198) whereas those with a longer half-life are left temporarily in the patient, and removed after a prescribed dose of irradiation has been administered (caesium-137).

During brachytherapy, it is important to achieve a uniform distribution of radiation in the adjacent tissues to avoid 'hot spots' which can cause excessive damage to the normal tissues, and 'cold spots' which can lead to under-treatment of the

TABLE 41.1 Brachytherapy

Technique	Amount and Type of Radium	Number of Applications	Duration
Paris technique	Intrauterine tube 33.3 mg—two vaginal ovoids 13.3 mg	One	Five days, each day, radium is removed, cleaned and replaced.
Stockholm technique	Intrauterine tube 50 mg—two vaginal ovoid 50–60 mg	Three	48 h each with a gap of 1 week between the 1st and 2nd, and 2 weeks between 2nd and 3rd.
Manchester technique	Intrauterine tube 50 mg and vaginal colpostat 30–50 mg	Two	72 h each at intervals of 1 week.

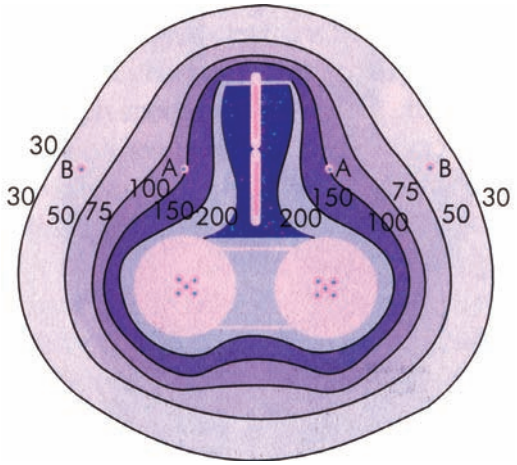

Figure 41.3 Isodose curves of a standard radium insertion using the Manchester technique for carcinoma of the cervix uteri. The dose at point A is taken as 100%. (From: Paterson R. *The Treatment of Malignant Disease by Radium and X-Rays*. Edward Arnold.)

tumour. In brachytherapy for cancer of the cervix, the limiting factor to be kept in mind is point A, a point 2 cm above the lateral fornix and 2 cm lateral to the cervical canal. It is the anatomical location of the ureter; hence, a dose exceeding 8000 rads should not reach this point. The second objective should be to irradiate maximally point B, located 5.0 cm from the uterine axis, laterally and at the same level as point A and dose is 5000 rads. This point represents the lateral pelvic wall. However, the radiation dose achieved at the lateral pelvic wall would be low due to the inverse square law (1000 rads).

The bladder and rectal mucosa cannot withstand over-irradiation (rectum: 5000 rads, bladder: 6000 rads); hence, adequate packing of the vagina and keeping the bladder and rectum empty are mandatory. Optimal safe dose depends upon the 'radiation tolerance' of the normal surrounding structures: bladder, rectum, intestines, liver and kidneys.

Teletherapy

It is a form of radiation therapy where the radioactive source is placed at a distance from the patient (external therapy). The source of radiation is placed at a distance 5 to 10 times greater than the depth of the tumour to be irradiated, in order to achieve uniform distribution of radiation to the tumour, and thereby avoid the large dose variations attributable to the inverse square law. This distance is also called source-to-skin distance (SSD). External radiotherapy irradiates mainly the parametrium and the pelvic lymph nodes. Brachytherapy is followed by teletherapy over a period of 4–6 weeks. In a few cases, where the primary tumour is large or the tumour has distorted the cervical canal and prevents the insertion of an uterine device, it is prudent to apply teletherapy first (3000 rads). This shrinks the primary tumour and enables the application of brachytherapy. Cobalt-60 and caesium-137 are the common sources of teletherapy (external radiotherapy).

Selectron reduces the period of application and shrinks the tumour quickly. Megavoltage therapy has the following advantages:

- Greater penetration allows deeper tissues to be effectively radiated
- Spares the skin effect
- Shorter treatment time
- No bone necrosis
- Can cover a larger field in the abdomen

Supplementary teletherapy through four or more portals is necessary to achieve uniform and adequate cancericidal dose or irradiation to the entire pelvis.

TABLE 41.2 Half-lives of commonly used isotopes

Radionuclide	Half-Life (Days)
Gold-198	2.7
Phosphorus-32	14.3
Iodine-125	60
Iridium-192	74.4
Cobalt-60	5.3
Caesium-137	30
Radium-226	1620

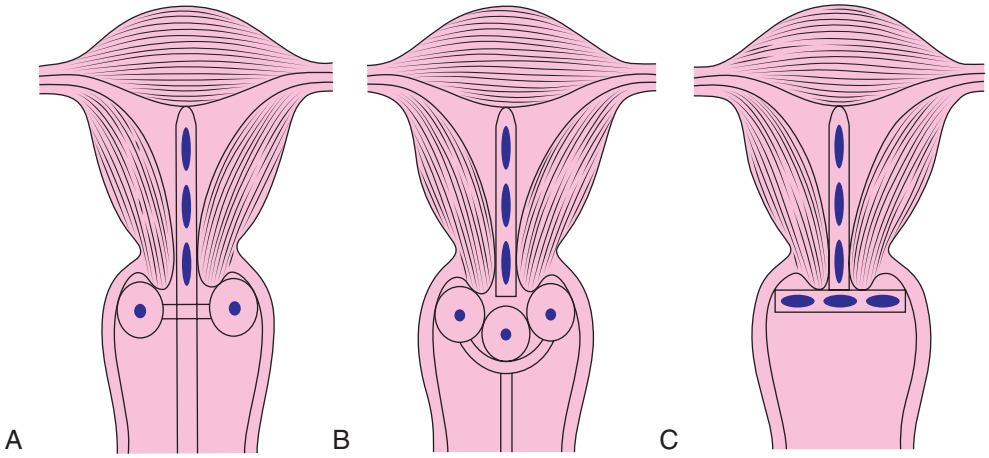

Figure 41.4 Different methods of brachytherapy. **(A)** Manchester technique. **(B)** Paris technique. **(C)** Stockholm technique.

The tumour tissue recovers more slowly or not at all as compared to the normal tissue. Therefore, fractionated course of radiotherapy (four to five times a week) allows normal tissues to recover before the next dose and reduces the toxicity.

In pelvic radiation, each fraction is 180–200 cGy. In abdominal radiation, it is reduced to 100–120 cGy to avoid damage to the liver, kidneys and intestines. A total of 25–30 fractions over 5–6 weeks is administered. This fractionation minimizes the side effects of radiation.

Interstitial Radiotherapy

In this, the radioactive source is placed directly into the tissue tumour. It may be removable implants or permanent implants which are placed in inaccessible tumours, such as radioactive iodine at the time of surgery. Removable implants can be used in the vagina and cervix. Iridium-192 is the radioactive isotope of choice in these cases. As with intracavity, afterloading devices are now available as safety methods. Other sources are caesium-137 and cobalt-60.

Complications of Radiotherapy

Complications of radiotherapy are divided into early and late complications.

1. *Early complications*. These include:
   - Transient nausea and vomiting. Antiemetic drugs help.
   - Bladder irritation causing frequency; dysuria or haematuria is treated with anticholinergic drugs or chlorpromazine.
   - Rectal irritation causing tenesmus and diarrhoea (1%). Anticholinergic drugs help.
   - Irritation of small intestine causing anorexia, nausea, vomiting, diarrhoea and weight loss (5%). Octreotide is used to relieve these symptoms.
   - Malaise and irritability, nervous depression, headache.
   - Flare-up of sepsis, tubo-ovarian mass, pyometra, peritonitis and septicaemia.
   - Pyelitis, pyelonephritis and cystitis.
   - Pyrexia.
   - Pulmonary embolism.
   - Skin reaction.

   Megavoltage therapy reduces these complications.
2. *Late complications.* These include:
   - Persistent anaemia.
   - Chronic pelvic pain due to fibrosis involving nerve trunks.
   - Pyometra due to cervical stenosis.
   - Proctitis, followed later by radiation ulcers, rectal bleeding, rectal strictures, occasionally rectovaginal fistula.
   - Post-irradiation ulcers in the bladder, causing dysuria, haematuria, vesicovaginal fistula.
   - Small bowel strictures, obstruction, ulceration and gut perforation.
   - Colonic ulcer, telangiectasia, perforation, stricture or obstruction.
   - Atropic vaginitis, fibrosis and vaginal stenosis causing marital discord.
   - Ureteric stricture and obstructive uropathy.
   - Osteoporosis, fracture neck of the femur.
   - Disturbed psyche.
   - Ovarian destruction causing severe menopausal symptoms and osteoporosis. This can be avoided by translocation of ovaries above the pelvic brim during primary surgery, or prescribing HRT.
   - Sarcoma is reported in 8% cases some years after radiotherapy, as some are suspected to be carcinogenic.

Contraindications to Radiotherapy

- Severe anaemia
- Poor general health
- Sepsis
- Pregnancy
- Presence of fibroids in the uterus
- Tubo-ovarian mass
- Uterovaginal prolapse
- Presence of genital fistulae
- Radioresistant tumour

Certain chemotherapeutic agents, such as cisplatin, carboplastin, 5-FU, taxol and interferon, are radiosensitizers and potentiate the radiation effect on hypoxic cells. They have been used concomitantly to improve the results of radiotherapy. *This is known as chemoradiation*.

Newer Techniques Sparing Adjacent Tissues

Normal tissue sparing with optimal target tissue radiation is known as 3D conformal radiotherapy. RapidArc is better than 3D.

Intensity modulated radiation therapy is being attempted.

3D conformal radiotherapy uses CT, MRI, PET to place the beam of radiation to conform only to the target area, to maximize dose to the tumour and minimize dose to the normal tissues.

Tomotherapy and cone-beam CT also allows precise localization of beam to the target tissue.

Role of Preoperative and Postoperative Radiation

Role of pre- and postoperative radiation is summarized in Table 41.3.

Clinical Applications of Radiotherapy

Cancer of the Cervix

Primary radiation therapy for cancer of the cervix combines teletherapy with brachytherapy. Radiation, like surgery, is a local therapy. It therefore influences only the tumour cells falling within the radiation volume. Intracavitary radiation by itself may therefore not be curative for patients in whom

TABLE 41.3 Preoperative and postoperative radiation: advantages and disadvantages

Advantages	Disadvantages
Preoperative radiation	
1. Surgically undisturbed tumour bed. Intact vascularity (good oxygenation)	1. Precludes accurate pretreatment staging of the disease
2. May facilitate surgical dissection, allowing a lesser procedure by shrinking the tumour	2. May be considered unnecessary on hindsight, in cases with high chances of cure with surgery alone
3. May decrease the likelihood of risk of implantation or dissemination of viable tumour cells during surgical handling of tissues	3. Interferes with tissue healing 4. Combined therapy increases the morbidity
Postoperative radiation	
1. Accurate surgical staging	1. Surgery may alter the kinetics of tumour proliferation
2. Extent of loco-regional disease accurately defined	2. Surgery often disturbs tumour vascularity causing hypoxia
3. Choice of omitting or selective use of radiation in some patients	

the tumour spread involves tissues beyond the effective radiation range and those with distant metastases. Additional external supplementary radiation to the pelvis is required to treat the pelvic lymph nodes. The tolerance of the normal tissues within the pelvis acts as the limiting factor in planning radiation therapy. Cervical cancer requires a radiation dose of 6000 cGy. The tolerance dose of irradiation for the urinary bladder is about 6000 cGy and for the rectum, it is about 5000 cGy. Doses in excess can damage these hollow viscera and cause radiation fistulae. The intracavitary radiation source is so calculated that it does not deliver a dose in excess of 8000 cGy to the point A located 2.0 cm above and lateral to the external cervical os. This point denotes the point of crossing of the ureter in the pelvis. The second point of consideration is point B located 5.0 cm laterally on the pelvic sidewalls where the obturator gland is located. The radiation dose at point B should not exceed 4500 cGy. This is to safeguard the bladder and rectum from over-irradiation. *Preoperative brachytherapy* is used in barrel-shaped endocervical growth of more than 2 cm. This is followed within a week or 4 weeks later by Wertheim's hysterectomy. Cisplatin prior to or during brachytherapy improves the response rate (Figure 41.4).

Cisplatin acts as a radiosensitizer and is employed as a neoadjuvant or concomitant chemoradiation (see also section on chemotherapy). The renal functions have to be checked.

Cisplatin 40 mg/m^2 IV given within 1 h prior to radiotherapy weekly improves the response rate of the latter. Other radiosensitizers are 5-FU, gemcitabine and taxol, carboplastin.

Postoperative external radiotherapy is required when the surgery has been incomplete or lymph nodes prove positive for malignancy.

Primary radiotherapy is mainly applied in advanced cancer of the cervix, but also preferred in Stages I and IIA by some gynaecologists, alternative to Wertheim's hysterectomy. The cure rates achieved in early stages are comparable by either method. However, realizing that radiotherapy causes vaginal stenosis leading to dyspareunia, ovarian destruction with menopausal symptoms, and osteoporosis and cervical stenosis causing pyometra, the choice of treatment in young women is Wertheim's hysterectomy. In a few cases, radiotherapy fails to irradiate the pelvic nodes completely, and recurrence occurs. In such cases, surgery is preferable to repeat radiotherapy, provided the woman is surgically fit. In primary radiotherapy normally, brachytherapy is applied first followed by external teletherapy. If the growth is large, first teletherapy is applied to shrink the tumour followed by brachytherapy.

Endocervical Cancer

In endocervical cancer, the best survival is seen when the concomitant cisplatin weekly and weekly pelvic radiotherapy for 6 weeks is followed by surgery. Postoperative radiotherapy is required if pelvic lymph nodes prove positive for cancer.

Endometrial Cancer

The importance of radiation therapy in the management of endometrial cancer is listed below:

- As an adjunct to surgery comprising TAH-1-BSO.
- By administering vaginal radiation via colpostat, vaginal vault recurrence drops to 2% from the previous 13%.
- The survival improves in Stages IC and II when postoperative radiotherapy is administered to sterilize the pelvic lymph nodes. Radiation is indicated in uterine sarcoma, though outcome is poor.
- To treat patients who are unfit for surgery.
- To treat patients with vaginal/pelvic recurrences.
- For palliation in cases of non-resectable intrapelvic or metastatic disease.

Ovarian Cancer

The primary treatment for ovarian cancer is total abdominal hysterectomy, removal of both ovaries and omentectomy. In inoperable cases, maximal debulking surgery is followed by chemotherapy in epithelial tumours, and most of the other malignant ovarian tumours. 'Moving-strip' technique of external radiotherapy is applied to para-aortic lymph nodes and abdominal metastasis. Dysgerminoma and granulosa cell tumours are highly radiosensitive.

In the 'moving-strip' technique, a strip of 2.5 cm area is irradiated front and back over 2 days, and the strip moved upwards, until the entire abdomen receives radiation. With the liver and kidneys shielded, the total tumour dose of 2600–2800 cGy is administered. CT and MRI are useful in detecting para-aortic lymph node involvement prior to radiotherapy.

The earlier instillation of radioactive gold, thiotepa and other chemotherapy drugs at the end of surgery is not widely used, because the drug needs to be evenly distributed to avoid intestinal adhesions. Besides, cyclophosphamide needs to be activated in the liver before its effect is felt. Therefore, systemic chemotherapy is more effective.

Approximately 40–50% 5-year survival rates can be achieved in Stage II disease having minimal pelvic residual disease. The 5-year survival rates drop to 5–15% in patients with larger residual lesions.

Vulvar Cancer

The aim of integrated multimodality therapy including surgery, radiation and possibly chemoradiation therapy is to reduce the risks of locoregional failure in patients with advanced primary or nodal disease, and to obviate the need for exenteration operations in women in whom the anus or lower urethra will be involved. The dose of radiation given is 4500–5000 cGy in women with microscopic disease and 6000–6400 cGy to women with macroscopic disease.

Preoperative radium needles (60 Gy in 6 days) shrink the tumour and facilitate extirpation of the tumour at a later date.

Postoperative pelvic radiotherapy is preferred to pelvic lymphadenectomy as it reduces the surgical morbidity. Pelvic radiotherapy is administered only if the inguinal lymph nodes prove histologically positive.

Vagina

Radiotherapy is often chosen in place of radical surgery, especially in children. If the tumour is located in the upper one-third of vagina, radiotherapy is similar to that of the cervix. If located in the lower one-third, interstitial needles (iridium-192) are placed in the vaginal tissue.

Choriocarcinoma

Choriocarcinoma responds extremely well to chemotherapy which has replaced surgery and radiotherapy in young women. Radiotherapy is applicable in the distal metastasis in a few cases.

Cancer Chemotherapy for Gynaecologic Cancers

The use of drugs to treat disseminated cancer has developed into a specialized discipline. The first successful effort to control cancer with the help of drugs is attributed to Li et al. (1956), who demonstrated permanent remission in trophoblastic disease. The understanding of the mode of action of the drugs at DNA level has brought out newer effective drugs with less toxicity and improved and prolonged the survival of women with genital cancers.

Tumour Cell Kinetics

A fundamental characteristic of malignant tumours is the rapid proliferation of malignant cells. These rapidly proliferating cells keep repeating a cycle of biochemical events continuously which culminate in cell division (Figure 41.5).

Since each proliferative cell gives rise to two daughter cells that continue the proliferative process, the cell population increases geometrically.

A tumour is described as consisting of four types of cells (Figures 41.5 and 41.6).

Dividing tumour cells. This is the only compartment that adds to the cell population. Cells in this compartment are most sensitive to cytotoxic agents.

Resting cells. These are non-dividing cells resting temporarily (cells in G_0 phase). They are refractory to chemotherapeutic agents.

Differentiated cells. These cells have lost their dividing potential and are awaiting natural death. Since they do not have malignant potential, they are of little concern to the chemotherapist.

Dying cells. These are terminal cells.

