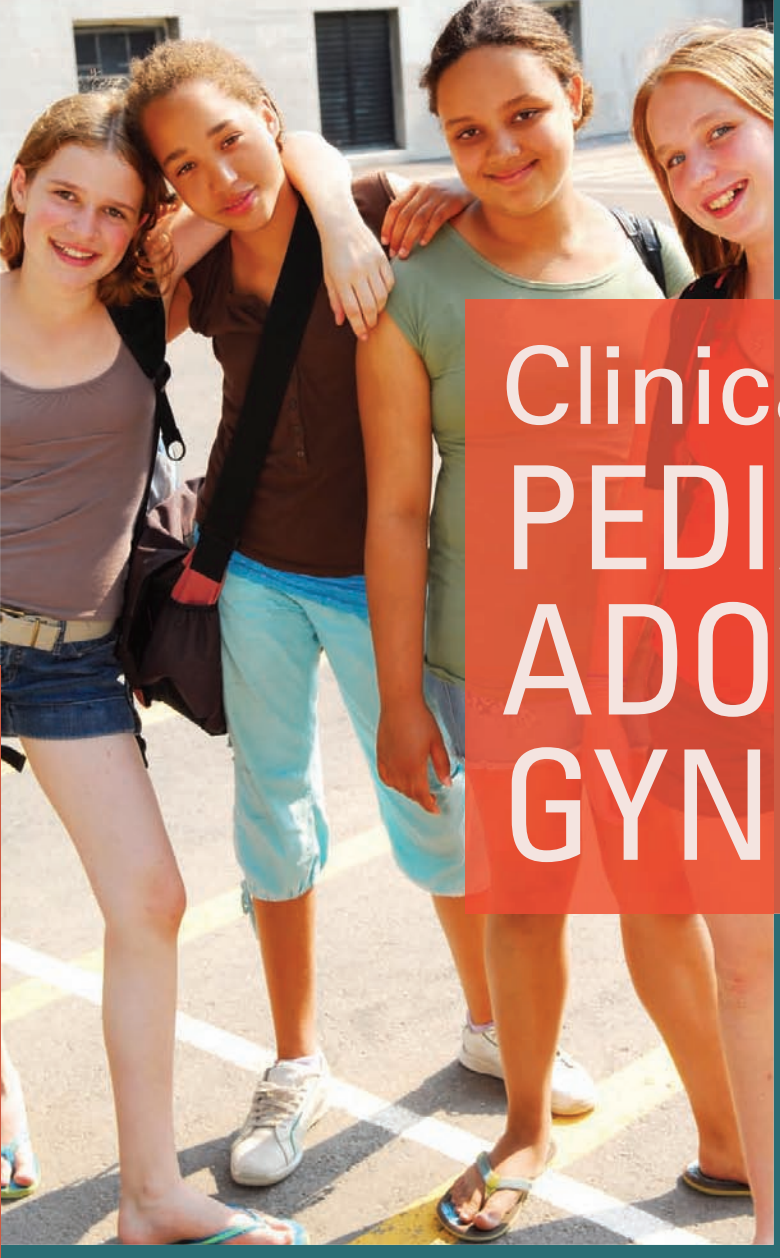

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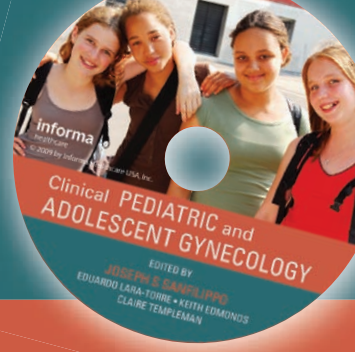

Clinical PEDIATRIC and ADOLESCENT GYNECOLOGY

EDITED BY

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Foreword

There are ever increasing numbers of physicians who specialize in the care of children with gynecologic problems. Yet few special areas of medicine have had to struggle to define its rightful place in the clinical arena as much as pediatric and adolescent gynecology. In fact, the twists and turns of pediatric and adolescent gynecology have been like a Wagnerian epic. This book helps to outline the scope of the specialty and should be required reading for those clinicians who work in this important area of medicine. Its chapters zigzag across the intersecting fields of endocrinology, urology, surgery, clinical genetics, oncology and psychiatry. The numbers of topics covered in the chapters of this book illustrate how much the clinical practice of pediatric and adolescent gynecology has evolved over the past several decades.

The authors are a remarkable sample of the people who have helped to galvanize this field and established it as a distinct and important area of clinical medicine. Together they carefully dissect each of the topics in this field, including perioperative care, sports medicine and confidentiality issues surrounding the care of children and adolescents. Their frequent references to randomized controlled trials, clinical prediction rates and treatment algorithms show that this field of medicine has effectively transitioned into the leitmotif of evidence-based medicine. The technologies that are essential to clinical care of the 2000s such as imaging (US, MRI) and DNA diagnostics are deftly woven into the content of each clinical topic. This is very important since magnetic resonance imaging (MRI) has assumed a role of unparalleled importance in diagnostic medicine and more recently in basic research.

This edition is especially designed for clinicians who work in the area of pediatric and adolescent gynecology on a daily basis. This is aptly reflected in the title *Clinical Pediatric and Adolescent Gynecology*. Throughout the book are many useful tips to assist the clinician in examining the small infant and difficult adolescent. The topics may seem to lack the cohesive spine of a more focused work, but there is an impressive body of information in this book by Joseph Sanfilippo and colleagues. The text is well written and some presentations are especially good at avoiding distracting details while providing useful approximations and novel insights for the busy clinician. It may not be possible to absorb all the chapters in this book in one sitting, but it is a treat to be able to return and reread certain topics frequently. There is much material here to learn and unlearn.

The editors led by Sanfilippo have taken up the gauntlet from a small number of historic "galvanizers" who turned people on to the importance of pediatric and adolescent gynecology as a distinct area of clinical medicine many decades ago. Though small in numbers these individuals (John Huffman, Vince Capraro, John Dewhurst, Alvin Goldfarb) transformed what was largely a descriptive science into a major tool for the study of pediatric and adolescent gynecology. Their role in setting the pace for scientific change in pediatric and adolescent gynecology is still underappreciated.

The authors of this book, who are literally the scientific grandchildren of the founding fathers, advance us further. They make us realize that translational research is not just taking results from the bench to the bedside, but reversing the process may be equally important. The unexpected responses of patients, observed by astute clinicians, constitute valuable human experiments and serve to generate new ideas and hypotheses that can advance the science of pediatric and adolescent gynecology.

Paul G McDonough

Preface

As medicine advances, as both art and science, we see specific focus on pediatric and adolescent gynecology. We live in an age in which the foundation for prevention of cervical cancer is being established. The advent of HPV vaccination appears to have a profound impact on prevention of cervical dysplasia and the sequela of a time-honored problem that oftentimes begins in adolescence. Strategies for fostering HPV vaccination beginning at nine years of age must be considered as we provide care to this unique age group. What about "attitudes" of health care providers rendering care to patients from birth through early twenties? This has taken on a whole new perspective as we advance both in the art as well as the science of pediatric adolescent gynecology. We now reflect on evidence-based data support for the presence of endometriosis in prepubertal girls. We remain aware of the fact that adolescent pregnancy rates are once again on the rise after a significant period of decline. We have learned much about communication with the teen and teen with parent or guardian. What are the barriers to communication and how should you the health care provider address such? Risk-taking behavior as well as emphasis on abstinence and "safe sex" have moved to the forefront of options when it comes to intimacy among adolescents.

We observe the evolution of new organizations across the world that provide cutting-edge information for those who provide care for the pediatric and adolescent age group. The North American Society for Pediatric and Adolescent Gynecology (NASPAG) and "FIGIJ" (the International Society for Pediatric and Adolescent Gynecology) were among the first to organize a forum for exchange of information and updating knowledge of the subspecialty area. EUROPAG (European Pediatric and Adolescent Gynecology Society), ALOGIA (South American Society for Pediatric and Adolescent Gynecology) and BRITSPAG (British Society for Pediatric and Adolescent Gynecology), as well as the Israeli Society for Pediatric and Adolescent Gynecology, continue to participate in fostering an environment of enhanced knowledge exchange for clinicians worldwide. The American College of Obstetricians and Gynecologists provides a committee, namely the Adolescent Health Care Committee, which is a multispecialty forum for the development of new educational tools to facilitate state-of-the-art care by obstetricians and gynecologists worldwide. The American Academy of Pediatrics and the American Academy of Family Practice have developed segments of their societies specifically designed to address adolescent gynecology. The Society for Adolescent Medicine is one other specialty society that includes a focus of gynecologic care. How to make an office or clinic environment "adolescent friendly" remains a goal of these specialty societies. The responsibility of making the first "gynecologic encounter" a pleasant and atraumatic event remains of paramount importance in the provision of care in this age group.

In this book's corresponding CD we have included an appendix to facilitate ready access of information at the clinician "office side" as opposed to the "bedside." The CD's video selections are designed to convey specific surgical technique for provision of care for problems in large part unique to this age group. The editors have made the decision to provide a portion of royalties from this textbook to NASPAG in an effort to expand the tools that can be utilized for education of providers of pediatric and adolescent reproductive health care worldwide. The editors remain indebted to the contributing authors for taking the time to share their time, talents and expertise with our reader audience. We have provided a comprehensive approach, designed to address virtually every problem the clinician is likely to encounter in evaluation and management of the pediatric and adolescent gynecologic patient.

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Section I: Growth and development

1. Embryology and prepubertal anatomy

Kunwar P Bhatnagar

Until recently female sexual differentiation was thought to be occurring in the absence of a Y chromosome. However, it is well accepted now that ovarian development is induced by specific genes such as DAX1 located on the short arm of the X chromosome, which down-regulates the steroidogenesis factor 1 (SF1) activity. The growth factor signaling molecule (WNT4) participates in ovarian differentiation.[1] Its early presence in the gonadal ridge is up-regulated in females but not so in males. In the absence of müllerian inhibiting substance (MIS), the paramesonephric (müllerian) ducts are stimulated by estrogens to form the upper vagina, cervix, uterus, and uterine tubes. Likewise, the external genitalia in the indifferent stage are acted upon by estrogens to develop into the lower vagina, labia majora, labia minora, and clitoris. Another line of evidence indicates that ovaries play no role in primary sexual development, as testes are required for masculinity and repression of femininity.[2] In the indifferent stage of development the gonadal sex is not determinable and both mesonephric and paramesonephric duct systems are present. Thus up to the 17 mm crown–rump length stage (estimated age 46 days[3]), the gonads cannot be identified externally either as ovaries or testes. However, genetically, the sex was already established as early as at the time of fertilization.

The female genital system comprises: (1) external genitalia – labia majora, labia minora with an interlabial gutter, frenulum of the labia minora (fourchette), gynecological perineum, mons pubis, clitoris with its prepuce, and frenulum, vestibule, bulbourethral glands, and lower vagina; (2) hymen, the upper vagina with its fornices, cervix, uterus, uterine tubes, and ovaries. The corresponding endocrine glands, such as the hypophysis, interact closely with the reproductive cycle. Several structures, such as the labia minora and its frenulum, prepuce and frenulum of the clitoris, anterior and posterior commissures of the labia majora, are highly variable in gross structure.

In the early embryo (beginning of week 4), the intermediate mesoderm gives rise to the excretory organs: the pronephroi, the mesonephroi, and the metanephroi. The majority of these develop into kidneys.[2] The gonads are intimately associated with the nephric system. The paired mesonephric ducts participate in the development of the genital system. In both sexes paired paramesonephric (müllerian) ducts develop lateral to the mesonephric (wolffian) ducts. In the female, the paramesonephric ducts form the major internal reproductive organs. In the male, the paramesonephric ducts regress and give rise to a few non-functional remnants (Table 1.1). The mesonephric ducts in the female likewise regress leaving a few non-functional remnants (Table 1.1), but in the male these ducts give rise to the ductal structures of the internal reproductive tract.

These so-called non-functional remnants remain a potential source of tumorigenesis and other cystic formations. The internal female genitalia develop independently of the ovarian influence. In the constitutive development of the external genitalia in the female, the undifferentiated fetal external genitalia become the vulva (Tables 1.2 and 1.3).

PRIMORDIAL GERM CELLS

The primordial germ cells are relatively large cells, first recognized in the 13-somite, 4-week human embryo, when as many as 30 of them are seen in the endoderm and the splanchnic mesoderm near the base of the allantois and the adjacent yolk sac.[4]

Table 1.1 Homologies of the female and the male genital systems*[2,10,16,17]

Female	Undifferentiated	Male
Oocytes	Primordial germ cells	Spermatozoa
Ovary	Gonad	Testis
Proper ovarian ligament and round ligament of the uterus	Gubernacular cord	Gubernaculum testis
Epoöphorantic (Gartner's) duct	Mesonephric (wolffian) duct	Duct of epididymis and ductus deferens (distal)
No homolog		Ductus deferens (proximal); ejaculatory duct and seminal vesicle
Appendices vesiculosae (?)	Mesonephric tubules	Appendix of epididymis (?)
Epoöphoron		Efferent ductules
		Lobules of epididymis
Paroöphoron		Paradidymis (tubuli)
		Paradidymis Aberrant ductules
Ostium abdominale of uterine tube; uterine tube	Paramesonephric (müllerian) duct	Appendix of testis
		No homolog
Uterus, cervix		No homolog
Vagina (? lower portion)		Prostatic utricle
Vagina (upper portion)		No homolog
Urethra	Urogenital sinus	Urethra (except navicular fossa)
Greater vestibular glands		Bulbourethral glands
Urethral and paraurethral glands		Prostate gland Remaining urethra and glands
Vestibule	—	Rest of urethra to glans
Labia minora	Genital folds	Penis, urethral surface
Labia majora	Labioscrotal swellings	Scrotum
Hymen	Sinus tubercle	Seminal colliculus
Urachus (median umbilical ligament)	Allantois	Urachus (median umbilical ligament)
Rectum and upper anal canal	Dorsal cloaca	Rectum and upper anal canal
Most of the bladder and the urethra	Ventral cloaca	Most of the bladder: part of prostatic urethra
Ureter, pelvis, calyces, and collecting tubules	Metanephric diverticulum (ureteric bud)	Ureter, pelvis, calyces, and collecting tubules
Broad ligament	Peritoneal fold	No homolog
	Generalized mesoderm (Phallus)	
Mesovarium		Mesorchium
Clitoris		Penis
Glans clitoridis		Glans penis
Corpora cavernosa clitoridis		Corpora cavernosa penis
Bulbs of the vestibule		Corpus spongiosum penis
Mons pubis		No named homolog; this region is similar to the mons pubis of the female†

*Corresponding male structures are given for comparison.

†In the *Nomina Anatomica*,[17] the term *mons pubis* has been listed both as a general surface feature and under the female external genitalia. No such listing occurs with the scrotum. On the basis of surface anatomy, the mons pubis (the rounded fleshy prominence over the symphysis pubis) should be a valid landmark in both sexes. The question remains whether males have either a mons pubis or at least its homolog. *Mons veneris* is the name of the prominence in the female. I suggest *mons martialis* as the term for this yet to be specified region in the human male.

Table 1.2 Chronology of the appearance of the components of the genital system

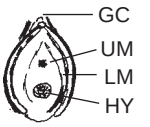
Fertilization Age	Crown–Rump Length (mm)	Developmental Event
Days		
Zero time	—	Chromosomal sex established
24–25	2.5–4.5 (13–20 somites)	Primordial germ cells; genital tubercle develops at the cranial end of the cloacal membrane
33–36	7.0–9.0	Undifferentiated gonad
41–43	11.0–14.0	Primordial germ cells incorporated in the primary sex cords: paramesonephric (müllerian) duct; nipples; urorectal septum fuses with the cloacal membrane; urogenital membrane ruptures (15-mm embryo)
56	27.0–31.0	Anal membrane ruptures; despite the fetus's human appearance, the external genitalia are still ambiguous
Weeks		
10	61	Ovary and vagina differentiate
12	87	External genitalia distinguished
16	140	Primordial follicles
18	160	Clitoris relatively large
Perinatal period	—	Hymen may rupture
Newborn	—	2 million primary oocytes in the ovaries
Childhood, puberty	—	Regression of primary oocytes; some 40 000 remain at puberty
Reproductive period (15–50 years)	—	Only about 400 become secondary oocytes and are expelled, one at a time, at ovulation
After menopause	—	Internal reproductive organs gradually regress

Data from Moore KL, Persaud TVN: The Developing Human. Clinically Oriented Embryology, 7th ed. Philadelphia: WB Saunders, 2003.

These primordial germ cells are believed to be derived from the endoderm, are 12–20 μm in diameter, with vesicular, centrally located nuclei, and distinct nuclear membranes (Figure 1.1).[4] Yolk granules persist in these cells much longer than in the somatic cells and become a diagnostic feature. The cytoplasm is rich in glycogen. Spindle-shaped germ cells are seen in the interstitial tissue, whereas the germ cells resting beneath or between the coelomic epithelial germ cells are round or oval. Migrating through the dorsal mesentery, they reach the medial mesonephric ridges, the sites for ovarian development. These sex cells become incorporated into the primary sex cords during the sixth week. Some of them may not reach the sex cords, and such ectopically oriented primordial germ cells may be the source for extragonadal teratomas and seminoma-like tumors.[5]

The ultrastructural characteristics of germ cells are unique.[4] A few pseudopodia extend from the cell surface. The round nucleus contains one or two nucleoli, finely dispersed chromatin, and numerous nuclear pores. In the cytoplasm are seen juxtanuclear Golgi complexes, centrioles, ribosomes, round mitochondria with vesicular cristae, some elements of rough endoplasmic reticulum, lysosome-like granules, lipid droplets, and pinocytotic vesicles (Figure 1.1). Glycogen particle aggregates and monofilament bundles are conspicuous. Microtubules and chromatid bodies are not observed. Occasional desmosomes are noted between germ cells and the surrounding coelomic epithelial or interstitial cells.

Table 1.3 Commonly observed hymenal types*[10–12]

Hymen	Hymenal Opening(s)	Illustrations†
i. Annular; circular; lunar	Circular or moon-shaped	
ii. Bifenestratus; biforis	Two side-by-side openings with an intervening septum between them	
iii. Crescentic	Half moon-shaped	
iv. Cribriform: fenestrated	Many small openings	
v. Denticular; fringed	Serrate-edged (as in a parous condition)	
vi. Falciform	Sickle-shaped	
vii. Imperforate	None; vaginal orifice completely closed	
viii. Infundibuliform	Centrally open with sloping sides	
ix. Septate	Opening divided by a narrow septum	
x. Subseptate	Opening partially blocked by a septum growing out of one edge but not reaching the other	

*After coitus the remnants of the torn hymen are known as hymenal caruncles.
†All illustrations (i–x) depict the hymenal condition in a 3-year-old child. The labia minora (LM) are pulled widely apart; the hymenal openings (HY) are diagrammatically exaggerated. GC, glans clitoridis; UM, urinary meatus.
Data partly from Anson BJ (ed), Morris' Human Anatomy. A Complete Systematic Treatise, 12th ed. New York: McGraw-Hill, 1966, p. 1523.

ULTRASTRUCTURE OF THE MATURE HUMAN OOCYTE

The normal mature human oocyte (Figure 1.2) is large and is enveloped by follicular cells. The nucleus is large, spherical, and eccentric in location, with a large nucleolus. Chromatin is mostly dispersed, and nuclear pores are numerous. A cluster of fine filaments is attached to the nuclear envelope. Attached to the nucleus is an aggregate of cytoplasmic organelles that corresponds to Balbiani's vitelline body;[6,7] these consist of multiple Golgi complexes, a single stack of annulate lamellae, randomly distributed mitochondria, lipid droplets, dilated smooth-surfaced endoplasmic reticulum, a centrosome, fine filaments, small aggregates of dense amorphous material, dispersed or aggregated vesicles, short and irregular tubules, multivesicular bodies, and a few membrane-attached and free ribosomes (Figure 1.2). The rest of the cytoplasm has a uniform texture with fewer organelles. The entire circumference of the subplasmalemmal cytoplasm of the oocyte and the cytocortical region of the first polar body show a heavy population of cortical granules.[8] Microvilli cover the entire oocyte surface, with the exception of the region in contact with the first polar body. The metaphase II spindle is characteristically organized.[8]

DEVELOPMENT OF THE INTERNAL GENITAL ORGANS

OVARIES

The ovary, in an undifferentiated stage, begins to develop in the fifth week as a region of multilayered coelomic epithelium (mesothelium), on the entire medial aspect of the gonadal (mesonephric) ridge. The coelomic epithelium is only one to two cells thick elsewhere on the mesonephric ridge. Primary sex cords, consisting of finger-like extensions of the epithelial cords, grow into the mesenchyme. An outer cortex and an inner medulla result. In embryos with 46,XX chromosomes, the cortex develops into the ovary, and the medulla regresses. In male

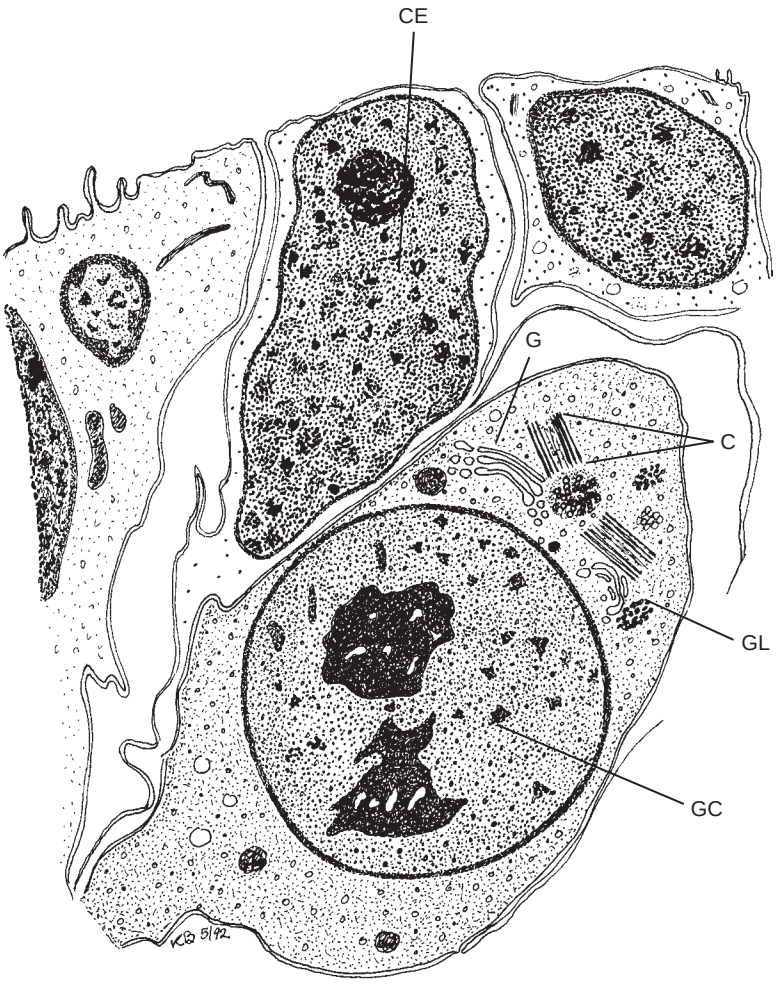


Figure 1.1 A diagrammatic illustration of the ultrastructure of a human primordial germ cell (GC) located beneath the coelomic epithelium (CE). The nucleus is round and contains two irregular and prominent nucleoli. The juxtanuclear cytoplasm shows the Golgi complex (G), centrioles (C), and glycogen particles (GL). (Modified from Fukuda T: Ultrastructure of primordial germ cells in human embryo. Virchows Arch [Cell Pathol] 1976; 20: 85–9.)

embryos this is reversed. A much thinner tunica albuginea develops at a stage later than in the males.

The ovary differentiates slowly. Nearly all primary sex cords remain in the cortex. After medullary regression, the primary sex cord clusters surround the primordial ova, which are now differentiated as primary oocytes that are in the prophase of the first meiotic division. The follicular cells proliferate from the coelomic epithelium. A full complement of primary oocytes – estimated to be 2 million – are present in the ovaries of a newborn. Regression occurs during childhood, and by puberty some 40 000 primary oocytes are said to remain.[2]

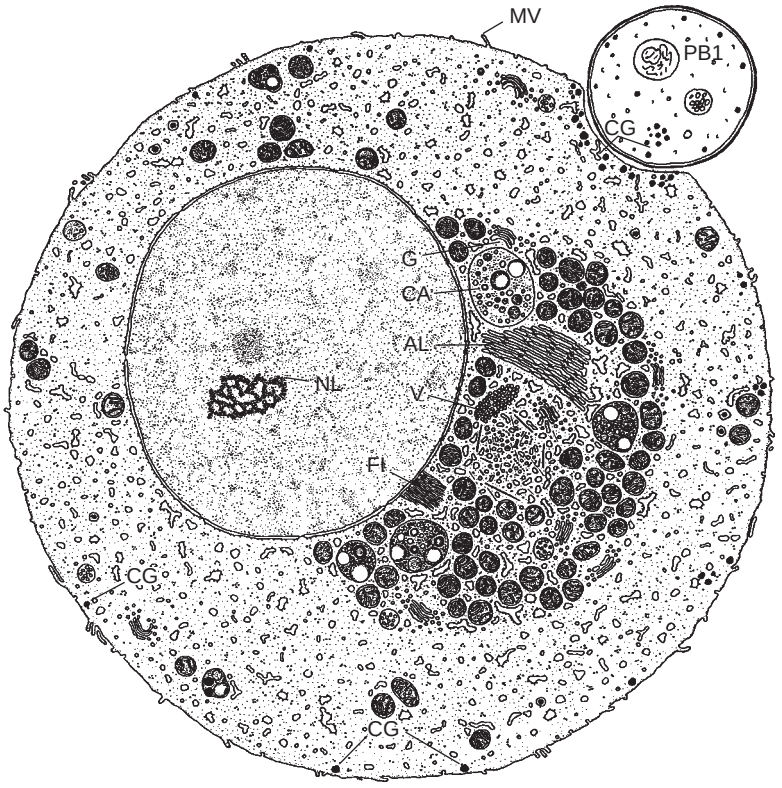


Figure 1.2 A diagrammatic illustration of the ultrastructure of a normal human oocyte in contact with the first polar body. Notice the cluster of cell organelles in the paranuclear complex of Balbiani's body (vitelline body). AL, annulate lamellae; CA, compound aggregates; CG, cortical granules; Fl, filaments; G, Golgi complexes; MV, microvilli; NL, nucleolus; PB1, first polar body; V, vesicles. (Modified from Lentz TL: Cell Fine Structure. An Atlas of Drawings of Whole-Cell Structure. Philadelphia: WB Saunders, 1971, and VanBlerkom J: Occurrence and developmental consequences of aberrant cellular organization in meiotically mature human oocytes after exogenous ovarian hyperstimulation. J Electron Microsc Technol 1990; 16: 324–46.)

Of these, only approximately 400 will develop into secondary oocytes by completing the first meiotic division, one by one, shortly before ovulation each month (Table 1.2). Virtually always, only one follicle matures and ruptures at midcycle each month. This continues until about 51.4 years of age, which is the average age when menopause occurs.[8] During the early fetal period, the ovaries are juxtarenal. They gradually descend into the lesser pelvis. Rarely, when the gubernaculum fails to unite with the uterine fundus, the ovarian and round ligaments become continuous, fail to lengthen, and as a result pull the ovary into the labia majora. In the newborn the ovaries are triangular in a cross-section made centrally through the longest plane and are rounded at the ends.[9–11] Surface furrows disappear within months after birth.[11] The ovaries in the adult are about 30 times larger in size compared with the infant (Table 1.4).[12]

ADNEXA[2,13–15]

The ovary traverses a short distance while descending to occupy its place in the ovarian fossa. It does not enter the inguinal canal. Through the mesovarium

Table 1.4 Data on the female reproductive organs[10,11]

	Ovaries	Uterine (Fallopian) Tubes	Uterus	Vagina†
Combined weight				
In the newborn	0.3 gm	—	3–4 gm	—
First 6 weeks postnatally	0.6 gm	—	—	—
Increase between birth and adulthood	5.0 gm*	—	— 14–17 gm (adult weight)	—
Size				
At birth	13 mm long/6 mm wide, 4 mm thick[10]	3.0 cm long, 5.0 mm wide	2.5–5.0 cm long, 2.6 cm wide, 1.3 cm thick	2.9–4.5 cm long, 1.5 cm wide, only potential cavity
In the adult	2.5–3.5 cm long, 2.0 cm wide, 2.0 cm thick	10 cm long, 0.1–3.0 mm wide	7.5 cm long, 5 cm wide, 2.5 cm thick, weighs 30–40 gm (1 kg at term)[10]	Anterior wall, 7.5 cm long posterior wall, 9.0 cm long, circumference about 4–5 cm^2
Long axis				
At birth	Vertical	—	—	—
During descent after birth	Horizontal	—	—	—
In ovarian fossa	Vertical	—	—	—
Epithelium				
Fetal	—	—	—	Greatly hypertrophic
During childhood	—	—	—	Remains inactive, growing slowly

*The ovaries weigh 11.3 gm at maturity, 32- to 37-fold increase from the birth weight.[16]
†The stated circumference of the orifice is about 5 cm.[11]

the ovary is attached to the medial aspect of the mesonephric fold. The inguinal fold attaches it to the ventral abdominal wall. A gubernaculum develops in the inguinal fold and later attaches to the uterus laterally near the entrance of the uterine tube. The lower part of the gubernaculum becomes the round ligament of the uterus, whereas the upper part becomes the ovarian ligament. The processus vaginalis peritonei (saccus vaginalis) also develops as a temporary peritoneal evagination. Usually its prolongation into the inguinal canal is completely obliterated. When patent (known as the *canal of Nuck*), it may form the sac of a potential umbilical hernia. The urethral and paraurethral glands remain rudimentary. The greater vestibular glands develop from the urogenital sinus.

PARAMESONEPHRIC (MÜLLERIAN) DUCTS AND FORMATION OF THE UTERINE TUBES, UTERUS, AND CERVIX[2,13–15]

The paired paramesonephric ducts develop as an invagination of the coelomic epithelium on the lateral aspect of the cranial end of the mesonephric ridge. The caudal end of this ridge grows blindly, subsequently acquires a lumen as it lengthens, and remains lateral to the mesonephric duct (Figures 1.3–1.6). At the caudal end of the mesonephros, the paramesonephric duct turns medially and, crossing ventrally to the mesonephric duct, enters the genital cord, where it bends caudally, juxtaposed with its companion on the opposite side by the third month of gestation. The blind ends of

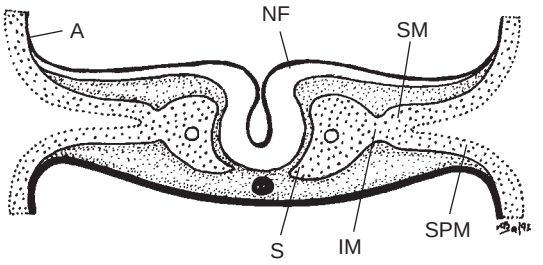


Figure 1.3 Cross section of an early (3-week) embryo showing the three divisions of the mesoderm. A, amnion; IM, intermediate mesoderm; NF, neural fold; S, somite (paraxial mesoderm); SM, somatic mesoderm; SPM, splanchnic mesoderm. (Redrawn from Moore KL, Persaud TVN: The Developing Human. Clinically Oriented Embryology, 7th ed. Philadelphia: WB Saunders, 2003.)

the two ducts produce an elevation on the dorsal wall of the urogenital sinus, the sinus (müllerian) tubercle. Each duct consists of vertical cranial and caudal segments with an intermediate horizontal section (Figure 1.6). The cranial segment forms the uterine tube, with its coelomic invagination forming the ostium of the tube (Table 1.1). The caudal vertical segments fuse to form the uterovaginal primordium, which develops into the lower uterine segment and, while enlarging, incorporates the horizontal aspects to give rise to the fundus and the body of the uterus. The endometrial stroma and myometrium develop from the surrounding mesenchyme.

The cervix is the tapered end of the uterus; its mucosa has irregular crypts unlike that of the uterine endometrium. The fused caudal portion of the paramesonephric ducts gives rise to the cervix. The paramesonephric ducts regress in the male and leave a few non-functional remnants (Table 1.1).

MESONEPHRIC (WOLFFIAN) DUCTS AND FORMATION OF NON-FUNCTIONAL REMNANTS[2,13–15]

The urogenital organs (kidneys, gonads in part, ducts, glands, adnexa) develop from the intermediate mesoderm (Figure 1.3). They are closely

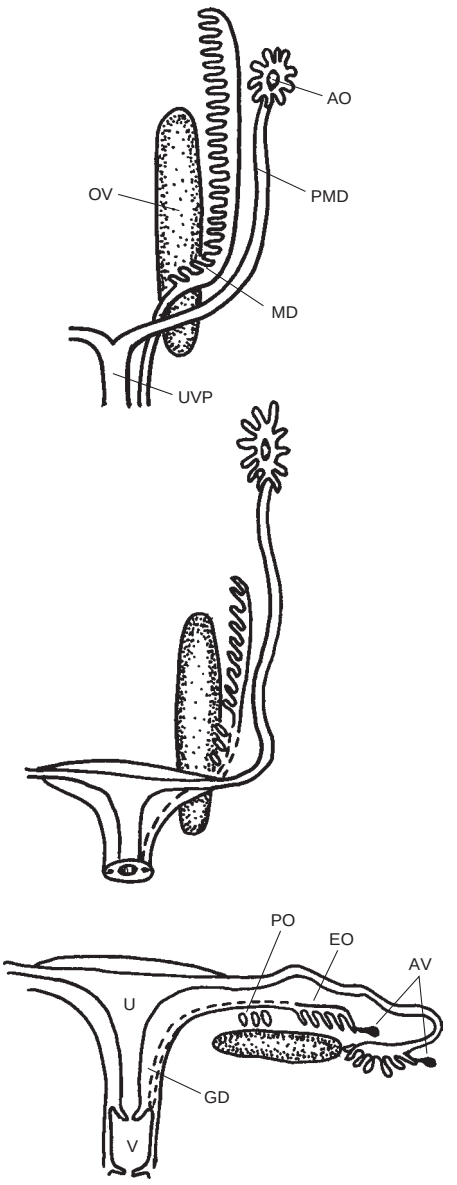


Figure 1.4 Transformation of the mesonephric (wolffian) and paramesonephric (müllerian) ducts into definitive structures. AO, abdominal ostium; AV, appendices vesiculosae (hydatids of Morgagni); EO, epoöphoron; GD, Gartner's duct; MD, mesonephric (wolffian) duct; OV, ovary; PMD, paramesonephric (müllerian) duct; PO, paroöphoron; U, uterus; UVP, uterovaginal primordium; V, vagina. (Modified from Anson BJ [ed]: Morris's Human Anatomy. A Complete Systematic Treatise, 12th ed. New York: McGraw-Hill, 1966. Modified with permission of McGraw-Hill, Inc.)

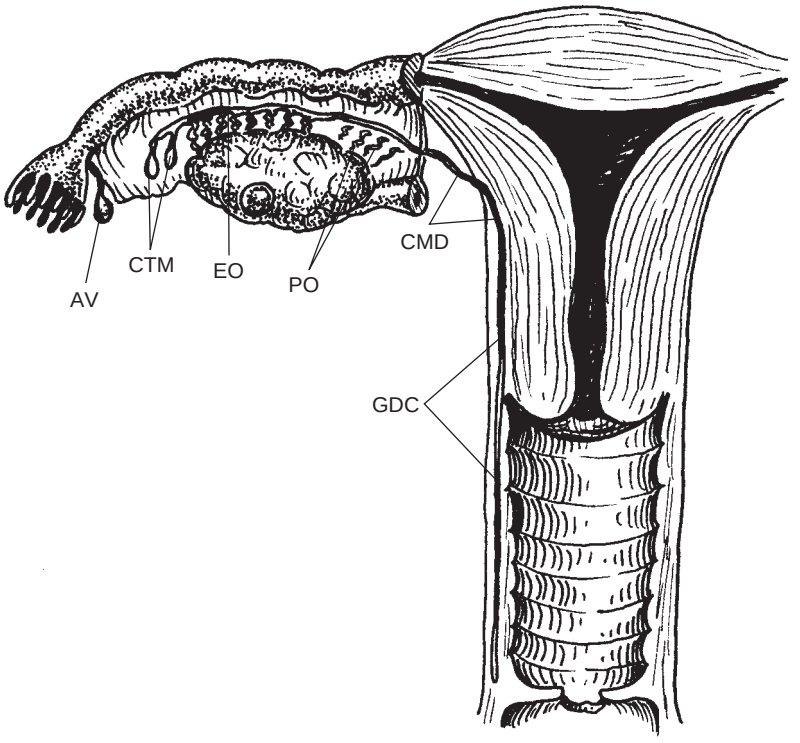


Figure 1.5 Persisting remnants of the mesonephric (wolffian) duct at puberty drawn in relation to the uterine tubes, uterus, and vagina. AV, appendices vesiculosae; CMD, cranial mesonephric duct remnants; CTM, cranial mesonephric tubules; EO, epoöphoron (cranial mesonephric tubule remnants); GDC, Gartner's duct cysts (caudal mesonephric duct remnants); PO, paroöphoron (caudal mesonephric tubule remnants). (Modified from Anson BJ [ed]: Morris' Human Anatomy. A Complete Systematic Treatise, 12th ed. New York: McGraw-Hill, 1966. Modified with permission of McGraw-Hill, Inc.)

associated with each other during early development. The fetal renal excretory system develops into the pronephroi, mesonephroi, and the metanephroi.[2] Only the mesonephros and its ducts participate in the formation of the female genital ducts (Table 1.1). Excluding the most cranial one or two tubules and the associated mesonephric duct, some five or six cranial mesonephric tubules form the epoöphoron, a vestigial structure associated with the ovary (Figures 1.4 and 1.5). The more caudal mesonephric tubules give rise to the paroöphoron, an inconsistent group of coiled tubules seen between the layers of the mesosalpinx. The paroöphoron usually disappears before adulthood. Additionally, one or more stalked, oval, pea-sized cysts known as *appendices vesiculosae epoöphorontis* (hydatids of Morgagni) are found near the epoöphoron and close to the ostium of the uterine tube. The vestigial remains of the lower portion of the mesonephric duct may be seen laterally on the upper half of the vagina as a minute tube or fibrous cord, the epoöphorantic duct (duct of Gartner). Occasionally, this duct transforms into cystic structures (Figures 1.4 and 1.5).

VAGINA AND THE HYMEN[2,13–15]

There is still no consensus on the development of the vagina. Earlier textbooks[1,2,13] describe the vagina

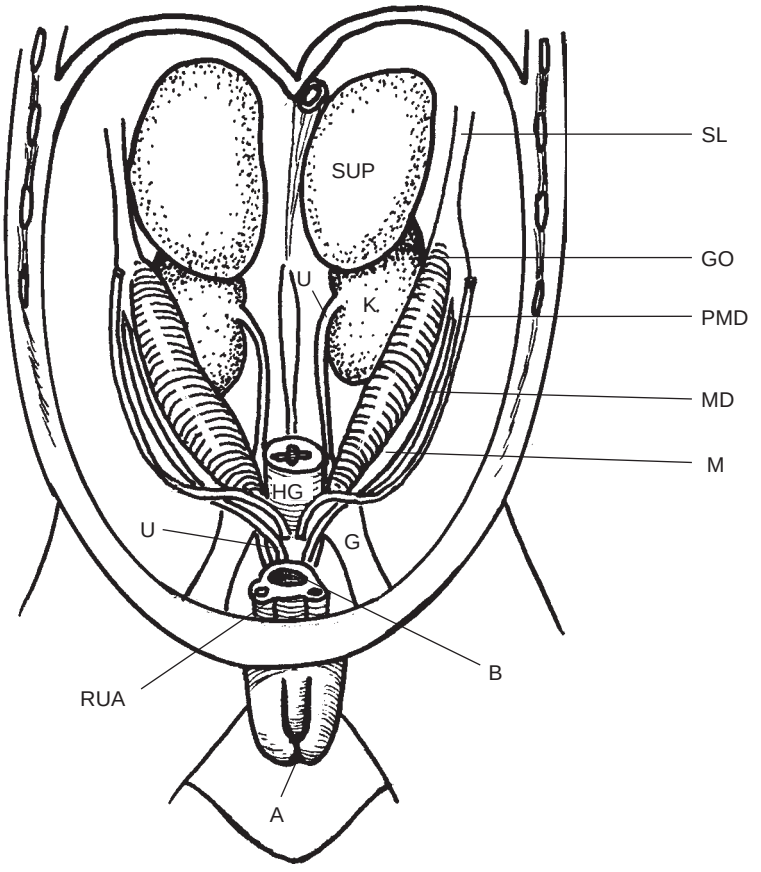


Figure 1.6 Dissection of a 26-mm human embryo at the end of the embryonic period (about 56 days) showing the developing mesonephric and paramesonephric ducts. A, anus; B, bladder; G, gubernaculum in inguinal fold; GO, gonad; HG, hindgut; K, kidney; M, mesonephros; MD, mesonephric duct; PMD, paramesonephric duct; RUA, right umbilical artery; SL, atrophying suspensory ligament; SUP, suprarenal gland; U, ureter. (Redrawn from Hamilton WJ, Boyd JD, Mossman HW: Human Embryology, 4th ed. Baltimore: Williams & Wilkins, 1972.)

as derived from two sources: the upper portion with its fornices are of paramesonephric origin; the lower is derived from the urogenital sinus. After the solid tip of the fused paramesonephric ducts reaches the urogenital sinus, which develops from the cloaca, paired solid evaginations from its pelvic part called the sinovaginal bulbs, grow out and proliferate forming a vaginal plate. By the fifth month, the entire vaginal plate is canalized. A bilayered tissue plate, the hymen (a vascularized structure made up of the sinus epithelial lining and a layer of vaginal epithelial cells) separates the lumen of the vagina from that of the urogenital sinus (later vestibule). The hymen develops a small lumen. In further development the hymen presents great variations in thickness, and the shape and size of the opening. The more commonly observed hymenal variations are described and illustrated in Table 1.3 (see also Chapter 7). In later development, the inferior hymenal surface and most of the vestibule are lined by an epithelium similar to that of the vagina. The urogenital sinus shortens to form the vaginal vestibule, which opens on the surface between the genital folds. The vaginal epithelium hypertrophies greatly

in the fetus under the influence of maternal hormones but remains unproliferated after birth and through childhood.

The walls of the vagina are seen through the hymenal orifice; the rugae in the lower part of the anterior wall of the vagina immediately beneath the urethra are more prominent in young females and in virgins.

DEVELOPMENT OF THE FEMALE EXTERNAL GENITALIA

The mons pubis, the rounded fleshy prominence over the symphysis pubis, is formed from subcutaneous adipose tissue. It remains devoid of hair until puberty, when it becomes covered by coarse hair limited above by a horizontal boundary.

The external genitalia initially develop in an undifferentiated state, and it is not possible to identify the sex externally before 12 weeks of gestation (Figure 1.7, Table 1.2). At the end of the embryonic period (8 weeks), the genital tubercle appears as a surface elevation at the cranial end of the cloacal membrane and lengthens into the phallus (Figures 1.8–1.11). Within it, the urethral plate grows towards the tip. The lower end of the plate abuts the ectoderm-lined primary urethral groove, which concomitantly develops along the

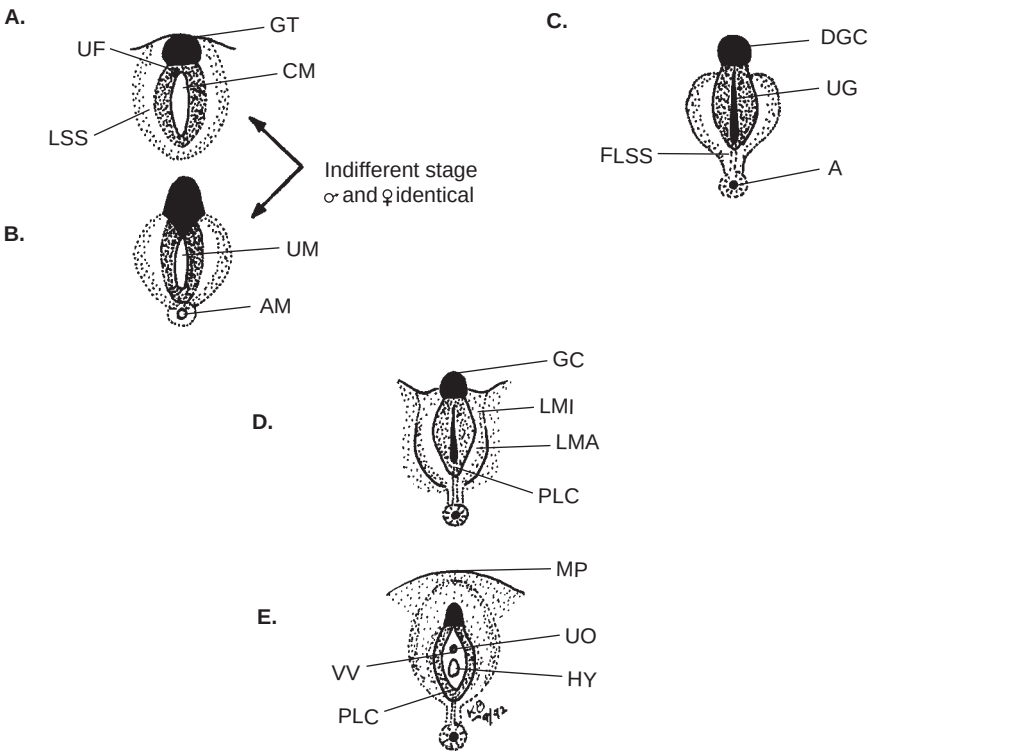


Figure 1.7 A series of diagrams illustrating the developing female external genitalia. *A, B,* The undifferentiated stages, 4 to 8 weeks. *C–E,* At 9, 11, and 12 weeks, respectively. A, anus; AM, anal membrane; CM, cloacal membrane; DGC, developing glans clitoridis; FLSS, fused labioscrotal swellings; GC, glans clitoridis; GT, genital tubercle; HY, hymen; LMA, labia majora; LMI, labia minora; LSS, labioscrotal swelling; MP, mons pubis; PLC, posterior labial commissure; UF, urogenital fold; UG, urethral groove; UM, urogenital membrane; UO, urethral orifice; VV, vestibule of vagina. (Redrawn from Moore KL, Persaud TVN: The Developing Human. Clinically Oriented Embryology, 7th ed. Philadelphia: WB Saunders, 2003.)

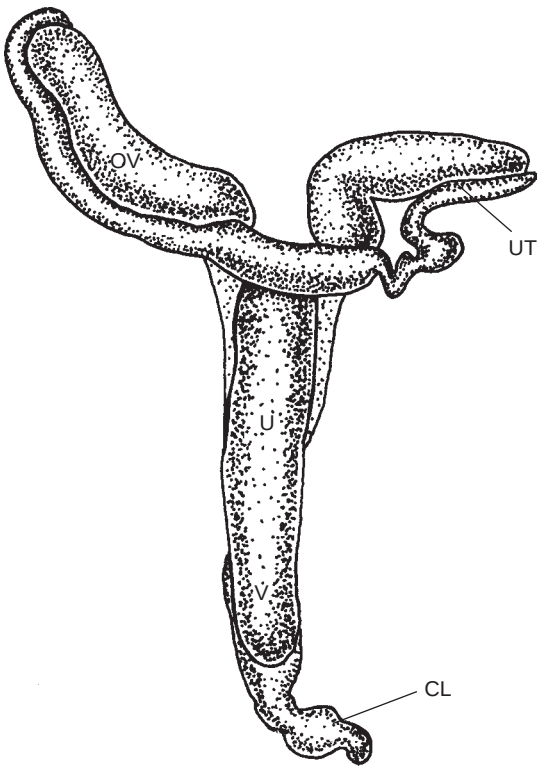


Figure 1.8 The female internal genitalia at 13 weeks (crown–rump length, 101 mm). CL, clitoris; OV, ovary; U, uterus; UT, uterine tube; V, vagina. (Redrawn from England MA: Color Atlas of Life Before Birth. Normal Fetal Development. London: Mosby–Year Book Europe Ltd., 1983.)

caudal surface of the phallus. The margins of the groove are the genital folds that surround the urogenital membrane and proximally terminate near the ventral end of the anus. The urogenital membrane ruptures at about 6 weeks, providing a common perineal space (the future vestibule) for the urinary and genital openings at the base of the phallus, bounded by the genital folds, which develop into labia minora. Two genital (labioscrotal) swellings form laterally and become the labia majora. The vestibule develops from the remains of the urogenital sinus. The urethral meatus, vaginal opening, the ducts of the greater and lesser vestibular glands, and the bulbs of the vestibule are found in the floor of the vestibule (Figures 1.10–1.12).

The phallus, which in the early stages is longer in the female than in the male, forms the clitoris. The prepuce develops first as a ridge proximal to the glans extending forward. Over the dorsum and the sides of the glans clitoridis, the shallow preputial sac is formed, but the ventral side remains free. Only in this manner does preputial development differ from the male homolog. The homologies of the external (and internal) genital organs are shown in Table 1.1.[10,16,17]

ACCESSORY STRUCTURES AND CONGENITAL MALFORMATIONS[2,13–15]

Supernumerary ovaries have been reported to occur in the mesovarium, in the broad ligament, and very rarely, in association with a third uterine tube. Bilateral absence of ovaries is rare. Unilateral absence has been associated with the absence of the corresponding uterine tube. Divided ovaries are common. Ectopically, an ovary can be drawn through the inguinal canal into the labia majora.

The uterus, Fallopian tubes, and the vagina are often absent in severe congenital malformations such as sympodia or sirenomelia. Unilateral absence of the paramesonephric duct, resulting in severe anomalies, has been reported. The anomalies of the female genital system result from faulty union or lack of the two paramesonephric ducts. This may result in either incomplete or complete duplication of the uterus combined with duplication of the vagina. Many variations between the two extremes are seen. The bicornuate uterus is a common condition in which a single vagina and cervix occur with duplication of the body of the uterus.

Hypospadias in the female, in which the urethra opens in the vagina, is quite different from that in the male. Epispadias in females is very rare and is similar to that in males. Usually there is an associated bifid clitoris and prepuce. A deep groove separates the two halves, and the urethral orifice may be in the clitoris or ventral to it.

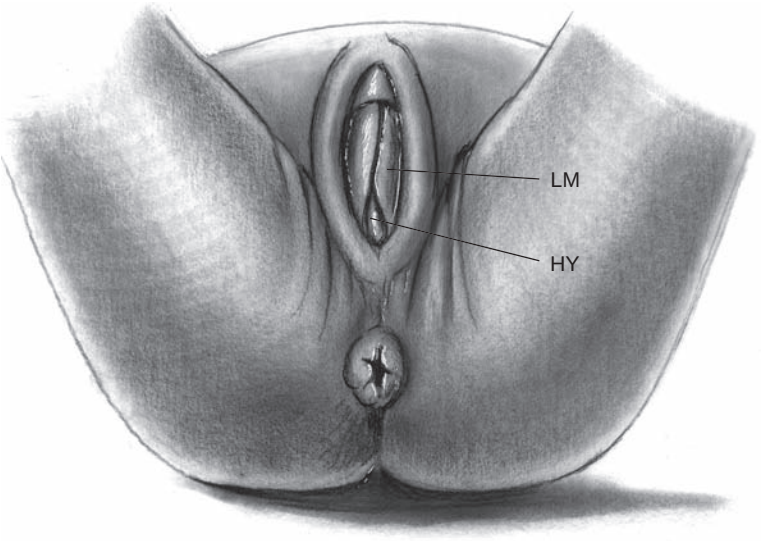


Figure 1.9 The perineum of a female fetus in the third trimester (crown–rump length, 254 mm). HY, pouting hymen; LM, labia minora.

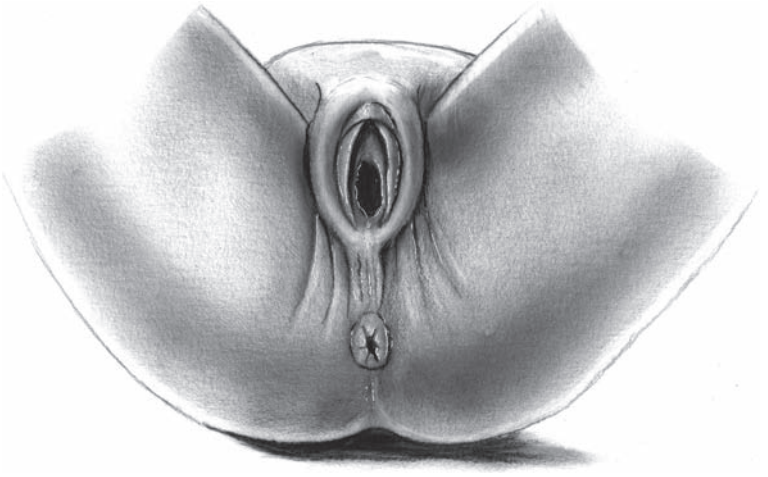


Figure 1.10 The perineum of a newborn female.

Errors in sexual development result in ambiguous genitalia. These may be the result of defective genetic direction, steroidogenesis, abnormal hormonal influences, or dyssynchrony during organogenesis. These disorders are discussed in Chapter 5.

GENITAL SYSTEM OF THE FEMALE NEWBORN AND THE CHILD[1,2,13–15]

The average weight of a full-term newborn infant is about 3300 g (7 lb), and the average crown–heel length is about 50 cm (20 in). In general, the

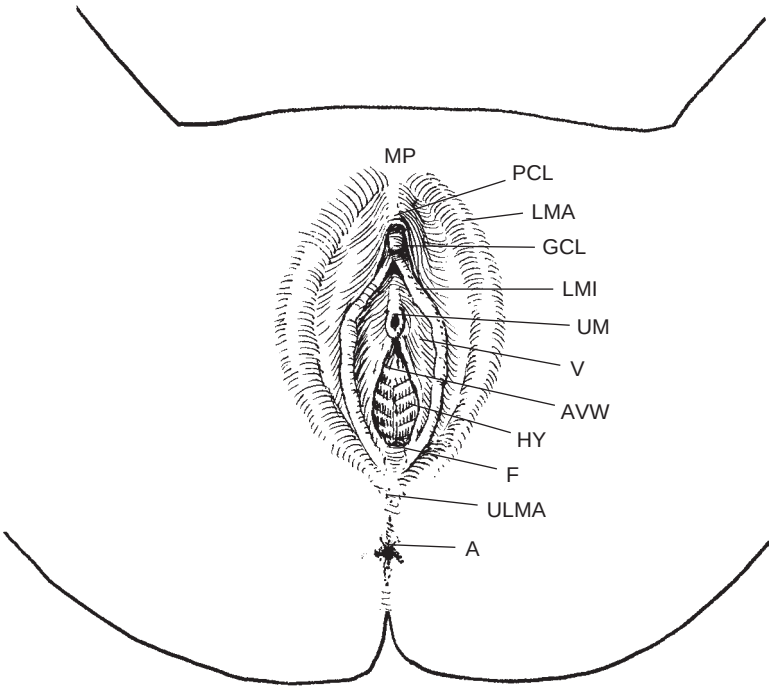


Figure 1.11 Illustration of the perineum of a 10-year-old female with labia separated. A, anus; AVW, anterior vaginal wall; F, fourchette; GCL, glans clitoridis; HY, hymen; LMA, labia majora; LMI, labia minora; MP, mons pubis; PCL, prepuce of the clitoris; ULMA, union of labia majora, posterior commissure; UM, urethral meatus; V, vestibule. (Redrawn from Snell RS: Atlas of Clinical Anatomy. Boston: Little, Brown, 1978.)

newborn female is slightly smaller and weighs less than the newborn male.[11] Water constitutes 80% of the total body weight, as compared with 60% at puberty. The newborn has 45% of water as extracellular fluid and 35% as intracellular fluid (as compared with 17% and 43%, respectively, at puberty). The development of the various components of the female genital system is summarized in Table 1.2.

In the newborn, the relatively large labia majora are bound inferiorly by a posterior labial commissure. Superiorly, they merge into the mons pubis (see footnote in Table 1.1). The labia minora are relatively larger at birth. The clitoris is also relatively larger and more prominent in the newborn than in the adult. The hymen in late fetal life and at birth consists of a membranous fold, which may protrude between the labia minora (Figure 1.9). The vaginal orifice has a circumference of about 5 cm and can permit speculum examination of the vagina. During early childhood the orifice is more deeply positioned. The rugae of the anterior vaginal wall are prominent and are seen through the vaginal orifice (Figure 1.11, Table 1.3). The vaginal wall is thin until puberty, and has a much redder appearance than in the adult. At puberty Döderlein's bacillus (*Lactobacillus acidophilus*), a large Gram-positive microorganism, appears in the vagina and breaks down glycogen in desquamated cells to form lactic acid. This protective phenomenon changes the pH of the vaginal secretions from alkaline to acidic, thus reducing the incidence of vaginitis. Mucous glands are absent in the vagina; cervical gland mucus keeps the vagina moist. Pubic hair appears at puberty; the labia minora do not develop hair.

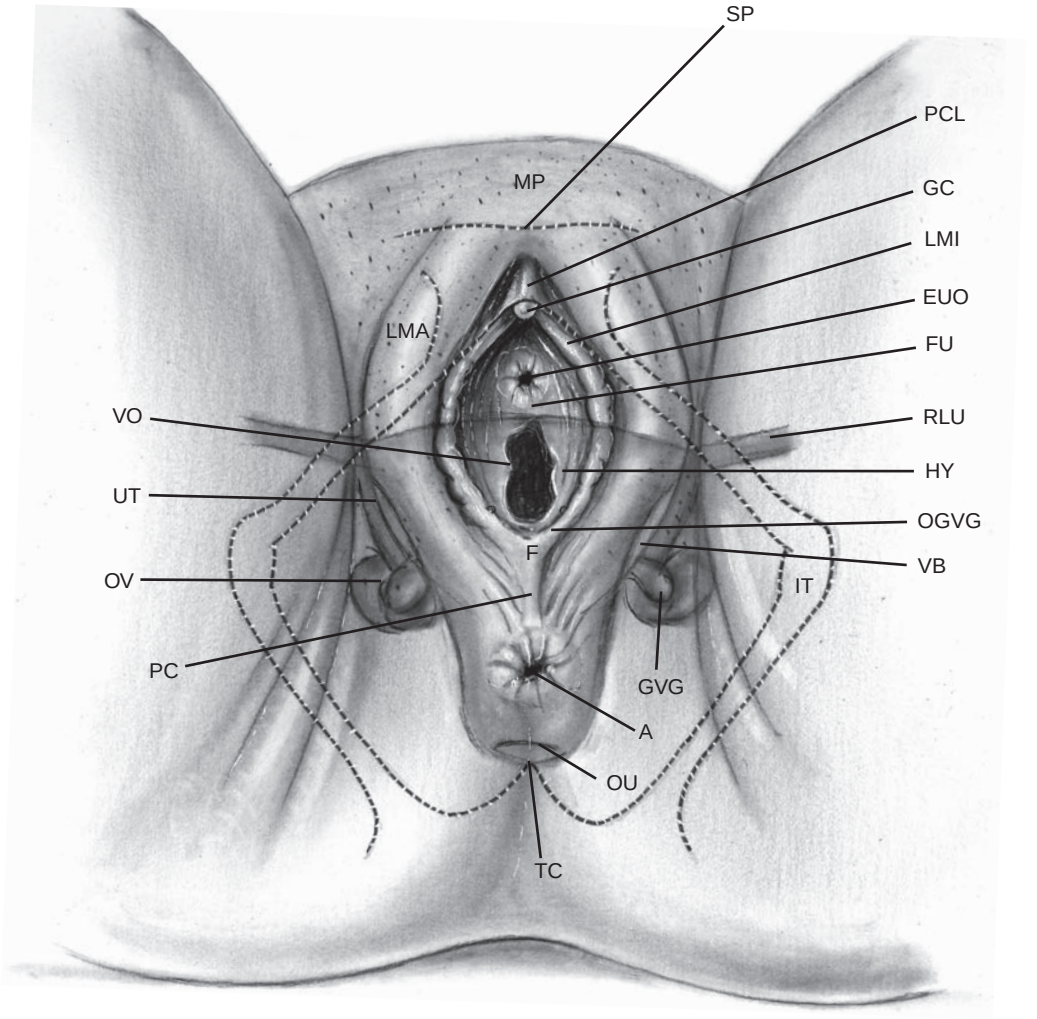


Figure 1.12 Illustration of the external genitalia shown in relation to the uterus, fallopian tubes, and ovaries, and the bony pelvis in a 10-year-old female. These internal structures are shown superimposed from an examining physician's view. A, anus; EUO, external urethral opening; F, fourchette; FU, fundus uteri; GC, glans clitoridis; GVG, greater vestibular gland; HY, hymen; IT, ischial tuberosity; LMA, labia majora; LMI, labia minora; MP, mons pubis; OGVG, opening of the greater vestibular gland; OU, ostium uteri; OV, ovary; PC, posterior commissure; PCL, prepuce of the clitoris; RLU, round ligament of the uterus; SP, pubic symphysis; TC, tip of coccyx; UT, fallopian (uterine) tube; VB, vestibular bulb: VO, vaginal orifice. (Modified from Anson BJ [ed]: Morris' Human Anatomy. A Complete Systematic Treatise, 12th ed. New York: McGraw-Hill, 1966. Modified with permission of McGraw-Hill, Inc.)

The vaginal vestibule is the cleft between the labia minora into which open the urethra, the vagina, and the multiple lesser vestibular glands. The greater vestibular glands open by a duct in the groove between the hymen and the labia minora on either side at the posterior or inferior aspect of the vaginal orifice (Figure 1.12). Between the vaginal orifice and the frenulum of the labia minora is a shallow vestibular

fossa. The hymen surrounds the vaginal orifice, which appears as an opening into it. The bulbs of the vestibule, the homolog of the corpus spongiosum penis, are paired erectile bodies on both sides of the vaginal orifice and are united in front of it by a commissura bulborum or pars intermedia. Posteriorly, they are in contact with the greater vestibular glands, and their anterior ends are joined to one another by a commissure and to the glans clitoridis by two bands of erectile tissue.

The form, size, position, and histologic appearance of the internal genital organs vary greatly between birth and attainment of puberty (Table 1.4).[11] Before birth, the uterus projects above the lesser pelvis, and the cervix is much larger than the fundus. The uterus is piriform at puberty and weighs 14–17 g. Usually the fundus is below the superior pelvic aperture, but its position depends on the contents of the bladder and the rectum. The organ is somewhat enlarged during menstruation because of increased vascularity. The ovaries are very large in the fetus, extending nearly the entire length of the Fallopian tubes (Figure 1.8). After birth, subsequent development reduces their overall dimension, and they reach adult size at puberty, gradually regressing after menopause.

APPLIED EMBRYOLOGY

IN VIVO TECHNIQUES TO AID FERTILIZATION[2,13]

In recent years several new methods have been developed and applied successfully to ensure fertilization and implantation, thus bridging the gap between sterility and fertility. Some of these new procedures are the following.

1. Intracytoplasmic sperm injection.
2. *In vitro fertilization* (IVF) and embryo transfer; zygote intrafallopian transfer, ZIFT. The first such IVF baby, Louise Brown, was born in England.[18] These procedures are detailed in Edwards and Brody.[19]
3. Assisted *in vivo fertilization* (gamete intrafallopian transfer, GIFT).
4. Cryopreservation of early embryonic stages.
5. Partial zona drilling (PZD).
6. Surrogacy.
7. Chorionic villus sampling for detection of chromosomal aberrations, X-linked disorders, and inborn errors of metabolism.

MOLECULAR BIOLOGY AS APPLIED TO HUMAN DEVELOPMENT

Molecular biological approaches such as recombinant DNA technology, transgenic animals, and chimeric models are important tools that examine specific gene expressions, their regulation of morphogenesis, and how various cells form specific embryonic parts. Homeobox-containing (*HOX*) genes are reported to control pattern formation during embryonic development.[13]

ACKNOWLEDGMENT

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2. Adolescent pubertal development

Shawn Smith, Kimberly McClanahan, and Hatim Omar

NORMAL PUBERTY AND GROWTH

Puberty is the transition that occurs between childhood and the attainment of the ability to reproduce. The definition of puberty alone can encompass the process of sexual maturation, but a more expansive approach is to think of puberty in combination with the term adolescence. This differentiation prompts the practitioner to consider the psychological, behavioral, and social changes of the adolescent who is experiencing pubertal development.

GROWTH

The correct assessment and measurement of growth in a child or adolescent is essential to competent health supervision, as growth is often first to be adversely affected by underlying pathology, both psychosocial and somatic. Failing to appropriately assess a child's growth can often cause a missed or delayed diagnosis of a systemic illness. Furthermore, when evaluating a child's growth it is imperative to determine growth rate, rather than simply relying on a cross-sectional analysis of one measurement in time. Correct monitoring of growth requires careful plotting of data on growth curves. Growth charts were originally published by the Centers for Disease Control and Prevention (CDC) in 1977 from the National Center for Health Statistics as a tool for health professionals to use to determine if a child's growth was adequate.[1] In 2000 the CDC revised these original growth charts based on several cross-sectional surveys from 1963 to 1994 (Figure 2.1).

The revised charts extend from 2 to 20 years, and have other important differences, which improve their utility to health-care providers and researchers. First, the revised edition includes two extra charts to encompass standards for assessing body mass index (Figure 2.2). The body mass index or BMI is an anthropometric index of weight and height combined with age and is a useful index in the evaluation of overall general health. The BMI is calculated by dividing weight in kilograms by the square of height in meters. An important difference between using BMI in children and adults is the influence of changing levels of sexual maturity. For example, among patients with similar BMI, the patients with higher sexual maturation will have a lower percentage of body fat.[2] The importance of including BMI in routine evaluation of growth is to screen for underweight or overweight children and adolescents with respect to age and height. A BMI for age greater than 95% is defined as overweight and between 85% and 95% as at increased risk for obesity. Second, the new charts represent a more diverse population, with regard to racial and ethnic background and, during infancy, the use of breast-feeding and formula for nutrition.