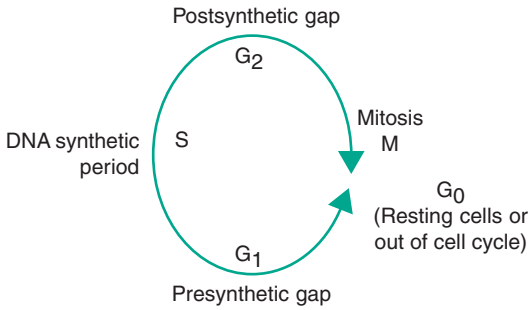

Figure 41.5 Scheme representing cell cycle: Prophase—Metaphase—Anaphase—Telophase (resting cells or out of cell cycle).

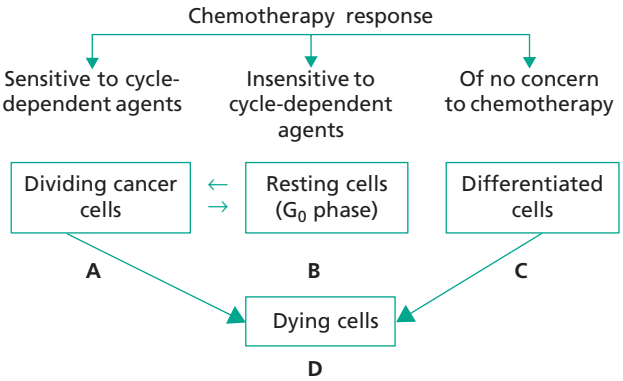

Figure 41.6 Cell types constituting tumour mass.

Small rapidly growing tumours have many more rapidly dividing and growing cells; hence, the doubling time is short. However, these are the same tumours which have a high number of cells sensitive to cell cycle-specific cytotoxic drugs. As the tumour mass enlarges, the growth rate progressively slows down, doubling time becomes longer, the cell input may equal loss, hence a stationary size may be reached, and the sensitivity to cell-specific drugs diminishes.

Another factor to be considered during cancer chemotherapy is the tumour load present at the commencement of therapy. Reduction in the burden of tumour cell load will bring an apparent remission, but during the interval between successive courses of cancer chemotherapy, the tumour growth recurs. This results in stepwise decrease in tumour cell mass.

In order to attain maximum tumour cell kill, the following principles must be considered:

- The chemotherapist must be well aware of the 'total tumour cell kill concept'.
- Tumour cell kill by cytotoxic drugs follows the pattern demonstrated by Skipper and Perry (1970) that the killing of tumour cells by cytotoxic agents occurs in an exponential fashion, so that a given dose kills a constant fraction of the population, irrespective of its initial size.
- There is a clear dose–response relationship.
- Prolonged treatment may be necessary to reduce the malignant cell population to a low number which will then be dealt with by the host immune mechanism.
- Chemotherapy is most effective when it is started early because the number of tumour cell population is low and the rapidly growing and dividing cells are sensitive to cancer chemotherapy.
- Chemotherapy must aim at different cell kill. The dose must be so adjusted that maximum destruction of tumour cell is achieved with minimal damage to normal cells.
- Many cytotoxic drugs in present use show some degree of tissue selectivity.
- Combination drug regimes and/or sequential drug regimes achieve superior tumour cell control with lowered side effects. Drugs with different actions yield better response and reduce drug resistance.
- The problem of drug resistance must be constantly borne in mind. This often happens with a single-drug therapy. Drug resistance may be temporary due to poor vascularity not allowing drugs to reach the tumour cells caused by fibrosis or bulky tumour, or permanent when it is either spontaneous or drug-induced mutation.

Chemotherapy has advanced tremendously in recent years, and is being increasingly used in the management of gynaecological malignancies. The drugs by virtue of prolongation of life and prolonged remission period allow a woman to live a 'tolerable' life.

Chemoradiation

It is now recognized that some chemotherapy drugs act also as radiosensitizers and lead to superadded cell kill prior to or preferably along with radiotherapy and prior to surgery. They are thus used as 'neoadjuvants' in a bulky tumour and locally advanced cancer in the pelvis. The most common drug used for this purpose is cisplatin either singly or as combined drugs. Cisplatin 40 mg^2 weekly is given 1 h before radiotherapy. The renal functions should be normal before instituting this regime. Other chemoradiation drugs in use are 5-FU, gemcitabine, cisplatin combined with gemcitabine 40 mg^2 in 200 mL saline 2 h before radiation—it takes 1 h to administer. *Post-radiation chemotherapy is not effective and poor response occurs on account of poor tissue oxygenation and poor vascularity not allowing the drugs to reach and penetrate the tumour*. In addition, myelosuppression of radiotherapy and high drug toxicity due to decreased renal function and ureteric obstruction (radiation fibrosis) caused by radiotherapy limit the use of chemotherapy drugs as post-radiation drugs.

Chemotherapy is also used for recurrent and advanced diseases that are not amenable to surgery or radiotherapy, to reduce the tumour volume and provide short-term palliation.

Combined agents are superior to a single-agent therapy; they enhance tumour cell kill, reduce dose toxicity and resistance, and yields a better therapeutic response with longer remission. They also yield better response than drugs acting similarly. Chemotherapy, however, does not prevent occurrence of distal metastasis. It must also be remembered that chemotherapy yields better response in distal metastasis as compared to post-radiated recurrence, as its vascularity is not compromised.

Role of chemotherapy is:

- Total response and cure is seen in 10–20%.
- Remission with partial response is seen in 40–50%.

Some drugs are nonspecific agents, i.e. alkylating agents, cisplatin, carboplatin and paclitaxel. These drugs damage the cells at any phase of cycle, though dividing cells are most vulnerable. The specific agents are methotrexate and adriamycin in gestational trophoblastic disease, 5-FU in vulval cancer, hydroxyurea, bleomycin and etoposide in cancer cervix.

Route. Drugs can be given orally (alkylating agents), intravenously or intraperitoneally at the end of surgery (but are not very effective).

Investigations required prior to chemotherapy are:

- Hb%, WCC and platelet count
- Serum electrolytes
- Kidney function tests
- Cardiac function with doxorubicin
- Pulmonary function with bleomycin
- Liver with methotrexate

Contraindications

- Hb% less than 10 g%, WCC less than 3000/mm^3 and platelet count less than 100,000/mm^3.
- Liver and renal dysfunction.

Complications of Chemotherapy

- Anaemia, thrombocytopenia, leucopenia
- Alopecia (reversible)
- Renal damage
- Liver damage
- Cardiac (doxorubicin)
- Pulmonary (bleomycin)

Classification of Drugs

- Alkylating drugs—Cyclophosphamide, ifosfamide, chlorambucil, melphalan, thiotepa (nonspecific drugs prevent DNA synthesis or its division), 6-mercatopurine.
- Antimetabolites—Methotrexate and 5-fluorouracil interfere with enzymes required for DNA synthesis.
- Antibiotics—Actinomycin-D, bleomycin, adriamycin, mitomycin (nonspecific), Doxorubicin. These inhibit RNA and DNA synthesis. They arrest mitosis.
- Plant alkaloids—Vincristine, vinblastine, taxol, docetaxel, etoposide (cell specific)—antimitotic.
- Hormones—Progesterone preparations, tamoxifen (anti-oestrogen). HRT if both ovaries are removed.
- Miscellaneous—Cisplatin, carboplatin, hydroxyurea, topotecan.
- Biological—Interferon. Improves host immune defence and maintains remission.

Newer Anticancer Drugs

The development of new chemotherapy improves the disease free interval and prolongs survival.

They are:

1. Vascular targeting agents (VTA)
   a. Angiogenesis inhibitors
      VEGF ligand bevacizumab (avastin, genetech)
   b. Receptor targeting VEGF
      Receptor tyrosine kinase inhibitor, cediranib, intedanib, anti-VEGF antibody inclone.
      The former primarily prevent development of new vessels in the tumour. The latter damage the established vessels in the tumour with cediranib 30 mg daily orally, 30% benefit is reported in recurrent epithelial ovarian tumours and fallopian tube cancer.
      Complication – Hypertension.
      Bowel perforation in intra-peritoneal tumours involving the bowel.
      Vascular disrupting agents (VDA) fosbretabulin, olaparib (oral 100–600 mg daily).
2. Alpha folate receptor targeting – farletuzumab EC145
3. Novel cytotoxic agents
   (a) Trabectedin
   (b) Epothilone analogues
   (c) Topoisomerase 1 inhibitors
   (d) Pemetrexed
   (e) Aurora kinase inhibitors

Vulva

5-FU is effective in cancer involving the anus. It shrinks the tumour which may even disappear.

Local excision of the residual tumour is then successful.

Vagina

The metastasis of choriocarcinoma responds to methotrexate and actinomycin-D.

Cervix

The use of cisplatin concomitant with radiotherapy and prior to surgery in endocervical growth is mentioned in Chapter 38. It also reduces the incidence of lymph node metastasis in bulky cervical tumour in Stages IB and IIB and improves the surgical outcome, though the survival rate has not shown improvement.

The drugs most sensitive are:

- Doxorubicin 120 mg/m^2 + cisplatin 50 mg/m^2 IV over 24 h weekly for 6 cycles (3 cycles as radiosensitizers).
- PVB:
  - Cisplatin 100 mg/m^2 IV day 1.
  - Vinblastine 6–12 mg/m^2 bolus in day 1.
  - Bleomycin 15–30 mg IM day 1, 8, 15 given 3-weekly for not more than 8 cycles.

Cisplatin requires adequate hydration.

Response rate of 50–70% is seen.

Chemoradiation also improves survival in distal metastasis.

Endometrial Cancer

Chemotherapy drugs are less used because of poor response in endometrial cancer; surgery and radiotherapy being the cornerstone in its management. Metastatic tumours respond better to progestogens.

Medroxyprogesterone acetate (MDPA) 1 g IM weekly or 400 mg orally daily, 1 g norethisterone IM weekly and 17-alpha-hydroxyprogesterone IM are effective in well-differentiated tumours containing oestrogen and progesterone receptors. Anaplastic tumour does not contain these receptors and fails to respond. Tamoxifen 10 mg bd by its anti-oestrogen action is also effective in advanced stage. Thirty per cent response is seen in lung metastasis with progestogens.

Sarcoma of the uterus is treated with cisplatin and ifosfamide. Doxorubicin is used as single-agent therapy following surgery. Recently, drugs like doxorubicin, platinum, taxane, carboplastin and paclitaxel have been tried.

Ovarian Cancer

Chemotherapy plays a major role after surgery in the management of ovarian cancer. Today, new drugs with less toxicity improve the survival as well as remission period. Multiple-drug therapy yields better survival.

Indications are:

- Prophylactic post-operative chemotherapy in Stage IC to prevent recurrence. Carboplatin alone is adequate prophylactically.
- In advanced stage as palliative therapy to keep the woman comfortable.

- In unresectable tumour, chemotherapy for 3–6 months followed by debulking surgery is recommended.

Chemotherapy for 3–6 months followed by debulking surgery and monitoring with tissue markers for regression and deciding on duration of therapy is the routine practice in residual tumour, recurrent and advanced cancer.

Cisplatin and taxol are the main drugs useful in ovarian cancer. Carboplatin is superior to cisplatin with less nephrotoxicity and less emetic and myelosuppression is reduced if used with granulocyte colony stimulating factor (G-CSF), G-CSF (175–200 mg/m^2). Corticosteroid and anti-histamine prevent hypersensitive reaction to paclitaxel, thromboplastin and stem cell harvesting. Carboplatin requires less hydration than cisplatin. Six cycles are usually given.

Second-line drugs when woman fails to respond to cisplatin are cyclophosphamide, topotecan, ifosfamide and doxycycline.

The woman should be monitored not only for the regression of the disease, but also for myelosuppression, vomiting, diarrhoea, nephrotoxicity, neurotoxicity renal toxicity and fungal infection.

The drugs used are as follows:

- Doxorubicin (adriamycin 120 mg/m^2 weekly for 6 cycles is cardiotoxic).
- Cisplatin 50 mg/m^2 IV over 24 h with good hydration 3-weekly for 6 cycles (30% response).
- Ifosfamide 1.2 g IV in 30 min.
- Methotrexate 50 mg/m^2 bolus weekly for 6 weeks.
- Topotecan 1–2 mg/m^2 day 1–5, 3-weekly. Response rate 20%.
- Paclitaxel 135–200 mg/m^2 over 24 h infusion, followed by cisplatin 75 mg^2 over 1 h 3-weekly. Cisplatin causes nausea, renal failure, peripheral neuropathy, myelosuppression, but no alopecia.
- BEP.
  - Bleomycin 15 mg IV weekly for 12 cycles.
  - Etoposide 100 mg/m^2 day 1–5, 3-weekly.
  - Cisplatin 20 mg/m^2 3-weekly.
- Carboplatin 300–400 mg/m^2 4-weekly. Response rate 30%.
- VAC
  - Vincristine 1.5 mg/m^2 IV day 1.
  - Actinomycin-D 0.5 mg IV 1–5 days.
  - Cyclophosphamide 150 mg/m^2 IV 5 days 4-weekly—germ cell tumours respond well.
- PVB
  - Cisplatin 100 mg/m^2 IV day 1.
  - Vinblastine 6–12 mg/m^2 bolus IV day 1.
  - Bleomycin 15–30 mg IV day 1, 8, 15, maximum of 8 doses 3-weekly.
- Cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2 bolus IV and cisplatin 50 mg/m^2 infused over 30 min 3-weekly for 6 cycles.
- Taxol derived from the bark of Pacific yew tree is in short supply, so it is expensive and available in semi-synthetic form. It promotes assembly and stability of microtubules and inhibits mitosis. A quantity of 175–250 mg/m^2 IV infusion over 3 h is useful in cisplatin-resistant cases. Side effects are neutropenia, paraesthesia, scotoma, myalgia, bradycardia, alopecia, vomiting and diarrhoea.
- Alpha interferon three times a week subcutaneously maintains emission period and improves survival.
- Gemcitabine 100 mg/m^2 + carboplatin first and eighth day 3-weekly for 6 cycles.

Extravasation should be avoided by using angiocatheter when giving doxorubicin, actinomycin-D and vincristine.

Topotecan is another new drug which inhibits nuclear enzyme DNA topoisomerase and is well-tolerated.

Germ cell tumour responds to bleomycin, etoposide (85%).

Choriocarcinoma

See Chapter 40.

Sarcoma

Cisplatin, ifosfamide, doxorubicin 60 mg/m^2 as single-agent therapy.

Breast Cancer

Although tamoxifen improves the survival period, it causes endometrial hyperplasia and cancer, and requires regular monitoring with ultrasound study of endometrium and endometrial biopsy.

The gynaecologist should be aware of the limitations of chemotherapy as well as its effectiveness. Tumour markers should be employed during chemotherapy to watch the effectiveness and decide the duration of chemotherapy in an individual case.

Immunotherapy

Realizing that immunosuppressed women are more likely to develop cancer, this therapy is receiving consideration. HPV vaccine is now available for cancer cervix prevention.

The best results are obtained if the tumour size is initially reduced by surgery, chemotherapy or radiation.

Immunotherapy includes:

- Vaccine against human papilloma virus for cancer cervix (prophylactic).
- Chemical immunostimulants—Levamisole, cimetidine.
- Cytokines, interferon (IFN), interleukins (IL-2), tumour necrosis factor (TNF).
- Chemotherapeutic drugs—cisplatin, doxorubicin.
- Passive immunization—Immunological active substances directly transferred to the host:
  - Cytoner, interferon, TNF.
  - Monoclonal antibodies.
  - Activated macrophages.
- Drug immune modifiers:
  - Anti-CA-125 antibody (oregovomab)
  - Bevacizumab-24 MAB antibody is not toxic, but bowel perforation and proteinuria are reported and the drug is very expensive. Bevacizumab-15 recombinant humanized monoclonal antibody directed towards VEGF-A, antiangiogenesis 15 mg/kg body weight every 3 weeks for 6 cycles with chemotherapy.

Gene Therapy

Familial cancer of ovary and endometrium has been observed in 5–10% cases. The genes BRCA-1 and BRCA-2 are responsible for ovarian malignancy. Gene study and gene therapy are under research. Stem cell therapy may play a major role in the future.

Taxane. Apart from being antimitotic it is also a radiosensitizer. It causes neutropenia, paraesthesia, myalgia, cardiac arrhythmia and alopecia.

The dosage is 135 mg/m^2 on 24-h infusion followed by 75 mg cisplatin.

Cisplatin sensitivity is the key predictor of response and survival. It is now replaced by carboplatin, because of its lesser toxicity. Cisplatin/carboplatin with paclitaxel is the first line of chemotherapy treatment in advanced cancer.

In ovarian cancer, chemotherapy is used as

- Neoadjuvant therapy
- Concomitant therapy
- Adjuvant therapy

Neoadjuvant (before surgery or radiotherapy)

The drug shrinks the tumour, reduces micrometastasis.

Disadvantage of neoadjuvant therapy is it delays specific therapy.

Drugs used are cisplatin, carboplatin, bleomycin, ifosfamide—with 50–70% response.

100 mg cisplatin + 1.2 g/m^2 ifosfamide.

Concomitant therapy (during treatment) acts as radiosensitizer, and enhances radiotherapy effect, but increases toxicity (Table 41.4).

Adjuvant therapy (drugs mentioned above) is employed following surgery or radiotherapy but response to local residual/recurrence is low, because of poor vascularity of the tumour. The distal metastasis however responds better to adjuvant chemotherapy, because of its intact vascularity.

With so many new drugs becoming available, tissue sensitivity test to various drugs may improve our decision regarding the best line of chemotherapy in the future.

TABLE 41.4 Toxicity of drugs

Drugs	Toxicity
Cisplatin	Vomiting, myelosuppression, renal toxicity, peripheral neuropathy, ototoxicity. No alopecia, hydration required
Carboplatin	Myelosuppression
Taxane	Hypersensitivity, myelosuppression, cardiac arrhythmia, alopecia

Key Points

- Radiotherapy and chemotherapy play an important role in the management of genital tract malignancies.
- Primary radiotherapy can be applied in cancer of the cervix as an alternative to Wertheim's hysterectomy in early stages, with equally good results and is the treatment in advanced inoperable cases. Surgery is however preferred in young women, because radiotherapy causes vaginal stenosis, pyometra, destruction of ovaries and menopause.
- Preoperative radiotherapy with cisplatin is recommended in endocervical cancer of more than 2 cm, and this shrinks the tumour.
- Postoperative radiotherapy is useful if surgery has been incomplete or lymph nodes are involved in cancer of the cervix and uterine cancer.
- Ovarian cancer is dealt with by primary surgery. Chemotherapy is the choice in the postoperative treatment. Granulosa cell tumour and dysgerminoma are highly radiosensitive and chemosensitive, suited in young women.
- 'Moving-strip' technique of radiotherapy is safe in dealing with abdominal and para-aortic lymph node metastasis.
- Choriocarcinoma responds well to chemotherapy which is considered the primary treatment. 90–100% success is reported with chemotherapy.
- Chemotherapy is now employed as neoadjuvant, concomitant and adjuvant therapy.
- The limitations and harmful effects of radiotherapy and chemotherapy should be understood.
- Chemoradiation is also used in residual and recurrent tumours as palliative measures.