Another useful tool for evaluating growth in a child is growth velocity charts. Determining and plotting growth rates is generally more sensitive for identifying growth problems than an isolated height-for-age. For example, if a child who was growing at a higher than average percentile line for his age began to fail to grow 1 year before evaluation, his height-for-age would still be in the normal range but his growth velocity assessment would show a significant reduction in growth rate.[3]

Some growth charts have been developed that allow for the variation in growth pattern of a specific syndrome (e.g. Down syndrome or Turner syndrome). These charts represent the standard

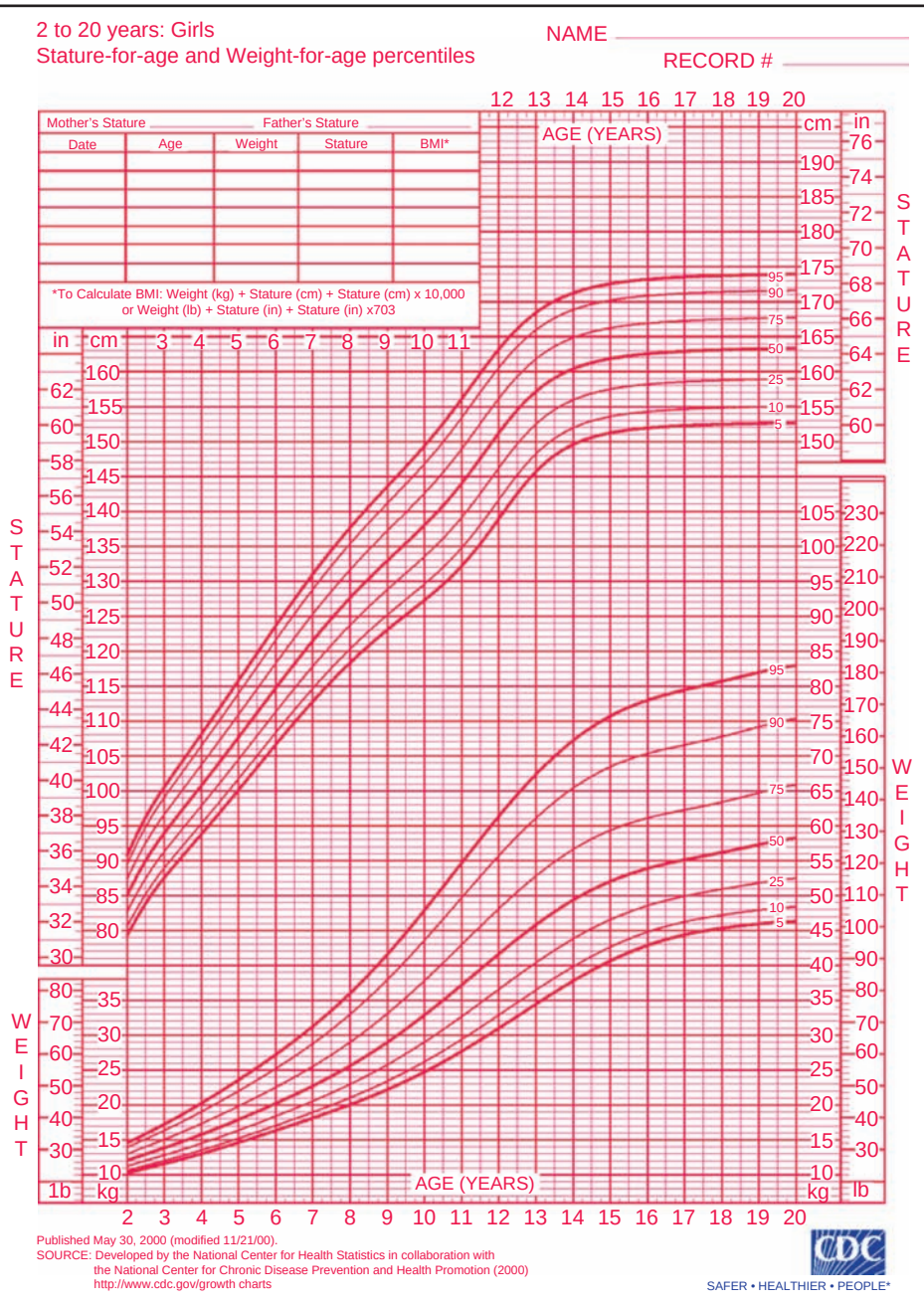


Figure 2.1 Growth chart for monitoring of growth in girls aged 2–20 years.

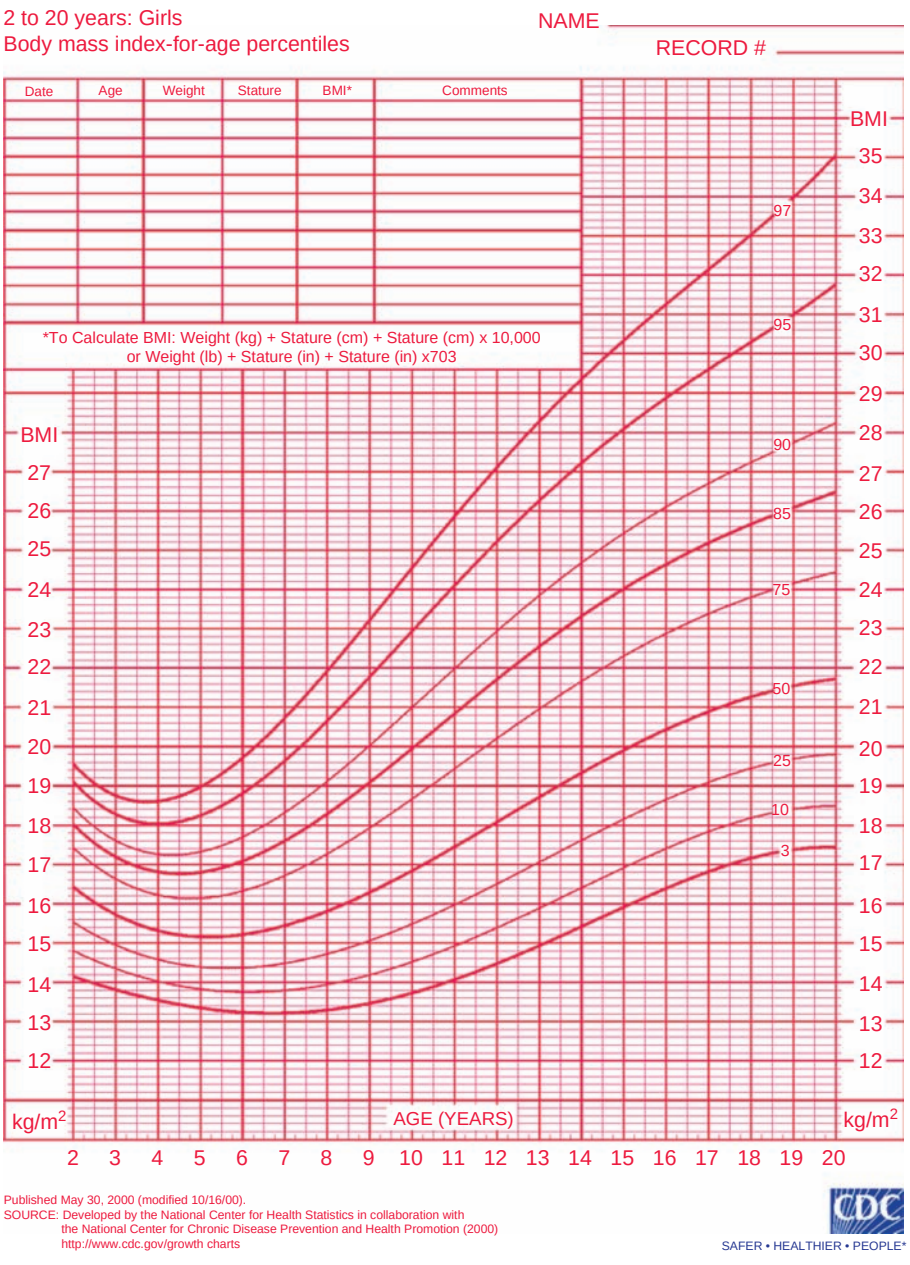


Figure 2.2 Chart for assessing body mass index (BMI) in girls aged 2–20 years.

growth for that particular syndrome, therefore allowing a child to be compared against standards in his or her own cohort.

It is important to address the fact that although we have excellent tools for evaluating growth, the tools are only useful if the correct measurements of the child are obtained and plotted on the curves. The child under the age of 2 years is measured supine and therefore this measurement is more appropriately referred to as the length. One examiner holds his head into contact with a fixed board while a second person stretches him out and then brings a firm board into contact with the heels. Feet are in plantar flexion at 90°. This measurement averages 1 cm more than the measurement of standing height.

PREPUBERTAL GROWTH

Growth during gestation through adulthood can be viewed in three phases. Infancy phase starts in mid-gestation and then rapidly decelerates to approximately 3–4 years of age. The childhood phase then begins, which is slowly decelerating growth until early adolescence and, finally, puberty is a sigmoid-shaped curve with a rapid adolescent growth spurt.[4]

Birth weight is determined more by maternal nutrition and health than by genetic factors. If a low birth weight infant is otherwise healthy it will likely 'catch up' or have a higher velocity of growth during the first year of life. Birth weights of most healthy infants tend to cluster around the population mean. Between 12 and 18 months genetic tendencies for eventual height play an important role. Infants who are predisposed to achieve a taller stature will attain an increase in the growth velocity to follow a percentile growth curve more consistent with genetic predisposition. Conversely, infants with a genetic predisposition for smaller stature will adjust their growth velocity to achieve the percentile for the genetic predisposition.[5]

This interesting 'catch up' growth is a phenomenon seen throughout childhood, especially in pathologic conditions. For example, if a child is severely malnourished or in a growth-restricted disease state and receives appropriate treatment for the condition, the growth velocity increases to place the patient at or closer to their genetic predetermined growth pattern.[3]

Growth velocity during childhood on the average is approximately 15 cm per year during the first 2 years of life and then slows to 5–6 cm during middle childhood until the onset of puberty.[6] Childhood growth rates are usually at their slowest in the 12–18 months immediately preceding puberty, an effect that is exaggerated when puberty is delayed. A mild childhood growth spurt with an increase in velocity around age 7 years will sometimes be observed, although this is not a consistent finding.

PUBERTAL GROWTH

During puberty males and females experience the greatest growth velocity since infancy. This growth can be conveniently divided into three stages.[7]

1. The nadir that occurs just before the growth spurt.
2. The stage when the adolescent is experiencing the maximum growth velocity.
3. The final stage when growth velocity decreases, which occurs before epiphyseal fusion.

It is important to remember, especially when examining patients during this period of rapid growth, that although growth is described in centimeters per year, this represents the average growth for that year and velocity may change throughout this time period. A good marker for following growth of an adolescent through puberty is the peak height velocity (PHV). During the year when PHV occurs, a girl may average 9 ± 1.03 cm per year, usually coinciding with Tanner breast stage 3. During puberty, girls will gain an average of 25 cm. For boys, the PHV ranges from 10.3 cm per year with a standard deviation of 1.54 cm per year. This occurs during Tanner genital stage 4. Boys will gain 28 cm on the average. For some this growth velocity is doubled compared with preadolescent

rates. The adolescent growth spurt occurs on the average 2 years earlier in females compared with males. Thus, for a temporary period of time, girls may be taller than many boys of the same age.[8–10]

CHANGES IN BODY COMPOSITION, SKELETAL GROWTH, AND BONE DENSITY

During the rapid growth during puberty, not only is there growth in all tissues, but there are also significant changes in body composition. These changes are highly sexually dimorphic. One of the greatest changes that boys and girls undergo is the change in percentage of body fat. From 5 to 10 years of age boys and girls have similar amounts of fat mass. The percentage of body fat is greater in females; specifically, they will tend to have 1% greater body fat at age 5 years, but 6% greater body fat by the age of 10. Males gain a greater amount of lean body tissue or fat-free mass and for a longer time. By ages 19–20 males will have finally attained total amount of fat-free mass, yet females will obtain this final total amount by 15–16 years of age.[11]

The increase in adipose tissue also accumulates in a sexually dimorphic pattern. Males increase more upper body mass in an 'android' distribution and females increase lower body mass with a 'gynecoid' distribution. These differences that exist between sexes are largely dependent on the effects of sex hormones.[12]

The skeleton also undergoes a great amount of growth, not only in length but also in density. Each bone begins with a primary center of ossification and will go through many stages of enlargement and shaping. The adult form is reached when epiphyses ossify and fuse with the main body of the bone. All these changes are evident on radiographics as the calcium content of the opacified bone is opaque. The sequence of the changes is the same in all individuals, thus using radiographs to evaluate skeletal bone age in comparison to chronological age is an excellent clinical tool. The photographic atlas of Greulich and Pyle is the most commonly used resource to compare radiographs of the hand with standards of maturation in a normal population.[13] Osseous maturation occurs at a faster rate in females than in males, so different standards are used for each sex.

As mentioned, bone density increases rapidly during the adolescent growth phase. The bone mineral accumulated during adolescence can be as much as one-quarter of adult mineral bone content. This occurs during the 2 years surrounding the peak of growth velocity. Many factors can affect the accretion of bone mineral including genetic factors, ethnicity, and body mass. Recent data support the theory that bone density obtained during adolescence is affected by the daily level of physical activity.

ENDOCRINE CONTROL OF PUBERTAL GROWTH

The action of multiple hormones in concerted fashion regulates linear growth in a child and adolescent. Growth hormone is the primary growth-stimulating factor during prepubertal growth. Sex hormone augmentations of growth hormone secretion, as well as direct growth-stimulating effects of sex steroids, cause growth acceleration during puberty. Growth hormone is a 191 amino acid protein secreted from the pituitary gland. The secretion of the hormone is controlled by somatostatin and growth hormone releasing hormone (GHRH). Somatostatin, or growth hormone release-inhibiting factor, is a tetradecapeptide which is a potent inhibitor of growth hormone secretion. It is secreted by the hypothalamus and is increased with high circulating levels of growth hormone and insulin growth-like factor (IGF-1). GHRH is also secreted by the hypothalamus. It binds to receptors to increase cAMP production by somatotrophs, thus increasing growth synthesis and secretion of growth hormone.

The action of growth hormone primarily affects linear growth. However, in concert with its major second messenger, IGF-1, there are multiple metabolic actions; some are dependent F IGF-1 and some are independent of IGF-1. Specifically, these

hormones act on bone to stimulate epiphyseal growth and increase the activity of osteoblasts. There is also an increase in endochondreal bone formation. Because it can bind weakly to the insulin receptor, IGF-1 has insulin-like effects. Growth hormone promotes lipolysis and accumulation of lean muscle mass, and can acutely have insulin-like effects, but causes insulin resistance when present in excess. And finally, there is an overall increase in lean muscle tissue.[6]

The secretory pattern of growth hormone is pulsatile, so that at any given time the level of growth hormone can be high or low. For this reason, unless one is evaluating for possible growth hormone excess, it is not appropriate to obtain random levels of growth hormone. In the prepubertal state the concentration of growth hormone is similar for males and females. There is day and night rhythmicity, but higher peaks during the early hours of sleep.[14] During puberty the pulsatile secretion of growth hormone increases, particularly during the daytime. Consequently, IGF-1 levels also increase dramatically. This large increase in secretion of growth hormone is due primarily to increase in pulse amplitude rather than pulse frequency.[15,16] Peak growth hormone secretion occurs earlier in puberty in females compared with males, helping to explain the earlier observed peak growth velocity in females.

Sex steroids, particularly estrogen, play a pivotal role in the increased secretion of growth hormone during puberty. Interestingly, this effect is most prominent in the early stages. Despite continued increased levels of steroids in late puberty, the levels of growth hormone and IGF-1 begin their gradual decline, which will persist throughout adulthood.[11,15]

Recently, research has focused on understanding the relationship between BMI and growth hormone. Studies show an inverse relationship between fat mass and growth hormone secretion. Gender also appears to play an important role in this relationship, with males being more sensitive to this obesity factor. Strikingly low levels of growth hormone after stimulation can be observed in male patients with a high BMI.[17]

Thyroid hormone also plays a key role in growth and development. The concerted actions of both growth hormone and thyroid hormone are largely responsible for skeletal growth. In rat models these hormones potentiate each other's effects; optimal growth occurs when both hormones are present, whereas growth is impaired when only one hormone is present.

The most impressive example of the importance of thyroid hormone in skeletal growth is in the condition of severe childhood hypothyroidism. Although the presenting signs and symptoms of acquired hypothyroidism in childhood are multiple, a dramatic decrease in the velocity of vertical growth is an early and common indication. There is delay in the ossification at the epiphyseal centers, and if the child remains untreated and ossification does occur the pattern is irregular and mottled, giving a porous fragmented appearance known as epiphyseal dysgenesis.[18] Thyroid replacement therapy leads to prompt resumption of linear growth and skeletal maturation.

Thyroid hormone also plays an important role in pubertal development, although it does not appear necessary for the development of the fetal reproductive system. For example, in congenital hypothyroidism, there appears to be normal development of the reproductive tract. However, there is a delay in sexual maturity if hypothyroidism is present at the time of normal transition to puberty.

ONSET OF PUBERTY

The age of onset of secondary sexual characteristics and attainment of reproductive potential is highly variable. For the average male, the first physical sign of the onset of puberty is the enlargement and softening of the testes, which occurs at a mean of 11.2 years of age (95% will range from 9.2 to 14.2 years of age). For the average female, the budding of the breast is the first clinical sign, occurring at a mean 10.9 years of age (95% will range from 8.5 to 13.3 years of age). A useful guideline is that sexual maturation before age 8 in females and 9 in males is premature; however, recent evidence

suggests that certain aspects of puberty in particular ethnic groups (e.g. adrenarche in African-American girls) can occur normally before the age of 8.[20]

FACTORS AFFECTING THE ONSET OF PUBERTY

There are many factors, that play a role in pubertal timing. Some of these factors, such as malnutrition and genetics, have been clearly identified to affect pubertal development. In developing countries, malnutrition is a known cause in delaying the onset of puberty, as well as dampening growth potential.[21]

Genetics clearly play a dominant role in affecting the age of onset. Parents exert equal influence on tempo of growth and timing of puberty. Multiple studies show a higher correlation in monozygotic twins for the onset of puberty compared with dizygotic twins.[3] Thus, it is critical to obtain a thorough family history when evaluating possible early or delayed puberty.

Research during the past has examined factors that may affect this timing. There has been increasing scientific research that demonstrates a trend toward earlier maturation in both boys and girls.[22,23] There is also evidence for racial differences in earlier maturation. Specifically, black females show an earlier age of pubertal onset compared with white females.[22,24–27]

Accumulating evidence that suggests there is an earlier age of maturation has prompted the question of etiology. Obesity is increasing in the childhood population of the United States owing to changes in lifestyle, eating habits, and activity levels,[28,29] and there is strong evidence linking higher BMI with earlier age of maturation, particularly in females.[26,30,31] One mechanism proposed to explain this relationship is the hormone leptin, a hormone produced by the adipocytes. Leptin serves as the primary signal to the hypothalamus to provide information on fat mass, thus regulating feeding behavior and body weight.[32] Although the exact role of leptin remains poorly understood, it does appear that circulating levels serve a permissive role in pubertal onset.[33–36]

CONTROL OF THE ONSET OF PUBERTY

Overview

During intrauterine life the hypothalamic-pituitary-gonadal (HPG) axis is active. This activity then diminishes as the inhibitory neurons of the HPG axis mature, but then rebounds with increased activity briefly after parturition due to an abrupt decline in maternal hormones. The HPG axis is then in a pattern of suppression that continues throughout childhood.

Sexual maturation is a result of the reactivation of the HPG axis. After birth, pituitary gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) rise to adult levels during the first several months of life, then decrease during a so-called 'latency' phase between late infancy and the onset of puberty. During this time the HPG axis is suppressed, more completely in males than in females. The hypothalamic hormone gonadotropin releasing hormone (GnRH) stimulates the production of LH and FSH from the anterior pituitary, which in turn stimulate the production of gonadal steroids. Specifically, in females LH induces maturation of the granulose cells, which then produce estradiol. FSH functions at the corpus luteum to secrete inhibin, which negatively feeds back to inhibit FSH. The interstitial cells of the testes produce testosterone. FSH stimulates spermatocytes in the presence of testosterone. The production of the hormonal changes induces secondary sexual characteristics, which will be discussed later.

The system that is responsible for the regulation of human reproduction includes the following:

1. The arcuate nucleus of the median basal hypothalamus is responsible for GnRH released at the median eminence into the primary plexus of the hypothalamic-hypophyseal portal circulation to the anterior pituitary gland.
2. The pituitary gonadotrophs release FSH and LH in reponse to GnRH.
3. The gonads, ovaries and testes, release estrogen/estradiol and testosterone.

Regulation of the gonadotropins

The pulsatile secretion of the gonadotropins LH and FSH is under the control of GnRH from the hypothalamus. During embryonic development, the neurons that will ultimately secrete GnRH originate in the olfactory placode and migrate through the forebrain to the hypothalamus.[37]

Secretion of the gonadotropins

FSH and LH have a common alpha subunit encoded by a single gene and specific beta subunit. LH beta subunit is encoded on chromosome 19 and FSH beta subunit is encoded on chromosome 11.[38] Third generation assays allow accurate measurement of low levels of the gonadotropins at all ages.[39]

As discussed previously, in early gestation, the human fetus synthesizes and secretes FSH and LH to peak serum concentrations reaching adult levels. However, after mid-gestation these levels decline. During the first few days after birth the concentration of both gonadotropins increases until approximately 6 months in males and 1–2 years in females, at which time the levels again decline.[40] A low level of FSH is detectable in pulsatile pattern in young prepubertal females and males. There is no detectable LH at this time.[41,42]

In the peripuberty phase, or the time period immediately before the onset of puberty, a sleep-associated pulsatile secretion of LH is the earliest hormonal phenomenon of puberty, observable before any outward clinical signs of puberty.[43] As the prepubertal phase progresses, a low frequency, low amplitude pulsatile LH pattern occurs during the night. This night-time secretion is the first sign of the initiation of puberty.[44–47]

This initially low pulsativity of LH gradually increases to encompass the daytime secretion pattern as puberty progresses. Throughout this period, gonadotropin levels increase, mainly reflecting higher pulse amplitude versus increasing frequency.[44,45] By the late stages of puberty the predominance of night-time LH disappears.

Feedback control of gonadotropins

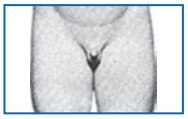
Changes in gonadal steroids cause reciprocal changes in pituitary gonadotrophs in both males and females.[21] That this negative feedback occurs not only at the level of the pituitary, but also at the hypothalamus is shown by the decrease in GnRH production following injection of estrogen into the arcuate nucleus of the hypothalamus. This decrease in GnRH leads to a decrease in gonadotopin levels and loss of LH pulsatile secretion pattern.[40,48] Conversely, in untreated males and females with testicular and ovarian failure, respectively, there is marked increase in pituitary gonadotropins.[49]

Interestingly, there are both negative and positive feedback mechanisms in the female, so that estrogen can also cause a stimulatory feedback mechanism on gonadotropins. This allows the level of circulating estrogen to increase until it has reached a critical level. This is sustained for a period of time at which there is a positive stimulatory effect on LH and FSH. This positive feedback mechanism is responsible for ovulation, and is not present until midpuberty. This delay in development of this positive feedback response may account for the anovulatory cycles initially seen after menarche.[50]

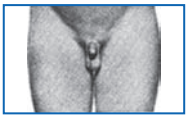
This biphasic effect of estradiol on gonadotopin secretion has also been shown in animal studies. Ovariectomized rhesus monkeys with abolished endogenous GnRH production were given exogenous pulsatile GnRH to control LH and FSH secretion. Following the administration of estradiol, the initial negative feedback mechanism was seen with a decrease in FSH and LH and then the positive stimulatory effect was seen with surges of gonadotropins.[51]

PHYSICAL CHANGES IN PUBERTY

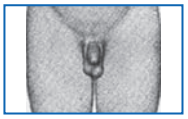
Objective measures to evaluate pubertal physical changes allow the clinician to better monitor the normal rate of development. The standard universal system used was initially described by Tanner in 1969 and is still used today (Figure 2.3). Pubertal growth and somatic changes are orchestrated by two different and independently controlled hormone-producing systems in the adrenal glands and the ovaries/testes. The development of breast tissue and growth of the penis and scrotum reflect activation



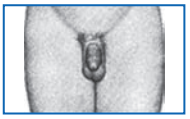
Stage 1. The penis, testes, and scrotum are of childhood size.



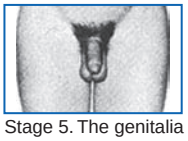
Stage 2. There is enlargement of the scrotum and testes, but the penis usually does not enlarge. The scrotal skin reddens.



Stage 3. There is further growth of the testes and scrotum and enlargement of the penis, mainly in length.



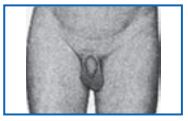
Stage 4. There is still further growth of the testes and scrotum and increased size of the penis, especially in breadth.



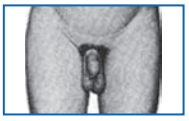
Stage 5. The genitalia are adult in size and shape.

(a)

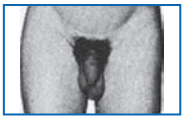
Stage 1. There is no pubic hair.



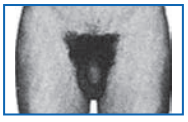
Stage 2. There is sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, primarilly at the base of the penis.



Stage 3. The hair is considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.

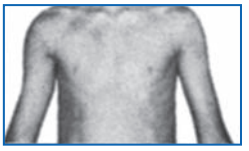


Stage 4. The hair, now adult in type, covers a smaller area than in the adult.

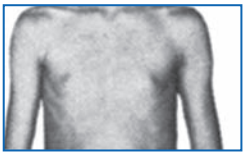


Stage 5. The hair is adult in quantity and type.

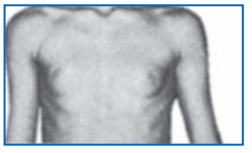
(b)



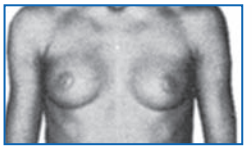
Stage 1. The breasts are preadolescent. There is elevation of the papilla only.



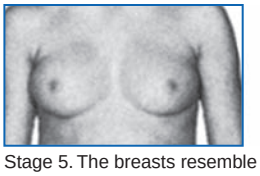
Stage 2. Breast bud stage. A small mound is formed by the elevation of the breast and papilla. The areolar diameter enlarges.



Stage 3. There is further enlargement of breasts and areola with no separation of their contours.



Stage 4. There is a projection of the areola and papilla to form a secondary mound above the level of the breast.



Stage 5. The breasts resemble those of a mature female as the areola has recessed to the general contour of the breast.

(c)

Figure 2.3 (a) Adolescent development in size of male genitalia. (b) Adolescent development in male pubic hair. (c) Adolescent development in size of female breasts.

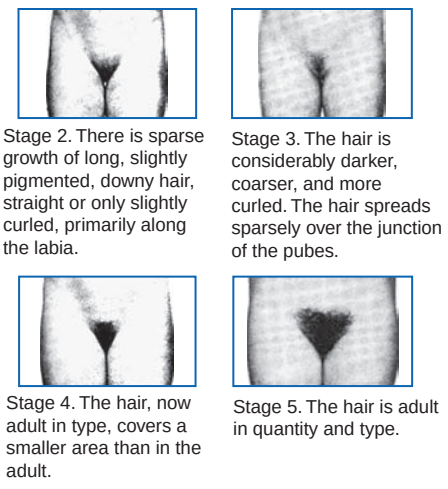


Figure 2.3 (*Continued*) (d) Adolescent development in female pubic hair. Used with permission of Ross Products Division, Abbott Laboratories, Inc, Columbus, OH 43214.

of the HPG axis and the production of estrogens or androgens, respectively, by the gonads. Androgens secreted by the adrenal gland contribute to body odor, and growth of pubic and axillary hair.

It is imperative when evaluating a patient to make an initial assessment based on history and physical exam of which hormone systems are active. This minimizes the drawing of extraneous and expensive laboratory tests in the evaluation of 'precocious puberty'; e.g. obtaining estrogen and LH levels in a girl presenting with adrenarche alone. Defining whether activation of the HPG axis and/or the adrenal sex steroid production is driving the physical changes is the key to performing a logical, cost-effective, and accurate diagnostic evaluation.

FEMALE

An increase in velocity of vertical growth is the initial physical sign of the onset of puberty. However, in females, breast development and enlargement, known as *thelarche*, is most commonly used as an indicator of the early stages of puberty. The initial breast tissue in the earlier stage of growth can be unilateral, which may persist for 6–9 months. Knowing this can not only provide reassurance to patients and families, but also may avoid unnecessary diagnostic tests. When evaluating the breast, it is important to include palpation of the breast tissue and visual inspection. This allows appropriate examination of the areola, papilla, and breast tissue. This is an important tool to differentiate breast tissue from adipose tissue in overweight females.

Tanner staging is used to describe breast development. In Tanner stage 1 or the preadolescent stage there is only elevation of the papilla. Stage 2 progresses to elevation of the breast and papilla as a small mound. Stage 3 represents further enlargement and elevation of breast and areola with no separation of their contours. Projection of the areola and papilla to form a secondary mound above the level of the breast is stage 4. Finally, stage 5 represents the mature stage, which is projection of the areola and papilla due to the recession of the areola to the general contour of the breast.

During puberty the vagina undergoes changes in appearance as well as growth. During the prepubertal stage the vagina has a glistening reddish appearance but during puberty estrogen dulls and thickens the mucosa. Furthermore, previously pink labia with relatively sharp, smooth edges undergo rugation, and there is increased fat deposition at the mons pubis. Peak growth velocity generally occurs around Tanner stage 4 of breast development, and coincides between stage 3 and 4 for pubic hair. Menarche occurs after the peak height velocity has occurred.

As discussed previously, there are two hormonal processes that control pubertal development. The action of the adrenal androgens is largely responsible for the development of axillary hair as well as pubic hair. In general, pubic hair appears first, and in ~20% of females precedes breast development. This phenomenon is even more common in African-American girls.

As with breast development Tanner staging is used to describe pubic hair development. When examining pubic hair it is important to make note of the distribution of the hair. For example, from the prepubertal stage 1 to stage 2, pubic hair begins

to grow along the labia, as maturity continues, growth occurs over the mons pubis, and finally at stage 5 growth has occurred on the medial thigh. During the progression through the Tanner stages the hair becomes more pigmented, coarser, and curlier. There is no Tanner staging for axillary hair. However, a gross scale of 1 (no hair) to 3 (adult pattern of hair) is sometimes used. There is an increase in the activity of glandular tissue, specifically sebaceous glands and merocrine sweat glands. During the initial appearance of pubic and axillary hair the apocrine glands begin to function.[8]

MALE

In males, enlargement and softening of the testes is usually the first sign of the onset of puberty. The measurement of the volume of the testis is a tool that can be used in the determination of pubertal development. The classic method for measuring testis volume is the use of the Prader orchidometer. This is a series of models on a string in increasing size. The clinician palpates the testis with one hand while comparing it to the models with the other. A volume of 4 ml usually indicates the onset of puberty.[8] This volume also correlates with a testicular length of 2.5 cm.[21]

Similar to the method used to describe the development in females, the stages of the growth of the penis and scrotum have been divided into five stages. Stage 1 represents the preadolescent stage and there is little growth until stage 2, which is defined by the enlargement of the testes and reddening and textural changes in the scrotal skin. This initial softening of the scrotal skin may be the first identified physical characteristic of pubertal onset. Stage 3 mainly consists of continued growth of penile length, scrotum, and testes. Stage 4 is distinct for the development of the glans penis. There is also darkening of the scrotal skin as well as continued growth. Stage 5 represents adult size and shape.[8]

With the growth of the penis, there is growth and development of the seminal vesicles, prostate, and bulbourethral glands. The time of the first ejaculation is approximately 1 year after the beginning of the accelerated penile growth. Enlargement of the larynx occurs at the same time as the increase in sitting height. The voice begins to deepen at the same time as the penis is reaching the final stage of maturity.

CONCLUSION

Puberty represents a time of acceleration of growth in many dimensions. An adolescent experiences not only sexual maturation, and an increase in growth velocity, but is also undergoing significant psychological and social changes that accompany the transition from childhood to adulthood. Many unknown factors affect the regulation of this process. Further research is needed to define these elements.

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3. Precocious puberty

Paul Kaplowitz

INTRODUCTION

Precocious puberty has become a hot topic in recent years because of concern that girls in the USA are starting puberty earlier now than in the past, and the uncertainty as to what might be causing this trend. Thus any discussion of this topic should begin with the problem of defining when puberty in girls should be considered precocious; this will involve a review of the data suggesting a trend towards earlier appearance of breast development and pubic hair, and the racial differences that have been reported. Distinctions will be made among two common normal variants, premature adrenarche and premature thelarche, central ('true') precocious puberty and the more serious but far less common peripheral precocious puberty, as well as the puzzling phenomenon of premature menarche. The most efficient and cost-effective laboratory evaluation based on the presenting signs of puberty will be discussed. Finally, there will be a brief discussion of the latest trends in the treatment of central and peripheral precocious puberty.

DEFINING WHEN PUBERTY IS PRECOCIOUS

The traditional definition of precocious puberty is the appearance of breast and/or pubic hair development before 8 years of age. This definition is based largely on Marshall and Tanner's classic study of white girls living in a group home in England in the 1960s, in which the average age of thelarche was 11 years and very few girls had breast development before age 8.[1] It was consistent with the results of a limited number of small studies from the US published in the 1940–1960 era. However, recent studies from the US suggest that in a significant number of girls (especially Afro-American girls), breast tissue and pubic hair are already present by age 8. One of these was the Pediatric Research in Office Settings (PROS) study done in 1992–93 in which 17 000 girls between the ages of 3 and 12 (90% white and 10% Afro-American) had their puberty staged by trained physicians in 65 mostly suburban offices.[2] The other study, the Third National Health and Nutrition Examination Survey (NHANES III), involved a smaller number of girls studied between 1988 and 1994. The subjects were selected so as to be representative of the population as a whole; Afro-American and Hispanic children were intentionally oversampled to facilitate racial/ethnic comparisons.[3] The key findings of these studies are summarized in Tables 3.1 and 3.2. Based on the large proportion of girls who already had breast or pubic hair development by age 8–9, it has been suggested that age 7 (or even age 6 for Afro-American girls) might be a more appropriate age cut-off for defining when signs of puberty are 'precocious'.[4] However, some endocrinologists have argued that it was dangerous to change the age cut-off points, in that pathology of concern might be missed if all girls with signs of puberty before age 8 were not evaluated.[5] Further discussion of secular trends in female pubertal development, both in the US and other countries, can be found in Anderson et al.[6]

When one considers the mean age of menarche in the equation, the situation becomes more complex. This is because recent US studies suggest that there has either been no decrease in the age of menarche from 1960 to the present,[1] or that any decrease has been rather small, on the order of 0.2 years, although for black girls, the decrease may have been greater.[6] This has led some to argue that the mean duration of puberty may be longer than in

Table 3.1 Comparison by racial/ethnic group of prevalence of breast development and pubic hair in 8-year-old girls from the PROS and the NHANES III studies

Racial/ethnic group	% with breast development		% with pubic hair	
	PROS study	NHANES III	PROS study	NHANES III
White girls	10.5	11.4	7.7	6.5
Afro-American girls	37.8	27.8	34.3	30.4
Hispanic girls	–	25.4	–	6.7

Adapted from Wu et al[3] and Kaplowitz et al.[4]

Table 3.2 Comparison by racial/ethnic group of the mean age of appearance of breast development and pubic hair in PROS and NHANES III

Racial/ethnic group	Mean age of onset of breast development		Mean age of onset of pubic hair development	
	PROS study	NHANES III	PROS study	NHANES III
White girls	10.0	10.3	10.5	10.5
Afro-American girls	8.9	9.5	8.8	9.5
Hispanic girls	–	9.7	–	10.3

Adapted from Wu et al[3] and Kaplowitz et al.[4]

the past, and that different factors may be influencing the onset of thelarche and menarche.[7]

Age guidelines should be only one consideration in deciding whether a young girl with signs of puberty needs an endocrine evaluation. It is as important, or perhaps even more important, to consider the presence or absence of progression of these findings over a period of observation and whether or not the growth chart demonstrates the growth acceleration suggestive of a pubertal growth spurt.

WHAT MAY BE CAUSING THE TREND TOWARDS EARLIER ONSET OF PUBERTY?

A variety of explanations have been put forth to account for the increasing prevalence of early breast and pubic hair development in US girls, and readers who desire a more detailed discussion are referred to a review article by Kaplowitz.[8] There has been much speculation that chemicals in the environment with estrogen-like activity, referred to as 'endocrine disrupters,' could be responsible for earlier breast development. Some of the chemicals implicated include phthalates, used in the manufacture of plastics and electrical equipment, 1,1-dichloro-2, 2-bis(4-chlorophenyl)ethane (DDE), a breakdown product of the now-banned pesticide 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT), estrogen contamination of meat and poultry, and estrogens or 'essential oils' with estrogenic activity in cosmetics and hair-care products. There is no solid evidence, however, linking any of these agents to the earlier appearance of breast tissue in large numbers of girls. Another theory proposed that a stressful home environment may accelerate the maturation of young girls. However, the most likely culprit is the increasing prevalence of obesity in Americans, including young girls. Between the 1960s and 2000,

the prevalence of obesity (body mass index, BMI > 95th percentile) in national surveys increased by approximately three-fold in 6–11-year-old girls.[9] It has long been known that overweight girls tend to mature earlier than normal-weight girls, and very thin girls (e.g. anorexics and athletes) tend to mature and reach menarche later. A reanalysis of the data from the PROS study showed that normal 6–9-year-old girls who already had breast development had a significantly higher mean BMI standard deviation score (SDS) than age- and race-matched girls who were prepubertal; this difference was greater for white than for Afro-American girls.[10] Increased BMI SDS also was related to early pubic hair development in 6–8-year-old girls. While these correlations do not prove cause and effect, at least two studies show that being overweight at a young age increases the likelihood of earlier appearance of breast development.[11,12] For example, the recent longitudinal study by Lee et al[12] of 354 girls followed from age 3 to sixth grade shows that increased BMI as early as age 3, plus the increase in BMI between the ages of 3 and 6, are important risk factors for whether or not a girl will be earlier than average age when entering puberty. It has been suggested that leptin, a product of fat cells that is required for normal reproductive function in women (i.e. rare patients with leptin deficiency have permanent gonadotropin deficiency), may be the critical link between increased BMI, increased fat mass, and earlier onset of puberty in girls.

THE DIFFERENTIAL DIAGNOSIS OF EARLY PUBERTY IN GIRLS

Premature adrenarche, due to a precocious increase in adrenal androgen secretion, is currently the most frequent cause of referrals for precocious puberty in girls. In the author's series of 104 consecutive children (90 girls) referred for evaluation between 1999 and 2002, 37 girls (over 40%) were found to have pubic and/or axillary hair and in most cases underarm odor, but no breast development.[13] Since many of these girls are overweight, in the sitting position they may appear to have breast development, so it is important to palpate for breast tissue in the supine position. While many girls with early pubic hair had tall stature and a few had rapid growth, none had signs of virilization such as clitoral enlargement, severe acne, or increased muscle mass, which might lead to concerns about a virilizing ovarian or adrenal tumor or late-onset congenital adrenal hyperplasia (CAH). This condition is unrelated to activation of the hypothalamic-pituitary-gonadal (HPG) axis. While its cause is unknown, pubic hair can appear at any age, even the first year of life.[14] The typical course is for the amount of hair to increase slowly over a period of years in the continued absence of breasts or other signs of androgen excess; no treatment is needed. Parents may be told that girls with premature adrenarche, particularly those who are overweight, have an increased risk of developing polycystic ovarian syndrome in their teenage years.[15]

Premature thelarche is the term used to describe girls (typically less than 3 years of age) who develop breast tissue that progresses very slowly or not at all over a period of observation. In some cases the breast tissue appears in infancy and concern increases when a year or more later it has not regressed. Height and the rate of growth are generally normal and, unlike girls with premature adrenarche, these girls are usually not obese. One follow-up study of 42 such girls diagnosed before age 3 found that only 13.5% had menarche before age 11, and that those with relatively early menarche were consistent with the age of maternal menarche.[16] Mean adult height was normal. While the cause of this benign condition is unknown, at least one study suggested that it may be due to small functioning ovarian cysts.[17] Some reports suggest that girls with premature thelarche may progress to full-blown precocious puberty, but this is extremely rare with girls in whom breasts appear before 3 years of age.

Central (true) precocious puberty (CPP) refers to girls who have progressive breast development starting before 7 or 8 years of age that is due to an early activation of the HPG axis. In most cases it is accompanied by growth acceleration so that these girls are usually above the 75th percentile in height

at the time of diagnosis. Pubic hair is frequently but not always present. While an elevated random luteinizing hormone (LH) level is suggestive of CPP, the best way to be sure is to re-examine the girl in 4–6 months. While the rate of progression is quite variable, it is typical for menarche to occur 2–3 years after breast budding is first noted. Most cases are idiopathic, and a positive family history of early puberty in parents and siblings is common. A French study found that the best predictor of the likelihood of a central nervous system (CNS) lesion is age at onset. For those starting between ages 6 and 8, only 2% had a relevant abnormality on brain imaging, while for girls with an onset of puberty before age 6, the figure was approximately 20%.[18] The most common CNS findings are malignant tumors, particularly optic glioma and hypothalamic astrocytoma, and a developmental defect called a hamartoma. Most but not all girls with tumors present with headaches or cranial nerve findings suggestive of increased intracranial pressure.

Peripheral precocious puberty is far less common than CPP and more challenging diagnostically; the entities listed below are all rare.

1. If a young girl has signs of androgen excess other than pubic/axillary hair and excessive body odor, particularly clitoromegaly, severe acne, or voice change, one needs to rule out four possibilities: a virilizing ovarian tumor, a virilizing adrenal tumor, late-onset (non-classical) CAH, or topical androgen exposure. Fortunately, three lab tests, testosterone (ovarian tumors), DHEA-S (dehydroepiandrosterone sulfate; adrenal tumors), and 17-hydroxyprogesterone (CAH) usually lead the clinician to the correct diagnosis if they are dramatically elevated, or will reassure the clinician that whatever is observed is not hormonally mediated. If the testosterone is elevated, one also needs to inquire about any potential exposure to topical testosterone used by males with whom the child has had close contact.[19] Imaging studies can be done to confirm the presence of a tumor if the DHEA-S or testosterone are markedly elevated, or in the case of CAH, an ACTH (adrenocorticotropic hormone) stimulation test looking for an exaggerated rise in 17-hydroxyprogesterone will confirm the diagnosis.
2. When there is rapid progression of breast development accompanied by a suppressed serum LH and a very elevated estradiol, the possibility of an estrogen-secreting ovarian tumor (generally a granulosa cell tumor) needs to be considered. Since these tumors are generally quite large at the time of diagnosis, an ovarian ultrasound is almost always diagnostic. If a large ovarian cyst is found, this could be an isolated finding, but it may be part of the McCune-Albright syndrome (MAS).[20] The other classic features are irregular café-au-lait pigmentation and cystic bone lesions called polyostotic fibrous dysplasia, which may result in fractures. Isolated cysts may regress over time but cysts in girls with MAS tend to progress over time, sometimes rapidly, and very early menarche is common.
3. Exposure to exogenous estrogens through birth control pills or other oral estrogen preparations is uncommon. However, there is increasing concern that some girls with early breast development may be exposed to estrogens or estrogen-like chemicals through use of lotions or hair-care products containing hormones, certain essential oils (lavender or tea tree oil), or extracts of placenta.[21] There are no reliable data at this time on how common this is among girls referred for precocious puberty or if it can cause the rapid increase in breast development that could be confused with precocious puberty due to endogenous overproduction of estrogens.

Premature menarche refers to the situation in which a young girl with no detectable breast development has one or more episodes of vaginal bleeding. One 1985 study of 17 such girls between the ages of 1 and 8 found that 11 experienced 2 or more episodes of vaginal bleeding and 6 experienced only 1.[22] By ultrasound the uterus was of normal prepubertal size in all subjects, but some of the ovaries contained follicular cysts. Gonadotropin levels were

prepubertal but estradiol levels were on the average slightly elevated. Although this scenario may bring to mind possibilities such as a vaginal foreign body, a uterine tumor, or child abuse, evidence of any of these is rarely if ever found. The bleeding generally resolves spontaneously, indicating that it is a benign process. It is not clear how there can be enough estrogen effect to result in vaginal bleeding but not enough to cause significant breast development.

LABORATORY EVALUATION

The best way to proceed when there are signs of puberty in a girl less than 7 or 8 years of age is to order a limited number of tests that target the specific findings or to simply observe for a period of 4–6 months without ordering any tests to see if there is progression. For a girl with early breast development who is 3 years of age or less, premature thelarche is by far the most likely diagnosis, and lab tests can usually be deferred. For a 4–7-year-old girl with breast development, particularly if there is evidence of growth acceleration, LH, follicle-stimulating hormone (FSH), and estradiol are sufficient; a random LH of > 0.3 IU/L is suggestive of true precocious puberty, while an LH of < 0.1 IU/L points to premature thelarche.[23] For cases that are not clear-cut (e.g. progressive breast enlargement with an LH of 0.2 IU/L), a gonadotropin-releasing hormone (GnRH) stimulation test may be helpful. Since synthetic GnRH is no longer commercially available, we generally give an injection of the daily formulation of the long-acting GnRH agonist leuprolide and obtain an LH and FSH 2–3 hours later. A rise in LH to > 5 mIU/ml is usually consistent with central precocious puberty, while a small rise in LH accompanied by a larger increase in FSH is typically seen in prepubertal girls and those with premature thelarche.

For girls with only pubic and/or axillary hair and axillary odor, but no virilizing signs and no growth acceleration, no lab tests are needed to make a diagnosis of premature adrenarche. The only lab test likely to be abnormal is the serum DHEA-S, which is generally in the range of 20–150 μg/dl. If there is growth acceleration and/or either clitoral enlargement or severe acne, the lab tests that are most useful are DHEA-S, testosterone, and 17-hydroxyprogesterone, which will identify the rare patient with a virilizing ovarian or adrenal tumor or late-onset CAH.

Table 3.3 provides a summary of lab tests used in the evaluation of precocious puberty in girls.

Table 3.3 Hormonal studies used for evaluation of children with signs of precocious puberty

Hormone	When most useful	Cautions
Luteinizing hormone (LH)	Distinguishing between premature thelarche and true precocious puberty	Some labs run assay with sensitivity < 0.5 IU/L; must request third generation assay, which has sensitivity of < 0.1 IU/L
Follicle-stimulating hormone (FSH)	High levels may indicate gonadal failure	Too much overlap between pubertal and prepubertal children to be of much help in early puberty
Estradiol	Is usually elevated in girls with precocious puberty; very high levels suggest tumor or cyst	Non-specific elevations common; some girls with precocious puberty have normal levels. *Do not order 'total estrogens'*
Dehydroepiandrosterone sulfate (DHEA-S)	Will usually be mildly elevated for age in children with premature adrenarche	Many labs do not provide good age-related normal values. DHEA levels much more variable; harder to interpret than DHEA-S
Testosterone	Marked elevation in a young girl (> 50 ng/dl) requires further evaluation; mild elevation (15–30 ng/dl) usually non-diagnostic	Many labs do not provide good age-related normal values; slight elevations often non-specific and hard to interpret. No need to order a free testosterone
17-Hydroxy-progesterone (17-OHP)	When late-onset congenital adrenal hyperplasia (CAH) needs to be ruled out	Minor elevations (100–200 ng/dl) usually not significant; obtaining levels after injection of synthetic ACTH (Cortrosyn) often necessary to make the diagnosis

RADIOLOGICAL STUDIES

A bone age is considered by many to be an essential part of the evaluation; in general it is most useful in girls who have rapid progression of findings and/or growth acceleration, when it is likely to be advanced by 1–3 years. An advanced bone age is quite common in children with typical premature adrenarche, especially those who are tall, but the finding does not generally affect how these girls are managed, which is in nearly all cases with reassurance.

A pelvic ultrasound is felt by some to be helpful in distinguishing between premature thelarche and CPP, in that girls with CPP will have a uterus and ovaries that are large for age.[24] However, clinical assessment, occasionally hormone levels, and follow-up will generally allow the clinician to make this distinction without the need for an ultrasound. The ultrasound is most critical in the rare cases when the hormonal findings are suggestive of an ovarian tumor or there are clinical features suggestive of MAS.

The question of whether all girls with CPP need a brain MRI is controversial. Some clinicians order one for every girl with any breast development before age 8, but as noted above, the incidence of relevant positive findings is low (only about 2%) when the onset of puberty is between the ages of 6 and 8[18] and there are no signs or symptoms of a central nervous system (CNS) mass. It is certainly not helpful if the LH is suppressed or if the main clinical findings are androgen-related, not estrogen-related.

TREATMENT OF PRECOCIOUS PUBERTY

WHO NEEDS TREATMENT?

Many girls with CPP do not require hormonal therapy. One reason is that some girls with early breast development have a variant referred to as unsustained or slowly progressive puberty and such girls do well with follow-up but no intervention.[25,26] The need for therapy is clearest if the patient has the onset of puberty before 6 years of age, which has progressed rapidly since its onset. In these cases, there is a high likelihood of menarche occurring before 9 years of age, which is often distressing for the child and her family, as well as a higher risk of short adult stature. In this age group, treatment results in an adult height that is significantly greater than would be expected if the child were left untreated. The far more common situation is the girl with onset of puberty between the ages of 6 and 8 who is generally tall at the time of diagnosis (above the 90th percentile). Even when the bone age is advanced by 2 years, such girls tend to finish their growth early but with a normal adult height. Some of these girls, mostly those starting puberty between ages 6 and 7, are at risk for having menarche by age 9. Those whose breast development starts closer to age 8 are not likely to have menarche before age 10, which is usually handled well by the child if she is adequately prepared for this. The exception would be a girl with developmental delay or very immature behavior, in whom a delay in menarche until age 11 may be desirable. Unlike in boys with precocious puberty, who often have difficulties due to increased libido, hypersexual behavior seems to be uncommon in girls with precocious puberty.

WHAT IS THE BEST TREATMENT?

The standard treatment for hormonally proven CPP is synthetic analogs of GnRH, which are agonists when given acutely but behave as antagonists when given chronically. This is because the pituitary gonadotrophs will respond only to pulsatile GnRH, and if GnRH levels remain elevated chronically, the gonadotrophs are desensitized and LH and FSH fall to prepubertal levels.[27] In the US, the GnRH agonist used most often is Lupron Depot (TAP Pharmaceuticals, Lake Forest, IL), which releases the GnRH agonist leuprolide acetate slowly, making it suitable for monthly injections. The starting dose is usually 7.5 mg/month, but occasionally higher doses (11.25 or 15 mg every 4 weeks) are needed to suppress gonadotropins. There is also a 3-month preparation of Lupron Depot (11.25 or 22.5 mg), which is only approved by the FDA for adults, but which has been

used by many pediatric endocrinologists in girls with precocious puberty. A recent study found that while gonadotropin levels during treatment were slightly higher when the 11.25 mg 3-month Lupron was compared to monthly 7.5 mg Lupron, suppression of breast development and accelerated growth was very satisfactory with the 3-month preparation.[28] The current cost of GnRH analog therapy using the 7.5 mg dose of Lupron Depot monthly is approximately $10 000 per year.

Another therapeutic option that is worth considering when the main goal is to prevent menses is DepoProvera, given at a dose of 150 mg every 3 months. Although it is considered less effective than Lupron in terms of slowing growth and rapid bone maturation, and breakthrough bleeding can occur, it is far less expensive. There is much experience with this formulation as a contraceptive in teenage girls and it should be considered in girls where adult height is not a concern but stopping menses for a prolonged period is, such as in girls with severe developmental delay.

TREATMENT FOR PERIPHERAL PRECOCIOUS PUBERTY

When precocious puberty is due to an ovarian or adrenal tumor, resection of the tumor is usually curative. For girls with androgen excess due to CAH, giving hydrocortisone at a dose of 10–15 mg/m^2/day will generally reverse androgen oversecretion. It should be noted, however, that prolonged exposure to elevated levels of androgen or estrogen can cause acceleration of bone maturation and parallel maturation of the HPG axis, such that after removal of the source of sex steroids, CPP may occur that can progress rapidly if not treated with a GnRH analog.

A more complex problem is treatment of precocious puberty associated with MAS. Since gonadotropin levels are usually very low, treatment with GnRH analogs is of no value. Some success has been reported with treatment with the estrogen receptor blocker tamoxifen, which results in slower linear growth and a decrease in the frequency of vaginal bleeding.[29]

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4. Delayed puberty

Loreta M Matheo and Pamela J Murray

Puberty derives from the Latin, *pubertas*, meaning adulthood.[1] The phenomenon of puberty is significant in all cultures and the delay or absence of this sentinel event can cause great anxiety in the teen and their family. While boys tend to present with a chief complaint of short stature, girls typically present later with concerns about absent breast development or absent menses. The exact biologic triggers of puberty remain unknown; however, numerous modulators of this process are recognized: genetics, ethnicity, body mass index (BMI), and exercise, as well as physical and emotional stress.

NORMAL PUBERTY

The onset of puberty in girls is most often identified by the physical finding of palpable breast buds or thelarche caused by estrogen. This sign, also referred to as Tanner or sexual maturity rating (SMR) stage 2, marks a transformation of the hypothalamic-pituitary-ovarian (HPO) axis. The stimulus is distinct from the appearance of pubic hair or pubarche, which occurs around the same age. Pubic hair is a marker for the onset of androgen secretion by the adrenal gland.[2]

While the development of secondary sexual characteristics is the most obvious sign of puberty, many other hormonal and physical changes are also taking place. The onset of the secondary sex changes is brought about by the reactivation of the HPO axis, which has been minimally active since infancy. Changes in sex hormones at this time include increased pulsatile secretion of gonadotropin-releasing hormone (GnRH) causing increased nocturnal pulsatile luteinizing hormone (LH). There is a decrease in the sensitivity of the hypothalamus and pituitary to estradiol and testosterone, leading to the increase of follicle-stimulating hormone (FSH) and LH. In girls the development of a positive feedback loop with critical estrogen levels causes a significant GnRH release, which stimulates LH leading to ovulation.

Simultaneously the body undergoes substantial growth. Peak height velocity in girls occurs at an average of 11.5 years between Tanner stages 2 and 3. Weight velocity peaks 6–9 months later in Tanner stage 3. The percentage of body fat increases in girls and the female pelvis widens. There is growth of the brain, heart, liver, and kidneys but they account for a smaller percentage of body weight. Bones increase in length. Then under the influence of larger concentrations of estrogen, the epiphyses close. Bone mass and bone density accrual increases in puberty and during the subsequent decade.[3]

The groundbreaking work of Marshall and Tanner[4] timed thelarche as occurring at a mean age of 11.5 ± 1.1 years and pubarche at a mean age of 11.69 ± 1.21 years among white British youth. Further research including that of Herman-Giddens et al[5] in the United States has lowered the observed mean age of thelarche for white girls to 9.96 ± 1.82 years and pubarche to 10.51 ± 1.67 years, and for African-American girls to 8.87 ± 1.93 years and 8.78 ± 2.00 years, respectively. Racial differences in the start of puberty are greater than the differences in average age of menarche.

DELAYED PUBERTY – DEFINITION

Delayed puberty is statistically set at 2 standard deviations (SD) above the mean age of onset. When derived from Tanner's data, this was clinically applied when there was a lack of initial breast

development (SMR 2) by age 13.7 years. Using Herman-Giddens observed data, the statistical upper limit of normal for the onset of thelarche is 13.85 for white girls and 12.73 for African-American girls. However, waiting until 14 years may postpone the identification of clinically important conditions. Similarly, waiting until the age of 16, a statement historically popular in textbooks and clinical teaching, to investigate the lack of periods may lead to a late diagnosis of a problem. In the opinion of the authors, the lack of pubertal signs by age 13 years warrants investigation. When chronic disease or highly demanding athletic participation is present, the evaluation may be delayed until the age of 14 years. Delay of puberty must also be considered if there is alteration or attenuation of the tempo of the pubertal process. Typically, girls move through SMR 2 to menarche within 2–2.5 years and delay is defined if the process extends to 4 years. If the tempo is slowed beyond this time frame, patients may present as having primary amenorrhea but need to be evaluated with the differential diagnosis of delayed puberty in mind. Age, secondary sex characteristics, linear growth, past medical and family history, and other findings on history and physical examination provide the context for clinical decisions about the evaluation for delayed puberty.

The American Academy of Pediatrics issued guidelines[6] recommending that clinicians begin discussing the onset of puberty during preadolescent well visits and continue explanations of body changes and the expected onset of menses 2–2.5 years after the onset of pubertal changes. Subsequently, the date of the last menstrual cycle (LMP) should be part of the vital signs of each visit. By making this discussion part of the routine exam, issues of delayed puberty can be promptly noted and evaluated.

While delay of puberty occurs in only 2.5% of the general population, the identification and evaluation of these patients are important to prevent potential medical and psychological problems. Medical consequences involve growth and bone development as well as effects of underlying medical conditions such as cystic fibrosis, celiac disease, Turner syndrome, and other genetic disorders.

Once it has been determined clinically that puberty is delayed the next step is a thorough history with attention to family history, as well as a complete physical exam as outlined in Tables 4.1 and 4.2. In a primary care practice the majority of patients will have a normal physical exam and a history that is only remarkable for delay of puberty in either parent or siblings. These patients will likely have a diagnosis of constitutional delay of puberty (CDP). It has been suggested that 50–80% of variance in pubertal onset is genetically based.[7] In a referral population of 232 patients with delayed puberty, however, only one-third of female patients were found to have CDP, followed by 26% who had hypergonadotropic hypogonadism and 19% with functional hypogonadotropic hypogonadism (FHH) associated with delayed but subsequent spontaneous puberty secondary to an underlying medical cause. Ultimately, only 7% were found to have Turner syndrome. In males, 63% will have constitutional delay and 20% FHH.[8]

There are various ways of categorizing and evaluating patients. One scheme is based on etiology (Table 4.3). Patients may be divided into those with constitutional delay of growth, hypergonadotropic hypogonadism (with elevated FSH and LH) or hypogonadotropic hypogonadism (low FSH and LH). When thinking about prognosis and treatment, as in Table 4.4, it is useful to categorize patients as those with pubertal delay (CDP or sequelae of chronic illness) or those with pubertal failure typically secondary to congenital enzymatic or receptor defects, or chromosomal abnormalities such as Turner syndrome. Initial laboratory evaluation is directed by findings of the physical exam and history but may include the tests listed in Table 4.5. Table 4.6 provides guidance in interpretation of the bone age obtained as part of the patient's initial evaluation. Figure 4.1 provides a summary algorithm for work-up of the patient with suspected delay of puberty.

CONSTITUTIONAL DELAY OF PUBERTY

When no organic pathology is found the term constitutional delay is applied. The growth spurt is

Table 4.1 Key elements of the history in the evaluation of delayed puberty

Exam element	Finding	Associated diagnosis
Family history	Age of pubertal milestones of both parents and all siblings	Constitutional delay of puberty
Neonatal history	Lymphedema Hypoglycemia	Turner syndrome Hypopituitarism
Childhood medical diagnoses	Cranial irradiation/CNS surgery Total body irradiation Chemotherapeutics Oopherectomy	Hypogonadotropic hypergonadism Hypergonadotropic hypogonadism
Review of systems		
Weight change	Decreased	Inflammatory bowel disease (IBD), anorexia nervosa, hyperthyroidism, diabetes mellitus, cystic fibrosis, celiac disease
	Increased	Hypothroidism, Prader-Willi syndrome
Skin/hair	Hair loss	Hypothyroidism
	Lanugo	Anorexia nervosa
	Striae	Cushing syndrome
Gastrointestinal	Abdominal pain, diarrhea, constipation	IBD, celiac disease
	Constipation	Hypothyroidism, anorexia nervosa
Neurologic	Headache	Cranial tumor
	Anosmia	Kallmann syndrome
Social history	Stress, depression, personality and behaviors associated with anorexia nervosa: obsessive, perfectionistic, unrealistic expectations	Anorexia nervosa, eating disorders
Substance use	Cigarettes, alcohol, stimulants, opioids	Substance use disorder
Athletics	Type of sport, hours of training per day/week	Female athletic triad
Medications	Phenothiazines, risperidone Anabolic androgenic steroids, radiation therapy, chemotherapeutic agents	Hyperprolactinemia Hypo- or hypergonadotropic hypogonadism
Diet history	Caloric intake (24 hour recall) Dieting, diet exclusions Purging behavior	Eating disorders spectrum

always delayed,[9] resulting in the frequently used alternative terms, constitutional delay of puberty and growth (CDPG) or constitutional delay of growth and maturity (CDGM).

Constitutional delay is a common outcome in the investigation of pubertal delay and is by definition a diagnosis of exclusion. In general the history and physical exam are normal but suggestive data include findings in regard to stature, growth velocity, and family history. Typically deceleration of height can be noted on the growth chart by the age of 2 years.[10] Additionally delayed epiphyseal maturation is seen, with bone age correlating more closely with pubertal stage than chronologic age. On physical exam there is relative shortening of the upper body segment.[11] Peak growth velocity is compromised and as a group these patients will have a mean deficit of final height which is 2.4 cm below mean predicted height.[12]

Sedlmeyer et al[13] looked at the pedigrees of 53 probands, boys and girls with CDP, and compared them to controls and found an autosomal dominant

Table 4.2 Key elements of physical exam in evaluation of delayed puberty

Exam element	Finding	Associated diagnosis
Height	Short stature	Turner syndrome, Prader-Willi syndrome, panhypopituitarism, renal failure, HIV/AIDS, inflammatory bowel disease (IBD)
	Deceleration of height beginning age 2	Constitutional delay of puberty
Upper/lower body segment (height measured from top of head to symphysis pubis/height from symphysis to floor)	> 1.0	Hypothyroidism
	< 0.9	Hypogonadism,[3] constitutional delay of puberty[11]
Weight	Increased	Hypothyroidism, Prader-Willi syndrome
	Decreased	Anorexia, exercise, chronic illness (Crohn's disease, celiac disease, diabetes mellitus, cystic fibrosis, HIV/AIDS)
Blood pressure	Increased	Turner syndrome (coarctation of the aorta), hyperthyroidism, renal disease
	Decreased	Anorexia nervosa
Skin	Lanugo	Anorexia nervosa
	Cyanotic	Cystic fibrosis
	Cool/dry	Hypothyroidism
	Sweaty	Hyperthyroidism
	Low hairline	Turner syndrome
	Multiple pigmented nevi	Turner syndrome
HEENT	High arched palate, webbed neck, low set ears	Turner syndrome
	Goiter	Thyroid disease
Chest	Shield chest	Turner syndrome
	Galactorrhea	Prolactinoma/drug-associated hyperprolactinemia
Cardiac	Bradycardia	Anorexia nervosa
	Tachycardia	Hyperthyroidism
	Murmur	Turners syndrome – coarctation of the aorta
Extremities	Increased carrying angle, short 4th metacarpal	Turner syndrome
	Clubbing	Cystic fibrosis
	Small hands and feet	Prader-Willi syndrome
Neurologic	Anosmia	Kallman syndrome
	Abnormal peripheral fields	Pituitary tumor

inheritance pattern with variable penetrance. Both maternal and paternal histories of delayed puberty were significant. Mothers of CDP probands had a mean age of menarche of 14.3 ± 1.4 years compared with 12.7 ± 1.4 years for mothers of the control group. In total, 67% of mothers of probands were delayed more than 1 or 2 SD for menarche. Also, 34% of fathers met 1 or 2 SD criteria for delay of

Table 4.3 Differential diagnosis of delayed puberty based on etiology

1. Constitutional delay of growth and puberty
2. Hypogonadotropic hypogonadism
   - Central nervous system abnormalities
     Neoplasms
     Histiocytosis
     Post-infectious lesions
     Post-radiation therapy
     Developmental abnormalities of brain formation
   - Isolated gonadotropin deficiency
     GnRH receptor gene defect
     Kallmann syndrome
     Congenital adrenal hypoplasia
     LH-β, FSH-β gene defects
   - Multiple pituitary hormone deficiency (e.g. *Prop-1* defect)
   - Other miscellaneous disorders (hypogonadotropism not permanent)
     Chronic systemic disease with a pattern of gonadotropin secretory developmental delay similar to that seen in constitutional delay
     Malnutrition
     Anorexia nervosa
     Impaired pubertal progression of trained female athletes (exercise amenorrhea)
     Psychogenic amenorrhea
3. Hypergonadotropic hypogonadism
   - Females
     Turner syndrome (gonadal dysgenesis)
     XX and XY gonadal dysgenesis (familial or sporadic)
     Autoimmune oophoritis
     Radiation and/or chemotherapy
     Galactosemia
     LH or FSH receptor gene mutations
     Polycystic ovary syndrome
   - Males
     Klinefelter syndrome (seminiferous tubule dysgenesis)
     Chemotherapy or radiation therapy
     Defects of Leydig cell testosterone biosynthesis
     LH or FSH receptor gene mutations
     Agonadism (vanishing testis syndrome)

LH, luteinizing hormone; FSH, follicle-stimulating hormone.
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Table 4.4 Differential diagnosis of delayed puberty based on prognosis and treatment

A. Pubertal delay
   1. Constitutional delay of growth and puberty (CDGP)
   2. Secondary to chronic illness
      Anorexia nervosa
      Asthma
      CNS disorders (Langerhans cell histiocytosis, congenital defects)
      Collagenosis
      Endocrine diseases (hypothyroidism, hyperthyroidism, hyperandrogenism, hypercortisolism, hyperprolactinemia, diabetes mellitus type 1)
      Gastrointestinal disease (coelic disease, inflammatory bowel disease, cystic fibrosis)
      Hematological/oncological disease (after radiotherapy and chemotherapy, β-thalassemia)
      Hepatic disease
      Infections
      Intense exercise
      Malnutrition
      Renal failure
      Stress

B. Pubertal failure
   1. Hypogonadotropic hypogonadism
      Idiopathic
      Syndromes (Kallmann, Prader-Willi, Laurence-Moon-Biedl)
      Hypopituitarism
        Isolated LH or FSH deficiency
        Panhypopituitarism
      Congenital abnormalities of CNS
      Secondary to Langerhans cell histiocytosis
   2. Hypergonadotropic hypogonadism
      Congenital
        Gonadal dysgenesis
        Biosynthesis and androgen receptor defects
        Anorchism or cryptorchidism
        Syndromes (Klinefelter, Turner, Noonan, Alstrom, Steiner myotonic, Del Castillo)
   3. Hypo/hypergonadotropic hypogonadism
      Secondary to:
        Surgery
        Chemo/radiotherapy
        Trauma, tumors, infectious disease

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puberty, while all fathers of control families reported pubertal onset at the same time as their peers. Because puberty and growth do ultimately occur, many consider CDP a variant of normal puberty with a slow tempo of maturation. In contrast, in patients with either fixed hypo- or hypergonadotropic hypogonadism, puberty is completely absent.[14] Exceptions can be seen in some girls who have FHH

Table 4.5 Initial laboratory evaluation of delayed puberty and associated disorders

- Thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin
- Bone age
- Karyotype if tall or short stature, or other Turner stigmata
- Complete blood count (CBC): anemia of chronic illness
- Erythrocyte sedimentation rate (ESR): elevated in many chronic, inflammatory, and infectious disorders
- Comprehensive metabolic panel: renal, liver pathology, diabetes mellitus
- Celiac screen – tissue transglutaminase, total IgA, anti-gliadin and anti-endomyseal antibodies

Table 4.6 Relationship between height age (HA), bone age (BA), and chronologic age (CA) in delayed puberty

Hypopituitarism	HA ≤ BA < CA
Hypothyroidism	BA ≤ HA ≤ CA
Hypogonadism	BA ≤ HA < CA
Systemic illness	BA = HA < CA
CDP	HA = BA < CA

CDP, constitutional delay of puberty.