Self-Assessment

1. Discuss the role of radiotherapy in cancer of the cervix.
2. Discuss the side effects of radiotherapy.
3. Discuss the role of chemotherapy in ovarian cancer.

Suggested Reading

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Chapter 42 Obesity

CHAPTER OUTLINE

Obesity until recently was considered a cosmetic nuisance, personal issue and social problem, but now it is realized that it also poses a major health hazard in later years, causing morbid conditions and at times, early death. Now considered a metabolic disorder, its prevalence has increased globally and threatens the health of the individual. Once acquired, it is difficult to get rid of, despite dietary control and exercise. It is therefore important to check the growth and weight of adolescents and adults before it creates health problems.

Prevalence

Increased prevalence over the previous years is due to several factors:

- *Lifestyle change:* Better social and economic environment has changed the lifestyle of people. Overeating and over-indulgence in wrong foods has led to obesity (fatty food).
- Lack of exercise due to heavy and prolonged hours at work, physical disability and sedentary life, causing less utilization of calories and accumulation of body fat.
- Genetic.
- Increased birth weight and maintenance of increasing weight through childhood and adolescence.

Definition

Obesity is defined in terms of body weight over height. Body mass index (BMI) is expressed as

$$\text{BMI} = \frac{\text{Weight in kg}}{\text{Weight in m}^2}$$

Normal BMI is between 18 and 25. Below 18 is considered underweight. Between 25 and 29.9 is overweight. Between 30 and 35 is obese.

BMI over 35 is considered morbidly obese. Waist-to-hip ratio should not exceed 0.8.

Aetiology

Apart from the above factors well known for gain in weight, obesity is considered a metabolic disorder originating in the fetus itself, partly contributed by mother's environment during pregnancy. Maternal conditions during pregnancy are over-nutrition, glucose intolerance and diabetes, leading to macrosomic fetus. The metabolic changes in this fetus persists through childhood, adolescence and adulthood leading to overweight and obesity.

Other factors are as follows:

- *Genetic*. Family history reveals obesity.
- *Pre-pregnancy weight*. Overweight mothers gain more weight than normal women during pregnancy. They also retain increased weight gain postpartum, and put on some extra pounds or so following each delivery; multiparae therefore tend to be overweight compared to primis and those with lesser pregnancies.
- *Menopause*. Low metabolic rate and inactivity add to the woman's weight after the menopause.
- Overeating, eating wrong food.
- Lack of exercise, sedentary lifestyle.
- *Diseases*. Thyroid—hypothyroidism, oedema due to hepatorenal disorders.
- *Drugs*. Corticosteroids over a prolonged period, androgens and oral hormonal contraceptives tend to increase the woman's weight.

Pathophysiology

Bones make up 12% of total body weight, muscles 35% and body fat 27%. The rest comes from other organs and blood and body fluid.

Of the total fat, abdominal and visceral fat (waist circumference) are linked to diseases in the adult life. Since women tend to accumulate more fat over the abdomen than the hips, as compared to men. Women tend to suffer from obesity more than men.

Leptin (167 amino acid protein) is a hormone secreted by adipocytes in the fat that influences hypothalamus regarding appetite. Increased leptin increases fat accumulation. Leptin secretion is also regulated by insulin which stimulates leptin secretion. In pregnancy, some women develop insulin resistance, and hyperinsulinaemia may be responsible for excessive weight gain through fat deposition and retention of weight gain postpartum.

Clinical Features

- *Age.* Pregnancy and menopause are linked to obesity in women.
- *Parity*. Multiparous women tend to be more overweight than less parous women.
- Family history (genetic).
- Many obese women are born overweight.

Complications and Sequelae (Figure 42.1)

- Obese adolescents tend to have precocious puberty which in turn reduces their height over all (see Chapter 4).
- Menstrual dysfunction due to hormonal and metabolic dysfunction.
- Polycystic ovarian syndrome (PCOS) is nowadays seen in young women who are overweight. They also demonstrate insulin resistance.
- Anovulatory infertility due to anovulation and PCOS.
- The success of in vitro fertilization (IVF) in infertile obese women is reported to be low.
- Breast, uterine and colonic cancer are reported to be higher in obese women than in lean women.
- Stress incontinence of urine is more prevalent amongst overweight women.
- Fungal and urinary infection is more common in obese women.
- *Diseases*. Obese women tend to suffer more from the following medical problems than lean women.
  - Gall bladder stones
  - Cardiovascular disease, especially myocardial infarct
  - Stroke, osteoarthritis
  - Thromboembolism, pulmonary embolism
  - Respiratory problem such as asthma
  - Sleeping disorders
  - Diabetes II
  - Hyperlipidaemia
- *Surgery.* It is difficult to procure a vein for intravenous drip during surgery.
  - Intubation during general anaesthesia and getting into an epidural space for spinal anaesthesia could be a problem.
  - Laparoscopic surgery is technically difficult.
  - During laparotomy, inadequate space and exposure of organs may make surgery difficult. Trauma to organs occurs more in obese women, so also bleeding during surgery.

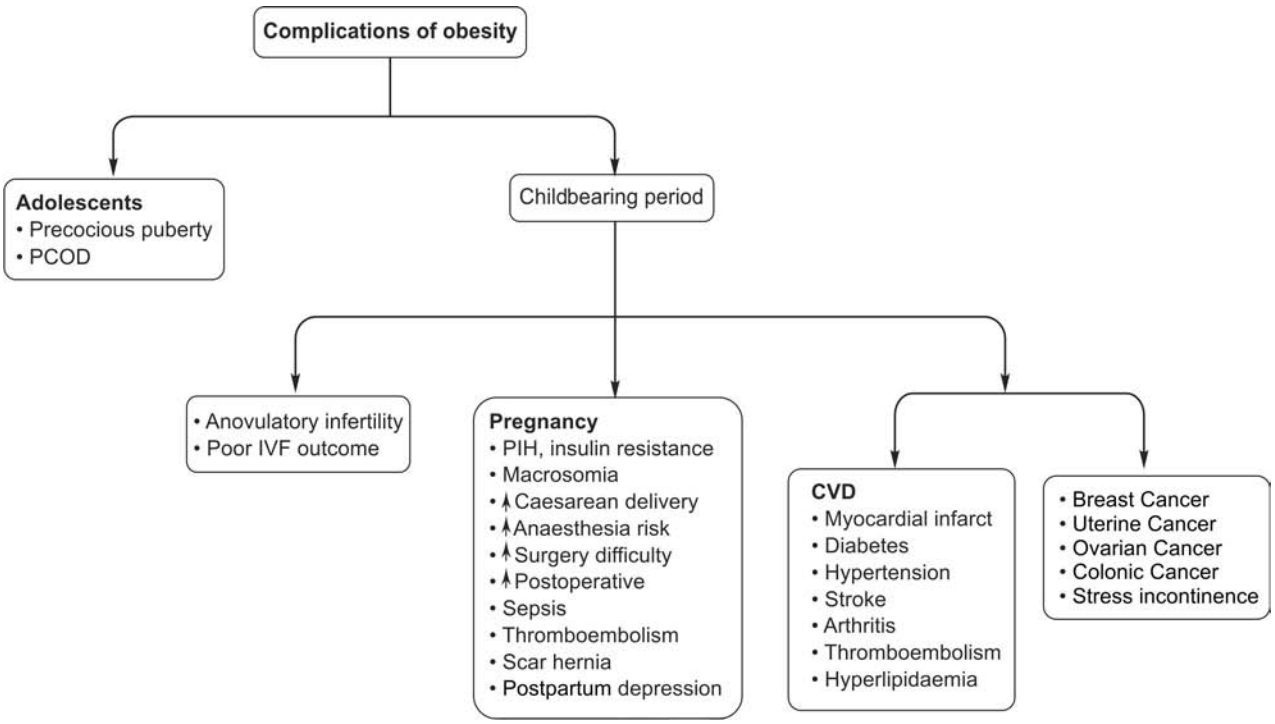

Figure 42.1 Complications of obesity.

  - Postoperative period may be complicated by infection, poor wound healing, thromboembolism and scar hernia.
- *Pregnancy*
  - Pregnancy-induced hypertension.
  - Insulin resistance and gestational diabetes.
  - Macrosomic baby.
  - Increased incidence of caesarean section is likely because of abnormal position caused by macrosomia, cephalopelvic disproportion and fetal distress.
- *Postpartum complications.* Retention of weight gain, postpartum depression, thromboembolism and poor lactation. Poor lactation is seen in obese women. This in turn causes overweight infants through bottle feeding.
- *Contraceptives*. Hormonal contraceptives are contraindicated in obese women.
- Functional limitations due to overweight are well known.

Management

Management comprises

- Prophylaxis (prevention)
- Treatment

Prophylaxis

Diet

Proper balanced diet is the essential step in maintaining normal weight. A balanced diet should contain 60% carbohydrate, 20% protein and 15–20% fat. Calorie intake of 1800–2000 daily is adequate, but also depends upon body weight (body weight in kg × 35).

A diet containing fibres delays absorption and lowers the glucose level.

Carbohydrates should be mainly of low glycaemic index. Animal proteins with amino acids are preferred.

Exercises

Yoga, meditation and regular exercises help in reducing weight. Rapid weight loss is not recommended, but 1 pound a week is safe.

Walking for half an hour daily for 5 days is sufficient to maintain weight.

Pregnancy

- Pre-pregnancy weight should be normal. Overweight women should be asked to reduce weight before conception.
- Weight gain should be monitored regularly.
- Postpartum weight should be carefully monitored. Most women reduce weight and return to pre-pregnancy weight by the end of 3 months postpartum; otherwise, diet control and exercises are recommended.

Breastfeeding prevents obesity in infants. Obese infants tend to remain obese throughout life, exposing themselves to diabetes, hypertension, hyperlipidaemia and certain cancers.

Management of Obesity

- Diet
- Exercises
- Drugs – lipase inhibitors
  - Orlistat
  - Rimonants
  - Sibutramine
- Surgery – Bariatric lipectomy
- Gene therapy

Drugs

Lipase inhibitors are prescribed for obese women. These are as follows:

- Orlistat (Reshape) is an anti-absorbent of fat and 120 mg daily reduces 30% of fat absorption from intestinal tract. It also prevents absorption of fat-soluble vitamins which is a disadvantage. It also causes fatigue and depression.
- Rimonank reduces food intake.
- Sibutramine enhances safety and is thermogenic by inhibiting serotonin and noradrenaline re-uptake. It acts centrally.

Fetal Obesity

Apart from changing lifestyle, diet and exercise, the important cause of adult obesity and its sequelae is fetal obesity or what is also known as macrosomia. It is now realized that fetal macrosomia due to a disorder in the maternal environment causes fat deposition in the newborn and infant. Metabolic disorder thus sets in and continues through adolescence and adulthood. Pregnancy adds to this metabolic disorder and increasing weight gain during pregnancy worsens the situation. Once obesity sets in, it is extremely difficult to shed it off. A sequelae of diseases follow, impairing life and even causing early death.

Prevention therefore lies in managing pregnancy, controlling weight gain and bringing back the original pre-pregnancy weight in the postpartum period. Controlling preconceptional weight and avoiding obesity before pregnancy are also very important for optimal outcome for the individual and long-term health benefit.

Treatment

Surgery

When medicines fail, surgery is resorted to:

- Bypass surgery takes 3 h to perform, but is a one-time procedure
- Lipectomy
- Laparoscopic adjustable gastric band (Lap band) takes half an hour to perform, but the band needs periodic adjustments, so follow-up is necessary.
- Gastrointestinal implantable electrical stimulation of nerves is being tried.
- Gene therapy may prevent obesity.

Key Points

- BMI decides who is overweight and obese.
- Obesity poses many health hazards in adult life and some can be life-threatening.
- Common causes of obesity are well known and can be rectified.
- Gynaecological problems originating from obesity are menstrual dysfunction, anovulatory infertility, PCOS and certain malignancies. IVF also yields poor results.
- Obstetric problems are considerable. Apart from maternal complications, fetal macrosomia is now considered a very important cause of adult obesity.
- Surgery increases morbidities in obese women in the form of infection, respiratory problems and thromboembolism.
- Medical problems in adults impair quality of life and may even cause early death.
- Prevention is better than treatment, which often fails and can be frustrating.

Self-Assessment

1. Discuss the hazards of obesity in reproductive functions.
2. Discuss the sequela of obesity.

Suggested Reading

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Chapter

43

Hormonal Therapy in Gynaecology

CHAPTER OUTLINE

Hormonal therapy is extensively used in gynaecological practice today. A few of these hormones are available in their natural form in adequate quantity, but most of them are now synthesized, and effectively and safely used in infertility, contraception, menopause and menstrual disorders. Lately, hormonal therapy has reduced the number of hysterectomies in abnormal uterine bleeding. The various hormonal assays and availability of a large range of synthetic hormones enable the application of correct dosage, optimal route and the suitable hormone for each individual condition. Different routes have been employed to cater to individual needs, convenience as well their effectiveness. They are used both for diagnostic and therapeutic purposes.

Broad groups of common hormonal preparations are discussed in this chapter.

Oestrogens

Oestrogens are naturally occurring C-18 steroidal sex hormones produced by the ovaries, adrenal glands and the placenta during pregnancy. In the ovaries, the luteinizing hormone (LH) induces theca cells to produce androstenedione which is aromatized to oestrogen by the granulosa cells. Adipose tissue in the peripheral areas and liver also contain aromatase which converts androstenedione to oestrone. The biologically active oestrogen is oestradiol. It is synthesized during pregnancy in the placenta. It is also synthesized from cholesterol and metabolized in the liver to conjugates of oestradiol, oestriol and oestrone which are excreted in the urine. Oestriol and oestrone are biologically weak oestrogens. After menopause, the source of oestrogen is adrenal glands and oestrone synthesized in the body fat mass peripherally by conversion of epi-androstenedione secreted by the ovary to oestrone. Oral oestrogen is extensively metabolized in the wall of the small intestine and liver and only 10% reaches the circulation as oestradiol (Table 43.1). The rest is converted to oestrone and oestradiol glucuronide. *These are weaker oestrogens; therefore, a large dose is required if the oral route is chosen. This effect is known as the 'first pass effect' in the liver*. Oestrogen increases the sensitive proteins in the liver, such as sex hormone binding globulin (SHBG), corticosteroid, thyroxine-binding globulin, renin substrate, and various coagulation and

TABLE 43.1 Advantages and disadvantages of oral oestrogens

Advantages	Disadvantages
1. Easy to take	1. Daily dose
2. Cheaper	2. First pass effect in the liver
3. Can be withdrawn quickly if side effects develop	3. Causes hypertension and thrombosis
4. Cardioprotective	4. Large dose is required because of the first pass effect

fibrolytic factors. *The risk of hypertension and thrombosis therefore increases with oral hormones.* However, HDL also increases and oral route is cardioprotective. While the non-oral route avoids the 'first pass effect' and the above complications, they do not protect the patient from cardiovascular risks. Synthetic oestrogens are derived from extracts of soya and Mexican yam, are inexpensive, effective and have found a wide application in clinical therapeutics.

Physiology

During the reproductive years of life, natural oestrogens are principally produced by the Graafian follicles in response to pituitary gonadotropins. Oestrogen is responsible for the development of secondary sex characters, including the breasts, provides the negative feedback signal to the pituitary gland and hypothalamus and maintains adequate mineralization of the bones.

The liver and adipose tissue also contain aromatase which converts androstenedione to oestrone. Sixty per cent of circulating oestrogen gets bound to sex hormone-binding globulin (SHBG) and 38% to albumin. The rest is left as free hormones circulating in the blood. Sixty per cent is excreted in the urine of which 20% is oestradiol and the rest are its metabolites. Ten per cent is excreted in the faeces, and the fate of the rest is not known. Oestrogen binds to the cytoplasmic receptors and is then translocated to the nucleus and influences the target tissues.

Oestrogenic preparations (Table 43.2) are used singly or in combination with progestogen in various gynaecological disorders (also see Chapter 3).

Commonly Used Oestrogens

1. *Ethinyl oestradiol (EE_2) and mestranol* are given orally, in the form of a skin patch and gel. It has a half-life of 12 to 14 h, reaching the peak level in 4 h. It is a common component in oral combined contraceptive pills (OCP) and is used in abnormal uterine bleeding (AUB) to regulate and control the amount of bleeding. Realizing that the side effects of breast cancer and thromboembolism in contraceptive pills were due to a high dose of oestrogen, the dose of EE_2 in OCP is now reduced to 20–30 μg of oestrogen in each pill. Synthetic oestrogens are most potent.

   Ethinyl oestradiol (EE_2) dose 0.01–0.05 mg. Estradiol valerate and succinate tablet 1–2 mg.

   Mestranol 0.01–0.05 mg.

   Mestranol is no more used in combined pills, because of increased risk of thrombosis.
2. *Conjugated oestrogen* is a natural oestrogen derived from mare's urine. *It is used in menopausal women to promote bone mineralization and cardioprotective effect*. It is also effective in controlling profuse bleeding of puberty menorrhagia, when given 25 mg intravenously or as the oral tablet premarin containing 0.625 and 1.25 mg oestrogen.
3. *Dienoestrol cream* is nonsteroidal oestrogen (oestriol) *for topical use in senile vaginitis (vaginal), kraurosis vulva and urethral syndrome in menopausal women.* Gel is also available.