Table 4.7 Constitutional delay of growth and puberty

Key historical information
- Positive family history (maternal *or* paternal) delayed puberty/menarche
- Short stature starting from age 2 as demonstrated on a growth chart

Key physical exam findings
- Short stature with relatively short upper body segment (U:L ≤ 0.9)
- Low or normal BMI

Key laboratory findings
- Delayed bone age for age consistent with pubertal state
- All other lab results are within normal limits

Treatment
- Typically none for females, need to individualize based on psychological and height impact

or genetic mosaicism for Turner syndrome. These patients may begin puberty on time but then not progress or later develop secondary amenorrhea.

The justification for treatment of children with CDGP is to prevent psychological and emotional problems in adolescence and adulthood. However, the conclusions of research evaluating these outcomes are mixed. Results vary from patient outcomes of dysfunctional eating patterns, victimization, and depression to no overt psychosocial problems but the perception of one's short stature as limiting to socio-economic standing.[15–17] Comparing populations of children with 'normal short stature' (NSS) who were referred to those with NSS who were not referred and to children with normal stature, Kranzler et al[18] found that non-referred children with NSS did not differ significantly from normal stature children. They suggest that psychosocial and behavioral problems in a referral population of patients with NSS were misattributed to their short height. Sandberg et al[16] looked at 956 boys and girls attending a public school. Participants included children of all heights. Self- and peer-rated assessments of social reputation and social acceptance were measured. They found no significant relationships between height and measures of friendship, popularity, or reputation with peers. With the notable exceptions of the studies by Kranzler et al and Sandberg et al, most studies of CDGP have few to no female participants. Where differences between male and female psychosocial adjustment are identified, females tend to have fewer negative sequelae if at all. Treatment for CDGP is suggested for male patients more frequently than for female patients. Data to support gender-specific treatment are limited. Table 4.7 summarizes key clinical points.

DELAYED PUBERTY IN THE ATHLETE

In 1970, one woman ran in the New York Marathon and did not finish.[19] In 1972, Title IX mandated equal financing for males and females in educational activities and programs in schools. This was interpreted to include participation in and support for sport activities. In 2006, 12 478 women ran in

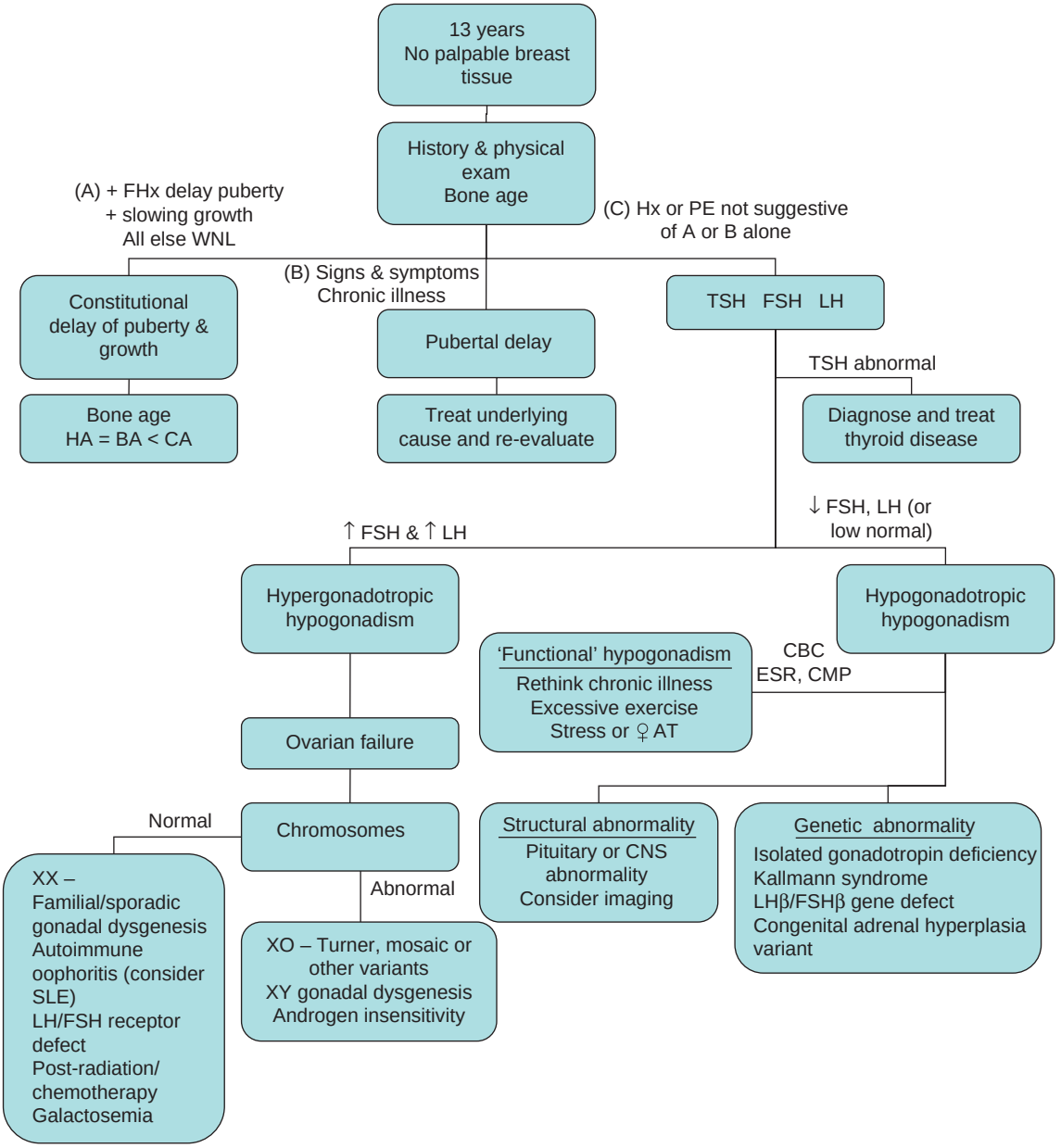

Figure 4.1 Female with Pubertal Delay: Suggested Approach to Evaluation. BA, bone age; CA, chronological age; HA, height/age; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; ESR (or CPR), erythrocyte sedimentation rate (or C-reactive protein); LH, luteinizing hormone; CMP, comprehensive metabolic panel; CBC, complete blood count; ♀AT, female athletic triad; WNL, within normal limits.

the New York Marathon and 12 321 finished (www.newyorkcitymarathon.org). There has been an impressive upsurge in female participation in sports, knowledge of the long-term sequelae of regular, strenuous exercise in young girls and women is not yet available. However, the ever-increasing number of athletic girls and women requires clinicians to recognize both the enormous benefits as well as the potential risks of training while long-term research continues.

The effect of training on the HPO axis of the athlete varies with the intensity of training, type of sport practiced, and the age at which the training began. Therefore a spectrum of presentations from delayed puberty to primary or secondary amenorrhea to the female athlete triad (disordered eating, amenorrhea, and osteoporosis) may be seen.

The highest risk is for those in sports where lean physique is important and training starts at a young age; these sports include gymnastics, ballet dancers, figure skaters, and long-distance runners. However, female basketball, volleyball, and tennis players, and swimmers tend to be above the 50th percentile for weight.[20] Interestingly, rowers can be found listed by different researchers in either weight category.[21]

The exact etiology of pubertal delay in elite athletes is debated, but centers around the combination of high energy output in the face of relatively low caloric intake leading to low body fat. Theodoropoulou et al[22] studied 423 elite rhythm gymnasts (RGs) and 427 artistic gymnasts (AGs) aged 11–23 years from 32 different countries. They found weight below average compared with controls for subjects. Both groups demonstrated pubertal and growth delay, which was greater for AGs who practiced on average 2.5 hours more per week and began training approximately 1 year earlier than RGs. The areas of delay in AGs compared with RGs were: thelarche (13.2 vs 12.9 years), menarche (14.9 vs 14.6 years), and bone age (2.13 vs 1.28 years). The combined average of training was 25–30 hours per week. This is considerably more than the average 15 hours per week for gymnasts in the 1970s, and 20 hours per week in the 1980s. In addition, on average these gymnasts attended seven major competitions a year.

In studying German elite gymnasts, 22 girls and 18 boys, Weimann et al[23] noted a low caloric intake of 1418.4 ± 525 kcal/day and minimal fat mass of 14.4% as compared with 22% in a normal age-matched control population. Swimmers tend to have a lower incidence of hypothalamic-pituitary-gonadal disorder. Nonetheless one study found swimmers concerned about weight, with 60% of average weight swimmers and 18% of underweight swimmers attempting weight loss by dieting.[6]

Because of intense training and low caloric intake athletes have low fat stores. Lack of fat stores leads to low leptin levels. Leptin, produced by the ob gene and secreted by adipocytes, is thought to influence the reproductive axis by a postulated permissive effect on puberty as well as its inhibitory effect on the appetite-stimulating neuropeptide Y (NPY). NPY levels increase with food intake and decrease with periods of starvation. It is theorized to be the link among fat stores, pubertal development, and LH-releasing hormone secretion.[21,24] In comparing leptin levels of patients with anorexia nervosa (AN) to elite gymnasts with anorexia athletica, Matejek et al[24] found the expected low levels of leptin in the AN patients, but even lower levels in the gymnasts, 2.9 vs 1.2 μg/l. An additional hypothesis postulates that the stress of regular sports training[25] has an impact on menarche; noting that for some elite athletes menarche is not reached even when critical BMI is achieved.

Puberty is a critical time for increased bone size and density. Most bone mass is acquired by the end of the second decade.[26] Therefore delay in puberty and menarche causes concern about possible osteopenia, increased stress fractures, potentially compromised final height, and bone mineral density (BMD),[27] as well as osteoporosis. Importantly it is not clear if diminished BMD is reversible with resumption of menses, estrogen replacement or calcium supplementation.[6] Long-term longitudinal studies in athletes with delay of puberty and absent menarche are lacking. However, Warren et al[28] carried out a 2-year study comparing osteopenia in dancers and non-dancers who had hypothalamic

amenorrhea. They evaluated if exercise affected the rate of bone accretion and the functional strength of bones and found that it did not. The subjects were 54 dancers, 22 of whom had amenorrhea and 57 non-dancers, 22 of whom also had amenorrhea. All amenorrheic subjects had normal to low LH and FSH and low estradiol levels. BMD was significantly lower in both amenorrheic groups. Low BMD persisted in all initially amenorrheic subjects despite the return of menses in seven and the continued weight-bearing exercise in the dance group. There were 108 stress fractures, with an increased frequency seen in those with lower BMD.

Table 4.8 Delayed puberty in the athlete

Key historical information

Type of sport practiced
- Sports that demand a particular lean esthetic to compete are at highest risk: ballet dancers, gymnasts, figure skating, long-distance running, and potentially rowing

Age of onset of training
- Estimate 5 month delay of puberty for every year of intense athletic training in childhood[78]

Hours of training
- < 15 hours/week training does not show menstrual changes or pubertal delay[18]
- > 18 hours/week intensive athletic training capable of attenuation of maturation
- New training routine or recent increase in hours

Diet history
- Review caloric intake and expenditures
- Average adolescent female requires 2500 kcal/day
- For every 2 hours athletic activity, require additional 800–1700 kcal[79]
- Restricting or purging behaviors
- 24 hour diet recall – use of low fat and low calorie food substitutes
- Dieting aids; vitamin or supplement use increases suspicion of abnormal eating behavior

Key physical exam findings
- Height: lack of pubertal acceleration of height and BMD
- Weight: low body fat, BMI < 18; recent significant weight loss; at low BMI all weight loss is significant

Laboratory findings
- Hypogonadotropic hypogonadism: low (to low normal) FSH, LH, and low estradiol

Treatment
- Should be individualized but may require a decrease in training routine and increase in caloric intake
- Consider estrogen replacement with hormonal contraceptives (see treatment guidelines section)

While pubertal delay and absence of menses may not be concerning to and at times may actually be desired by the athlete, coach or parents, it is important to recognize the associated medical consequences of osteopenia and osteoporosis and counsel the patient and family appropriately. It is equally important not to simply attribute delayed puberty and absence of menses to athletic training and miss the patient with a pituitary lesion, Kallman syndrome, Crohn's disease or celiac disease. Table 4.8 summarizes key clinical points in evaluating pubertal delay in the athlete.

DELAYED PUBERTY IN CHRONIC ILLNESS

Many serious illnesses and congenital anomalies are now experienced as chronic illnesses, allowing affected children to survive through adolescence and into adulthood. In addition to their medical problems, these teens require attention to their developmental needs, both psychological and physiologic. A frequent finding is delayed puberty and growth failure. Across the spectrum of chronic illnesses, an overall mean delay in puberty of 2 years is seen in both genders. Table 4.9 lists many of the chronic illnesses associated with delayed puberty.

It is important for subspecialists caring for these patients, as well as their primary care providers, to be aware of the effect of chronic illness and treatment on pubertal development. Recognition of the potential for pubertal delay or pubertal failure can allow the teen and their family to anticipate this issue and develop a timely plan for consultation with growth and reproductive specialists. Prompt recognition and treatment where possible may minimize psychological stress and maximize height. Additionally, increased survival among these patients raises questions about future fertility, contraception, and preconceptual concerns.

Delayed puberty in chronic illnesses can be caused by multiple factors. It can be a direct consequence of a disease process, as in acidosis and uremia of chronic renal failure, or a side effect of therapy, as in total body irradiation in preparation

Table 4.9 Main chronic diseases responsible for delayed puberty

- Malnutrition
  - Caloric-protein
  - Micronutrients (Ca, Zn, etc.)
- Recurrent infections/infestations
- Immunodeficiency
  - Congenital
  - AIDS
- Gastrointestinal diseases
  - Malabsorption
    - Celiac disease
    - *Giardia lamblia* infestation
    - Pancreatic cystic fibrosis
  - Inflammatory bowel disease
  - Chronic hepatopathies
- Renal diseases
  - Glomerular nephropathies
  - Congenital tubular defects
  - Interstitial nephropathies
  - Nephrotic syndrome
  - Chronic renal failure
- Respiratory diseases
  - Chronic asthma
  - Pancreatic cystic fibrosis
- Hematological diseases
  - Leukemia
  - Chronic anemia
    - Thalassemia major
    - Pancytopenic anemia
  - Histiocytosis
- Endocrinopathies
  - Hypogonadotropic hypogonadism
  - Hypergonadotropic hypogonadism
  - GH deficiency
  - Hypothyroidism/hyperthyroidism
  - Poorly controlled type 1 diabetes
  - Hypercortisolism
  - Hyperprolactinemia
- Eating disorders
  - Anorexia and bulimia nervosa
- Strenuous exercise (athletic amenorrhea)
- Miscellaneous
  - Connective tissue inflammatory diseases
  - Psychological stress
  - Gaucher's disease
  - Cancer and tumor therapy
  - Chronic cardiopathies

Ca, calcium; Zn, zinc; AIDS, acquired immunodeficiency syndrome; GH, growth hormone. Reproduced with permission. This table was published in Best Practice and Research Clinical Endocridinology and Metabolism, Vol. 16/1, Poso J, Argente J, The main chronic diseases responsible for delayed puberty, 73–90, Copyright Elsevier (2002).

for bone marrow transplant. Malnutrition and high caloric needs, a frequently overarching presence in chronic illness, may be causative in delayed puberty, secondary to malabsorption, decreased appetite or increased nutritional losses. However, researchers have demonstrated delayed pubertal onset in patients in whom nutrition and disease control are adequately managed, as in HIV/AIDS and cystic fibrosis. Frequently, delayed puberty in chronically ill patients can be the result of all these factors. An example of this interplay is Crohn's disease, where malnutrition, inflammation, and steroid therapy can all be factors. Conversely, clinicians need to be cognizant when evaluating patients that delayed puberty and growth failure may be the presenting signs for previously undiagnosed chronic illness such as HIV/AIDS or celiac disease.

Modulating the effects of chronic illness on puberty is the age of onset of illness, severity, and duration of illness. For example, prepubertal total body irradiation in preparation for bone marrow transplant may cause only delay of puberty, while irradiation during puberty can lead to ovarian failure. Patients with severe Crohn's disease requiring prolonged high doses of corticosteroids are more at risk for delay of puberty than individuals with milder disease requiring less steroid therapy. More difficult to quantify is the impact of an individual patient's emotional response to the stressors of illness.

INFLAMMATORY BOWEL DISEASE

In the review of delayed puberty and inflammatory bowel disease by Ballinger et al,[29] the mean onset of puberty in these patients was found to be 12.6 years. Delay was seen more frequently in Crohn's disease than ulcerative colitis (UC). Ferguson and Sedgwick's series[30] of patients with juvenile onset inflammatory bowel disease found that 13 of 22 women with Crohn's disease reported pubertal delay, whereas only 3 of 11 patients with UC experienced delay. Delays are most typically seen in patients with frequent relapses or for whom remission is never achieved. Induction of sustained remission often results in pubertal onset.[29] Malnutrition, active

inflammation, and corticoid therapy contribute to the effects of inflammatory bowel disease on puberty.

MALNUTRITION

In Crohn's disease caloric intake may be only 43–82% of recommended values. Simultaneously, patients have increased nutritional requirements and the potential for ongoing nutrient loss through diarrhea and intestinal bleeding. Prepubertal levels of sex steroids are noted in patients with rapid weight loss, despite previous evidence of pubertal progression.[29]

INTESTINAL INFLAMMATION

Intestinal inflammation itself is postulated to be a significant factor, as there are patients who do not enter puberty despite adequate nutritional supplementation. In these patients, when remission is induced either medically or particularly via surgical intervention, rapid growth with onset of puberty is frequently seen within a year.[29]

CORTICOSTEROID THERAPY

While treatment can limit the effects of disease it may also cause an array of side effects. Steroids can interfere with the retention of nitrogen and minerals, thus further aggravating nutritional deficits. It also can inhibit pulsatile GH secretion, reduce GH receptor expression, and inhibit bioactivity of insulin-like growth factor 1 (IGF-1). However, many patients will have growth acceleration after the initiation of glucocorticoid therapy, probably due to decreased inflammation and overall increased nutrition.[14]

THERAPY

Principles of therapy for delay of puberty and growth in patients with IBD aim to maximize nutrition and minimize inflammation. When adequate nutrition is achieved and medical management has suppressed inflammation but the patient does not show signs of pubertal onset or accelerated growth, surgical resection of areas of active disease may be indicated.[14] Typically, onset of puberty is noted within 1 year of surgery.[29]

CELIAC DISEASE

With the introduction of improved screening and diagnostic modalities the recognized incidence of celiac disease has grown. Recent investigations show its prevalence in the US general population to be 1:133 and significantly higher in first- and second-degree relatives of affected individuals.[31] In European populations the prevalence can be higher. Hypogonadism and resultant delay in onset of puberty have been described, as well as subsequent reproductive consequences such as amenorrhea, infertility, spontaneous abortion, low birth weight, and early menopause. In one study menarche occurred in untreated girls at a mean age of 16.6 years.[32] Delayed puberty in these patients is felt primarily to be related to issues of malnutrition; however, consideration of immunologic effects is also emerging.

MALNUTRITION

Protein calorie malnutrition and deficits in micronutrients such as iron and folate are described.[14] Leptin levels were decreased in untreated patients with celiac disease, and increased with gluten-free diet therapy.[33]

IMMUNOLOGIC ASPECTS

It is postulated that high levels of autoantibody directed against self-antigens could be directed against hormones, receptors, or organs critical for pubertal development. Several celiac patients with hypopituitarism have been described presenting

with abnormal levels of gonadotropins, raising the possibility that the pituitary gland may be a target organ for an autoimmune process in some patients with celiac disease.[32]

THERAPY

Initiation and maintenance of a gluten-free diet corrects pubertal delay; however, this may not correct all subsequent reproductive problems,[14] which may be related to other factors associated with the disease, possibly immune-related.

DIABETES MELLITUS

Previously it was felt that patients with insulin-dependent diabetes mellitus (DM) were at risk for delayed puberty.[34,35] Recent studies looking at patients with good glycemic control demonstrated that the timing and onset of puberty are similar to those of healthy matched controls. A small but significant delay in menarche as well as in the late stages of pubertal development was noted.[36] Delay in puberty in patients with poor glycemic control is common. For discussions of the multifactorial contributions of poor glycemic control, the reader is referred to the article by Schroeder et al.[37]

THERAPY

Maintenance of good glycemic control is the cornerstone of therapy.

HIV/AIDS

Delay of growth and puberty is a significant finding in 25–100% of children with HIV infection and may precede other manifestations of the disease by months.[14] Two recent studies[38,39] showed significant delay of pubertal onset in HIV-infected girls (and boys). The studies looked at different populations and found delays of differing degrees. De Martino's group looked at Italian children and found a median age of pubarche (P2) in those with severe immunosuppression to be 13.0 years.[38] Buchacz's group included non-Hispanic whites and blacks, and Hispanics, and found a median age of P2 to be 12.1 years. Buchacz et al found a significant association between CD4 count and delay of pubertal onset.[39] This was not seen in the Italian group.

The underlying mechanism of pubertal delay in HIV/AIDS remains unclear. Malnutrition alone is not felt to be responsible, as delay is also seen in patients with adequate nutrition. Correlation has not been found between delay and incidence of opportunistic infections or protease inhibitor use. However, patients with growth failure have decreased levels of insulin-like growth factor, insulin-like growth factor binding protein-3, and acid labile subunit, all of which are normal in HIV children without delay.[14] Additionally infected children have euthyroid sick syndrome with increased basal thyrotropin levels and reduced free thyroxine levels. This condition is felt to partly be related to proinflammatory interleukin overproduction triggered by the HIV-1. Finally, delayed sexual maturation through altered neural activity may be induced by the virus.[38]

THERAPY

Treatment is primarily directed at controlling the disease, as growth and puberty correlate with the degree of immune dysfunction.[40] In addition it is important to maximize nutrition. Androgen deficiencies are a part of the spectrum of AIDS in adults and adolescents,[41] and multiple endocrine abnormalities described in HIV-infected children are associated with differences in growth and body composition.[42] In some instances, the use of hormonal therapy is considered.

CYSTIC FIBROSIS

Patients with cystic fibrosis (CF) often have significant delay of puberty, typically by 2 years.[14] The etiology

for this has traditionally been thought to be related to malnutrition, with 34% of teens being malnourished.[43] However, with ongoing advances in care, the nutritional status of patients with CF has continuously improved but delay in puberty and onset of menarche is still seen. The mean menarcheal age from various series ranges from 14.2 to 14.9 years.[43] In a retrospective study of 17 patients with CF no correlation was found between menarcheal age and nutritional or clinical status.[44] However, correlation was noted between delayed puberty and menarche and patients with abnormal oral glucose tolerance tests (OGTT) compared with patients with normal OGTT. Additionally, patients who were homozygous for the Δ F508 mutation were significantly older at menarche (mean age 15.2 ± 1.9 years).

Mechanisms are not completely understood nor solely a consequence of malnutrition. Postulated theories include mutated CF transmembrane conductance regulator (CFTR) gene in the brain that could dysregulate neuroendocrine secretion and lead to delayed pubertal onset despite good clinical status. Patients with Δ F508 have a 25% increased resting energy expenditure compared with patients with other mutations.[44] Other possible contributors include the effects of insulin, which declines in patients with CF and is necessary for the ovary to reach its full steroidogenic potential.[43] Estradiol and FSH levels are delayed and do not reach normal levels until girls with CF are approximately 16 years old.[44]

TREATMENT

Optimize nutrition, identify and treat abnormal glucose metabolism, and provide hormonal replacement therapy when indicated.

CANCER

A majority of children with cancer will survive into adolescence and adulthood. The possibility of delayed puberty is usually not an immediate concern at the time of diagnosis but subsequently may be raised as treatment options are discussed, or after treatment has finished. Questions about menstrual cycles or future fertility often lead to a discussion of the effects of disease or treatments. The mechanisms underlying menstrual cycle and fertility vulnerability are some of the same that influence puberty. Geenen et al[45] investigated adverse outcomes in long-term survivors of childhood cancer and found that patients increasingly confront multiple late treatment sequelae. They report a high rate of post-treatment adverse events, with 75% having one or more and 25% having five or more adverse events, including cardiovascular events, fertility problems, and second malignancies.

The effect of cancer on puberty may be either direct or indirect. It can directly exert a mass effect as a brain tumor or secrete hormones from a distant location. Treatment using radiation therapy or chemotherapy may cause damage to the HPO axis. The extent of gonadal injury is dependent on the age and pubertal status at the time of treatment, dose and fractionation schedule of radiation, and dose of chemotherapy.[46] Cyclophosphamide damage is dose-dependent and may be increased and less reversible when used with busulfan. In theory, ovarian suppression with combined hormonal contraceptives (CHC) may provide some protection from damage. GnRH agonists may be more effective than CHC in protecting ovaries from therapies that attack dividing cells. Surgical relocation of the ovary away from radiation has been effective in improving ovarian outcomes after pelvic irradiation.[47]

Alkylating agents used in chemotherapy such as cyclophosphamide, chlorambucil, and the nitrosoureas, as well as procarbaxine, vinblastine, cytosine arabinoside, and cisplatinum have known gonadal toxicity.[43]

Radiation doses exceeding 5000 cGy to the hypothalamic-pituitary axis may render a child gonadotropin-deficient. In some cases, lower doses of radiation can cause precocious puberty, only to be followed by gonadotropin deficiency years later.[43]

Total body irradiation (TBI) is used in preparation for bone marrow transplant (BMT) in patients with acute lymphocytic leukemia (ALL), as well as

in other cancers and diseases such as sickle cell anemia. TBI has an effect on gonadal function that is highly dependent on age at treatment. Single-dose and fractionated TBI during pubertal and early adulthood have an incidence of ovarian failure of close to 100%. In contrast, treatment during prepuberty is followed by normal pubertal development in 50% of girls.[48] However, in patients with Hodgkin's disease receiving lower doses of radiation therapy, chemotherapy, or both, Papadakis et al[49] found that while gonadal dysfunction was seen early after the end of treatment, ovarian function remained or returned to normal in most young women.

TREATMENT

When there is ovarian or pituitary failure, treatment is low-dose estrogen for pubertal induction followed by estrogen and cyclic progesterone for maintenance of puberty and pubertal changes, as with other gonadotropin deficiencies or Turner syndrome. Because of documented changes in ovarian function over time it is critically important to follow these patients. Patients who enter puberty normally may still be at increased risk for spontaneous abortions or early menopause. Conversely those requiring hormonal therapy may have return of gonadal function. Therefore it is advisable to periodically halt therapy and re-evaluate gonadotropin levels.[50] Elevated gonadotropins at the time of evaluation do not necessarily indicate permanent ovarian failure. Sarafoglou et al[46] reviewed 16 girls retrospectively who underwent high-dose chemotherapy and hyperfractionated TBI. Of these, nine had spontaneous puberty with a mean menarchal age of 13. Six of these girls had elevated LH and FSH, with two showing normalization during 4–7 years of follow-up.

SYSTEMIC LUPUS ERYTHEMATOSUS AND JUVENILE RHEUMATOID ARTHRITIS

Delayed puberty, short stature, and osteoporosis are known to accompany systemic lupus erythematosus (SLE), especially when the disease presents early. Attention to these issues may be overlooked in young patients with SLE, since it most commonly presents in post-pubertal individuals. Delayed puberty is seen in approximately 11% of patients.[51] The mechanism for delay of puberty is unclear but is thought to be related to the inflammatory process of the disease as well as secondary to treatment with high-dose steroids in SLE and juvenile rheumatoid arthritis (JRA). Anti-corpus luteum antibodies have been identified in post-menarcheal women with SLE.[52] Cyclophosphamide causes ovarian toxicity in individuals with cytochrome P450 polymorphism.[53]

TREATMENT

When possible, minimize disease and complicating morbidities such as renal compromise with immune suppression or modulators and other steroid-sparing regimens.

EATING DISORDERS

Amenorrhea is a diagnostic criterion for anorexia nervosa; when illness begins during prepuberty, delay of puberty may be seen. Low weight and FHH with low FSH and LH, as well as low estradiol and leptin contribute to pubertal and menarcheal delays and disturbances. However, low weight is not the sole issue causing delay. Amenorrhea precedes weight loss in about 20% of patients with AN. The mechanism of this hypothalamic or pituitary dysfunction is not understood. Disturbances of peptides involved in food control, growth hormones, and the HP-adrenal axis also accompany anorexia nervosa.

TREATMENT

Psychological and medical management geared toward raising BMI and promoting psychological and physical health are the essential treatment

elements. On average patients who recover and maintain weight at 90% of ideal for 6 months have been shown to have return of function of the HPO axis with return of menses.[54] Comorbidity with affective disorders and the chronicity of the condition often predict persistent amenorrhea or recurrent menstrual symptoms.[55,56] In contrast to individuals with AN, thin elite athletes who also have delayed puberty are more likely to have pubertal advancement when strenuous exercise and activity are interrupted, despite continued low BMI.[14]

HEMOGLOBINOPATHIES

Delay in growth and puberty occurs in various hemoglobinopathies associated with chronic anemia. Thalassemia major and sickle cell disease (SCD) with SC hemoglobin are associated with moderate delays in puberty of a year or less in several studies conducted in different countries. SCD with SS hemoglobin is associated with greater delays in growth, puberty, and menarche.[57] This depends on the type of anemia and its severity but is generally related to chronic intermittent hypoxemia, decreased IGF-1, a hypermetabolic state, and malnutrition. Zinc deficiency is implicated in delay of puberty in sickle cell anemia. Youth with SCD-SS followed prospectively demonstrated pubertal delay of 1–2 years and a delay of skeletal age of 1.3 ± 1.5 years. Growth delays were more pronounced in the second decade of life compared with the first, and in girls were associated with hematological and nutritional parameters.[58] In hemoglobinopathies requiring transfusions such as thalessemia major, pubertal delay can be related to iron deposits in the endocrine glands including the hypothalamus and pituitary glands leading to hypogonadotropic hypogonadism.[14] Serum ferritin concentrations are associated with growth velocity.

TREATMENT

In a group of children with thalassemia major treated with long-term chronic transfusions and chelation, no pubertal development was noted in 42% of the 13–17-year-old girls; 72% had primary amenorrhea. Breast development and menarche were delayed in the cohort with SCD-SS.[59] Bone marrow transplantation (BMT) for SSD is accompanied by the standard pretransplant chemotherapy routines including busulfan and cyclophosphamide. Brachet et al[60] reported that of 10 females with normal growth parameters pretransplant, 7 had persistent ovarian failure following BMT. The other three received lower busulfan dosing and had subsequent spontaneous puberty. FSH levels were elevated during post-transplant puberty, and are not a reliable indicator of subsequent ovarian function. Puberty may be normalized by maximizing nutrition and managing hemoglobin to optimize oxygen-carrying capacity, but there is a lack of published studies on long-term growth and reproductive outcomes.

CHRONIC RENAL DISEASE

Delayed puberty is a common problem and is typically associated with normal to slightly elevated gonadotropins. It may be seen in glomerular, interstitial, and tubular disorders, and frequently in patients with chronic renal insufficiency. The average delay is 2.5 years.[14] Various mechanisms contribute to pubertal delay including hypothalamic-pituitary dysfunction, and decreased excretion of gonadotropins and prolactin by the kidney. Additionally, malnutrition, metabolic acidosis, electrolyte loss, and accumulation of toxic substances can be involved.[14,61] However, some patients may have other specific causes for delayed puberty such as Frasier syndrome; a syndrome marked by gonadal dysgenesis associated with end-stage renal disease of unknown etiology.[61]

TREATMENT

Renal transplant, but not dialysis, reverses hypothalamic-pituitary dysfunction.[10] In instances of Frasier

syndrome, estrogen replacement followed by estrogen and cyclic progesterone is indicated.

ENDOCRINE DISORDERS

Endocrinopathies causing delay of puberty can be divided into those without the possibility of spontaneous pubertal onset and those where puberty is only delayed. Conditions associated with pubertal failure include: gonadotropin deficiency, gonadotropin resistance to LH or FSH, and receptor mutations. Conditions where puberty is delayed or halted include: growth hormone deficiency, hypothyroidism, hyperthyroidism, hyperprolactinemia, hypercortisolism, and poorly controlled diabetes. With these disorders, identification and treatment of the underlying endocrinopathy correct the pubertal delay or arrest.

SOLID ORGAN FAILURE WITH TRANSPLANT

Successful organ transplant in the pediatric population continues to grow, reaching 1816 in 2004.[62] Many of these patients will have delayed growth and puberty as a consequence of their organ failure. The pubertal delay is typically 1–2 years. Pubertal development occurs after transplantation but its tempo varies by age at transplantation, type of organ transplanted, and steroid use.

MISCELLANEOUS DISEASES

As pointed out in the comprehensive review of delayed puberty in chronic illnesses by Pozo and Argente,[14] numerous other medical conditions may be associated with delay of puberty and growth. They include connective tissue pathologies, chronic cardiomyopathies, Friedreich's ataxia, Gaucher's disease, and hyperprolactinemia, among others. Clinicians encountering delayed puberty in these patients should seek endocrinologic consultation.

CONGENITAL DISORDERS, ENZYME DEFICIENCIES, AND SYNDROMES

Several congenital disorders are associated with delayed puberty or pubertal failure. They may manifest as either hypergonadotropic or hypogonadotropic hypogonadism.

HYPERGONADOTROPIC HYPOGONADISM

Elevated gonadotropin levels indicate absent or unresponsive gonads. Disorders of hypergonadotropic hypogonadism include: Turner syndrome, gonadal dysgenesis, LH and FSH receptor defects, FSH β subunit deficiency, autoimmune oophoritis, and infectious causes such as mumps oophoritis. Most hypergonadotropic hypogonadism is idiopathic.

Acquired gonadal failure may be caused by trauma, torsion, infection, chemotherapy, or radiation. An uncommon form of congenital adrenal hyperplasia (CAH) with deficiency of steroidogenic acute regulatory protein (StAR) may present similarly. Inborn errors of metabolism, especially galactosemia where metabolites may poison the ovary if not identified and treated early, can cause premature ovarian failure. Autoimmune polyglandular syndrome 1 may present initially as ovarian failure and progress to involve other endocrine organs.

When there is incomplete pubertal delay, in phenotypic females with breast development and no pubic hair, androgen insensitivity is a likely diagnosis. Individuals with androgen insensitivity (1/20 000) have breast development, no body hair, and 46,XY karyotype. The disorder is caused by an androgen receptor mutation on the X chromosome that produces regression of müllerian and wolffian structures *in utero*. Young women with sparse to normal pubic hair and no breast development, elevated gonadotropins, and 46,XY or 46,XX karyotypes have Swyer's syndrome. In both cases, further imaging for reproductive structures and possible laparoscopic exploration for gonadal tissue are needed. Other mutations of the SRY gene abnormalities have been associated with mixed gonadal dysgenesis. Absence of the SRY gene and some

Table 4.10 Hypergonadotropic hypogonadism – gonadal dysgenesis and genetic variants

I. Turner syndrome

Key historical information
- Lymphedema at birth; feeding problems
- Short stature; absent pubertal growth spurt and secondary sex characteristics
- Learning disabilities, especially poor space-form perception, and average intelligence
- Increased risks of types 1 and 2 diabetes, autoimmune hypothyroidism, celiac disease, osteoporosis, inflammatory bowel disease, hypertension, ischemic heart disease, aortic dilatation and dissection
- No associated risk factors or familial clusters for classic Turner syndrome

Key physical exam finding
- Congenital cardiac and renal anomalies, especially coarctation of the aorta and horseshoe kidneys
- Ptosis, down-slanting palpebral fissures, retrognathia, short 'webbed' neck, and low hairline
- Lymphedema of hands and feet, short 4th metacarpal, and nail dysplasia
- Broad chest, widely spaced nipples, tubular breasts
- Cubitus valgus
- High arched palate, strabismus, chronic otitis and consequent hearing problems, low set ears, sensorineural hearing loss
- Multiple pigmented nevi
- Gonadoblastoma – 12% if Y chromosome abnormalities or inclusion

Key laboratory findings
- Elevated FSH and LH
- Low or unmeasurable estrogen and ovarian androgens
- Delayed bone age for age consistent with pubertal state
- Abnormal karyotype – complete or partial absence of the X chromosome
- Perform fluorescent *in situ* hybridization (FISH) to confirm absence of Y chromosome material on X chromosome
- Mixed picture of normal and hypergonadotropins may occur with Turner mosaic
- After chemotherapy- and radiation-induced hypogonadism, both hypo- and hypergonadotropin levels may be found over time

II. Genetic variants and other syndromes
- Turner syndrome: 'pure' gonadal dysgenesis – 45,XO
- Mosaicism – 45,X/46,XX – does not predict severity or expression because of tissue-specific variability
- XX pure gonadal dysgenesis
- Other sex chromosome anomalies – isochrome Xq, ring X, deletion Xp
- Perrault syndome – autosomal recessive – gonadal failure with sensorineural deafness
- Frasier syndrome – XY females with gonadal dysgenesis and progressive glomerulopathy, and variants
- Swyer syndrome 46,XY pure gonadal dysgenesis including SRY mutation – tall individuals with increased risk of gonadal malignancy
- Multiple X syndromes – rare with skeletal dysplasia, neurodevelopmental delay, gonadal failure – XXX and Xq deletions – pubertal arrest more common

(*Continued*)

Table 4.10 (*Continued*)

- CYP 17 gene deficiency caused by allele of cytochrome P450 enzyme with 17-hydroxylase and 17-20 desmolase activity necessary for cortisol, progestin, androgen, and estrogen production
- Aromatase deficiency – CYP 19 gene mutation interferes with conversion of androgens to estrogens – ambiguous genitalia at birth, multicystic ovaries clinically expressed in females primarily

mutations interfere with differentiation to male gonads, associated structures and ultimately male phenotype. Gonadal histology is variable and gonads may be found in the abdomen or inguinal canal.

TURNER SYNDROME

With a prevalence of 32–50 per 100 000 females (~1/2000), Turner syndrome will be the most frequently encountered chromosomal abnormality associated with delayed puberty. Key physical and laboratory findings and other genetic variants are listed in Table 4.10. The concerns of individuals with Turner syndrome include fertility, short stature, sexual development and function, and general health.[63] A comprehensive clinical practice guideline by Bondy[64] for the Turner Syndrome Consensus Study Group provides recommendations for diagnostic evaluations and subsequent surveillance and treatment for children and adults with this disorder.

HYPOGONADOTROPIC HYPOGONADISM

Disorders with hypogonadotropic hypogonadism include Kallmann, Prader-Willi, and Bardet-Biedl syndromes, and familial hypogonadotropic hypogonadism. In this collection of disorders, GnRH stimulation does not produce an elevation of FSH or LH. Some of the identified genetic disorders only affect the HPO axis, but others may have an effect on other endocrine axises in addition. Molecular genetic techniques have identified an array of new disorders and associated mutations of hormones and their receptors including leptin, FSH, LH, and

GnRH. Gracia and Driscoll[65] summarized many of the newly delineated molecular genetic disorders disturbing puberty. Farooqi et al[66] and Meduri et al[67] have made recent contributions to the literature, describing leptin and FSH receptor mutations, respectively.

Kallman syndrome, an X-linked disorder with a defect on the KAL gene, occurs in 1/50 000 females. Females with a defect in the β subunit of FSH present with delayed puberty. Others with a FSH or LH receptor defect manifest with delayed puberty and ovarian failure.[68] Table 4.11 outlines findings associated with specific etiologies. Prader-Willi syndrome is a genetic disorder of paternal chromosome 15s occurring in 1/15 000 of all births. Its hallmark is obesity with rapid weight gain between ages 1 and 6 years. Females demonstrate hypothalamic hypogonadism, hypoplastic labia minora and clitoris, and delayed or incomplete puberty.[69] Behavioral characteristics include excessive hunger, food seeking and consumption, and other obsessive/compulsive attributes.

The aforementioned disorders cause a delay in puberty by producing a hypogonadotropic state. In addition to the specific disorders detailed above, many acute illnesses and stressors can perturb the HPO axis, as discussed earlier in this chapter. Prolonged disturbances in the peripubertal stage can delay puberty or its progression. Treatment of the underlying condition may need to be augmented by the more general approach to pubertal hormone replacement described below.

Table 4.11 Hypogonadotropic hypogonadism

Multiple genetic syndromes

Key historical information
- Kallmann syndrome and variants – positive family history (maternal *or* paternal) of associated findings in some variants with incomplete expression, and delayed puberty/menarche, abnormal color vision, hypoosmia (autosomal dominant inheritance)
- Prader-Willi – poor infant feeding, failure to thrive, followed by rapid weight gain between 1 and 6 years, compulsive eating and food-related behaviors (autosomal dominant inheritance)
- Bardet-Biedl – decreased vision (rod-cone dystrophy), developmental delay, autosomal recessive
- β subunit gonadotropin and gonadotropin receptor mutations – rare mutations with variable pubertal presentation

Key physical exam findings
- Kallmann syndrome and variants – unilateral renal agenesis, sensorineural hearing loss, icthyosis, abnormal eye movements, synkinesia (mirror image movements), midfacial defects of cleft lip/palate and hypertelorism
- Prader-Willi – obesity, developmental delay, picking and associated scars
- Bardet-Biedl – central obesity, mental retardation, other genital anomalies

Key laboratory findings
- Low or unmeasurable FSH and LH
- Delayed bone age consistent with pubertal status
- FSH and LH levels unresponsive to GnRH stimulation test
- Normal pituitary on MRI, if indicated; aplasia of the olfactory bulbs on MRI – Kallmann
- Karyotype normal; genetic testing positive for transcription factor mutations (e.g. PROP-1)
- All other lab results are within normal limits or abnormal because of associated anomalies, e.g. Bardet-Biedl syndrome is accompanied by renal disease

TREATMENT OF HYPOGONADISM

Estrogen initially stimulates breast development and linear growth. At higher levels it inhibits height growth by promoting epiphyseal closure. Following normal puberty girls usually grow an additional 2–3 inches post menarche. Growth expectations for individuals with Turner syndrome treated with growth hormone and estrogen are improved, although there is controversy about the optimal timing of the hormone administration.[64,70–72] Expected height increases after induced puberty and menarche are unknown for other conditions. In all cases, evaluation with an endocrinologic specialist to consult about both pubertal delay and stature, and to advise on diagnostic testing and treatment is recommended.

Current guidelines[64] advise the initiation of hormone therapy at the age of normal puberty or when diagnosed, whichever is first. Follow-up includes monitoring secondary sex development, linear growth, and hormone levels, when measurable, and if the values contribute to decisions about dosing of hormones or other clinical questions.

Common recommendations are empirically based. Several authors[64,70,73,74] recommend that clinicians initiate a 'lowest dose' of estrogen by pill or patch,

to mimic the physiologic estrogen secretion of early puberty and stimulate height and breast growth, such as 0.3 mg conjugated estrogens (or lower), or 0.5 mg estradiol daily for 6 months. Some clinicians recommend the low dose estrogen only two or three times per week initially, then increasing to daily dosing for 6 months followed by an increase to a higher daily dose of 0.625 mg conjugated estrogens or 1 mg estradiol.

There are some theoretical advantages to transdermal estrogen, since the liver metabolism of oral estrogens may decrease IGF-1 levels. Transdermal estradiol patches offer steady-state delivery and a wide range of doses, and can be adjusted to approximate physiologic increases in estrogen. With transdermal delivery, doses as low as 0.025–0.05 mg/day of estradiol may be used initially, increasing every 6 months. Monthly injections of estradiol are another theoretically attractive, but unpopular option, until persuasive data about superiority are available. Currently, the standard treatment for Turner syndrome involves growth hormone in addition to estrogen and should be orchestrated by a pediatric endocrinologist to maximize height and pubertal outcomes.

Once puberty is established, estrogen doses are usually increased every 6 months over 1–2 years as the clinical and hormonal response is monitored. Transdermal (0.05–0.1 mg/day) or oral estradiol, or conjugated estrogens are prescribed to produce expected clinical responses. When the clinical response is questioned, or when medical concerns about the metabolism of sex steroids are raised, serum levels of estradiol can be obtained. In all cases, secondary sex development and linear and weight growth are followed. Measurements of hormones, bone age, and bone density are not routine but may have clinical indications. When a uterus and normal outflow tract are present, after 12–48 months, depending on the patient's response to hormones, the rate of escalation of estrogen dose, or if breakthrough bleeding begins, cyclic progestins for 10–14 days should be added to produce a withdrawal bleed every month. Oral medroxyprogesterone in 5 or 10 mg tablets daily is the most common progesterone used, but there are a number of alternative preparations. Conventional guidelines for estrogen replacement recommend 1 week off estrogen after 3 weeks of hormone. For convenience, combined hormonal contraceptives in oral, transdermal, or intravaginal delivery systems, provide an easy and 'normative' alternative for hormonal replacement and controlled menses. Concerns regarding potentially immature uterine development on oral contraceptive pill (OCP) hormone replacement have led some authors[75,76] to recommend a minimum of 6 months on the daily estrogen and cyclic progesterone regimen before initiating CHC. Extended cycles and 24/4 regimens of CHCs will minimize the number of no-estrogen days in these women with no endogenous estrogen production. No androgen supplementation is recommended for young females with hypogonadism.

TREATMENT OF DELAYED PUBERTY: GENERAL CONSIDERATIONS

Long-term concerns in individuals with delayed puberty include fertility, and related concerns of contraception, bone health, related general health matters, and the origins, genetics, and transmissibility of their disorder.[63]

Fertility in hypogonadotropic hypogonadism requires exogenous gonadotropin development therapy and consultation with a reproductive endocrinologist. Other associated reproductive and medical concerns may dominate the clinical picture. Fertility in hypergonadotropic hypogonadism requires, minimally, donor eggs and initial hormonal support of the fetus in a normal uterus if present, or surrogate pregnancy. Expert consultation with a reproductive endocrinologist is critical.

Bone health may be a concern because of delayed initiation of hormone replacement, steroid use, undernutrition, malnutrition, and other medical or behavioral concerns. If these factors add risk, or if stress or complete fractures are found, measurement of BMD using the age-appropriate parameters is warranted. Additional adjustments may be required to adjust norms for body size.[77] If osteopenia or osteoporosis is identified, consultation with a

bone disorder specialist is advised. Treatment of these disorders in young women is an emerging field, and automatically applying solutions that are recommended in menopausal women is not generally accepted or recommended care at this time.

Delayed puberty may be anticipated or identified relatively early in individuals who are followed for other diseases or growth delay. In the context of chronic disease and genetic disorders, diagnosis and treatment can be anticipated. Early consultation with a pediatric endocrinologist and long-term care with reproductive and adult endocrinologists are recommended. Adolescent medicine specialists are often familiar with the hormonal replacement regimens and may play a role in management through the teen years in consultation with endocrine specialists. Late diagnosis of delayed puberty requires immediate referral to an endocrine specialist for diagnostic testing and treatment plans.

Consideration of long-term goals of growth and fertility, but concomitant consideration of contraception, STD prevention, and preconceptual concerns, are part of comprehensive reproductive health care in individuals with delayed puberty. Expert resources for evaluation and treatment are likely to be found in pediatric, adult, and reproductive endocrinologists, other system-specific pediatric subspecialists, and adolescent medicine practitioners. Behavioral health, genetic counseling, and nutritional support professionals should be considered for inclusion in a team approach to the treatment of the disorders causing delayed puberty.

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5. Disorders of sexual differentiation

Joe Leigh Simpson

INTRODUCTION

Disorders of sexual differentiation are individually rare but in aggregate not uncommon. In this chapter we consider those disorders most likely to occur in adolescent females or infants with genital ambiguity. This chapter reflects a number of research contributions.[1,2]

REPRODUCTIVE EMBRYOLOGY

Primordial germ cells originate in the endoderm of the yolk sac and migrate to the genital ridge to form the indifferent gonad, which is initially indistinguishable in 46,XY and 46,XX embryos. Indifferent gonads develop into testes if the embryo – or more specifically the gonadal stroma – is 46,XY. This process begins about 43 days after conception. Testes become morphologically identifiable 7–8 weeks after conception (9–10 gestational or menstrual weeks).

Sertoli cells are the first cells to be morphologically distinguishable in testicular differentiation. Sertoli cells organize the surrounding cells into tubules. Both Leydig cells[3] and Sertoli cells[4] appear before testicular morphogenesis *per se*, consistent with their role in directing gonadal development. These cells secrete the hormones that direct different aspects of male differentiation (Figure 5.1).

Fetal Leydig cells produce testosterone, which stabilizes wolffian ducts and permits differentiation of the vasa deferentia, epididymides, and seminal vesicles. Testosterone is converted by 5α-reductase to dihydrotestosterone (DHT), which virilizes external genitalia. These actions can be mimicked by the administration of testosterone to female or castrated male mammalian embryos, and are demonstrated in humans by the effects of certain teratogenic forms of female pseudohermaphroditism.

Fetal Sertoli cells produce anti-müllerian hormone (AMH, also called müllerian inhibitory substance or MIS). This glycoprotein diffuses locally. If its receptor (AMHR) is intact, regression of müllerian derivatives (uterus and fallopian tubes) occurs. AMH also plays a role in gonadal development. If AMH is chronically expressed in XX transgenic mice, oocytes fail to persist, tubule-like structures develop in gonads, and müllerian differentiation is abnormal.[5]

In the absence of a Y chromosome, an indifferent gonad develops into an ovary. Transformation into fetal ovaries begins at 50–55 days of embryonic development. Oocytes differentiate in 45,X embryos, but then undergo atresia more rapidly than that occurring in normal 46,XX embryos. Thus, the pivotal ovarian genes on the X actually control ovarian maintenance.

Ductal and external genital development occurs independent of gonadal differentiation. In the absence of testosterone and AMH, external genitalia develop in a female fashion. Müllerian ducts form the uterus and fallopian tubes; wolffian ducts regress. These changes occur in normal XX embryos, as well as in XY animals that were castrated as embryos before testicular differentiation.

GENETIC CONTROL OF SEX DIFFERENTIATION

Both sex chromosomes (X and Y) as well as autosomes contain genes that must remain intact for normal sexual development. Location of these loci becomes important for clinical management. That autosomal factors influence sexual development

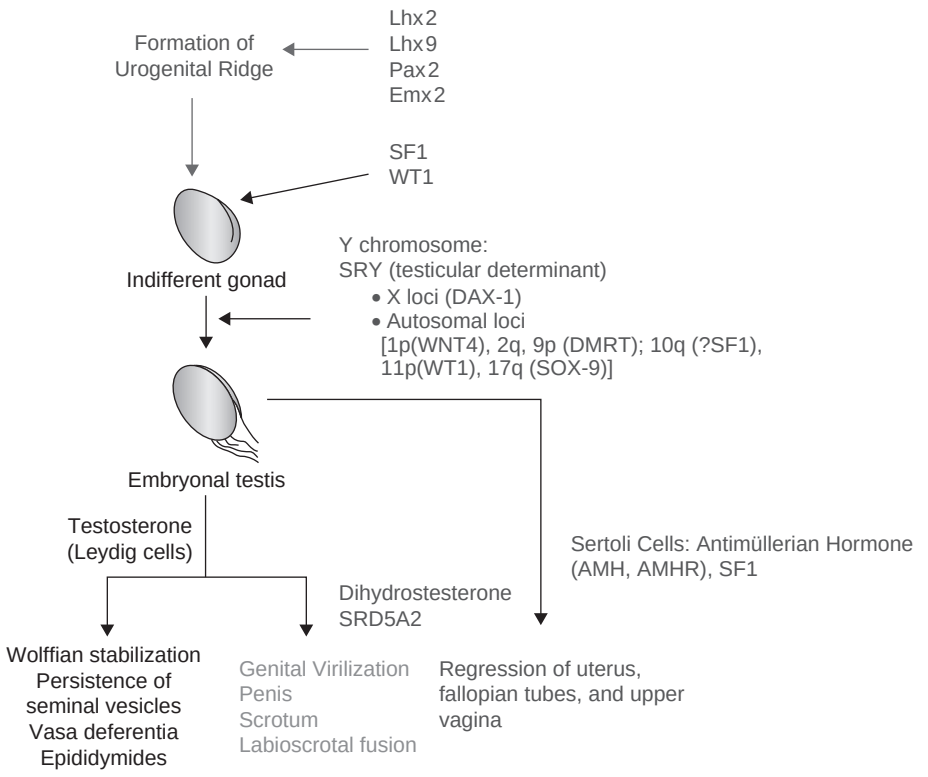


Figure 5.1 Schematic diagram illustrating embryonic differentiation in the normal male. The role of certain genes in the formation of the urogenital ridge and indifferent gonad have been deduced in rodents but not necessarily confirmed in humans. Known human genes are designated by standard nomenclature. Reproduced with permission from Simpson JL: Mammalian Sex Determination, Encyclopedia of Life Sciences, 2008, John Wiley & Sons, Ltd, published online March 2008, doi: 10.1002/9780470015902.a0001886.pub2).

predicts that autosomal translocations may clinically be associated with genital or gonadal abnormalities. A corollary is that health-care professionals managing pediatric gynecologic patients should anticipate gonadal abnormalities in autosomal chromosomal abnormalities.

GENES ACTING BEFORE DIFFERENTIATION INTO GONADS

Based largely upon animal models, a series of genes are assumed to be necessary for development of the urogenital ridge. In mice, these include Lim 1 and 9 (Lhx1; Lhx9), Emx2, and Pax 2. Development of the indifferent gonad from the urogenital ridge probably requires different genes, currently believed to include SF1 and WT1. Germ cell formation and migration logically require other genes, postulated at present to include SCF (c-kit) and SDF (KCR4). Most of these genes have been recognized, and their roles postulated, on the basis of murine knockout models. Extrapolations to the human phenotype are imprecise, but one would predict that both male and female gonads would be affected if the above genes are perturbed.

Y CHROMOSOME AND TESTICULAR DEVELOPMENT

That 46,X,i(Yq) individuals were female in appearance demonstrated decades ago that the key

testicular determinants (testis determining factors or TDFs) were localized to the Y short arm (Yp). SRY (Sex-determining Region Y) is now known to be the pivotal gene. In confirmation, 10% of sporadic XY gonadal dysgenesis cases show point mutations within SRY,[6] as will be discussed below. The pivotal sequence in *SRY* involves a high-mobility group (HMG) box that shares features with other DNA-binding sequences. When XY gonadal dysgenesis is associated with a point mutation or deletion in *SRY*, perturbation almost always involves the HMG box. *SRY* is evolutionarily conserved, present in all male (XY) mammals. *SRY* is expressed before testicular differentiation.[7] Transgenic XX mice with *Sry* predictably show testicular differentiation.[8]

X CHROMOSOMES AND TESTICULAR DIFFERENTIATION

Various clinical disorders indicate that testicular differentiation requires genes on X. The importance of genes on the X chromosome was first well established by the X-linked recessive form of XY gonadal dysgenesis.[9,10] In addition, Xp contains a region that when duplicated suppresses testicular development despite presence of SRY. The duplicated gene responsible for this phenomenon[11] was originally called *dose-sensitive sex reversal* (DSS). The term DAX is now applied. The locus is near or identical to that for adrenal hypoplasia (AHC), but the exact relationship remains unclear.

AUTOSOMES AND TESTICULAR DEVELOPMENT

Autosomal loci are also pivotal for testicular differentiation. These genes could act either upstream or downstream to SRY, i.e. exerting their action either before or after SRY. Complex scenarios have been proposed. Based on murine knockout models, absence of WT-1 results in failure of both males (46,XY) or females (46,XX) to develop gonads (and kidneys).[12] Both SRY and WT-1 are found in the testes, but the latter is expressed earlier. This is the basis for hypothesizing that WT-1 is required upstream of SRY (i.e. before SRY is expressed).[13]

SF1, SOX9, and SOX8 are considered to be genes downstream from SRY. Like SRY, SOX9 has a DNA-binding HMG box. Deletion or perturbation of SOX9, which is localized to 17q23, is responsible for campomelic dysplasia and XY gonadal dysgenesis (sex reversal). Duplication of 17q23.1→q24.3 conversely has resulted in a 46,XX individual having bilateral scrotal gonads (presumptive testes), a small male phallus, and a perineal urethral orifice (incompletely sex-reversed XX male).[14] In aggregate, this suggests that female differentiation involves derepression, perhaps by SRY, of an otherwise constitutive autosomal testicular-determining autosomal region. Indeed, in mice insertional mutagenesis to SOX9 produces a not dissimilar phenomenon; the gene involved is called odd sex (ods).[15] Overall, the assumption is that SRY normally depresses an autosomal locus to allow testicular differentiation.

Other autosomal regions affect testicular development. These deletions include 9p24.3 (DMRT),[16] 10q26 (SF1),[17] 11p (WT1), and 2q33.[18] Further details concerning these genes are provided elsewhere.[2] Duplication of 1p35, the region in which WNT4 is localized, also perturbs testicular development. Overexpression of WNT4 up-regulates DAX1 and, hence, causes XY sex reversal.[18]

Less well-defined evidence for autosomal control over testicular development consists of the occurrence of testicular differentiation in 46,XX true hermaphrodites (see later). Almost all 46,XX true hermaphrodites cases lack SRY, suggesting that loci permitting testicular differentiation must therefore be autosomal.

OTHER GENES ON THE Y

The Y contains other genes of clinical relevance. Deletions of the Y long arm are associated with male infertility. Approximately 15% of azoospermic men have such deletions; 5–10% of oligospermic men have deletions. The most popular model assumes three loci. AZFa is the rarest abnormality and is

associated with absence of spermatogenesis and stem cells. AZFb produces maturational arrest and corresponds to the locus entitled RNA-binding motif (RBM). The most common locus is AZFc, associated with azoospermia and severe oligospermia. AZFc contains the locus DAZ (Deleted in AZoospermia). Using intracytoplasmic sperm injection (ICSI), affected males can sire offspring. However, their DAZ deletions are obligatorily transmitted to all sons.

Gonadoblastoma Y (GBY) is the other locus relevant to pediatric gynecology. Loss of the fluorescent (and presumably some contiguous euchromatic nonfluorescent) portion of Yq[19] protects against germ cell neoplasia in sex-reversed XY females. XY females having deletion of Yq fail to develop neoplasia as would otherwise occur. (See below for further details.) XY females having an intact Y often may develop neoplasia. A candidate gene for the locus[20] is TSPY, a multicopy gene located in interval 3.[21] TSPY is normally expressed in spermatogonial cells in normal testes[22] and up-regulated in gonadoblastomas.[23]

X CHROMOSOME AND CONSTITUTIVE OVARIAN DIFFERENTIATION MAINTENANCE GENES

Pathogenesis of germ cell failure in humans involves increased germ cell attrition. If two intact X chromosomes are not present, ovarian follicles in 45,X individuals typically degenerate by birth. As stated already, genes on the second X chromosome can be deduced to be responsible for ovarian maintenance, rather than primary ovarian differentiation. A specific gene product(s) may or may not be required for primary ovarian differentiation. DAX1 was once a popular candidate gene. Indeed, we have noted that duplication of Xp21 results in 46,XY embryos differentiating into females.[11] Given this, it was reasoned that Xp21 could play a primary role in ovarian differentiation in 46,XX individuals. The region contains the locus AHC (adrenal hypoplasia congenital), which as noted includes or is identical to DAX1 (Dosage sensitive sex reversal/Adrenal hypoplasia critical region X); its mouse homolog is Ahch. However, XX mice lacking Ahch proved to have normal ovarian differentiation, ovulation, and fertility;[24] XY mice mutant for Ahch show testicular germ cell defects. Thus, Ahch cannot plausibly be responsible for primary ovarian differentiation. Current interest focuses on the anti-testes actions of FOXL2, a gene that if perturbed causes blepharophimosis-epicanthus syndrome (BPES), type 1.[25]

OVARIAN GENES ON THE X SHORT ARM (Xp)

Deletions and other structural abnormalities of the X chromosome (short arm or long arm) are associated with ovarian failure, either complete or partial. The phenotype is discussed elsewhere.[1,2] Genes on Xp must be pivotal for ovarian germ cell function, but progress in their identification has been scant. Here we shall review selected candidate genes. The search is clinically relevant because any common causative gene might be subjected to testing for diagnostic as well as potentially management decisions.

USP9X (UBIQUITIN-SPECIFIC PROTEASE 9)

This gene maps to Xpl1.4, as noted a pivotal region.[26] The *Drosophila* ortholog of *USP9X* is required for eye development and oogenesis in that species.

ZFX (ZINC FINGER X)

ZFX drew attention on the basis of its mapping to Xp22.1–21.3 and being homologous to ZFY, once a candidate gene for male sex determination. Mice null for ZFX are small, less viable, less fertile, and characterized by diminished germ cell number in ovaries and testes.[27]

BONE MORPHOGENETIC PROTEIN (BMP15)

Perturbations of BMP15 and other members of the transforming growth factor-beta (TGFβ) superfamily

are accepted causes of premature ovarian failure (POF). BMP15 is located in Xp11.2. The phenotype of mouse knockout models is consistent with a key role; follicular dysfunction is observed and mice are infertile.

In 2004, Di Pasquale et al observed two sisters with POF who were heterozygous for c.704A>G substitution.[28] A later study involved 79 American and 87 European caucasian women with POF.[29] Nine women had one of four different non-synonymous sequence variants; only one was found in control women. Among 203 European caucasians, Laissue et al[30] reported 3 non-synonymous variants in 13 women with POF; only one variant was present in the control sample. Dixit et al[31] sequenced 202 Indian women with ovarian failure and found 18 (9%) with heterozygous *BMP15* variants. These perturbations involved 11 different non-synonymous sequences; none were present in controls. However, many variants in the POF cases were found in only a single POF subject, raising doubts about causation.

If heterozygous BMP15 mutations exert a deleterious effect, the mutation must exert a dominant negative effect. The possibility of the homologous allele being dysfunctional but lacking a discernible coding perturbation seems less likely on statistical grounds. The basis of a dominant negative effect might involve disturbed dimerization of TGFβ proteins. BMP15 protein not only forms homodimers, but also heterodimers with the GDF9 protein, an autosomal TGFβ protein.

GENES ON THE X LONG ARM (Xq)

XIST (X INACTIVATION SPECIFIC TRANSCRIPT)

It has long been speculated that disturbances of X inactivation *per se* lead to ovarian failure, but the concept of such a 'critical region' is still arguable. Loss of germ cells in X autosomal translocation and X deletions involving Xq13 may or may not be the direct result of perturbation of XIST, which is encoded in this region.

DIAPH2

Diaphanous (DIAPH2) is the homolog of *Drosophila melanogaster* diaphanous (dia). This family of proteins helps to establish cell polarity, govern cytokinesis, and reorganize the actin cytoskeleton. In both male and female flies, dia causes sterility. Disruption of the last intron of *DlAPH2*[32] was observed in Xq21/autosome translocation associated with ovarian failure.

DACH2

Originally identified through an X/autosome translocation, this gene is mapped to distal Xq21 in the region encompassed by a vaguely defined but officially labeled locus called POF2. Bione et al[33] found novel single nucleotide polymorphisms (SNPs) in 7 of 257 women with primary amenorrhea ($n = 19$), POF ($n = 212$), or early menopause ($n = 26$). Of the five different perturbations in the seven women, three were also found in controls; the remaining two involved heterozygous mutations in conserved regions and, hence, were plausible explanations for POF.

POF1B

POF1 is the official designation for a 'gene' located on Xq21.3-27. Distinct from DACH2 and DIAPH2, POF1B is not inactivated. Lacombe et al[34] used the term POF1B to describe a mutation in a Lebanese family in which five consanguineous sisters had primary amenorrhea. The sisters were stated to have premature ovarian failure, but in fact never developed menses or secondary sexual development. All five showed a homozygous R329Q perturbation (exon 10). Protein function predictions suggested homology with myosin, a protein that plays a pivotal role in cell division.

XPNPEP2

This gene (X-propy1 aminopeptidase 2) maps to Xq25, and has also been proposed as relevant to a

'gene' called POF2 that maps in this region. Bione and Toniolo[35] and Prueitt and colleagues[36] reported that XPNPEP2 was disrupted in an Xq/autosome translation associated with primary amenorrhea.