TABLE 43.2 Oestrogen preparations in therapeutics

Generic Name	Doses in Common Use	Indications
1. Oral		
• Ethinyl oestradiol	0.01, 0.02, 0.03, 0.05, 1.0 mg	Irregular menses, OC pills
• Conjugated equine oestrogen (Premarin)	0.325, 0.625 , 1.25 mg	HRT puberty menorrhagic
• Micronized oestrogen (E_2)	1–2 mg	Menorrhagia, irregular menses
• Combined pills		Contraceptives
2. Injectable		
• Conjugated equine oestrogen	25.0 mg slow IV	Puberty menorrhagia Menorrhagia
3. Topical vaginal		
• Dienoestrol cream, Evalon cream	0.01% in cream base	Senile vaginitis, urethral syndrome
4. Transdermal patches		
• 17 β-oestradiol (3–7 days)	0.03–0.1 mg	HRT
• Combined E + MPA	0.625 mg + 5.0 mg	HRT
• Oestradiol implant	25, 50, 100 mg	Long-acting HRT—6-monthly

The cream is applied once or twice daily for 2 to 10 days each month for 3 to 4 months. It has no protection against bones.

4. *Implants* are used as part of a long-term hormonal replacement therapy (HRT) in spontaneous or surgically induced menopausal women. While providing a good compliance, its surgical insertion and removal, if side effects develop, are the disadvantage.
5. *Oestrogen patch* is a transdermal patch applied over the outer aspects of the buttocks or lower abdomen, but not over the breasts, in HRT. By avoiding the first pass effect in the liver, the side effects are minimized; it lowers triglycerides. The skin patch can cause skin irritation. The gel gets absorbed in 2 min and does not cause skin irritation.
6. *Micronized oestrogens* are used orally.
7. Stilboestrol—synthetic nonsteroid used in prostatic cancer.

Contraindications

Oestrogen is contraindicated in:

- Suspected malignancy of the genital tract
- Breast cancer
- History of thromboembolism
- Liver and gall bladder disease
- Cardiac, hypertensive and diabetic woman
- Lactation—Reduced milk production
- Sickle cell anaemia because of thrombosis
- With rifampicin, barbiturates, phenytoin and anticoagulants, as these drugs interfere with its metabolism and reduce its efficacy.

Indications

- Short-term use for menopausal symptoms. Premarin 0.625 mg or Evalon 1–2 mg orally daily for 3 to 4 months is effective (see Chapter 5). Oestrogen cream is prescribed for local symptoms such as dry vagina and urethral syndrome.
- Long-term HRT prevents or delays osteoporosis and is also cardioprotective (see Chapter 5).
- Oestrogen cream is prescribed in vulvovaginitis in children, senile vaginitis and urethral syndrome in menopausal women.
- Oral contraceptives—see Chapter 20.
- Abnormal uterine bleeding—see Chapter 24.
- *Intersex*. Patients suffering from Turner's syndrome and testicular feminizing tumour should receive oestrogen combined with progestogens cyclically throughout life to develop secondary sex characters, avoid cardiovascular accidents and osteoporosis.
- Oestrogen is used in prostatic cancer.
- Supresses lactation.
- Improves mood in postpartum and menopausal depression.
- Premenstrual tension syndrome.

Side Effects

- Nausea, vomiting when given orally.
- Mastalgia, water retention and increase in weight.
- Thromboembolism, cerebral thrombosis.
- Endometrial and breast cancer if given for a long period without progestogen.
- Hepatic adenoma, gall bladder disease.

Tibolone and selective oestrogen receptor modulators (SERMS) have both oestrogenic and anti-oestrogenic action. They have anti-oestrogenic action on the breast tissue, but agnostic action on the endometrium and bones. They can cause endometrial hyperplasia and cancer.

Progesterone

Progesterone is the natural hormone produced by the theca cells of the corpus luteum and the placenta. It is metabolized in the liver and excreted in the urine as sodium pregnanediol glucuronide. Natural progesterone is not active orally and is given only by intramuscular injection in an oil base. Progesterone acts on target tissues only when the latter are primed with oestrogen, as oestrogen produces progesterone receptors.

A large number of synthetic compounds which can be taken orally have been marketed in recent years.

Preparations

Progestogens are synthetic compounds belonging to two main groups—the oestrone or 19-norprogestins which are structurally similar to testosterone and pregnane or 17-acetoxy compound structurally similar to progesterone. The oestrone compounds are mainly incorporated in oral contraceptive pills, and pregnane compounds used in pregnancy and AUB.

Classification

- Pure progesterone—Oral and vaginal micronized progesterone have no adverse effect on lipid profile.
- Pregnane (derived from progesterone molecule), lynestrenol (allyloestrenol), medroxyprogesterone, megestrol acetate.
- Estrane (derivative of testosterone)—Norethisterone, norethandriol (first generation).
- Gonane—Levonorgestrel, norgestrel (second generation). They reduce the level of SHBG, have androgenic, anti-E effect.
- Third-generation progesterone (desogestrel, gestodene, norgestimate). These are less androgenic and cause less metabolic disorders, but increase the risk of thrombosis.
- Hybrid drospirenone (3 mg equivalent to 25 mg spirinone) now used in oral pills for acne and PCOS. Yasmin contains 30 µg of EE_2 (21 days), Janya contains 20 µg EE_2 for 24 days in a cycle.

- Hybrids (drospirenone) have anti-androgens, anti-mineral corticosteroid effect; are used in premenstrual tension; causes hyperkalaemia by decreasing potassium excretion in the urine, less water retention and weight gain.

These have no influence on lipid profile and have a very good control on menstrual cycles.

Micronized progesterone—Oral tablet (100 mg) causes vomiting, giddiness and liver damage.

Micronized vaginal tablet (100 mg) is without these oral side effects, but causes vaginal irritation.

Progestogens are administered:

- Orally—Singly or with oestrogen.
- Intramuscular injection monthly, three-monthly as contraceptives.
- Implants—Norplant (contraceptives).
- IUCD impregnated with levonorgestrel (Progestasert, Mirena).
- Vaginal tablet and rings.
- Skin patches.

Crinone 8% (90 mg) vaginal gel is a micronized progesterone in dilute emulsion system.

Therapeutic Applications

- Pure progesterone as injection in oil or micronized vaginal or oral capsules are used in threatened and recurrent abortions, and in corpus luteal phase deficiency (CLPD).
- High doses of injections are used in advanced endometrial cancer.
- Contraception—Oral in combination with oestrogen, minipills and injectables are used as contraceptives. Implants (Norplant) are effective over 5 years (see Chapter 20). IUCDs impregnated with progesterones are available (Mirena). Mirena is effective for 5 years.
- Abnormal uterine bleeding (see Chapter 24).
- Dysmenorrhoea, premenstrual tension syndrome.
- *Endometriosis*. Though danazol is the drug of choice, owing to the cost and hirsutism, progestogens continue to be employed in endometriosis.
- Endometrial ablation in AUB. Prior to the TCRE (transcervical resection of endometrium), endometrial shrinkage is achieved by progestogens given over 4 to 6 weeks.
- *Amenorrhoea*. Progesterone challenge test—A single injection of 100 mg progesterone will induce withdrawal bleeding if endometrium is primed by oestrogen (see Chapter 23). Oral tablets also work. (Primolut-N 5 mg tid × 3 days)
- Post-coital pill—Levonorgestrel 0.75 mg tablet given within 72 h of unprotected coitus and repeated 12 h later will prevent pregnancy in 98% cases.
- With oestrogen in HRT (Chapter 5).
- Postponement of menstruation—5 mg norethisterone tid for 4 to 5 days or longer will delay onset of menstruation (starting 3 days prior to anticipated period).
- Allyl progesterone is used in abortions.
- Progestogens are used as 'add back' therapy with GnRH to prevent osteoporosis and allow prolonged GnRH therapy.

Contraindications

- Undiagnosed vaginal bleeding.
- Breast cancer, breast tumour.
- Thromboembolism.

Side Effects

- Nausea, vomiting.
- Headache, mastalgia, water retention, cramps in the legs, weight gain.
- Hirsutism in androgen-related compounds.
- Depression.
- Increased low-density lipoproteins and cardiovascular accidents.
- Deep venous thrombosis, pulmonary embolism with desogestrel and gestodene.
- Breast tumours, cancer.
- Medroxyprogesterone acetate causes bone loss.
- Increase in LDL and decrease in HDL.

Androgens (Figure 43.1)

Androgens are 19 carbon steroids derived from cholesterol and formed in the adrenal gland, ovaries and peripherally.

Types

- Testosterone—potent (T)
- Dihydrotestosterone by conversion of (DHT) testosterone by 5 α reductase—most potent hormone acting at the target organs, i.e. hair follicles
- Androstenedione—weak androgen
- Dehydroepiandrosterone (DHEA)—weak androgen
- Dehydroepiandrosterone sulfate (DHEAS)—weak androgen

Testosterone is a natural androgen hormone secreted by the ovarian stroma and the adrenal glands. The normal level is 0.2–0.8 ng/mL. Its use in modern gynaecology is

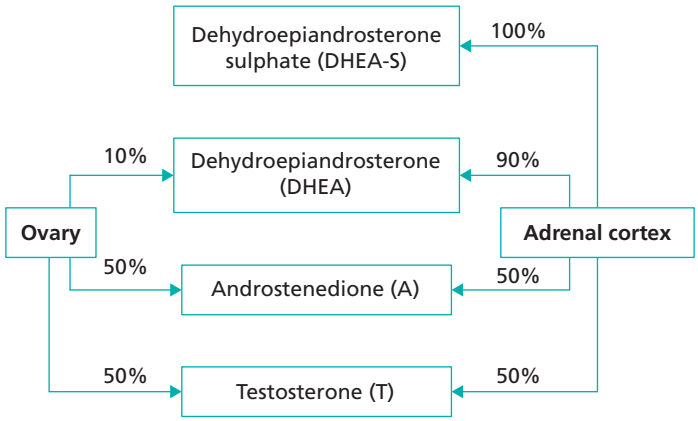

Figure 43.1 Sources of androgens.

limited on account of hirsutism and availability of synthetic progestogens which have similar biological effects. Fifty per cent androgen in women is derived from the ovaries and 50% comes from the adrenal cortex. Ninety per cent is bound to SHBG and some to albumin and remains inactive, and the rest (1%) circulates in the blood. At the target tissues, it is converted to dihydrotestosterone which is biologically active and causes acne and hirsutism in excess as seen in polycystic ovarian syndrome.

DHEA—90% from adrenal gland; 10% from the ovary

DHEA >8000 ng/mL is seen in the adrenal cortex tumour. The compound is quickly metabolized and cannot be estimated clinically. Its normal level is 40–340 μg/dL. Plasma level more than 700 μg/dL occurs in adrenal tumours. Serum 17 hydroxyprogesterone level more than 5 ng/mL is seen in adrenal hyperplasia. Ovarian production of testosterone is 0.2–0.3 mg daily and is responsible for 50% total testosterone, the other 50% is derived from the adrenal gland. Androstenedione contribution is 50% each from the ovaries and the adrenal gland.

DHEAS comes exclusively from the adrenal gland.

LH stimulates production of ovarian testosterone hormone in the ovarian stromal tissue as in PCOS. Insulin resistance is often the cause of LH stimulation to produce ovarian androgens.

It is used orally, IM or as a 6-month implant.

Androgens cause masculinizing effect such as

- moustache, beard, hair on the chest
- frontal baldness
- acanthosis nigricans is often associated with insulin resistance.

Uses

- Endometriosis—Danazol is effectively used.
- Male infertility—Oligospermia.
- Decreased libido—100 mg implant for 6 months is available for menopausal women to improve libido.
- In mastalgia and fibrocystic disease of the breast.

Side Effects

Virilization and hirsutism.

Danazol

Danazol is an isoxazole derivative of 17-alpha ethinyl testosterone. It acts directly on the endometrium causing atrophy, by displacing oestrogen receptors in the endometrium. Its indirect suppressive action on the pituitary gland also reduces oestrogen and progesterone secretion. By reducing the SHBG, it frees bound testosterone into circulation. It has androgenic and anabolic properties.

Uses

- It is largely used in endometriosis either as a primary treatment or following surgery to eradicate residual tumour and prevent recurrence. The oral dose varies from 400 to 800 mg daily in divided doses. Seventy-five to ninety per cent improvement is seen within 6 months.
- *Abnormal uterine bleeding*. Danazol should not be offered to young women in view of risk of hirsutism, but in older women, it is used when oestrogen is contraindicated and progestogens fail to cure menorrhagia. With the availability of several drugs like NSAIDs and antifibrinolytics, the role of danazol is limited in this disorder.
- Danazol is given in a dose of 200 mg daily for 4 to 6 weeks prior to transcervical resection of endometrium in AUB to produce endometrial thinning and atrophy.
- Danazol is effective in cyclical mastalgia: 100 mg twice daily will improve 60% cases.
- Fibrocystic disease of breasts is also treated with danazol.
- Gynaecomastia.
- It improves libido in menopausal women.
- It shrinks fibroid and is used prior to surgery.
- Improves spermatogenesis in male infertility.

Side effects

Danazol should not be given for more than 6 to 9 months at a time because of anti-oestrogenic action and virilizing effect.

Other side effects are:

- Weight gain, headache, water retention and oedema.
- Acne, hirsutism and muscle cramp.
- Breast atrophy, amenorrhoea; deepening of voice which is irreversible.
- Liver damage, increased low-density lipoprotein, lowers HDL with its associated cardiovascular complications.
- It is teratogenic in early pregnancy causing masculinization of a female fetus.
- Glucose intolerance.

Contraindicated in liver disease and cancer prostate.

Gestrinone

Gestrinone is a trienic 19-norsteroid derivative of testosterone which has androgenic, anti-oestrogenic, anti-progestogenic and anti-pituitary action. Its mode of action is similar to danazol, and its clinical applications are similar, but is more expensive.

Oral dose of 2.5–5 mg twice weekly to be taken at the same time and same day in the week will induce amenorrhoea in 85% cases of AUB. Its side effects are milder and are therefore preferred to danazol. Vaginal tablet 2.5 mg is applied weekly.

Anti-Oestrogens

Apart from androgens which are anti-oestrogenic (inhibit the ovarian function through the pituitary and oppose the action of oestrogens on the target organs), the drugs which antagonize oestrogens at the receptor level are clomiphene and tamoxifen.

Clomiphene Citrate

Greenblatt first introduced clomiphene in gynaecology in 1956, for inducing ovulation.

Clomiphene citrate is a nonsteroidal compound related to diethylstilbestrol (DES). It is a mixture of two isomers, cis (now known as zuclomiphene) and trans (now known as enclomiphene citrate). Cis fraction is responsible for inducing ovulation. Clomiphene citrate contains 38% cis and 63% trans isomers. It has a half-life of 5 days. It is metabolized in the liver and excreted in bile and faeces.

Mode of Action

Clomiphene is the first drug of choice in induction of ovulation. By competing with cytoplasmic oestrogen receptors in the hypothalamus, it blocks the negative feedback of circulating endogenous oestrogen. This allows release of GnRH into the pituitary portal system and stimulates LH and FSH secretion. Starting on the second day of the cycle and given for 5 days, E_2 level starts increasing 5–6 days after stopping the drug and induces maturity of the Graafian follicle and ovulation with LH surge. The best action is seen if a certain amount of oestrogen is present in the body. However, it exerts anti-E action on the endometrium and cervical mucus, causing slight decrease in the fertility rate.

Indications

Clomiphene is indicated in:

- Anovulatory infertility.
- Polycystic ovarian syndrome (PCOD) associated with infertility.
- In in vitro fertilization. Gamete intrafallopian transfer (GIFT) technique and assisted reproduction therapy (ART).
- 25 mg orally for 25 days each month for 3 to 6 months to stimulate spermatogenesis.

Contraindications

Clomiphene is contraindicated in:

- Ovarian cyst—the cyst can increase in size.
- Chronic liver disease, because it is metabolized in the liver.
- Scotoma.

If the woman suffers from amenorrhoea, clomiphene can be started any day. In normal cycles, the drug is started on the second day of the period in a dose of 50 mg daily for 5 days. Monitoring is done by serial ultrasound from the 10th day onwards, until the signs of ovulation are observed. Normally, the follicle increases in size daily by 1–2 mm. When the dominant follicular size reaches 20 mm, hCG 5000 IU is injected intramuscularly. About 36 to 40 h after hCG is injected, ovulation occurs—the couple is advised intercourse around this time. Not only does the hCG injection indicate the precise time of ovulation, it also compensates for corpus luteal phase defect (CLPD) caused by clomiphene.

On clomiphene administration, 80% ovulate and about 50% conceive. This low pregnancy rate may be attributed to the anti-oestrogenic effect of clomiphene on cervical mucus, CLPD on endometrium. The cyclical therapy is recommended for 6 months after which a break is given for 2 to 3 months. Further attempt to induce ovulation is repeated after that. If ovulation fails to occur and follicular size does not attain 20 mm, the dose of clomiphene is increased by 50 mg each cycle to the maximum of 150 mg daily. Alternately, the tablets may have to be taken for 7 days each cycle. If this too fails, the patient is offered FSH/LH therapy.

To reduce the peripheral anti-oestrogenic action and improve the fertility rate, clomiphene is lately replaced by letrozole 2.5 mg daily for 5 days. However, the drug can cause drowsiness.

In endometriosis, 30% conceive and in PCOS, although 80% ovulate, 40% become pregnant.

In PCOS, the high level of DHEAs reduces the pregnancy rate. Adding 0.5 mg dexamethazone lowers DHEA levels and improves conception rate.

Side Effects

The side effects are: (i) ovarian enlargement in 10%, (ii) hot flushes, sweating due to oestrogen deficiency, osteoporosis, (iii) nausea, vomiting, (iv) visual disturbances, blurring, scotoma, (v) headache, dizziness, urticaria, (vi) hair loss 3%, (vii) weight gain, (viii) anti-oestrogenic effect on cervical mucus and endometrium (ix) CLPD, (x) hyperstimulation syndrome, (xi) two- to threefold increased risk of neural tube defect has been reported by many, though not proved, (xii) multiple ovulation and multiple pregnancy in 10%, (xiii) abortion rate 25 to 40% due to CLPD, (xiv) ovarian malignancy if the treatment is extended beyond 1 year and (xv) premature ovarian failure, caused by exhaustion of follicles through multiple ovulation.