SRY RELATED HMG – BOX (SOX) 3

The pivotal role of SRY and homeobox genes, whose proteins bind DNA, has already been noted. SOX-3 maps to Xq26-q27[37] and thus becomes a candidate gene for POF. Its close homology to SRY is also intriguing. Wolff et al[38] found a gene deletion in males who had multiple malformations including small testes. However, no perturbations were found in 164 isolated POF cases.[39]

FMR1

Fragile X syndrome is the most common cause of mental retardation in males. This phenotype is the result of an increase in the number of CGG triplet repeats in a 5′ region of the X-linked gene FMR1, which is located on Xq27.3. FMR1 is a translational suppressor of a number of other genes. Hypermethylation occurs, FMR1 protein is suppressed, and other genes are secondarily overexpressed. Fragile X syndrome occurs when there are greater than 200 CGG repeats, the normal number being 29 or 30.

Of relevance in this chapter, POF may occur when the number of repeats is between 55 and 200, a situation defined as premutation. The term 'premutation' arose because during maternal meiosis the number of CGG repeats in a premutation carrier may expand, and if expanded to greater then 200 will result in mental retardation in males. Of female 'premutation' carriers, 15–20% show POF.[40] In turn, premutation carriers have been identified in perhaps 1–5% of women with sporadic premature ovarian failure and in 10–15% of women with familial POF.[40]

MONOSOMY X (TURNER SYNDROME)

The chromosomal complement most frequently associated with ovarian dysgenesis is 45,X. The proportion of 45,X individuals in a given sample of ovarian failure cases depends on mode of ascertainment. Fewer 45,X individuals are detected if primary amenorrhea is the presenting complaint than if short stature or other somatic anomalies are also present. Logically, primary amenorrhea is more likely to be the presenting complaint in 45,X cases identified by gynecologists, whereas short stature is more likely in cases identified by pediatricians. Overall, about 50% of all patients with complete ovarian failure have a 45,X complement; 25% have sex chromosome mosaicism with a structural abnormality (e.g. 45,X/46,XX).[41,42] Structurally abnormal X or Y chromosomes are less common.

In 80% of cases it is the paternally derived X that is lacking. This percentage (80%) probably means that X^m and X^p chromosomes are lost randomly.[43] The reason is that assuming 45,Y is lethal, the theoretical percentage of 45,X^m cases would be 67%, not much different from the 80% actually observed. In structurally abnormal X chromosomes, the paternal X is usually lost.[43] The phenotype does not generally differ between 45,X^m and 45,X^p cases (X^m,X of maternal origin; X^p,X of paternal origin).

GONADS IN MONOSOMY X

In most 45,X adults having ovarian failure, the normal gonad is replaced by a white fibrous streak, 2–3 cm long and about 0.5 cm wide, located in the position ordinarily occupied by the ovary (Figure 5.2). Histologically, a streak gonad is characterized by interlacing waves of dense fibrous stroma that are indistinguishable from normal ovarian stroma (Figure 5.3). That germ cells are usually completely absent in adults but present in 45,X embryos indicates that the pathogenesis of germ cell failure is increased atresia, rather than failure of germ cell formation. Ovarian rete tubules,

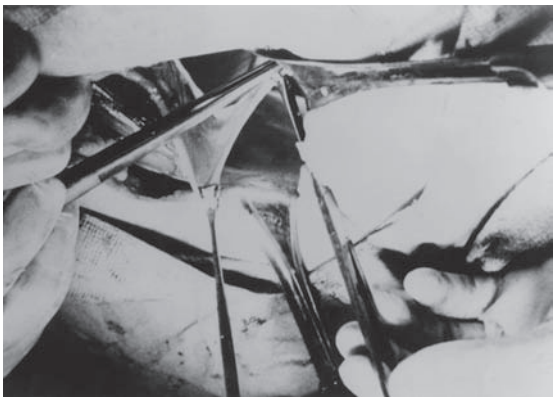


Figure 5.2 A streak gonad. Reproduced with permission from Simpson JL: Disorders of Sexual Differentiation: Etiology and Clinical Delineation. New York: Academic Press, 1976.

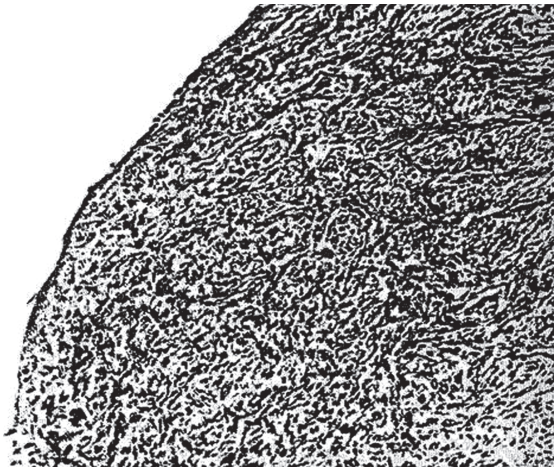


Figure 5.3 Histologic appearance of a streak gonad demonstrating absence of oocytes. Reproduced with permission from Simpson JL: Disorders of Sexual Differentiation: Etiology and Clinical Delineation. New York: Academic Press, 1976.

which probably originate from either mesonephric tubules or the medullary sex chords, are present in the medial portion of most streak gonads. Hilar cells are usually detected in streak gonads derived from patients past the age of expected puberty.

SECONDARY SEXUAL DEVELOPMENT

About 3% of monosomy X adults menstruate spontaneously and 5% show breast development (Table 5.1). Occasionally, fertile patients have been reported. An occult 46,XX cell line is one explanation for a 45,X woman who menstruates. It is, however, plausible that a few 45,X individuals could be fertile, inasmuch as germ cells are clearly present in 45,X embryos. Offspring of 45,X women are rare, but probably not at greatly increased risk for chromosomal abnormalities.[44]

Once hormone therapy is instituted, uterine size becomes normal. This permits 45,X women to carry pregnancies in their own uterus after transfer of donor embryos. Counseling must take into account overall maternal health, particularly the presence of cardiac anomalies like coarctation of the aorta.

SOMATIC ANOMALIES

45,X individuals usually are short (less than 4 ft 10 in) and also often exhibit many Turner stigmata. No single somatic anomaly is pathognomonic of Turner syndrome, although in aggregate a characteristic spectrum exists that is likely to occur in women with a 45,X complement. The pediatric gynecologist should consider evaluation of renal, vertebral, cardiac, and auditory function obligatory. Details on somatic anomalies are covered elsewhere in more detail.[1,42]

GROWTH

Birth weight of 45,X neonates is decreased. Total body length at birth is more normal, often near to the 50th percentile. However, by the expected time of puberty the height lies in the 10th to 15th percentile.[45] The mean height of 45,X adults (16 years and older) is 141–146 cm.[42]

Various treatments for short stature in 45,X patients have been proposed: growth hormone,

Table 5.1 Somatic features associated with 45,X chromosome complement

Growth
Decreased birth weight
Decreased adult height (141–146 cm)
Intellectual function
Verbal IQ > performance IQ
Cognitive deficits (space–form blindness)
Craniofacial
Premature fusion of spheno-occipital and other sutures producing brachycephaly
Abnormal pinnae
Retruded mandible
Epicanthal folds (25%)
High-arched palate (36%)
Abnormal dentition
Visual anomalies, usually strabismus (22%)
Auditory deficits, sensorineural or secondary to middle ear infections
Neck
Pterygium (46%)
Short, broad neck (74%)
Low nuchal hair (71%)
Chest
Rectangular contour (shield chest) (53%)
Apparently wide-spaced nipples
Tapered lateral ends of clavicles
Cardiovascular
Coarctation of aorta or ventricular septal defects (10–16%)
Renal (38%)
Horseshoe kidneys
Unilateral renal aplasia
Duplication of ureters
Gastrointestinal
Telangiectasias
Skin and lymphatics
Pigmented nevi (63%)
Lymphedema (38%) due to hypoplasia of superficial vessels
Nails
Hypoplasia and malformation (66%)
Skeletal
Cubitus valgus (54%)
Radial tilt of trochlear surface of humerus
Clinodactyly V
Short metacarpals, usually IV (48%)
Decreased carpal arch (mean angle 117°)
Deformities of medial tibial condyle
Dermatoglyphics
Increased total digital ridge count
Increased distance between palmar triradii a and b
Distal axial triradius in position t'

anabolic steroids, and low-dose estrogen. Currently the most popular protocol involves administration of recombinant growth hormone. Effect on ultimate height is still not clear, but the consensus is that height increases by 6–8 cm.[46,47] Mitigating against fully beneficial effects of treatment are abnormalities involving epiphyses. Not only are long bones abnormal but so are the teeth and skull. Women with 45,X karyotype could thus be said to have skeletal dysplasia.

INTELLIGENCE

Most 45,X women have normal intelligence, but any given patient has an increased chance of being retarded. Performance IQ is lower than verbal IQ, the latter being more similar to 46,XX matched controls. 45,X individuals often have a specific cognitive defect characterized by poor spatial-processing skills ('space–form blindness').[48,49] Psychosocial deficits secondary to short stature include immaturity and immature social relationships.

X CHROMOSOMAL MOSAICISM: 45,X/46,XX AND 45,X/47,XXX

45,X/46,XX is predictably associated with fewer anomalies than is 45,X. Simpson[41] once calculated

that 12% of 45,X/45,XX individuals menstruate, compared with only 3% of 45,X subjects. In that series, 18% of 45,X/46,XX individuals exhibited breast development, compared with 5% for the 45,X genotype. Mean adult height was greater in 45,X/46,XX than 45,X; more mosaic (25%) than nonmosaic (5%) patients reach adult heights greater than 152 cm. Somatic anomalies are less frequent in 45,X/46,XX than in 45,X.

The complement 45,X/47,XXX occurs less often, but the phenotype is similar to that of 45,X/46,XX. Individuals with 45,X/46,XY may also have bilateral streak gonads, but more often they have a unilateral streak gonad and a contralateral dysgenetic testis (mixed gonadal dysgenesis).

OVARIAN FAILURE ASSOCIATED WITH NORMAL CHROMOSOMAL COMPLEMENTS: MENDELIAN AND MITOCHONDRIAL CAUSES

Autosomal genes play a role in POF, as long evident on the basis of indirect evidence. In the prototypic form of 'XX gonadal dysgenesis' somatic anomalies are by definition not found. Affected individuals are normal in stature; Turner stigmata are absent. Inheritance is usually autosomal recessive. Considerable heterogeneity exists; thus, the different genes probably exert different mechanisms of action.

AUTOSOMAL GENES OF KNOWN ENDOCRINE FUNCTION

FOLLICLE-STIMULATING HORMONE β

Mutations in follicle-stimulating hormone (FSH)β are rare, but the two affected women who have been reported have predictably shown neither thelarche nor menarche. Affected women predictably have hypogonadotropic hypogonadism. Matthews and colleagues[50] described a homozygous 2 bp deletion (GT) in exon 3, codon 61. Layman et al[51] reported a woman in whom one allele showed a missense mutation (exon 3, codon 51), and the other allele showed a deletion (exon 3, codon 61).

FSH RECEPTOR

FSH receptor (FSHR) is the only gonadotropin-related gene in which a mutation has been found in significant numbers of women with an ovarian abnormality. Homozygous FSHR mutations are the most common cause of XX gonadal dysgenesis in Finland, but are rare elsewhere. Aittomaki and colleagues[52,53] found FSHR missense mutation C566T (Ala566Val) in many (but not all) Finnish families. Sometimes ovaries show follicles as predicted in ovarian resistance, but other cases show traditional streak gonads.[54] Females heterozygous for the mutation showed normal fertility.

Outside Finland Ala566Val mutations (C566T) are rare. None were found in 46,XX hypergonadotropic hypogonadism or POF cases studied in the United States,[55] Brazil,[56] and Mexico.[57]

LUTEINIZING HORMONE β

In a single family in Brazil a homozygous luteinizing hormone (LH)β mutation was found in two hypogonadal males and their female sib. The mutation involved a 5′ splice site (IVs2 + IG→).[51] The female sib underwent pubertal development, but shortly thereafter experienced secondary amenorrhea.[58]

INACTIVATING LH RECEPTOR

LH receptor (LHR) mutations in 46,XX women cause gonadal dysgenesis or premature ovarian failure. Reported female cases have been ascertained in sibships with affected 46,XY sibs, who have Leydig cell hypoplasia and show sex reversal (female phenotype with streak gonads).

An example is the report of Latronico and co-workers[59] of a 22-year-old 46,XX woman with primary amenorrhea; her three 46,XY sibs (also phenotypic female) had the same homozygous C544→X mutation. The truncated protein consisted of five rather than seven transmembrane domains.[60]

The 46,XX sib failed to ovulate, even though gametogenesis proceeded until the preovulatory stage. Ovarian histology (follicle dysfunction) is consistent with mouse knockout models.

INHIBIN α

Inhibins (INH) are heterodimeric glycoproteins, synthesized by granulosa cells. Inhibins consist of an α subunit and one of two B subunits (B_A and B_B), producing INHA and INHB, respectively. These genes exert negative feedback inhibition on FSH. By contrast, activins enhance FSH secretion. In premature ovarian failure serum inhibin is low and FSH is elevated. Elevated FSH and low inhibin thus indicate reproductive aging. Perturbation of inhibins should cause ovarian failure.

Three studies have shown an association between POF and a particular INHα missense mutation – G769A. Shelling et al[61] found G769A in 3 of 43 New Zealand POF patients (7%); only 1 of 150 controls (0.7%) showed G769A. However, the fact that the mother of one of the three G769A cases had the same perturbation and was clinically normal casts doubt on causality. Marozzi et al[62] found G769A in 7 of 157 Italian POF cases, 3 of 12 primary amenorrhea cases, and 0 of 36 early menopause (40–45 years) women. Dixit et al[63] reported that familial POF cases were relatively more likely to show G769A (9/80 cases) than were sporadic cases.

Concluding causation on the basis of gene association studies *per se* is never possible because of pitfalls like ethnic stratification, and there is reason to be skeptical. The G769A transition may not be pivotal, given that normal individuals also have the G769A transition and given that individuals with G769A may be normal even in a family in which a G769A relative has POF. However, INHα remains an attractive candidate gene, and *in vitro* functional studies have revealed positive findings.

CYP17 (17α-HYDROXYLASE/17,20 DESMOLASE DEFICIENCY)

46,XY individuals with a homozygous mutation in this gene show male pseudohermaphroditism or XY sex reversal. Less commonly reported are 46,XX cases, who present with primary amenorrhea or premature ovarian failure.[64] Ovaries are hypoplastic and may be streak-like in appearance. Oocytes appear incapable of reaching diameters of more than 2.5 mm.[65] However, ovarian stimulation can produce oocytes capable of fertilization *in vitro*.

CYP19 (AROMATASE)

Conversion of androgens (Δ4-androstenedione) to estrogens (estrone) requires cytochrome P450 aromatase (CYP19), an enzyme that is the gene product of a 40-kb gene located on chromosome 15q21.1.

Ito and co-workers[66] reported an aromatase mutation (CYP19) in a 46,XX 18-year-old Japanese woman with primary amenorrhea and cystic ovaries. Compound heterozygosity existed for two different point mutations in exon 10. The mutant protein lacked functional activity.

Conte and colleagues[67] reported aromatase deficiency in a 46,XX woman presenting with primary amenorrhea, elevated gonadotropins, and ovarian cysts. Compound heterozygosity for two different exon 10 mutations was found: a C1303T transition (arginine to cysteine) and a G1310A transition (cysteine to tyrosine). The phenotype differed from that reported by Ito et al[66] in that genital ambiguity was present.

GENES REQUIRED FOR OOGENESIS

NOBOX

NOBOX (Newborn Ovary homeoBOX gene) encodes a homeobox transcriptional regulator.[67] NOBOX is oocyte-specific and expressed from the primordial follicle through metaphase II. Female null mice (knockout) show ovarian failure, whereas males are normal. One study failed to show NOBOX perturbations in 30 Japanese women,[68] but our group later found two novel missense mutations (Arg355His and Arg360Gln) among 96 caucasian

POF cases.[69] Arg355His was found in 278 controls. A functional effect was shown: by electrophoretic mobility shift array (EMSA); Arg355His disrupted binding of the NOBOX homeodomain to DNA, showing capacity for a dominant negative effect.

LHX8 (LIM DNA-BINDING PROTEINS)

LIM homeobox (LHX) genes encode DNA-binding proteins, serving as transcriptional factors that play critical roles in embryonic differentiation. Lhx8 transcripts localize to mouse oocytes from germ cells through antral follicles. Null mice lack germ cells.[70]

Our group sequenced LHX8 in 95 caucasian women with POF,[71] and found no abnormalities. Additional studies are necessary before it can be concluded that perturbation of this gene can cause POF in humans.

NANOS3 (RNA-BINDING PROTEIN)

NANOS3 is an RNA-binding protein. Both female and male knockout mice are infertile.[72] Human NANOS3 gene consists of two exons and is expressed in germ cells.

Our group sought NANO3 perturbations in 80 Chinese and 88 American caucasians, but the only sequence variant found was a synonymous nucleotide substitution that had already been reported.[73]

GDF9 (GROWTH DIFFERENTIATION FACTOR 9) AND TRANSFORMING GROWTH FACTORS

The X-linked TGF family member BMP15 has already been discussed. Other TGFβ superfamily genes are also transcription factors, and encoded by autosomes. Located on chromosome 5 (5q31.1), GDF9 has three subunits: signal peptide, pro-domain, and mature region. This arrangement is similar to other TGFβ family members. BMP15 and CDF9 gene products can form heterodimers.

Expressed in oocytes, GDF9 is believed to play an essential role in both early and late folliculogenesis.[74] GDF9 protein promotes cumulus expansion; its suppression (double-stranded interfering RNA) prevents cumulus expansion. In null mice oogenesis does not proceed, mutations thus causing disorders of follicle function rather than primordial germ cell formation. Immunization against GDF9 in sheep disrupts early folliculogenesis and leads to the absence of normal follicles beyond the primordial stage.

Human POF cases have been interrogated for GDF9 perturbations. Of 127 Indian women with POF, Dixit et al[75] found 5 to have the missense mutation A199C and 2 to have a G646A mutation. All mutations were heterozygous, occurring in the preprotein region. Our group more recently surveyed 61 American women with POF. A single woman showed a heterozygous perturbation (c.307C>T) that resulted in proline being replaced with serine (P103S).[76] Supporting plausibility of a deleterious effect was that the perturbation involved a conserved region and involved replacement of a hydrophobic amino acid (proline) with a hydrophilic amino acid (serine) residue. Among 100 Chinese POF cases, we found a novel propeptide mutation (Thr238Ala) not present in 96 Chinese controls.[77] Again, substitution of the hydrophobic alanine for the hydrophilic threonine could be deleterious. As for BMP15 and other TGFβ gene family members, the plausibility of a deleterious GDF9 heterozygous change rests on the assumption that a dominant negative mutation exists.

GPR3 (G PROTEIN RECEPTOR 3 AND G PROTEINS)

G proteins (GPs) and their receptors (GPRs) constitute a family of regulatory proteins involved in intracellular and intercellular transduction. Disparate stimuli (e.g. hormones, light, glycoproteins) all exert conformational changes on GPRs to allow binding to GPs. GPs and GPRs are crucial for reproductive function. The oocyte-specific G-stimulating protein-coupled receptor GPR3 is a known factor in maintaining meiotic arrest in the mouse oocyte.

Female mice lacking GPR3 develop premature ovarian aging as a result of spontaneous resumption of meiosis in antral follicles, independent of the LH surge.[78] Oocyte attrition results.

Our group sought GPR3 perturbations in women with POF; none of 82 showed perturbations of significance.[78] A single caucasian subject showed heteroduplex formation due to a heterozygous nucleotide substitution, C to A at position 51 (c.51C>A). However, this substitution does not alter the amino acid sequence, and had already been identified in normal women. Although GPR3 mutations do not appear to be a common explanation for POF in North American caucasians, studies in other populations are needed.

ANGIOTENSIN II TYPE 2 (AT2) RECEPTOR

This gene is expressed in fetal tissue and in a diverse group of disease states. Atretic granulosa cells express the gene in rodents, which provides a plausible relationship for POF. Perhaps an even more attractive reason is its location on Xq22-23, a region of known significance, so-called POF2. Katsuya et al[79] studied two families, in each of which sibs each had POF; no AT2 mutations were found.

PIEBALDISM (KIT)

Piebaldism is an autosomal dominant disorder characterized by patches of depigmentation (white) skin and hair.[80] Unlike vitiligo, the condition is evident at birth and progressive. Hyperpigmented macules are present on both normal and depigmented skin. Some cases are caused by mutations of KIT, an autosomal (4q12) gene that encodes for the tyrosine kinase transmembrane regulator for mast/stem cell growth factor.[80] Mutations exerting causality are unassailable, and include missense, nonsense, deletions, insertions, and splice junction mutations.

The c-kit receptor and its ligand (KL) have long been identified to cause germ cell loss in mice if perturbed, corresponding to the white spotting (W) and steel (Sl) loci. Human KIT is thus a good candidate gene for POF. Shibanuma et al[81] studied 40 women with unexplained POF, sequencing the entire coding region. One synonymous missense mutation was found, but this is not a plausible explanation for POF.

MIS AND MIS RECEPTOR TYPE II

In addition to its role in müllerian duct regression in males, MIS (AMH) is an oocyte inhibitor in the rat. The locus for AMH is on 19p, whereas that for the AMH receptor is 12q. The murine knockout model shows early depletion of primordial follicles.[82] However, Wang et al[83] failed to find plausible perturbations in 16 POF cases in humans.

RET FINGER-LIKE PROTEIN 4 (RFLP4)

The RING finger-like protein is expressed exclusively in murine oocytes, functioning as an E3 ubiquitin protein ligase. Ubiquitin ligase regulates protein degradation. Human RFLP4 is located on 19q13.4, and specifically has been shown to interact with oocyte proteins of the ubiquitin-protease degredation pathway.[84] In a review by Suzumori et al[85] no mutations were found 'in Japanese POF patients with 46,XX POF'.

FORKHEAD TRANSCRIPTION FACTORS (FOXL2, FOX03A, FOX1A)

See next section.

OTHER GENES CAUSING POF

Over 200 murine genes cause male or female infertility,[86] as judged by null (knockout) models in mice. Many but not all genes are oocyte gonadal specific. The genes discussed in this chapter

represent only those genes in which human POF cases have been interrogated for mutations.

Especially attractive candidate genes include SOHLH1, SOHLH2, OBOX, NR6A1, TAF4B, and BAX. These represent different mechanisms of gene action, some related to gonadotropins. Data are awaited, but it seems unlikely that any given gene will be responsible for more than perhaps 1–2% of POF. Possibly non-traditional mutations such as copy number variants will prove more informative than missense or nonsense mutation. Whole genome associations using SNPs or copy number polymorphisms (CNPs) are planned, potentially identifying chromosomal regions of interest.

PLEOTROPIC MENDELIAN GENES COMMONLY CAUSING OVARIAN FAILURE

FRAGILE X SYNDROME

This X-linked disorder has been discussed above.[40]

BLEPHAROPHIMOSIS-PTOSIS-EPICANTHUS (FORKHEAD TRANSCRIPTION FACTORS) (FOXL2)

Type 1 blepharophimosis-ptosis-epicanthus syndrome (BPES) is an autosomal dominant disorder in which POF coexists with the listed eyelid abnormalities.[87] Perturbations of forkhead transcription factor FOXL2 are the cause. In BPES type 1, FOXL2 mutations of unassailable significance (e.g. stop codon and truncated protein) have been found.[88,89] In the absence of eyelid abnormalities, however, mutations in this single exon gene are uncommon explanations for POF. De Baere and colleagues[90] found no FOXL2 mutations in 30 POF patients with normal eyelids; Harris and co-workers[91] found 2 mutations among 70 POF cases; Watkins et al[92] found 8 mutations among 233 cases (3.4%).

FOX03A

Other forkhead transcription genes cause ovarian follicular depletion when genes are knocked out (null) in mice. FOX03A regulates G1/S transition in granulosa cells. Watkins et al[92] sought mutations in the coding region of FOX03A. Of 60 POF cases (30 in New Zealand, 30 in Slovenia) 2 showed potentially significant mutations not present in controls. One mutation was a single heterozygous mutation in a Slovenian woman. The non-conserved amino acid change (Ser421Leu) was potentially capable of inducing a conformational protein change. The other mutation found was Arg506His in a New Zealand woman. Because of its location in the amino acid sequence, this mutation is believed to be less likely to exert an untoward effect.

FOX01A

Watkins et al[92] found a single conservative change (P84L) in FOX01A among 90 POF cases. The patient was of Slovenian descent.

GALACTOSEMIA (GALACTOSE 1-PHOSPHATE URIDYL TRANSFERASE DEFICIENCY)

Ovarian failure occurs in galactosemia, an inborn error of metabolism caused by galactose 1-phosphate uridyl transferase (GALT) deficiency. Kaufman and co-workers[93] found POF in 12 of 18 (67%) galactosemic women. Waggoner and colleagues[94] reported ovarian failure in 8 of 47 (17%) galactosemic women. Pathogenesis presumably involves galactose toxicity after birth, given that toxic metabolites should be cleared rapidly *in utero* by maternal enzymes. Consistent with this explanation, neonates with galactosemia show normal ovarian histology.

There is no evidence that galactosemic heterozygotes (GALT heterozygotes) show POF. Human homozygotes do not obligatorily have POF, nor do transgenic mice in which GALT is inactivated (knockout).

CARBOHYDRATE-DEFICIENT GLYCOPROTEIN (CONGENITAL DISORDERS OF GLYCOSYLATION)

In type 1 carbohydrate-deficient glycoprotein (CDG) deficiency, mannose-6-phosphate cannot be

converted to mannose-1-phosphate. This lipid-linked oligosaccharide is necessary for formation of secretory glycoproteins. The gene is located on 16p13; the perturbation usually causing CDG is a missense mutation.[95] In addition to ovarian failure, neurologic abnormalities exist.

AIRE (AUTOIMMUNE POLY-ENDOCRINOPATHY-CANDIDIASIS ECTODERMAL DYSTROPHY, APECED)

The AIRE (autoimmune regulation) gene is located on 21q22.3 and is responsible for APECED. Many different AIRE perturbations have been found in this autosomal dominant disorder, a pleiotropic condition[96] of varied expressivity. These include nonsense mutations and frame shifts, so causality is not in doubt.

Ovarian hypoplasia exists in 50–60% of cases.[97] Other findings include alopecia, vitiligo, keratopathy, malabsorption, hepatitis, and mucocutaneous candidiasis. The wide range of features makes it unclear when to apply the APECED appellation. This becomes relevant to isolated POF; AIRE thus may or may not be a good candidate gene. There has been no attempt to determine if a particular mutation leads to ovarian failure, as distinct from its association with other autoimmune phenomena of APECED.

More specific mutations could otherwise be sought in isolated POF. AIRE mutations have not yet been sought in POF cases lacking autoimmune findings. The more specific mutation or group of mutations in POF-associated APECED could thus be sought.

SYMPHALANGISM AND NOGGIN (NOG)

Noggin is responsible for the autosomal dominant disorder proximal symphalangism (SYM1).[98] Characteristic features include ankylosis of the PIP (proximal interphalangeal) joints, carpal–tarsal fusions, brachydactyly and deafness. NOG is expressed in the ovary and is an antagonist of bone morphogenic protein 4 and 7, a member of a family of genes (e.g. BMP15) already considered as a candidate for POF.

One SYM1 case has shown POF.[98] As predicted, a NOG mutation was found. Apparently NOG perturbations have not been sought in isolated POF subjects.

PERRAULT SYNDROME (POSSIBLE CONNEXIN MUTATIONS)

When XX ovarian dysgenesis coexists with neurosensory deafness, Perrault syndrome is said to exist.[99–102] This disorder is inherited in autosomal recessive fashion. Attractive candidate genes exist in the connexin gene family, given that disturbances of connexin genes explain approximately half the cases of congenital deafness. In a murine knockout model for connexin 37[103] (also called gap junction A4 or GJA4), null mice show gonadal failure with arrest at the antral stage of oogenesis.

CEREBELLAR ATAXIA WITH XX GONADAL DYGENESIS

Hypergonadotropic hypogonadism and ataxia were first reported to be associated by Skre et al,[104] who described cases in two families. In one family a 16-year-old girl was affected, whereas in the other family three sisters were affected. In the sporadic case and in one of the three siblings, ataxia was observed shortly after birth; in the two other sibs the ages of onset were during childhood. Cataracts were present in all individuals described by Skre et al.[104] Hypergonadotropic hypogonadism and ataxia were subsequently reported by De Michelle et al[105] and Amor et al.[106] In these and other reports, the nature of the ataxia differed. Ataxia was usually not progressive, cataracts were sometimes observed, and amelogenesis as well. Neurosensory deafness has been reported, as has mental retardation. Genetic heterogeneity must be assumed in hypergonadotropic hypogonadism disorders showing cerebella ataxia.

GERM CELL FAILURE IN BOTH SEXES

In a few sibships both males (46,XY) and females (46,XX) have each shown germ cell failure. Affected

females show streak gonads, whereas males show germ cell aplasia (Sertoli cell-only syndrome). The clinical significance of both these families as well as those in the previous section is that the same autosomal gene may be capable of deleteriously affecting germ cell development in both sexes. Presumably action involves a site common to early germ cell development. The causative genes might disturb the urogenital ridge, formation of the indifferent gonad, or migration of germ cells.

In two families parents were consanguineous, and in neither were somatic anomalies observed.[107,108] This contrasts with other families in which male and female sibs were not only affected but also showed unique patterns of somatic anomalies have been noted. Al Awadi et al[109] reported germ cell failure and an unusual form of alopecia. Scalp hair persisted only in the midline, with no hair present on the sides of the face and head ('mane-like'). Mikati et al[110] reported germ cell failure, microcephaly, short stature, mental retardation, and unusual facies (synophrys, abnormal pinnae, micrognathia, loss of teeth). The sibs reported by Al Awadi et al[109] were Jordanian; those reported by Mikati et al[110] were Lebanese. In both families, parents were consanguineous.

46,XX AGONADIA

In agonadia the gonads are absent, external genitalia are abnormal, and all but rudimentary müllerian and wolffian derivatives are absent. Almost all reported cases are 46,XY. Relevant here, however, are the rare reports of 46,XX agonadia. In 46,XY, agonadia mimics the much more common XX gonadal dysgenesis with warrants.

Sporadic XX cases were reported by Duck et al[111] and Levinson et al.[112] Mendonca et al[113] reported agonadia without somatic anomalies in phenotypic sibs having unlike chromosomal complements (46,XY and 46,XX). Kennerknecht et al[114] reported agonadism, hypoplasia of the pulmonary artery and lung, and dextrocardia in XX and XY siblings.

MITOCHONDRIAL GENES

Perturbations of mitochondrial DNA (mtDNA) cause various disorders, usually involving muscle and neurological systems. Searching for perturbations of mitochondrial DNA in POF should be fruitful because the mature oocyte contains the greatest number of mDNA copies of any human cell.

POLYMERASE GAMMA PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA (PEO)

Proximal myopathy, sensory ataxia, and parkinsonism occur in this disorder. The cause is a mutation in the mitochondrial gene polymerase gamma. Among seven families studied by Luoma et al,[115] POF co-segregated with PEO in three of them. The mutation Y955C was found in two of the three families. This tyrosine to cytosine change involves a highly conserved region, making a functional effect highly plausible. In the third family compound heterozygosity (N468D/A1105T) was observed in an affected woman.

MENDELIAN CAUSES OF 46,XY GONADAL FAILURE (XY SEX REVERSAL)

Phenotypic females may have apparently normal male (46,XY) chromosomal complements. The phenotype is not surprising; predictable loss of testicular tissue before 7–8 weeks would be expected to produce such a phenotype. (See earlier section on Reproductive embryology.)

By definition all types of XY gonadal dysgenesis are characterized by structurally normal female external genitalia, vagina, uterus, and fallopian tubes. In at least some cases the gonads of human XY females were unequivocally ovaries.[116] At puberty secondary sexual development does not occur. Height is normal, and in prototypic cases somatic anomalies are not present. External appearance is thus identical to 46,XX gonadal dysgenesis without somatic anomalies. As in 45,X or 46,XX gonadal

(ovarian) failure, FSH and LH are elevated; estrogens are decreased.

Clinically important to pediatric gynecologists is that in contrast to 45,X and 46,XX ovarian failure 20–30% of 46,XY phenotypic females develop a dysgerminoma or gonadoblastoma. Neoplasia may arise in the first or second decade, necessitating prophylactic gonadal extirpation. Laparoscopic removal of gonads and sometimes the gonadoblastoma or dysgerminoma is possible.[117] The uterus and fallopian tubes should *not* be removed because the patient may wish to carry a pregnancy through donor oocytes or donor embryos. Somatic anomalies may coexist as a result of several syndromes. These will be discussed below.

SRY MUTATIONS

A predictable cause of XY sex reversal is mutation or deletion of SRY. This usually but not always involves the HMG box. Approximately 10–15% of sporadic XY gonadal dysgenesis result from perturbations of SRY.[6]

DAX1 DUPLICATION

XY sex reversal may involve duplication of the X-linked gene Dose Sensitive Sex reversal region (or DAX1) on Xp21, as previously described. Only 1 of 27 '46,XY sex-reversal females' studied by Bardoni et al[11] showed duplication of Xp21.2-22.1.