Incidence of unruptured luteinized follicle is increased.

Ovarian Hyperstimulation Syndrome

Ovarian hyperstimulation syndrome (OHSS) (Figure 43.2 and Table 43.3) is a complication of assisted reproductive

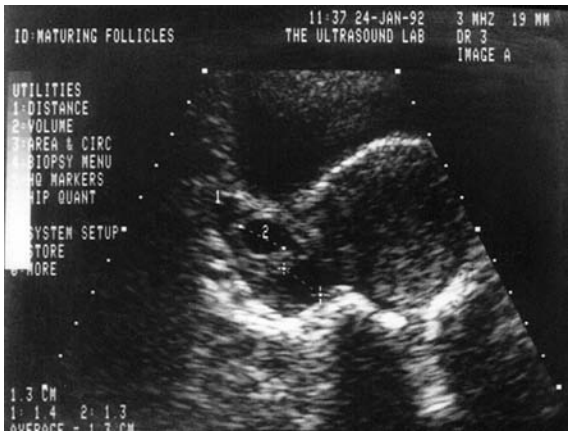

Figure 43.2 Ultrasound showing multiple maturing follicles. (Courtesy: Dr Ashok Khurana, New Delhi.)

TABLE 43.3 Grading of OHSS

Degree	Grade	Clinical Features
Mild stimulation (10–30%)	Grade I	Abdominal distension, pain
	Grade I + nausea	Vomiting, diarrhoea, ovarian enlargement less than 5 cm
	Grade II	Weight gain <3 kg
Moderate (3–4%)	Grade III	Features of mild OHSS + ultrasonic evidence of ascites, hyponatraemia, hypokalaemia, hypoproteinaemia
		Reduced renal output, ovarian size up to 10 cm, weight gain of 10 lb
Severe (0–5%)	Grade IV	Features of moderate stimulation + clinical ascites and/or hydrothorax, adult respiratory diseases, ovarian size >12 cm, weight gain >5 kg
	Grade V	Grade IV+hypovolaemia, hyponatraemia, hyperkalaemia, increased blood viscosity, hypercoagulability, decreased renal perfusion, oliguria, hypotension, hypoproteinaemia, thrombosis, coagulation failure, electrolyte imbalance, leucocytes >15,000/mm^3, hepatic, renal failure Haematocrit > 55% and serum creatinine >1.6 mg%

technologies and an iatrogenic complication occurring in the luteal phase or early pregnancy. It is a potentially life-threatening condition, occurring in 1–10%. It results from induction of ovulation in infertility cases. It is more common in FSH/LH therapy than clomiphene and pulsatile GnRH drugs. Its incidence is higher in PCOS and anovulatory infertility as compared to infertility caused by amenorrhoea. Raised LH in PCOS is responsible for hyperstimulation, and hCG should not be included in the therapy in these cases. hCG administration increases the risk, so also the dose of drugs, size and number of ovarian follicles. It is also common in a conceptional cycle if multiple ovulation occurs. It is characterized by ovarian enlargement, pleural and peritoneal effusion, oliguria, liver damage and thromboembolism. Severe form of OHSS occurs if the woman conceives during that cycle.

Pathogenesis

The main reason for OHSS is the increased vascular permeability leading to fluid shift from intravascular to extravascular space. This causes decreased blood volume and decreased albumin as well as electrolyte levels. It leads to accumulation of fluid such as ascites and hydrothorax. The increased vascular permeability is due to prostaglandin, cytokines and growth factors secreted by multiple growing follicles.

The risk factors for OHSS are:

- Young age of the woman
- PCOS
- Previous OHSS
- Increased oestradiol level >3000 pg/mL
- 20 or more small follicles
- Increased renin and angiotensin factors
- Vascular endothelial growth factor (VEGF) causes neovascularization of granulose cells and increased E_2 level
- PCOS high LH/FSH ratio, HCG and pregnancy in stimulated cycle
- FSH/LH causes higher incidence of OHSS (30%) than clomiphene (10%) and GnRH (1%)

OHSS can be predicted by high level of E_2 (>3000 pg/mL), more than 20 follicles on ultrasound and increased doppler blood flow. There is increased release of rennin and angiotensin.

Complications

Complications of OHSS are:

- Vascular—cerebrovascular accidents, thromboembolic phenomenon, deep venous thrombosis
- Coagulopathy
- Liver dysfunction
- Adult respiratory distress caused by ascites/hydrothorax
- Renal failure due to hypovolaemia
- Gastrointestinal—Related to E_2 level
- Torsion and haemorrhage in the ovarian cyst

Prevention

hCG should be withheld in a cycle if more than 20 follicles are seen on ultrasound and E_2 level rises to 3000 pg/mL. In PCOS, it is prudent to withhold hCG. Albumin 5% infusion in 500 mL lactated Ringer's solution during and after oocyte retrieval prevents OHSS. Dopamine agonist cabergoline 0.5 mg daily for 8 days starting on day 1 of hCG avoids OHSS.

Ovarian hyperstimulation syndrome occurs with smaller than larger follicular size 5 to 8 days after hCG administration. It is an iatrogenic condition of increased vascular permeability resulting in exudation of fluids from the intravascular to the extracellular compartment. Progesterone support helps.

Treatment

Ovarian hyperstimulation syndrome requires hospitalization. Medical therapy includes:

- *IV fluids for hypovolaemia.* Colloids, plasma expanders or human albumin infusion 5% in 500 mL Ringer's lactate. Half-life of albumin is 3 to 10 days. Fifty grams of albumin (25% albumin in 50 mL) raises blood volume to 500 mL. Human albumin 20% with 2 L of dextrose may

be needed. Gelofusine for hypovolaemia may be required—continuous autotransfusion of ascitic fluid (CATAF) is performed for 5 h each day.
- Diuretics and NSAIDs should be avoided because of hypovolaemia and poor renal perfusion except in pulmonary oedema and to correct electrolytes.
- High thigh venous support stocking prevents deep venous thrombosis.
- Immunoglobulins IV may prove to be effective.
- Glucocorticoids.
- Anticoagulants—heparin.
- Dopamine improves renal blood flow, oliguria and prevents renal failure.
- Correction of electrolytes.

Investigation and monitoring

Investigation and monitoring are done by

- Hb%, WCC, platelet count—WCC15,000 and haematocrit.
- Urea, electrolyte estimation, serum protein level
- Repeat ultrasound to monitor size of ovarian cyst and ascites.
- Weight recording.
- Renal function tests.
- Liver function tests.
- Coagulation profile.
- Central venous pressure recording.
- X-ray chest for pleural effusion.

Surgery is required if the ovarian cyst ruptures, undergoes torsion or haemorrhages. Aspiration of ovarian cyst, ascites, pleural and pericardial effusion may be required.

Aromatase Inhibitors

Letrozole

Letrozole (nonsteroidal aromatase inhibitor) is used in the induction of ovulation. It has a half-life of 45 h and is eliminated via the kidneys. It prevents conversion of androstenedione to oestrone. A dose of 2.5 mg daily for 5 days in a cycle has the following advantages over clomiphene:

1. It has no anti-oestrogenic action on the endometrium and the cervix—yields better pregnancy rate.
2. It induces mono-follicular stimulation, adequate LH surge and avoids multiple pregnancy.
3. Better implantation.
4. No hyperstimulation syndrome. It is suited in cases of PCOS. Lately, a single dose of 20 mg on day 3 is being tried. It is contraindicated in hepatic dysfunction.

It can however cause drowsiness and liver dysfunction. Anastrozole is useful in endometriosis (1 mg day).

Selective Oestrogen Receptor Modulators Acting as Anti-Oestrogen (Table 43.4)

Tamoxifen

(Tamoxifen, cytofen, eldtam, mamofen, oncomox)

Tamoxifen is a nonsteroidal anti-oestrogenic drug. It acts by binding to and reducing the availability of oestrogen receptors. It is mainly used in the palliative treatment of advanced breast cancer in postmenopausal women. It has also been used successfully in cases of PCOD. Tamoxifen is effective in primary and secondary prevention of breast cancer; it prevents spread to the other breast and recurrence by 50% and mortality by 25%. It is also bone and cardioprotective. Primary chemoprevention is indicated in $BRCA_1$ and $BRCA_2$ gene positive women, usually first relatives of breast cancer patients.

Side effects (two-fold increase) are hot flushes, vaginal dryness (anti-E_2 action), endometrial hyperplasia, polyp, endometrial carcinoma and sarcoma.

Hyperglyceridaemia, deep venous thrombosis, ischaemic heart disease and retinopathy are other complications to watch for during tamoxifen therapy.

Progestogens do not protect against tamoxifen induced endometrial hyperplasia.

TABLE 43.4 Varieties of SERMs and comparison of their therapeutic effects

Therapy	Hot Flashes Insomnia	Genital Atrophy	Endometrial Proliferation	Ovulation	Osteoporosis	Breast Cancer	CVD
Oestrogen[a] ERT/HRT	↓	↓	NA	NA	↓	↑	↑
Clomifen	NA	↑	↓	↑	NA	NA	NSC
Tamoxifen	↑	↑	↑	NA	↓	↓	↑
Raloxifene	↑	NSC	↓	NA	↓	↓	↑
Genistein	↓	↓	NSC	NA	↓	NSC	↓
Centchroman	NA	NSC	NSC	NSC	↓	↓	NSC

NA: Not applicable in the clinical situation, CVD: Cardiovascular disease including deep venous thrombosis, NSC: No significant change.
[a]ERT alone used following hysterectomy.

Dosage

The dose is 10–20 mg twice daily for not more than 5 years in breast cancer because it becomes ineffective after that.

Precautions

Tamoxifen enhances the effects of warfarin. It is known to cause endometrial hyperplasia and cancer. It is mandatory to monitor endometrial growth by serial sonography and uterine aspiration.

The important second-generation SERM is raloxifene, which has less beneficial action on the breast than tamoxifen. It is cardioprotective, maintains bone density and has no adverse effect on the endometrium unlike tamoxifen. However, it is anti-oestrogen and it does not cure menopausal symptoms such as hot flushes.

The dose is 60 mg daily. It is mandatory to discontinue therapy before, during and after surgery, to avoid the risk of superficial and deep venous thrombosis.

Raloxifene, 60 mg daily used in endometriosis, do not cause endometrial hyperplasia.

Ormeloxifene (Centchroman)

It is a nonsteroidal anti-oestrogen developed for its contraceptive potential. Due to its long half-life, it is available in Indian market as a 'weekly nonsteroidal pill'. It is free from adverse effects on the breast, endometrium, ovary, liver and coagulation factors. It does not inhibit ovulation and exerts contraceptive effect on implantation. It has anti-oestrogen activity on endometrium (also see chapter on birth control).

Antiprogesterone

The antiprogesterone in common use is mifepristone (RU 486).

Mifepristone

Mifepristone—RU 486 (mifegest, mifeprine)

Mifepristone is a 19-norsteroid derivative of the synthetic progestogen norethindrone. The drug binds to the receptors in the cell nucleus and blocks progesterone action at the target organs. It also binds to glucocorticoid and androgen receptors. About 85% of the drug is absorbed after oral therapy. Peak level is reached in 1 to 2 h. The half-life of the drug is 24 h. It is excreted in bile and faeces. Bioavailibility is 60%.

Administration of the drug (150 mg) during the first 3 days of the follicular phase has no effect on the menstrual cycle. Drug administration in the late follicular phase suppresses LH surge and ovulation fails to occur. A single dose of the drug given within 2 days of the LH surge does not alter menstruation. Late administration in the luteal phase causes luteolysis and prevents pregnancy. Epostane is another progesterone synthesis inhibitor.

Therapeutic Applications

- This drug has been approved for medical termination of pregnancy (MTP) up to 49 days. Successful abortion occurs in about 85% of cases. Usually the abortion takes place within 5 days of drug administration; however, one has to wait for 28 days to judge success. In 15% cases, when abortion fails to occur or is incomplete, or the patient continues to bleed, surgical evacuation becomes necessary. The drug is administered in the form of three tablets (200 mg each), followed by two tablets of misoprostol 200 µg, each orally or preferably vaginally 48 h later. Just 200 mg mifepristone has also been proved effective. Lately, medical termination of pregnancy extended up to 9 weeks of gestation with mifepristone and misoprostol has proved successful. By reducing the level of β-hCG, it causes necrosis of the decidua and death of the embryo.
- It is useful in ripening of the cervix prior to prostaglandin induction of mid-trimester abortion. A dose of 200–600 mg RU 486 followed by prostaglandin 24 to 48 h later (400 µg) shortens induction–abortion interval, and reduces the dose and the side effects of prostaglandin.
- It is effective in missed abortion (same dose as in MTP).
- Ectopic pregnancy—Mifepristone injected into the unruptured ectopic pregnancy causes its resolution (see Chapter 21 on Ectopic Gestation).
- Cushing's syndrome—because of its anti-glucocorticoid therapy.
- Post-coital contraception. Ten milligrams given within 72 h of unprotected coitus is used as a post-coital contraception.
- It has some beneficial influence on shrinkage of fibroids and endometriosis (10–25 mg daily for 3 months).

Side Effects

- Headache (5%).
- Gastrointestinal symptoms of nausea, vomiting (3.5%). Occasional diarrhoea.
- Faintness, skin rash.
- Adrenal failure if massive dose is employed.
- Teratogenic. If medical method fails with RU 486, pregnancy should be terminated.
- Endometrial hyperplasia by reducing progesterone effect.
- Low potassium level, increase in creatinine level.

Anti-Androgens

Cyproterone Acetate (Dianette, Androcur)

Cyproterone is chemically related to progesterone, is derived from 17-alpha-hydroxyl progesterone and exerts a mild progestation activity. It is a potent anti-androgen, and competes with dihydrotestosterone for intracellular androgen receptor sites—it inhibits its binding. It has a weak corticosteroid effect. Small doses have no effect on

the pituitary function, but large doses cause amenorrhoea, loss of libido, suppression of spermatogenesis and gynaecomastia in males. By lowering LH level, it also reduces production of androstenedione in the ovary.

It is used in the treatment of hirsutism. A dose of 50–100 mg cyproterone acetate is given during the first 10 days of the cycle along with 30 μg of ethinyl oestradiol (EE_2) given cyclically for 3 weeks every month. *The effects begin to be seen only after 3 months of therapy*. Cyclic administration should continue for 6 to 12 months, followed by a maintenance dose of 5–10 mg of cyproterone acetate with EE for a prolonged period to prevent recurrence of hirsutism. Combination with EE is necessary to prevent pregnancy and thereby avoid teratogenic effects; it also regulates the cycles. In cases of PCOS, treatment regularizes menstruation, increases the levels of serum sex binding globulins which bind the free testosterone thereby reducing hair growth, acne and dry skin. On stopping therapy, results of induction of ovulation protocols improve. The drug is also useful to treat acne. The dose for acne is 2 mg with EE_2 to be taken daily for 21 days of each cycle (also see Chapter 10).

Spironolactone

Spironolactone is an aldosterone antagonist and was used as a diuretic. Its anti-androgenic properties have been put to use in the treatment of hirsutism. Its beneficial effects are observed after 3 to 4 months of therapy. The drug blocks the androgen effect at the receptor level in the hair follicles. It also reduces the 17-alpha-hydroxylase activity, lowering the plasma levels of testosterone and androstenedione (Chapter 10).

Dosage

A daily dose of 150 mg along with cyclic administration of EE provides relief in about 60% of the cases. It is useful in cases of PCOS. The maintenance dose of 50 mg is continued after 6 to 12 months of therapy.

Side Effects

Transient diuresis; polymenorrhoea is encountered in 10% of users; breast engorgement; and electrolyte disturbances (hyperkalaemia) when high doses are used.

Flutamide

(Cytomid-250, Drogenil, Flutacare, prostamid, flutide)

Flutamide is a substituted anilide. It is a nonsteroidal, anti-androgenic drug blocking the action of androgen at the receptor levels.

Dosage

A dose of 125–250 mg twice daily for 6 months along with OC pills is useful in the treatment of hirsutism. In males, it has been used in the treatment of prostatic hyperplasia and cancer.

Side Effects

Hepatotoxicity, dry skin, oligomenorrhoea and decreased libido.

Finasteride

(Finast, fincar, fistide, finpecia)

Finasteride is a competitive inhibitor of the enzyme 5-alpha reductase, which converts testosterone to dihydrotestosterone. It has no affinity to androgen receptors. It has no effects on other hormones and it does not influence the hypothalamus–pituitary–gonadal axis.

It is also used in benign prostrate hyperplasia.

Dosage

A dose of 5.0 mg/daily for 6 months is recommended.

Side Effects

Hypersensitivity to the drug; decreased libido; teratogenic effect on the fetus during pregnancy.

Glucocorticoids

Dexamethasone 0.25–0.5 mg or prednisone given at night daily for 6 months reduces ACTH secretion and hirsutism. It is contraindicated in obese women. The drug is also used in PCOS, with clomiphene in infertility, and adrenal hyperplasia.

Pituitary Hormones

Gonadotropins

The anterior pituitary gland secretes follicle-stimulating hormone (FSH), LH and prolactin. The physiology of their secretion is described in Chapter 3.

FSH is extracted from the urine of menopausal women and is available in injection form. One ampoule contains 75 IU FSH as a frozen dried powder along with a solvent.

Human β-chorionic gonadotropin hormone, which simulates LH in action, is extracted in a similar manner. It is available in 1000, 2000 and 5000 IU as frozen dry powder with an ampoule of solvent.

Both recombinant FSH and recombinant gonadotrophin are now available. They are self-administered subcutaneously, very effective and has lesser risk of hyperstimulation.

Therapeutic Uses

Gemzell first reported its use in 1958.

Therapeutic uses of gonadotropins are:

- Induction of ovulation in anovulatory infertility. Those who fail to respond to clomiphene are treated with FSH and LH. Infertility caused by pituitary hypofunction also needs this therapy. The dose is adjusted according to ultrasonic findings of follicular growth and E_2 level. The treatment is started on the second day of the cycle and continued until ovulation occurs.

- Induction of multiple ovulation using hyperstimulation protocols for infertile women going through ART as in in vitro fertilization, GIFT, zygote intrafallopian transfer (ZIFT) and ICSI.
- Hypogonadotrophic hypogonadism in males.
- Cryptorchism.
- In primary and secondary amenorrhoea caused by pituitary failure in hypogonadotropic hypogonadism.
- hCG is used in CLPD, infertility and early abortions.

No teratogenicity is reported.

250 μg recombinant hCG is equal to 5000 IU of hCG with less local side effects.

Side Effects

The side effects are:

- Hyperstimulation syndrome.
- Multiple pregnancy in 10%.
- Local reaction at the site of injection, fever, arthritis.

Anti-FSH and anti-LH are in the process of being developed as contraceptives.

Growth Hormone

Growth hormone (GH) is a polypeptide secreted by the anterior pituitary gland. Its action is to induce and promote linear growth at puberty. The growth of the long bones are indirect and is mediated via insulin-like growth factor I (IGF I), secreted mainly by the liver in response to GH. Subcutaneous administration of GH causes rise in the serum IGF I within 4–6 h and IGF I in turn has a direct negative feedback on the pituitary hormones. GH is secreted in a pulsatile fashion during sleep. At puberty, its level rises.

Recombinant GH is available as a subcutaneous injection and is used in Turner's syndrome and those of short stature. In adults, it reduces the body fat mass, decreases protein catabolism, but increases protein synthesis. It causes carbohydrate intolerance. Side effects include ankle oedema, carpal tunnel syndrome, arthralgia, arthritis and diabetes. It however improves osteoporosis.

Gonadotropin Releasing Hormone and its Analogues

Gonadotropin releasing hormone (GnRH) is a decapeptide first isolated by Matsuo et al. and Scally et al. in 1971. Pulsatile administration of this hormone or its analogues causes a rapid rise in FSH and LH. The rate and intensity of pulsatile release determines the secretion of pituitary hormones. Continuous administration however suppresses the pituitary gonadotropins. It has a half-life of 15 min. Because of its inactivation in the gut, parenteral route (subcutaneous and nasal spray) are employed. Agonists and antagonists are available.

Agonists and Antagonist GnRH: Mode of Action

In in vitro fertilization, GnRH agonists cause an initial rise in FSH and oestrogen called 'flare up' followed by gonadotropin suppression (down-regulation). Therefore, it takes longer for induction of ovulation.

Synthetic antagonists (cetrorelix and ganirelix) compete with receptors in the anterior pituitary gland and directly suppress gonadotropin secretion. They, therefore, have the advantage of:

- Smaller amount of gonadotropin required for ovulation.
- Shorter stimulation period with FSH.
- Reduced incidence of OHSS and multiple pregnancy.
- Comparable success as agonists in IVF.

Cetrorelix 0.25 mg is started 6 days after FSH therapy until the time of hCG administration, or a single 3 mg dose given at the end of FSH stimulation.

Clinical Uses

Diagnostic

GnRh stimulation test, 50–100 μg, IV causes rise in FSH, LH in hypothalamic failure. In pituitary failure , there is no secretion of FSH, LH. This differentiates between hypothalamic and pituitary failure in amenorrhoea.

Synthetic GnRH analogues (buserelin, factrel, goserelin) have been used in clinical practice as follows:

- Pulsatile GnRH analogues 5–10 μg intravenously every 90 to 120 min (infusion pump), pulsatile 15–20 μg subcutaneously or intranasal 200 μg every 2 h have been useful in hypothalamic amenorrhoea to stimulate the hypothalamic-pituitary-ovarian axis and induce cyclical menstruation in delayed puberty.
- Pulsatile GnRH, in the above doses, has been used with success in hypothalamic hypogonadal infertility or in those who fail to respond to FSH/LH. Monitoring of ovulation is done ultrasonically and by estimation of E_2 level and the dose either reduced or replaced by hCG in the luteal phase following ovulation. 50–100 μg IV induces FSH secretion in 30–60 min and LH in 15–30 min.
- GnRH analogues are used in down-regulation protocol to bring down pituitary hormones before starting on FSH/hCG regime in inducing ovulation.
- GnRH in infertility caused by PCOS and endometriosis yields a lower success rate.
- Cryptorchism in males.

Continuous administration or monthly depot injections (Zoladex 3.6 mg) are useful in the following:

- Precocious puberty to suppress pituitary–ovarian hormones until such time that normal puberty is desired.
- Contraception, but administration is difficult and expensive. Buserelin 6.6 mg implants suppress E_2 for 6 months.
- Abnormal uterine bleeding if other measures fail.
- Endometriosis.

- To shrink the size of uterine fibroid preoperatively. Depot injection of 3.6 mg injected intramuscularly every 28 days for 3 months shrinks the volume and vascularity by 50 to 80%. The size of the fibroid starts growing again after stoppage of the drug; therefore, surgery should be undertaken soon after the therapy.
- To shrink the endometrium prior to transcervical resection of endometrium in menorrhagia.
- Breast cancer to suppress oestrogen.
- Prostatic cancer, cryptorchidism.

When given intravenously or subcutaneously in a pulsatile manner, a special infusion pump is used and the site of infusion changed every 2 to 3 days.

Side Effects

The following are the side effects:

- Hyperstimulation syndrome is reported between 0.6 and 14% (normally 1%).
- Multiple pregnancy is the same as in the general population, i.e. 1%.
- Abortion rate may be slightly increased.
- In gynaecological use, prolonged administration for more than 6 months causes hypo-estrogenic state and menopausal symptoms, osteoporosis. For this reason and considering the high cost, GnRH therapy should not be given beyond 6 months at a time; 'add-back therapy' can be used.

Add-Back Therapy

The concept of add-back therapy is to counteract the hypo-oestrogenic side effect, without affecting the condition for which GnRh therapy is employed. This allows prolonged use of GnRH therapy. The drugs used in add-back therapy are oestrogen, progestogens, tibolone and bisphosphonates especially to prevent osteoporosis. Norethisterone 5–10 mg daily is better than MDPA, as the latter causes osteoporosis. Tibolone is also effective.

Agonists as well as antagonists are now available in GnRH therapy. Antagonists such as cetrorelix and ganirelix act faster (3–4 days) against agonists which may take 3 weeks, and carry some advantage in certain situations.

Other side effects are:

- Insomnia, nausea, decrease in breast size, myalgia, dizziness, decreased libido, low high-density lipoprotein and increased cholesterol.
- Allergic reaction and infection at the site of injection or spray, bronchospasm.

Drugs used are:

- Nafarelin 400 µg intranasally for 6 months. Half-life is 4.4 h.
- Buserelin 300 µg tid subcutaneously or intranasally for 3–6 months or 6.6 mg 3 monthly injection (nanopeptide).
- Goserelin (Zoladex) 3.6 mg implant or IM monthly (nanopeptide).
- Leuprolide 3.75 mg 4 weekly for 3–6 months or 10.8 mg 3 monthly.
- Superfact 200–500 mg subcutaneously daily.
- Buserelin implant 6.6 mg suppresses ovarian hormones for 3 months.
- Triptorelin 3–7 mg IM 4 weekly

Antagonists of GnRh are:

- Antarelix
- Cetrorelix

These prevent premature LH surge. Advantages of antagonists over agonists are:

- They are cost-effective.
- Short duration of drugs are required compared to prolonged therapy with agonists.
- Smaller doses are required.

Disadvantage: Weekly subcutaneous injection against monthly and 3 monthly injections of agonists.

Prolactin

Prolactin (PRL) is a polypeptide hormone resembling growth hormone and human placental lactogen. It contains 198 amino acids and is secreted by pituitary lactotrophs in a pulsatile manner. Extra pituitary sites for prolactin production are endometrium, decidua, hypothalamic neurons, intestine, lungs and renal cancer. Prolactin is normally under the inhibitory influence of prolactin inhibiting factor, dopamine, which acts directly on lactotrophs. Prolactin contains native or little PRL (50%) which is biologically most active, a big PRL which is elevated in pregnancy and a big big PRL which is inactive.

Stimulating factors for prolactin are:

- Prolonged lactation.
- Thyroid-releasing hormone.
- Oestrogen promotes PRL release by inhibiting dopamine of hypothalamic level as well as by directly stimulating lactotrophs.
- Endorphins, tricyclic antidepressants methyldopa phenothiazine stress.
- Sleep increases its secretion.
- Empty sella turcica and pituitary tumours, craniopharyngoma.
- Some cases of endometriosis.
- Some cases of PCOS.
- Liver and renal disease reduce its excretion.

Clinical features of hyperprolactinaemia are oligomenorrhoea, amenorrhoea, galactorrhoea, infertility and recurrent abortions through corpus luteal phase defect (see Chapter 23 also).

Normal prolactin level determined by radio-immunoassay (RIA) is up to 25 ng/mL. It is up to 100 ng/mL in hyperprolactinaemia, but level crosses 100 ng/mL in the presence of a tumour. Apart from CT and MRI to detect a brain tumour,

visual examination is necessary to detect pressure on the optic nerve.

Treatment is by antiprolactin drugs or surgery for macroadenoma. Antiprolactin drugs are bromocriptine and other derivatives.

Drugs are used in:

- Hyperprolactinaemia
- Microadenoma <10 cm
- Macroadenoma (>10 cm) to shrink the tumour prior to surgery.

Bromocriptine

Bromocriptine, a synthetic ergot derivative (lysergic acid derivative of ergoline) and a powerful dopamine agonist, was discovered in 1971. It suppresses prolactin while promoting the secretion of gonadotropins. It thus induces menstruation, ovulation and promotes pregnancy. It also suppresses lactation.

Bromocriptine is available as parlodel, proctinal, cabergoline, serocrip tablets.

Pergolide is now also available as a vaginal tablet and intramuscular injection by the name parlodel-LAR (glycolipid microspheres).

Contraindications

Hypertension, cardiovascular disease.

Therapeutic Applications

Bromocriptine's therapeutic uses are:

- Suppression of lactation—2.5–5 mg daily orally.
- Cyclical mastalgia.
- Anovulatory infertility caused by hyperprolactinaemia.
- Treatment of microadenoma and preoperatively in macroadenoma to shrink the tumour prior to surgery.

In infertility due to hyperprolactinaemia, 70% to 90% ovulate and menstruation is established, 70% pregnancy rate is also encouraging. If pregnancy follows, the treatment should be discontinued, though no teratogenic effect is reported in the fetus.

In pregnancy, the level of prolactin rises and the follow-up is mainly by fundus examination which suggests optic nerve pressure by the tumour. Bromocriptine can be continued during pregnancy if the tumour appears to increase in size as suggested by fundus examination. Cabergoline is safe during pregnancy.

Dose

The dose starts with 1.25 mg at bedtime and gradually increases to 2.5 mg bid or more as required. The effect lasts 12 h.

In those who cannot tolerate the oral drug or in resistant cases, the vaginal tablet or cream is to be used daily. Alternately, the long-acting tablet in the name of cabergoline (dostinex) is available. Starting with an initial dose of 0.25 mg twice weekly, the dose is gradually built up to 1 mg twice weekly. It acts at a D_2 receptor site.

Parlodel-LAR monthly intramuscular injection, used in the initial dose of 50 mg increasing to 100 mg if necessary, causes acute reduction in prolactin level by 30% to 80%, reduction in tumour volume by 25% with minimal side effects.

Quinagolide 25–150 µg daily in divided doses followed by maintenance dose 75 µg daily.

Side Effects

The side effects are seen in 10%:

- Nausea, vomiting; the patient is advised to take the tablet at night.
- Hypotension and dizziness due to postural hypotension.
- Nasal congestion, headache, constipation.

Results

The drugs normalize prolactin level in 86% of idiopathic hyperprolactinaemia and 77% in microadenoma. The macroadenoma shrinks in 70%. Some require surgery.

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a glycoprotein containing two linked subunits alpha and beta. Alpha unit contains 92 amino acids similar to LH, FSH and thyroid-stimulating hormone. Beta unit contains 145 amino acids, and has specific biological activity in pregnancy and ectopic pregnancy.

hCG starts rising soon after fertilization and is detected in the serum 1 week before the due menstrual period. The level doubles every 2–3 days, peaks on the 100th day and then gradually declines. The hormone secreted by the syntiotrophoblast is luteotropic and secretes progesterone by the corpus luteum until the tenth week when the placenta takes over the hormonal functions. With progesterone, it provides endometrial support to the embryo.

Role of hCG

- It supports early pregnancy.
- In ectopic pregnancy and missed abortion, the level is low and does not double every 2–3 days. In hyperemesis and in hydatidiform mole, the level is high, so also in multiple and diabetic pregnancy.
- While the level is high in trisomy 21 (Down syndrome), it is low in a fetus with trisomy 18.
- Its role in ovarian stimulation in anovulatory infertility has already been described.
- hCG is detected by
  - Urine pregnancy test.
  - Quantitative test in serum is useful in monitoring ectopic pregnancy and follow-up of molar pregnancy.
- In management decision-making in ectopic pregnancy.

Therapeutic Applications

- In habitual abortion, it provides support to the embryo.
- IVF programme: hCG given when the follicular size reaches 20 mm causes follicular rupture 36–38 h following injection, and provides support in implantation and endometrial vascularization.
- In corpus luteal phase deficiency.

Key Points

- Oestrogen preparations in clinical use include ethinyl oestradiol used in contraceptive pills and conjugated oestrogens in HRT in menopausal and urethral syndrome. Implants are mainly employed for long-term use. Vaginal cream is effective in atrophic vaginitis and urethral syndrome.
- Progesterone as injectable in oil or micronized preparation is used in corpus luteal phase defect and early pregnancy support.
- Progestogens are used in abnormal uterine bleeding and as combined contraceptive pills and mini-pills. They are required in HRT.
- Androgens (danazol) are effective in the treatment of endometriosis and fibrocystic disease of the breasts.
- Clomiphene and tamoxifen are employed in infertility. Tamoxifen is mainly useful in breast cancer.
- Mifepristone (anti-P) is recently introduced in termination of early pregnancy.
- Anti-androgens are used to treat hirsutism in PCOS.
- Hypothalamic gonadotropin-releasing hormones (GnRH) are employed in various gynaecological conditions, for not more than 6 months. Add-back therapy allows prolonged use of GnRH therapy, however.
- Bromocriptine is useful in hyperprolactinaemia and suppression of lactation.
- The side effects of all hormonal preparations should be known and avoided in clinical practice.
- Human chorionic gonadotropin hormone is used in the induction of ovulation and pregnancy support in early gestation.
- Anti prolactin drugs are employed in hyperprolactinaemia and microadenoma. They induce menstruation, and ovulation and improve pregnancy rate. Macroadenoma may require surgery.
- FSH, HCG are used in the induction of ovulation if clomiphene fails, and in IVF to induce multiple ovulation.

Self-Assessment

1. Describe the physiological role of oestrogens in the body. Enumerate the indications and the commonly used oestrogenic medications in clinical practice.
2. Classify progestogens and their clinical applications.
3. Name the androgenic medications and their clinical applications.
4. Name the pituitary gonadotropins and their role in therapeutics
5. What are GnRH analogues? What is their role in clinical practice?
6. A woman, 28-year old, complains of galactorrhoea. How will you investigate and manage this case?
7. Discuss the hormones used in anovulatory infertility.

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Chapter

44 Pelvic Adhesions and Their Prevention

CHAPTER OUTLINE

Until recent years, less attention was paid to the occurrence of pelvic adhesions and their sequelae in a woman's life. Re-surgery for various conditions has discovered a high incidence of such adhesions and the increased morbidity associated with them.

It has therefore become important to understand the causes of abdominal and pelvic adhesions and attempt to prevent them. Various pharmacological and anti-adhesive agents have been manufactured that may prevent or reduce the risk of such adhesions.

Adhesions are unfortunately a common sequel of abdominal surgery. However, they may also occur due to pelvic inflammatory disease, endometriosis and abdominal tuberculosis.

Incidence

It is recognized that 95% women develop adhesions following infection, trauma and surgical procedures, though not all manifest the symptoms. Flimsy adhesions may remain asymptomatic and may never be discovered unless repeat surgery is performed for other indications.

In obstetrics, the rate of caesarean section surgeries has gone up two- to threefold, and that alone has increased the risk of abdominal adhesions.

Sequelae

As mentioned earlier, flimsy adhesions that remain asymptomatic are not recognized unless the woman undergoes another surgery. Dense adhesions develop symptoms within a few days, months or years later.

- The woman develops chronic pain in the abdomen (75%) which incapacitates and affects her quality of life.
- Infertility (20–40%) may follow tubal adhesions and may require tubal surgery or in vitro fertilization. The risk of an ectopic pregnancy in these women is somewhat higher than in the normal population.
- Menorrhagia and dysmenorrhoea are secondary to pelvic adhesions, so also dyspareunia and backache.
- Intestinal obstruction is another sequelae of abdominal adhesions. The obstruction may be acute, developing shortly after the surgery, or may be chronic with long-term illness and malnutrition.
- Re-surgery may be very difficult adding morbidity in the form of trauma to the organs, bleeding and infection.
- Re-admission for pain may prolong her postoperative period or will cost money.

Aetiology

Nonsurgical and surgical causes for pelvic adhesions are listed below.

Nonsurgical Causes

- Pelvic infection and pelvic inflammatory diseases mostly affect the fallopian tubes and the ovaries. These lead to tubal infertility. Fitz-Hugh–Curtis syndrome forms a band between the right tube and the undersurface of the liver.
- Peritonitis causes abdominal as well as peritoneal adhesions that lead to chronic abdominal pain or intestinal obstruction.
- Tubercular peritonitis.
- Appendicitis.
- Intestinal perforation leading to peritonitis.
- Pelvic endometriosis, infected dermoid cyst, uterine fibroids.
- Radiotherapy for cancer.

Surgical Causes

The following are the most common causes of adhesions due to surgery:

- Trauma to the organs or peritoneal membrane abrasions caused by rough handling, dry pack, prolonged surgery leading to damage to the peritoneal surface.
- Poor haemostasis resulting in blood oozing into the abdominal cavity.
- Infection during intestinal surgery or lapses in aseptic technique, prolonged surgery.
- Ischaemia causing avascularity and damage to the peritoneal surface.
- Foreign body such as pack and sutures.
- Excessive use of diathermy to coagulate bleeders. Laser causes minimal adhesions.
- Inherent in the woman (constitutional).
- Desiccation causing dryness of organ surfaces during prolonged exposure to air.

Pathophysiology of Formation of Adhesion

Adhesions are the connective tissues (fibrin) that bridge two organs or surfaces together. They are also known as 'internal scars'.

The plasma protein leaks and oozes causing fibrin deposition which starts as early as after 3 h of surgery. Normally, the fibrin process is reversed through enzymatic degradation by locally released fibrinolysin. Trauma and other factors such as ischaemia and infection during surgery reduce the level of fibrinolysis, thus initiating adhesion formation. Adhesion is formed as early as 5–7 days after surgery, though they may not manifest for some time.

Clinical Features

- Many remain asymptomatic, especially if the adhesions are flimsy. The site and extent of adhesions are responsible for clinical manifestations.
- Chronic abdominal pain. The pain increases with certain movements. It may be dull, constant or intermittent. Acute pain occurs with intestinal obstruction, when vomiting, inability to pass flatus and abdominal distension occur. Acute intestinal obstruction occurs within a few days of surgery. Chronic obstruction causes intermittent symptoms, with tubercular peritonitis causing cysts or chronic symptoms.
- Infertility. Twenty to forty per cent women with previous pelvic inflammatory disease (PID) suffer tubal infertility.
- Menorrhagia and dysmenorrhoea may follow pelvic adhesions of PID.
- Re-surgery will be difficult and prolonged.

Trauma to intestines and bladder may occur while opening the abdomen. Injury to viscera occurs during surgical dissection. Haemorrhage and incomplete haemostasis are other problems.

Prophylactic Measures

Nonsurgical Adhesions

- Early diagnosis and treatment can prevent or reduce the amount of adhesions.
- Placentrex is recommended in pelvic inflammatory disease. It is an extract of the placenta containing enzymes that prevent or dissolve early adhesions.

Surgical Adhesions

- Laparoscopy is said to cause less abdominal and pelvic adhesions. Of late, this is disputed, if surgery is prolonged or trauma to the abdominal organs occurs.

Laparotomy

- The quicker the surgery and lesser the time, less is the risk of adhesions.
- There is less risk of adhesions if organs and tissues are handled gently and trauma to the visceral peritoneum avoided.
- Complete haemostasis avoids adhesions.
- Ischaemia is to be avoided as it causes trauma to the visceral peritoneum.
- Desiccation is to be avoided—dry packs should not be used. Wet packs soaked in saline keep the tissues healthy and moist. Irrigation at the end of surgery is effective.
- Excess diathermy causes more trauma to the peritoneum of the visceral organs.
- Microsurgery avoids trauma.
- Monofilament sutures should be used. Sutures over the visceral peritoneum (peritonization) and parietal peritoneum should be avoided—this is expected to reduce adhesions.
- Prophylactic antibiotics should be used.

Earlier, when postoperative adhesions were anticipated, omental or peritoneal graft was placed over the suture line.

Intraoperative Prophylaxis

Although adhesion formation may be inevitable in inflammatory conditions, it is possible to reduce the risk by early diagnosis and adequate management. Placentrex seems to help in dissolving adhesions if given early in the management.

Since trauma and bleeding form part of any surgery, formation of postoperative adhesion of whatever degree and severity appears to be inevitable. Lately, some steps have been introduced to reduce postoperative adhesions in the form of insertion of adhesion-reducing agents.

Nonsteroid anti-inflammatory drugs were tried, but they failed to reach the site of adhesion due to reduced vascularity. Locally, they get absorb-Assed too quickly into systemic circulation to be effective.

Physical barriers were next introduced to keep the two traumatic surfaces separate or to cover the raw sutured area.

Methods Used

- Hydroflotation
- Solid mechanical barriers
- Films and gels
- Omental and peritoneal graft as mechanical barriers

Hydroflotation

- Hyskon (32% Dextran 70) solution (plasma expander) caused anaphylactic reaction and even death, and is no more used.
- Hydroflotation with saline: Ringer lactate with or without heparin 5000 IU in 200 mL provides a fluid barrier between organs. These crystalloids are however rapidly absorbed (within 24 h) from the peritoneal cavity before adhesion formation and are not effective.
- Adept (4% icodextrin) solution has a sufficiently long peritoneal residence and provides hydroflotation during the crucial period of adhesion formation (5–7 days). It looks like saline, is isomolar and does not potentiate infection. It is easy to instil and is inexpensive. Adept can also be sprayed laparoscopically. It has been shown to reduce the incidence, extent and severity of postoperative adhesions. Besides, it does not interfere with the healing process of the scars and administration of intra-peritoneal drugs.

Solid Material Barriers and Gels

Earlier, omental or peritoneal grafts like preclude were placed whenever adhesion risk was high. They were placed over the organ scar.

Preclude (expanded polytetrafluoroethylene)—Gore-Tex—has the disadvantage that it is nonabsorbable and needs to be sutured to the scar. It also needs to be removed laparoscopically a week later.

- Interceed (oxidized regenerated cellulose) is an absorbable barrier introduced in the 1990s. It prevents adhesion formation and at the same time does not interfere with the healing process. However, the presence of blood makes it ineffective—perfect haemostasis is necessary. Interceed can however form adhesions if not properly applied and in the presence of incomplete haemostasis and infection. In the presence of blood, it does not adhere to the organ, remains as a foreign body and encourages adhesions.
- Seprafilm (hyaluronic acid with carboxymethylcellulose) is a film placed over the suture line. It remains during the period of re-epithelization and gets spontaneously absorbed. The sheet is firm and non-compliant and difficult to insert during laparoscopic surgery. It is mainly used underneath the anterior abdominal wall to prevent intestinal adhesions, so that repeat surgery is safe.

Conclusion

It is difficult to realize the incidence, extent and severity of postoperative adhesions following abdominal surgery. In a high-risk case or as a routine, some form of anti-adhesion device needs to be placed at the end of surgery. Research is on for a safe, effective barrier to reduce this complication and make repeat surgery safe.

Key Points

- Adhesion formation is inevitable following pelvic infection but specifically following abdominal surgery.
- Postoperative adhesions increase morbidity and result in early or late complications, affecting the quality of life in a woman.
- Various methods such as mechanical barriers and hydroflotation are attempted; we are yet to discover an agent which is safe as well as effective in preventing adhesions.

Self-Assessment

1. Describe the causes of pelvic adhesions.
2. Discuss the clinical features and management of pelvic adhesions.

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Chapter

45

Preoperative and Postoperative Care, and Surgical Procedures

CHAPTER OUTLINE

Surgical procedures have become very safe today, because of improved anaesthesia, availability of blood transfusion, antibiotics as well as good preoperative and postoperative care of the woman. Advanced surgical technologies have also contributed to reduced surgical morbidities and operation-related complications.

It is therefore important to pay due attention to preoperative and postoperative management of a woman undergoing surgery.

Preoperative Investigations

Prior to the submission of the patient to any major gynaecological surgery, it is necessary to evaluate her fitness for it. The preoperative investigations include the following:

- *Complete blood count*. This includes haemoglobin assessment and total and differential leucocyte count.
- *Urinalysis.* This includes routine and microscopy urinalysis. Culture examination is requisitioned if microscopy reveals significant number of pus cells (more than five) or history of urinary tract infection (UTI), especially in women with cystocele, urinary complaints and fistula.
- *Fasting and post-prandial blood sugar* estimations.
- *Kidney function tests.* Blood urea, serum creatinine and uric acid.
- *Liver function tests.* Particularly in women giving a history of jaundice and in all women undergoing cancer surgery.
- *Blood tests for VDRL.* Australia antigen and HIV-I and II.
- *Serum electrolytes.* Na, K, Cl and HCO_3.
- *Radiograph of the chest*, preoperatively or in genital cancer for metastasis.
- *ECG and stress test* whenever indicated.
- *Intravenous pyelography (IVP)* in case of cancer cervix and urinary fistulae.
- *Blood group and Rh factor*.
- *Bleeding time and clotting time*.

Preoperative Care

Purpose of Preoperative Care

It is the cornerstone for successful surgical outcome.

- To make the correct diagnosis.
- To decide on the need of surgery and its correct selection.
- Investigations to:
  - confirm the diagnosis.
  - fitness for anaesthesia and surgery.

Identify the risk factors, any abnormal condition and rectify this before undertaking surgery.

Correct Diagnosis

Detailed history and clinical examination can lead to correct diagnosis in most cases. History includes the presenting symptoms, drugs taken, any allergy and previous blood transfusion and surgery.

Clinical Examination

Apart from abdominal, speculum and bimanual examination, general examination rules out hitherto undetected anaemia, thyroid enlargement, breast disease and cardiovascular

examination besides blood pressure. Pap smear is taken as required.

Investigations

These include the following:

- Confirmation of clinical diagnosis by ultrasound, CT and MRI.
- To assess the extent of the disease, any anatomical distortion of bladder, ureter by the pelvic tumour and malignancy.
- Staging and feasibility of surgery. In case of uterine fibroids, the number, size and location of fibroids decide the type of surgery appropriate to the case.
- Decide on the type and route of surgery.

Fitness for Surgery

It is necessary to make sure that the woman is fit for surgery, by performing the following investigations:

- BP check up.
- Hb% white cell count, differential count, blood group-RH.
- Routine urine examination for pus cells, sugar and protein.
- Kidney function tests.
- Liver function tests in cancer surgery and in previous liver disease.
- Blood sugar. In a known diabetic, to check on sugar control.
- X-ray chest, routine and for secondary malignancy.
- ECG.
- Thyroid function tests if required.

If any abnormality is detected, the woman is referred to the appropriate specialist for treatment and the operation is postponed until the woman is considered fit.

To protect the surgical staff regarding hepatitis B virus, HIV in high-risk patients.

In an emergency and life-saving condition, minimal essential investigations are done, blood arranged and the risks of operation explained.

In a planned surgery, some gynaecologists prefer autotransfusion, and blood of the woman is withdrawn 2 days before surgery and preserved. Alternately, a relative donor is arranged. This avoids the risk of HIV and other sexually transmitted diseases, hepatitis B virus.

By assessing the fitness this way, sudden cancellation and prolonged postoperative hospitalization due to complications are avoided.

Drugs

Woman on any drug needs counselling, regarding temporary stoppage or addition of alternative drugs or a new drug. Any allergy to a particular drug should be noted. History of previous blood transfusion, the reason for transfusion and any adverse reaction is noted.

Oral contraceptive pills should be stopped 4 weeks before surgery. These can cause thromboembolism. Warfarin should be stopped and replaced by heparin with good monitoring. Aspirin is also best avoided as it can cause bleeding. Anaemia should be treated and Hb% should be at least 10 g%. Any infection should be cleared with antibiotics.

Smoking and alcohol should be stopped for a few days before surgery. Lithium and tricyclic anti-depressants should also be stopped. The drugs for hypertension and diabetes should continue. Many prefer to switch to insulin before and after the surgery. Thyroid drugs need to be continued.

Thromboprophylaxis

Prophylactic heparin is needed in a high-risk woman for thromboembolism and it should be continued for a variable period postoperatively.

Consent

Proper counselling and informed consent should be obtained in writing. A girl below 18 years and a woman with a psychiatric problem are considered unfit to give consent and the guardian's signature is required.

Preoperative Preparation

- The woman should not take any food or liquid at least 12 h before surgery.
- **Bowel preparation**. The patient is advised to take dulcolax or other laxatives at night so that her bowels move well, and it is empty during surgery. It is important so that the bowels do not move and soil the operation table, and also intestines are not distended and obstruct the surgery. Some recommend enema early in the morning, but this is cumbersome and some enema water may be retained.

Preoperative bowel preparation is required for laparoscopic surgery and surgery for a malignant tumour. This is necessary in case bowel injury occurs during surgery.

Today, the vaginal wall is cleaned just before surgery with Betadine after the bladder is catheterized. The bladder needs to remain empty throughout the surgery. If spinal or epidural anaesthesia is employed, the woman may not be able to micturate as such and bladder catheter for 24 h postoperatively becomes necessary.

In prolapse, if infection or a decubitus ulcer is present, vaginal packing with Betadine for a few days heals the ulcer. Menopausal woman may require oestrogen vaginal cream for a few days.

Most women are now admitted early on the day of the operation, and this saves the cost. Only those at high risk or with a medical disorder get admitted one day prior to surgery.

Shaving the part is essential. The area for surgery is cleaned with Savlon and spirit in the operation theatre. The vagina is cleaned with Savlon or Betadine lotion. The bladder catheter keeps the bladder empty throughout the surgery. This avoids injury to the bladder.

Anaesthesia

It is left to the choice of the anaesthetist, and this partly depends upon the condition of the woman.

Antibiotics

Today's practice is to start intravenous antibiotics intraoperatively. In caesarean section, antibiotic is administered after the delivery of the baby.

Postoperative Care

Postoperative care is important if surgical complications are to be avoided.

Immediate Care (24 H)

Vital signs such as

- Pulse, temperature, BP and respiration chart to be maintained.
- The patient needs intravenous fluid for 24 h. Following a minor surgery, oral fluids are allowed 4 h after the surgery, and soft diet is given on the day of surgery.

The average patient needs 2 L of fluid intravenously for 24 h. This comprises 1 L of 5% glucose, 1/2 L of glucose saline and 1/2 L of Ringer's lactate to maintain electrolyte balance. If the woman vomits, extra fluid is required to make up for the loss.

- Intake–output chart should be maintained to monitor renal function as well as to decide on the amount of intravenous fluid required. Catheter for 24–48 h prevents urinary retention.
- Antibiotics are best administered intravenously in the first 24 h. The first dose is given during surgery. Later, oral antibiotics can be started. The choice of antibiotics depends upon the surgeon, but it is prudent to administer IV Metrogyl for the first 24 h to combat anaerobic organisms in addition to other antibiotics.
- Analgesics are required for a day or two, and the choice depends upon the need of the woman. A night sedation allows the woman to sleep well and wake up fresh. NSAID should be avoided in a woman with asthma and gastric ulcer.
- The patient should be observed for respiratory complications and pain in the legs (thrombosis).
- The abdomen is watched for distension and bowel sounds. Once the bowel sound returns, oral soft diet is started.
- Urine culture should be obtained if the indwelling catheter is placed for 2 days or more.
- The patient should be watched vaginal bleeding. A slight bleeding is noted during the first few days, and this wears off gradually.
- Blood transfusion should be avoided as far as possible. If postoperative haemoglobin falls below 8 g%, iron therapy will restore it to normal. It should be noted that one unit of blood raises haemoglobin by just 1 g, with its other associated risks of blood transfusion.
- Early ambulation is practiced today to avoid thromboembolism. The patient is advised to move out of bed once the intravenous fluid is stopped.
- Bowels should be moved with dulcolax or enema on the third or fourth day once she is on solid diet.
- The abdominal dressing should be changed on the third day and when the sutures are removed. Nowadays, subcuticular catgut suture for the skin does not require removal.
- The woman is normally discharged home on the fourth or fifth day of operation. The patient is advised against intercourse for one month.

Follow-up is done a month after the surgery to check all is well. The woman needs counselling regarding lifestyle, sexual activity and any special precaution. A woman operated for cancer needs prolonged chemotherapy and radiotherapy and should be under observation for recurrence.

Immediate postoperative complications are:

- Haemorrhage
- Infection such as wound infection, chest infection, urinary infection
- Paralytic ileus
- Embolism
- *Burst abdomen*. Burst abdomen in gynaecological surgery is now rare that Pfannenstiel incision and subcuticular VICRYL Suture material is used.

Pelvic vein thrombosis with fever and tachycardia is less common with early ambulation and prophylactic antibiotics. CT is useful in the diagnosis of pelvic vein thrombosis. Heparin and antibiotic are needed.

Late sequelae are:

- Scar hernia
- Dyspareunia in vaginal surgery
- Abdominal adhesions causing chronic pain
- Recurrence of fibroids and endometriosis
- Recurrence of malignancy

Surgical Procedures: Dilatation of the Cervix and Endometrial Curettage (D&C)

D&C is a minor gynaecological procedure of dilatating the cervix and curetting (scraping) the endometrial tissue from the uterine cavity.

It is mainly a diagnostic procedure, rarely done for therapeutic purpose (mainly obstetric).

Dilatation of the cervix alone is required in the following conditions:

- Prior to curettage (commonest).
- For cervical stenosis.
- To prevent cervical stenosis following Manchester operation for prolapse of the uterus.
- To prevent postoperative cervical stenosis in cauterization of cervical erosion and conization.
- To drain haematometra.
- To drain pyometra.

- Prior to insertion of radium into the uterine cavity in cancer of the cervix and endometrial cancer.
- Prior to removal of embedded intrauterine contraceptive device (IUCD).
- Prior to breaking uterine adhesions in Asherman syndrome.
- Prior to endocervical curettage for endocervical cancer.
- Prior to hysteroscopy.
- To diagnose incompetent os. If No. 9 dilator goes in easily, the internal os of the cervix is considered as an incompetent os with the risk of habitual abortion and preterm labour.

Obstetric indications are:

- Prior to evacuation in missed abortion, incomplete abortion, evacuation of hydatidiform mole. It is also necessary in medical termination of pregnancy.

Curettage is mainly diagnostic. This is required in:

- Abnormal uterine bleeding (AUB) to study the hormonal pattern causing abnormal bleeding.
- Secondary amenorrhoea to detect tubercular endometritis.
- Postmenopausal bleeding to rule out endometrial cancer.
- Endometrial cancer to study the endocervical tissue and the extent of spread. This helps in staging and deciding on treatment.
- *Infertility*. Until recently, D&C was performed premenstrually to detect if ovulation has occurred. Secretory endometrium indicates that ovulation has occurred. Proliferative endometrium in the premenstrual phase indicates non-ovulation. Now, ultrasound has replaced D&C for monitoring ovulation. It is however required if tubercular endometriosis is suspected. The endometrial tissue is preserved in saline for culture. The tissue is also subjected to polymerase chain reaction. Corpus luteal phase defect is diagnosed when the endometrial histology lags behind the menstrual date by 2 days.
- A menopausal woman on hormonal replacement therapy; she should be watched for endometrial hyperplasia and cancer.
- A woman on tamoxifen for breast cancer should undergo curettage 6-monthly to diagnose endometrial hyperplasia and cancer.

Therapeutic D&C is indicated:

- To remove endometrial polyp (polypectomy).
- Obstetric indications mentioned for dilatation of cervix.

The dilators used are:

- Hegar double-ended dilator (Figure 45.1).
- Hawkins' single-ended dilator (Figure 45.2).
- Fenton's dilator (Figure 45.3). They come in different sizes (No. 3–10 dilators).

Slow cervical dilatation is performed with prostaglandin E_1 (misoprostol) vaginal pessary (200–400 µg). The pessary is inserted in the vagina 3 h prior to D&C, and this slow dilatation avoids cervical trauma.

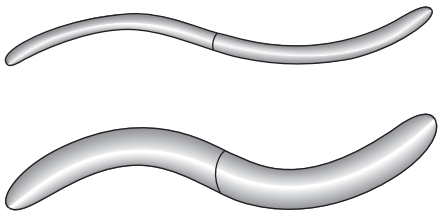

Figure 45.1 Hegar's double-ended dilator used to dilate the cervix.

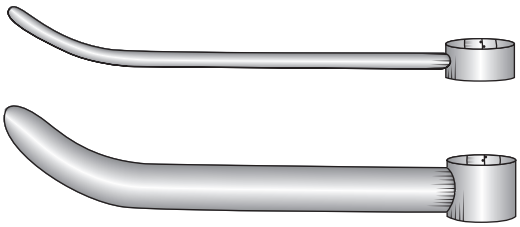

Figure 45.2 Hawkin's single-ended dilator.

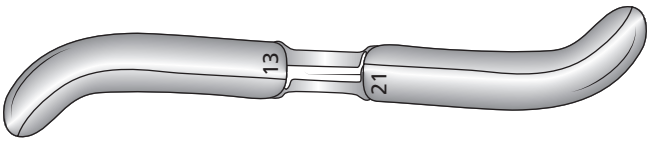

Figure 45.3 Fenton's dilator.

Curettage is performed usually with a sharp curette. The blunt curette is used in obstetric conditions to avoid uterine perforation (Figures 45.4 and 45.5).

Karman plastic curette is mainly used for suction evacuation in medical termination of first-trimester pregnancy. These come in sizes no. 3–10.

Procedure of D&C

The equipments required are as follows:

- Sim's speculum
- Anterior vaginal wall retractor
- Vulsellum or Allis forceps to hold the anterior lip of the cervix
- Uterine sound
- Cervical dilators
- Curette

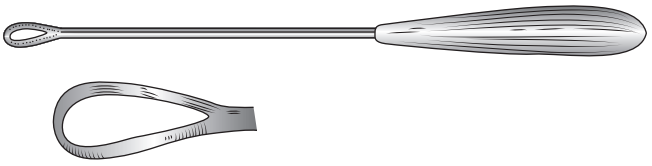

Figure 45.4 Sim's uterine curette.

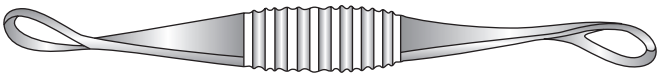

Figure 45.5 Blake's double-ended uterine curette.

- Sponge-holding forceps and sponges to clean the area and vagina
- Savlon, Betadine
- 10% formalin to preserve the endometrial tissue
- Saline to preserve endometrial tissue for culture

D&C is performed under either sedation, paracervical block or general anaesthesia. Local anaesthesia is adequate in a multiparous woman, but a nulliparous or an apprehensive woman may require general anaesthesia.

- The woman is put in the lithotomy position. The perineal area and inner thigh area and vagina are cleaned with Savlon or Betadine. The area is draped with sterile sheets.
- Bimanual examination is done to ascertain the size of the uterus and its direction and to rule out adnexal mass.
- With the help of Sim's speculum and anterior vaginal wall retractor, the cervix is exposed and the anterior lip held with Vulsellum or Allis forceps.
- The uterine sound confirms the size of the uterine cavity and its direction (normal length is 5–6 cm).
- The cervix is dilated starting from No. 3 up to 10 mm.
- The curette is introduced into the uterine cavity and the uterine lining scraped from above downwards all round.
- A gritty sensation indicates the end of curettage.
- The tissue is preserved in 10% formalin. For culture and PCR, the tissue is sent in saline. Other methods of obtaining endometrial tissue for the histological study are:
- *Fractional curettage*
- *Endometrial biopsy*

Fractional curettage is indicated in suspected endometrial carcinoma. In this procedure, endocervical curettage is done prior to cervical dilatation. Following dilatation, the isthmic portion is curetted and the tissue kept in a separate bottle. Thereafter, the uterine cavity is curetted and sent separately.

Normal endometrium appears pink and healthy. Profuse, pale looking and friable tissue suggests malignancy. Fractional curettage determines the extent of spread of malignancy down the uterine wall, so that staging can be done and appropriate treatment planned. Involvement of endocervical lining places the malignancy in stage II of the disease.

Endometrial biopsy is performed as an outpatient procedure without anaesthesia or under sedation. The cervix is not dilated and a biopsy curette is inserted and a strip or two of endometrial tissue is obtained for histological study.

Contraindications

Contraindications to D&C are:

- Suspected pregnancy
- Lower genital tract infection

This surgical procedure is performed only after the infection clears up with antibiotics.

Complications

Complications of D&C are few and rare.

Dilatation of cervix can cause:

- Ascending infection.
- Cervical tear and bleeding.
- Incompetent os.
- Uterine perforation occurs mainly in a soft uterus, i.e. pregnant, puerperal uterus, and in atropic postmenopausal or scarred uterus. It can also occur in a malignant uterus.

Perforation is suspected when the dilator or curette goes further in without resistance beyond the measured length of the uterine cavity. The first thing to do is to remove the instrument and postpone surgery. If the bleeding is slight, the woman is observed for internal bleeding. Heavy bleeding requires immediate laparoscopy and sometimes laparotomy. Laparotomy is required when intestinal injury occurs.

Sequelae of D&C

- Infection of upper genital tract.
- Asherman syndrome—This condition is caused by vigorous curettage, in tubercular endometritis and following packing of the uterine cavity to control postpartum haemorrhage. It also follows uterine sepsis.

Asherman syndrome is classified as mild, moderate or severe depending upon the degree and extent of adhesion. The woman presents with hypomenorrhoea, secondary amenorrhoea, infertility or habitual abortions.

The diagnosis is confirmed with hysterosalpingography or hysteroscopy. Hysteroscopy enables adhesiolysis. Reformation of adhesions is prevented by insertion of IUCD for 3 months and giving oestrogen cyclically (21 days) for 3 months to develop endometrium or by inserting the Foley catheter into the uterine cavity for 7 days and giving oestrogen.

- Infertility due to pelvic inflammatory disease (PID) caused by ascending infection.
- Ectopic pregnancy due to PID.
- Rupture uterus during subsequent pregnancy or labour.
- Adherent placenta following Asherman syndrome.

Instruments Used

Sim's speculum is a double-ended speculum which retracts the posterior vaginal wall, in dorsal and left lateral positions (Figure 45.6). It comes in different sizes.

Sim's anterior vaginal wall retractor is a double-ended instrument with a loop at either end (Figure 45.7).

Vulsellum forceps is a long forceps with teeth at one end which ensures a firm grip on the cervix when the Vulsellum is locked. It is applied to the anterior lip of the cervix during D&C, Fothergill operation and vaginal hysterectomy. It can also be applied to the posterior lip during culdocentesis for aspirating pus in pelvic abscess and blood in ectopic pregnancy. In a pregnant uterus and menopausal uterus, it is safer to use Allis forceps—this will avoid cervical trauma and bleeding (Figures 45.8 and 45.9).

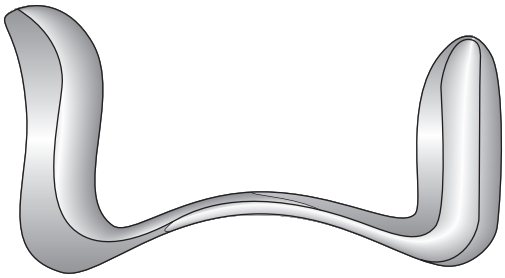

Figure 45.6 Sim's speculum. It retracts the posterior vaginal wall to expose the cervix; also used during vaginal surgery.

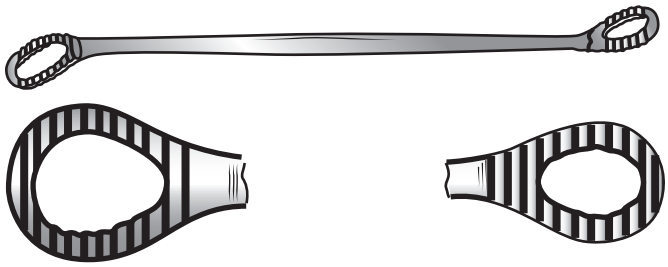

Figure 45.7 Sim's anterior vaginal wall retractor retracts the anterior vaginal wall to expose the cervix.

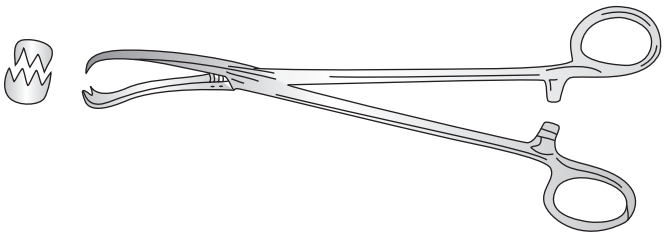

Figure 45.8 Vulsellum forceps. It is used to grasp the cervical lip and steady the cervix during vaginal surgery.

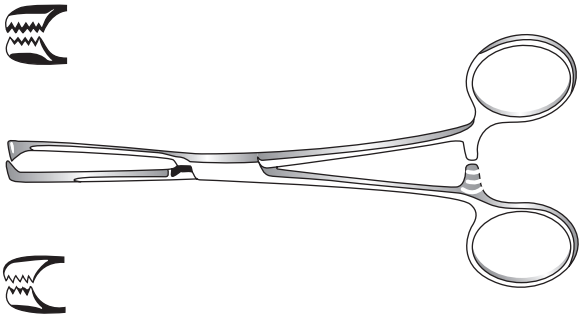

Figure 45.9 Allis forceps. It can also hold the cervix, edges of the vagina during colporrhaphy and edges of the rectus sheath during abdominal surgery.

Sponge-holding forceps is used to hold the soft cervix during obstetric D&C. Apart from its use to clean the area with sponge, the sponge forceps is also used to hold the cut edges of the lower uterine segment in caesarean section and the cut edges of the cervical tear following vaginal delivery and as a haemostatic as well.

Uterine sound is a 30 cm long angulated instrument with a handle at one end and a rounded blunt tip at the other. It is marked in inches or centimetres. The angulation accommodates for flexion of the uterus (Figure 45.10).

Uses of uterine sound

It measures the uterine cavity and the cervical length.

- It is used to diagnose cervical stenosis.
- It is used to sound a polyp, IUCD or uterine septum.
- It helps to break adhesions in Asherman syndrome.
- It differentiates between chronic inversion and fibroid polyp.
- In a misplaced IUCD, the uterine sound can be inserted and X-ray of the pelvis taken, and the position of IUCD in relation to the sound shows if IUCD is perforated.

Other Types of Speculum

- Cusco speculum. (Ch. 6)
- Auvard speculum (Figure 45.11) is a heavy retractor provided with a heavy metal ball and is self-retaining. It is employed in vaginal hysterectomy to retract the posterior vaginal wall. A channel is provided in the handle to collect the blood and drain.

The ovum forceps is a non-crushing forceps which does not have a catch or lock on its handle and is meant to grasp the products of conception. The forceps is introduced closed into the uterine cavity. It is then opened, the products of conception grasped, the instrument closed and rotated to detach the products from the uterine wall.

Figure 45.10 Simpson's uterine sound. It measures the uterine cavity, sounds a polyp and IUCD.

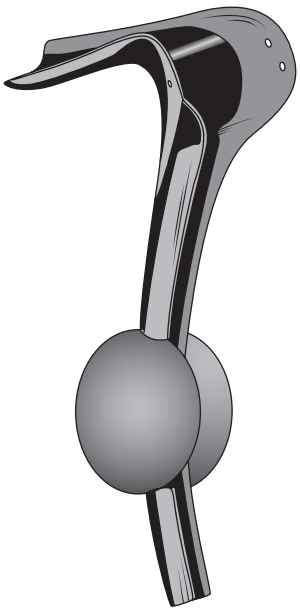

Figure 45.11 Auvard speculum. Auvard speculum retracts the posterior vaginal wall during vaginal hysterectomy and is self-retractory.

Apart from D&C, the following are the other methods employed to study the endometrium:

- Ultrasound which shows endometrial thickness (hyperplasia and cancer) and detects endometrial polyp. Doppler ultrasound shows increased blood flow and decreased resistance to the flow in endometrial cancer.
- Hysteroscopic evaluation and biopsy.

Conization of Cervix

Conization of cervix is required when Pap smear and colposcopy reveal CIN II or CIN III. It is done under general anaesthesia, using cold knife or laser to cut into the tissue. The vaginal wall is incised all round 1 cm above the external os or above the visible lesion, and dissected off the cervix. The cone is dissected extending up to or short of the internal os. Haemostasis is secured and the area is left to granulate and not covered with the vaginal flap, as this gives a wrong reading on the follow-up Pap smear (Figures 45.12 and 45.13).

Since conization causes bleeding, it is now mostly replaced by colposcopic selective biopsy or large loop excision of the transformation zone (LLETZ) and Leep (see Chapter 38 on cancer of the cervix). Conization is used as a therapeutic procedure in CIN III in young women desirous of future pregnancy.

Complications

Apart from bleeding and infection, conization can cause cervical stenosis and incompetent os. This can lead to haematometra, habitual abortions and cervical dystoria during labour.

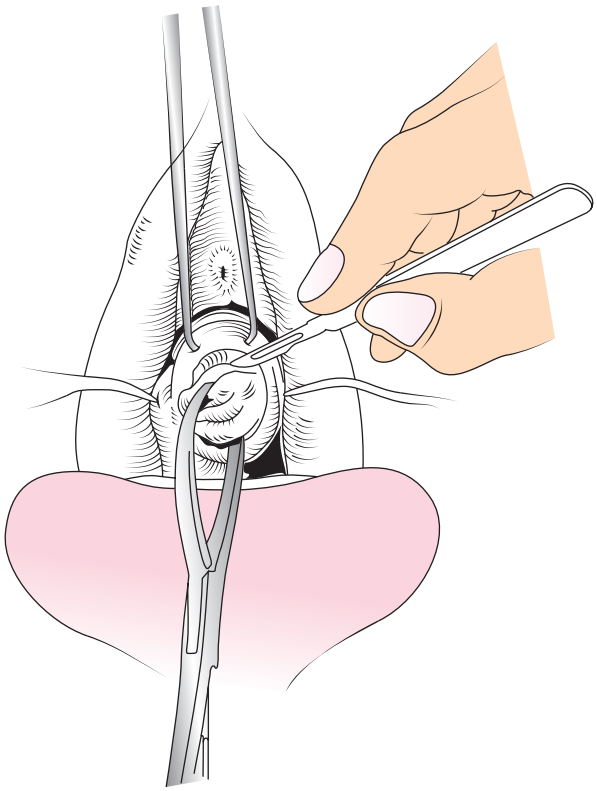

Figure 45.12 Grasping the cone biopsy.

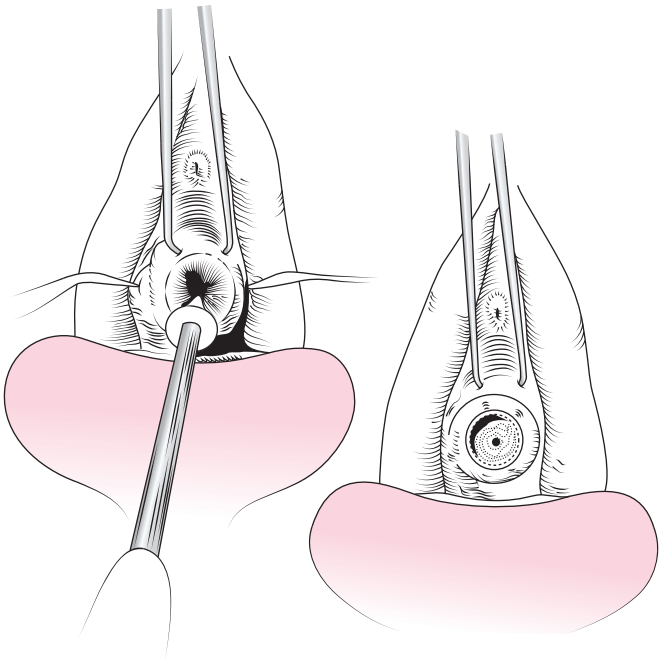

Figure 45.13 Haemostasis and removal of cone of the cervix.

Key Points

- To make any surgery safe, preoperative and postoperative care are as important as the surgical technique.
- Preoperative care includes confirmation of the clinical diagnosis, assessment of the extent of the surgery required and making the patient fit for anaesthesia as well as surgery.
- Postoperative care looks after her nutrition, prevention of infection with appropriate and adequate antibiotics, prevents thromboembolism by early ambulation and makes this period as pain-free and comfortable as possible.
- D&C is a minor diagnostic procedure.
- Dilatation of cervix is required in a few cases.
- Endometrial study is required in AUB, secondary amenorrhoea and postmenopausal women suspected of endometrial cancer.
- Conization of the cervix is restricted to therapeutic procedure in young women with CIN III. As a diagnostic procedure, it is mainly replaced by colposcopic biopsy, LLETZ and Leep.

Self-Assessment

1. Discuss the indications of D/C.
2. What are the complications of D/C?
3. Discuss the role of conization.

Suggested Reading

Hacker and Moore's Essentials of Obstetrics and Gynecology 2010.

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