X-LINKED XY GONADAL DYSGENESIS

XY gonadal dysgenesis may be caused by an X-linked recessive mutation.[9,10] The locus involved appears to be distinct from that for DAX1.

XY GONADAL DYSGENESIS AND WILM'S TUMOR ONCOGENES: (WT-1); DENYS-DRASH SYNDROME; FRASIER SYNDROME

One such syndrome is Denys-Drash syndrome,[118] in which duplication of WNT4 causes XY reversal, and is believed to do so through up-regulation of DAX1. 46,XY sex reversal may be part of several different malformation syndromes, causative genes for which are distinct. It is these conditions that have allowed the existence of autosomal genes acting upstream or downstream from SRY to be deduced. One such set of syndromes involves the gene WT1 (Wilms tumor oncogene), which in complex fashion causes genital abnormalities.

The relevance of WT1 perturbations to sex differentiation became evident when the association of nephropathy, genital ambiguity, and Wilms tumor was initially reported in a male child. These features became known as Denys-Drash syndrome. Mental retardation, aniridia, and Wilms tumor were later shown to be associated with deletions of 11p13, where the WT1 gene is located. The molecular basis is most often a heterozygous mutation in exons encoding a DNA-binding zinc finger motif. The mutant protein presumably exerts a dominant negative effect.

In Denys-Drash syndrome phenotypic males usually show genital ambiguity (male pseudohermaphroditism), but a few 46,XY cases are sex-reversed.[119] The gonadal phenotype thus extends from streak gonads through dysgenetic testes to true hermaphrodites.[119] Müeller[119] stated that half the phenotypic females were 46,XY.

XY sex reversal and renal parenchymal disease occur in Frasier syndrome.[120,121] This disorder is the result of a complex WT1 defect, namely an imbalance between two transcripts that reflect differential splicing involving the amino acids lysine, serine, and threonine.

XY GONADAL DYSGENESIS AND CAMPOMELIC DYSPLASIA (SOX-9)

XY gonadal dysgenesis may be associated with campomelic dysplasia, a disorder in which bowing of the long bones is characteristic. Located on 17q24.3-q25.1, the cause is perturbation of the DNA-binding protein SOX9. In the absence of

CPD, SOX9 mutations have not been reported as XY sex reversal.[122]

Olney and colleagues[123] reported an interstitial deletion of 17q (q23.3q-24.3) associated with absence of SOX9 and presence of campomelic syndrome. This suggests haplo-insufficiency as a molecular mechanism.

XY GONADAL DYSGENESIS AND ATX

The ATX (Alpha Thalassemia X chromosome) gene is an X-linked member of the DNA helicase family. ATX mutations cause mental retardation, α-thalassemia, and abnormal facies (upturned nose, 'carp-shaped mouth'). The molecular perturbation generally involves a prematurely truncated protein.[124,125] Complete sex reversal (female external genitalia) may occur. Affected cases have streak gonads and lack müllerian derivatives, suggesting transient early expression of AMH. The genital phenotype may be milder hypospadias or micropenis.

XY GONADAL DYSGENESIS WITH AUTOSOMAL DELETIONS (2p, 9p, 10q)

As discussed when considering the genetics of sexual differentiation, deletions of certain autosomal regions deleteriously affect male sex differentiation. The best known deletion involves 9p, which has often been associated with XY gonadal dysgenesis.[16] 9p24.3 contains a domain homologous to key sex-determining genes in *C. elegans* (mab3) and *Drosophila melanogaster* (double sex, or dsx). Initially called DMT, the human locus is now labeled DMRT1 (Doublesex and Mab3 Related Transcription factor 1). Ferguson-Smith and colleagues[126] concluded that del(9)(p24.3) was a frequent cause of SRY-positive 46,XY gonadal dysgenesis, but others found fewer or no cases.

Waggoner et al[17] observed sex reversal associated with deletion of 10q26, a region that encodes Sf1. Slavotinek et al[18] reported sex reversal with deletions of 2q33.

XY GONADAL DYSGENESIS WITH AUTOSOMAL DUPLICATIONS (1p; 17p)

Wieacker and colleagues reported XY sex reversal in association with duplication of 1p22.3→p32.2.[127] Jordan et al[128] studied another XY female with duplication of 1p (1p31-p35). Plausibility relates to the location of WNT4 on 1p35. As discussed, WNT4 up-regulates DAX1, duplication of which can impede testicular development.

46,XY AGONADIA

Agonadia is defined as completely absent gonads (not even streaks), external genitalia that are abnormal but usually female-like, and müllerian *or* wolffian derivatives no more than rudimentary. External genitalia consist of a phallus about the size of a clitoris, underdeveloped labia majora, and often nearly complete labioscrotal fusion. Less often, external genitalia are nearly female in appearance. In about half the cases, somatic anomalies coexist: craniofacial anomalies, vertebral anomalies, and mental retardation.[129]

Although rare 46,XX cases were discussed earlier, agonadia is almost always 46,XY. Pathogenesis of 46,XY cases is based on the assumption of loss of testes early in embryogenesis. Pathogenesis must take into account not only absence of gonads (presumably testes), but also external genitalia that are abnormal and internal genital ducts that are lacking. Transient presence of fetal testes is postulated, sufficiently long to initiate male differentiation and suppress müllerian differentiation yet not sufficiently long to complete male differentiation. Consistent with this hypothesis, SRY is present in XY gonads.

The other major hypothesis is disturbance of somatic tissue, especially connective tissue.

Given the existence of both heritable tendencies,[130] as well as frequent coexistence of somatic anomalies, defective connective tissue seems especially plausible for certain cases.

FEMALE PSEUDOHERMAPHRODITISM

In female pseudohermaphroditism 46,XX individuals fail to develop the external genitalia expected of normal females. The predictable reason is excess androgens *in utero*. The most common cause is congenital adrenal hyperplasia due to deficiencies of the various enzymes required for steroid biosynthesis (Figure 5.4): 21-hydroxylase, 11β-hydroxylase, and 3β-ol-dehydrogenase. The common pathogenesis involves decreased production of adrenal cortisol, which regulates secretion of adrenocorticotropic hormone (ACTH) through negative feedback inhibition. If cortisol production is decreased, ACTH secretion is not inhibited. Elevation of ACTH leads to increased quantities of steroid precursors, from which androgens are synthesized.

Syndromes of adrenal hyperplasia must be excluded soon after birth. Cortisol and corticosterone deficiencies result in sodium wasting that can be life-threatening. Standard texts provide debated discussions.[131,132]

ADRENAL HYPERPLASIA

DEFICIENCY OF 21-HYDROXYLASE (CYP21)

Clinical aspects

Deficiency of 21-hydroxylase is the most common cause of genital ambiguity among 46,XX individuals. If 21-hydroxylase is deficient, this cytochrome P450 enzyme fails to convert 17α-hydroxyprogesterone (17α-OHP) to 11-deoxycortisol (see Figure 5.4). Serum cortisol and deoxycortisol are decreased; androstenedione, estrone, levels of 17α-OHP, and testosterone are increased. A diagnosis can be made by increased levels of 17α-OHP, in serum (affected neonate) or amniotic fluid (affected fetus).

Females deficient for 21- or 11β-hydroxylase show clitoral hypertrophy and labioscrotal fusion. The urethral orifice is displaced to a site more nearly that expected in a male. The extent of virilization

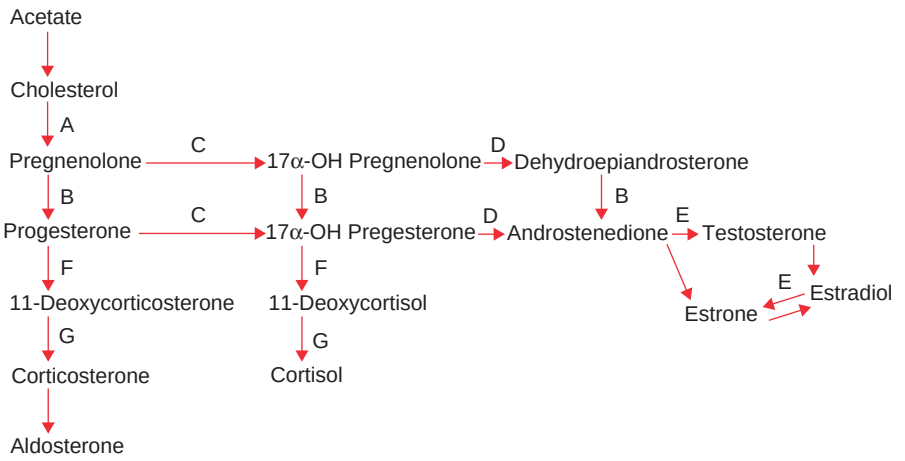


Figure 5.4 Important adrenal and gonadal biosynthetic pathways. Letters designate enzymes required for the appropriate conversions. A, 20α-hydroxylase, 22α-hydroxylase and 20,22-desmolase; B, 3β-ol-dehydrogenase; C, 17α-hydroxylase; D, 17,20-desmolase; E, 17-ketosteroid reductase; F, 21-hydroxylase; and G, 11β-hydroxylase. Adapted with permission from Simpson JL: Mammalian Sex Determination, Encyclopedia of Life Sciences, 2008, John Wiley & Sons, Ltd, published online March 2008, doi: 10.1002/9780470015902.a0001886.pub2).

may vary among individuals who have the same enzyme deficiency. Wolffian derivatives (vas deferentia, seminal vesides, epididymides) are absent, probably because fetal adrenal function begins too late in embryogenesis to stabilize the wolffian ducts. Müllerian derivatives develop normally, as expected in the absence of AMH (MIS). Ovaries likewise develop normally. Scrotal and areolar hyperpigmentation may occur, presumably as a result of increased pro-opiomelanocortin (POMC), the parent hormone of MSH and ACTH. Hyperpigmentation suggests 21- or 11β-hydroxylase deficiency in males, whose genitalia are normal at birth. If not detected before birth, these enzyme deficiencies may be unrecognized until age 2 years or later. Genital enlargement, pubic hair, and prematurely tall stature are then noted.

Sodium wasting may or may not occur in 21-hydroxylase deficiency. If not observed (nonsodium wasting 21-hydroxylase deficiency) ACTH secretion is assumed to have been sufficient to raise aldosterone and cortisol levels and prevent sodium wasting. Mineralocorticoid and sodium chloride are usually needed to correct hyperkalemia and restore fluid–electrolyte balance. If not treated, hyponatremia, hyperkalemia, dehydration, and death may occur. Cortisol administration remains necessary into adulthood, although requirements (per unit of weight) may diminish with age. Long-term replacement with sodium-retaining hormone (e.g. fluorinated hydrocortisone) may be necessary.

Molecular aspects

21-Hydroxylase is a cytochrome P450 enzyme encoded by a gene (CYP21) on chromosome 6p21, closely linked to human leukocyte antigen (HLA). When the precise molecular perturbation is unknown, linkage facilitates heterozygote identification and antenatal diagnosis. The CYP21 gene is arranged in tandem with the gene for the C4 component of complement.[131,132] In addition, CYP21 has a pseudogene (CYP21P), also in tandem with C4. The pseudogene is the result of an 8 bp deletion in exon 3 that results in an altered reading frame and, hence, a truncated nonfunctional protein. The actual sequence reads C4A-CYP21P-C4B-CYP21, oriented with the sense strand reading left to right. It is presumed that this CYP21/C4 tandem configuration arose by gene duplication through recombination. The configuration is the same in mice, great apes, and cattle, but not all mammals. Although both complement genes (C4A and C4B) are active, only a single CYP21 gene is active.

The CYP21/C4 tandem arrangement predisposes to unequal crossover owing to chromosomal misalignment. Irrespective, the resulting deletions (25%) and gene conversion (15%) are still less common explanations for 21-hydroxylase deficiency than single point mutations.

The relative frequency of various CYP mutations varies among ethnic groups. Simple virilizing 21-hydroxylase deficiency is associated with a nucleotide substitution, whereas the salt-wasting form is predictably more likely to be associated with deletions, frame shifts, and nonsense mutations. However, the phenotype cannot always be predicted from the molecular mutation.

DEFICIENCY OF 11β-HYDROXYLASE (CYP11B1)

Much less common than 21-hydroxylase deficiency, 11β-hydroxylase deficiency is also an autosomal recessive condition.[131,132] It is characterized by decreased conversion of 11-deoxycorticosterone to corticosterone. As the principal metabolite of 11-deoxycortisol, tetrahydrocortisol is increased. Because deoxycortisol and deoxycorticosterone are potent sodium-retaining hormones, their increased levels may lead to hypervolemia and, hence, hypertension. Infants with 11β-hydroxylase deficiency thus manifest not only the genital virilization characteristic of 21-hydroxylase deficiency but also hypertension.

Two separate 11β-hydroxylase genes code for the mitochondrial cytochrome P450 enzymes, CYP11B1 and CYP11B2. The latter is expressed in zona glomerulosa and is important for aldosterone synthesis. Located on 8q22, CYP11B1 is mutant in female pseudohermaphrodites. The most common perturbations are point mutations.[132]

DEFICIENCY OF 3β-HYDROXYSTEROID DEHYDROGENASE (3β-HSD)

In 3β-ol-dehydrogenase (see Figure 5.4) deficiency, the principal androgen synthesized is dehydroepiandrosterone (DHEA). This relatively weak androgen cannot be converted to either androstenedione or testosterone. Females with 3β-ol-dehydrogenase deficiency are thus less virilized than females with 21- or 11β-hydroxylase deficiencies. In fact, DHEA is such a weak androgen that males with 3β-ol-dehydrogenase deficiency fail to masculinize completely (male pseudohermaphroditism). Thus, 3 β-ol-dehydrogenase deficiency is the only form of adrenal hyperplasia that produces genital ambiguity in both males and females. One might expect the external genitalia to be identical in affected males and females, but 3β-ol-dehydrogenase activity peaks earlier in embryonic testes (third month) than the adrenals and ovaries (fourth month).

Complete deficiency of 3β-ol-dehydrogenase results in severe sodium wasting secondary to deficiency of sodium-retaining hormones. Sodium wasting may be so pronounced that affected infants die precipitously; however, less severe deficiencies are compatible with long-term survival. Inherited in autosomal recessive fashion, this condition is best diagnosed on the basis of serum steroids measured before and after ACTH stimulation.

Unlike CYP21 and CYP11B, 3β-HSD is not mitochondrial but rather microsomal. That is, 3β-ol-dehydrogenase is not a cytochrome P450 enzyme. There are two 3β-HSD genes (I and II), both located on chromosome 1 (p11-13). Type II is expressed in gonads and adrenals. Point mutations are the most common molecular perturbations in 3β-ol-dehydrogenase deficiency.[133]

DEFICIENCY OF 17α-HYDROXYLASE/17,20-LYASE (CYP17)

Deficiency of the cytochrome P450 enzyme 17α-hydroxylase/17,20-lyase results in failure of pregnenolone to be converted to 17α-hydroxypregnenolone. If the enzyme defect is complete, cortisol, androstenedione, testosterone, and estrone cannot be synthesized; however, 11-deoxycorticosterone and corticosterone can. As ACTH secretion compensatorily increases, 11-deoxycorticosterone and corticosterone increase. The result is hypernatremia, hypokalemia, and hypervolemia. Clinically, hypertension is evident. Aldosterone levels are decreased, presumably because hypervolemia suppresses the renin-angiotensin system.

Deficiency of this enzyme does not cause female pseudohermaphroditism. As discussed previously, females with 17α-hydroxylase/17,20-lyase deficiency have normal external genitalia, but at puberty fail to undergo normal secondary sexual development (primary amenorrhea). Thus, these cases are encountered in differential diagnosis of XX gonadal dysgenesis, as discussed above.

TERATOGENIC FORMS

Pregnant women receiving testosterone or other androgens may give birth to masculinized female fetuses, who have phallic enlargement, labioscrotal fusion, displacement of the urogenital sinus invagination, and wolffian duct development. These forms of female pseudohermaphroditism are rare, but still important because they are preventable.

To interfere with genital differentiation, a teratogen must exert its action during organogenesis. Before that time, organ-specific structure cannot be affected. In humans, the genital tubercle first becomes evident at approximately 5 weeks embryogenesis (7 weeks gestation). If an androgenic teratogen is administered before 12 weeks of gestation, labioscrotal fusion or urogenital sinus displacement may occur. After 12 weeks, the teratogen can cause clitoral enlargement, but not labioscrotal fusion. Excessive androgen production predictably does not affect müllerian differentiation or ovarian differentiation.

Androgen-induced female pseudohermaphroditism was more common decades ago, when women were more frequently treated during pregnancy with high doses of synthetic progestins. Virilized female offspring were not rare. Administration of androgenic progestins during pregnancy, especially

in high doses, is now less commonly indicated;[134] thus, the problem arises only rarely.

Testosterone, ethinyl testosterone, norethindrone acetate, norethindrone, and danocrine are potent teratogens that are sometimes administered to women of child-bearing age. If doses are administered therapeutically to women pregnant with female embryos, female pseudohermaphroditism could result. Large doses of progestins are required to produce virilization. A single oral contraceptive pill taken daily should not produce teratogenic female pseudohermaphroditism. Virtually a pack a day would be necessary to mimic serum concentrations incurred in the 1960s during 'therapeutic' regimens, usually to prevent pregnancy loss. Of note, 17α-hydroxyprogesterone caproate is an acetoxy-progestin that is far less androgenic than the nor-testosterone progestins. Norethynodrel, medroxy-progesterone, and 17α-hydroxyprogesterone caproate have rarely been implicated in female pseudohermaphroditism.

Fetal masculinization has been reported in pregnancies associated with Sertoli cell tumors (arrhenoblastoma), Leydig cell tumors, luteomas of pregnancy, and adenocarcinomas that metastasize to the ovary (e.g. Krukenberg tumor). Although frequently cited in texts as a cause for masculinizing female fetuses, androgen-secreting tumors in pregnant women are actually an extraordinarily rare cause of female pseudohermaphroditism. Moreover, patients with pre-existing androgen-secreting tumors rarely become pregnant.

Marked clitoral enlargement of unexplained origin sometimes results from hemangiomas, neurofibromas, or tumors. In other cases, enlargement seems to be idiopathic and may reflect end-organ hyperresponsiveness.

OTHER FORMS OF FEMALE PSEUDOHERMAPHRODITISM

Other rare (genetic) forms of female pseudohermaphroditism exist, seemingly not the result of adrenal abnormalities. Elucidation is awaited. An example is the report by Park et al[135] of two siblings, both of whom had clitoral hypertrophy, a single perineal orifice leading anteriorly to a urethra and posteriorly to a vagina, and numerous skeletal anomalies (hypoplasia of the mandible and maxilla, brachycephaly, narrow vertebral bodies, relatively long slender bones, dislocation of fusion of the radial heads leading to abnormal elbows, coax valga, and phalangeal fusion of several toes). Müllerian derivatives and ovaries were normal. Both siblings developed breasts and pubic hair but failed to menstruate. Their parents were consanguineous; thus, autosomal recessive inheritance seems probable.

Female pseudohermaphroditism (genital ambiguity) can also be associated with one or more of the following anomalies: absence or duplication of the uterus; renal absence, duplication, or hydronephrosis; and imperforate anus. Short stature, mental retardation, deafness, ear and nose malformation, and a blind colon are less often associated; the ovaries are usually normal. Whether this entity is a single disorder or different presentations of a field defect is unclear.

Genital abnormalities may also result from maldevelopment of the genital tubercle, cloacal membrane, urogenital membrane, or the entire hind end of the embryo (i.e. claudal regression syndrome). Sometimes the external genitalia may be so abnormal that the sex of rearing is in doubt. These rare disorders include exstrophy of the bladder, exstrophy of the cloaca, and sirenomelia.

MALE PSEUDOHERMAPHRODITISM

Individuals with a Y chromosome who have external genitalia that fail to develop as expected for normal males have traditionally been called male pseudohermaphrodites. More recently, 'contemporary' nomenclature, has been proposed, replacing the term 'male pseudohermaphroditism'[136] with such descriptors as the designation Disorders of Sex Development (DSD). In this chapter, we shall, however, continue to retain traditional terminology, not failing to appreciate the virtue of enhanced sensitivity. Use of new nomenclature is held in abeyance pending widespread clinical acceptance.

To warrant the omnibus diagnosis of male pseudohermaphroditism, external genitalia must be sufficiently ambiguous to generate confusion concerning sex of rearing. Cytogenetic forms of male pseudohermaphroditism (45,X/46,XY and variants) are discussed in this section in order to contrast their phenotype with those of genetic male pseudohermaphroditism, given that both groups of disorders must be considered concurrently in the differential diagnosis of genital ambiguity.

TERATOGENIC FORMS

If administered in sufficiently high doses in the first trimester to a woman pregnant with a male fetus, various drugs would be expected to produce female external genitalia (male pseudohermaphroditism). With cyproterone acetate, the mechanism of action involves blocking the androgen receptor. With flutamide, the action of androgen receptors is also impeded. Finasteride inhibits 5α-reductase, which is necessary to produce dihydrotestosterone. Actual cases have fortunately not been reported, and some agents have not even been marketed in the USA. However, these drugs are approved in other countries for treatment of hirsutism or for contraception; thus, potential for teratogenic male pseudohermaphroditism exists.

Controversy persists concerning whether administration of progestins or progesterones during pregnancy can produce hypospadias. In this author's opinion, the weight of evidence is very much against these agents adversely affecting genital development.[134]

45,X/46,XY MOSAICISM

Phenotypes associated with this mosaicism range from near-normal males with cryptorchidism or mild penile hypospadias to those with genital ambiguity or even sex reversal (females). Based on follow-up cohort studies of 45,X/46,XY mosaicism detected *in utero* (prenatal genetic diagnosis), 90% of cases are normal males. Cases ascertained postnatally differ phenotypically from cases ascertained prenatally.[137] The differing phenotypes presumably reflect differing tissue distributions of the various cell lines. A structurally abnormal Y chromosome is not uncommon. Structurally abnormal chromosomes are unstable (e.g. dicentric), for which reason the 45,X line may arise secondarily following loss of a structurally abnormal Y. Three general phenotypes are associated with 45,X/46,XY mosaicism.

45,X/46,XY UNAMBIGUOUS FEMALE EXTERNAL GENITALIA

45,X/46,XY cases with female external genitalia are usually normal in stature and show no somatic anomalies. A few are short, have Turner stigmata, and thus are clinically indistinguishable from 45,X individuals. Irrespective, external genitalia, vagina, and müllerian derivatives remain unstimulated because of the lack of sex steroids. Breasts fail to develop; pubic and/or axillary hair is scanty. If breast development occurs in a 45,X/46,XY individual, the estrogen-secreting tumors gonadoblastoma or dysgerminoma should be suspected. In the absence of neoplasia virilization has been reported, perhaps from gonadotropin stimulation of streak gonads.

Although streak gonads of 45,X/46,XY individuals are histologically indistinguishable from those of 45,X individuals, gonadoblastomas or dysgerminomas nonetheless develop in about 15–20% of 45,X/46,XY individuals.[138] As discussed previously, the GBY locus (GonadoBlastomere Y chromosome) on Yq must predispose to neoplasia, because if deleted in sex-reversal XY females the risk of neoplasia is decreased.

Removal of gonads is recommended for all 45,X/46,XY individuals having female external genitalia, probably even if the gonadoblastoma-predisposing locus GBY is ostensibly absent. Neoplasia may develop in the first or second decade of life. Gonadectomy can usually be accomplished by laparoscopy. The uterus should be retained because pregnancy may be desired through donor oocytes or donor embryos.

45,X/46,XY AMBIGUOUS EXTERNAL GENITALIA

In individuals who have ambiguous external genitalia and a 45,X/46,XY complement, a uterus is usually (90%) present. Many investigators believe that the phenotype is invariably associated with 45,X/46,XY mosaicism, sometimes cryptic given that only 45,X or only 46,XY cells may be demonstrable. The term *asymmetric* or *mixed gonadal dysgenesis* is applied to individuals having one streak gonad and one dysgenetic testis.

A uterus is an important diagnostic sign in evaluating male pseudohermaphroditism because it is absent in almost all other forms of male pseudohermaphroditism (described below). If an individual has ambiguous external genitalia, bilateral testes, and a uterus, it is thus reasonable to infer that individual actually has 45,X/46,XY mosaicism, irrespective of whether both lines can be demonstrated cytogenetically. This means that risk of neoplasia exists.

MALE PSEUDOHERMAPHRODITISM (GENITAL AMBIGUITY OR SEX REVERSAL) IN MULTIPLE MALFORMATION SYNDROMES

Genital ambiguity is one component of a number of multiple malformation syndromes. Among the more common are the Meckel-Gruber syndrome, Smith-Lemli-Opitz syndrome, brachioskeletal-genital syndrome, esophageal-facial-genital syndrome, and genitopalatocardiac syndrome. These disorders are usually inherited in either autosomal recessive or X-linked recessive fashion. See Simpson[2] for further discussion.

TESTOSTERONE BIOSYNTHETIC DEFECTS

Male pseudohermaphroditism may result from deficiencies of these adrenal or gonadal enzymes: 3β-ol-dehydrogenase, the bifunctional enzyme 17α-hydroxylase/17,20 desmolase, 17-ketosteroid reductase, and the enzymes necessary to convert cholesterol to pregnenolone (congenital adrenal lipoid hyperplasia). The common pathogenesis involves testosterone levels too low to virilize external genitalia. Deficiencies of 21- or 11β-hydroxylase, which are the most common adrenal biosynthetic defects and the most common causes of female pseudohermaphroditism, do not result in *male* pseudohermaphroditism.

Testicular biosynthetic defects should be suspected in 46,XY male pseudohermaphrodites whenever levels of testosterone or its metabolites are decreased. Diagnosis may be difficult during infancy because neonatal testosterone levels are physiologically low. Provocative tests (i.e. human chorionic gonadotropin (hCG) stimulation) may be helpful.

CONGENITAL ADRENAL LIPOID HYPERPLASIA (StAR)

In congenital adrenal lipoid hyperplasia, 46,XY cases show external genitalia that are ambiguous or female-like. 46,XX cases show female external genitalia. Sodium wasting is severe, adrenals are characterized by foamy-appearing cells filled with cholesterol.[139] Accumulation of cholesterol has long been assumed to reflect inability to be converted to pregnenolone (Figure 5.4). Levels of C18, C19, and C21 steroids are almost undetectable. Inheritance is autosomal recessive. Neurodegeneration and hyperpigmentation are observed; respiratory distress is common (25%).

Congenital adrenal lipoid hyperplasia results from perturbation of the gene encoding Steroidogenic Acute Regulatory protein (StAR). The term 'acute' reflects ability to respond rapidly ('acutely') to corticotropin stimulation, specifically by producing a 30 kD mitochondrial protein in adrenal cells. The StAR protein delivers precursors for cholesterol side chain cleavage; thus, its perturbation has major consequences on hormone action in gonads and adrenals. Most reported StAR mutations have been in Japanese or Korean[139] populations, in which the affected allele is most often (18%) Gln258 stop, producing a truncated protein. In Arabs the mutation is more likely missense (Arg182 Leu), and in Palestinians a deletion.[140] Other mutations have been found in other ethnic groups. Founder effects

are presumably responsible for different alleles in different ethnic groups.

3β-HYDROXY-STEROID DEHYDROGENASE (3β-HSD)(3β-OL-DEHYDROGENASE DEFICIENCY)

In this enzyme deficiency, synthesis of both androgens and estrogens is decreased. The major androgen produced is DHEA. Relatively weaker than testosterone, DHEA alone is not capable of adequately virilizing the male fetus; thus, genital ambiguity occurs. The phallus is small, the urethral opening is proximal on the penis, and labioscrotal fusion is incomplete. Testes and wolffian ducts differentiate normally. Diagnosis is usually established on the basis of disproportionately increased serum DHEA following ACTH stimulation. In addition to genital abnormalities, 3β-ol-dehydrogenase deficiency is associated with severe sodium wasting. This is predictable given that both aldosterone and cortisol are decreased.

There are five 3β-HSD genes, but only type II is expressed in adrenal and gonads. External genitalia of males with type II 3β-HSD deficiency do not completely develop. Mutations are scattered among the four exons, most commonly in the third exon[141] (Figure 5.4).

Affected females (46,XX) also show genital ambiguity. 3β-ol-dehydrogenase (3β-HSD) is thus the only enzyme capable of producing both male pseudohermaphroditism in males and female pseudohermaphroditism in females. 46,XX individuals with this enzyme deficiency show genital ambiguity and virilization due to elevated DHEA and androstenedione. These androgens are relatively weaker than testosterone, but nonetheless potent enough for limited virilization.

17α-HYDROXYLASE AND 17,20-DESMOLASE (LYASE) DEFICIENCY

17α-Hydroxylase/17,20 desmolase is a bifunctional cytochrome P 450 enzyme, possessing both 17α-hydroxylase and 17,20 desmolase (lyase) activities. That a single gene/enzyme was responsible for both 17α-hydroxylase and 17,20-desmolase functions was surprising because pedigree studies had suggested two genetically distinct conditions and presumably two separate genes. Indeed, in some families only 17α-hydroxylase activity seemed deficient, whereas in others only 17,20-desmolase activity seemed deficient. Males deficient in 17α-hydroxylase/17,20 desmolase (lyase) usually show ambiguous external genitalia, but occasionally external genitalia are female-like. Wolffian duct development and testicular development are normal. Males deficient for 17α-hydroxylase usually have normal blood pressure. Affected females (46,XX) may show hypertension, and fail to undergo normal sex differentiation.

The responsible P450c17 enzyme is coded by the CYP17 gene, which lies on chromosome 10(q24-25). Missense CYP17 mutations are scattered throughout the gene. A four base duplication initiated in codon 480 is the usual explanation for affected Mennonites, a group in which 17α-hydroxylase deficiency is not extraordinarily rare.[142] Otherwise, no consistent mutation is found.

DEFICIENCY OF 17β-HYDROXYSTEROID DEHYDROGENASE (17-KETOSTEROID REDUCTASE)

Inability to convert dehydroepiandrosterone to testosterone results from deficiency of the microsomal enzyme 17-ketosteroid reductase, also called 17β-hydroxysteroid dehydrogenase (17βHSD) or 17β-ol dehydrogenase (Figure 5.4). This enzyme reaction is reversible; thus, there are multiple designations, connoting both oxidative and reductive steps.

Plasma testosterone is usually decreased, whereas androstenedione and dehydroepiandrosterone are increased. Affected males show ambiguous or female-like external genitalia, bilateral testes, and wolffian derivatives; no müllerian derivatives are present. Breast development may or may not be present, depending upon the estrogen to testosterone ratio. Pubertal virilization may be greater than in many other enzyme deficiencies, and sometimes gynecomastia is not evident.[143] The sex of rearing

has even been changed from female to male after puberty.

17βHSD is microsomal, rather than mitochondrial. Thus, its action involves gonads rather than adrenals. Of the five isozymes of 17β-HSD, type III is of relevance here (17βHSD3). Molecular perturbations typically involve single amino acid substitutions: missense, frameshift, and splice junction mutations. Most missense mutations lack residual activity. This is not, however, true for the most common aggregation of cases, Gaza Arabs who show an R80Q missense mutation.[144] In that population the phallus is typically bound by chordee, and only 4–8 cm in length; gynecomastia is not rare. The R80Q missense mutation (Arg80-Gln) reduces enzyme activity to 20% of normal. R80Q has also been found in Portugal, Spain, the Netherlands, and Brazil. This is believed to be consistent with a founder effect, perhaps derived from Phoenicians.

Eleven 46,XX females have shown mutations at both alleles. All are asymptomatic,[145] consistent with 17βHSD3 expression being limited to the testes.

DEFICIENCY OF STEROIDOGENIC FACTOR-1

Steroidogenic factor-1 (SF1) is an orphan nuclear receptor whose structure is closely related to steroid receptors. However, SF1 has no known ligand, thus the designation 'orphan'. The SF1 gene is encoded on human 9q33.

The first human case involving SF1 deficiency was reported by Achermann et al.[146] The affected 46,XY female showed primary adrenal failure, female external genitalia, streak gonads, and normal müllerian derivatives responsive to hormones. The proband was heterozygous for a 2 bp substitution at codon 35 (G35E). The assumption of compound heterozygosity was made. The mutated amino acid involved glycine in the last amino acid of the first zinc finger of SF1, suggesting disturbance of a DNA-binding site.

A second XY sex-reversal case was homozygous for an Arg92Gln mutation.[147] Two heterozygous family members were normal. A case reported by Biason-Lauber et al had adrenal insufficiency.[148]

Of clinical significance is presence of a uterus in the SF1-deficient female (46,XX). This forms the basis for assuming that SF1 regulates repression of anti-müllerian hormone (AMH).

COMPLETE ANDROGEN INSENSITIVITY

Clinical aspects

In complete androgen insensitivity (CAI, complete testicular feminization), 46,XY individuals show bilateral testes, female external genitalia, a blindly ending vagina, and no müllerian derivatives (Figure 5.5). These clinical findings are predictable, given the underlying pathogenesis involving inability to respond to testosterone. AMH or MIS is synthesized normally by Sertoli cells. The body responds appropriately to AMH, as a result of which the uterus does not persist. Testes synthesize estrogens in unimpeded fashion; thus, breast development and pubertal feminization occur given that circulating androgen fails to antagonize the cellular action of estrogen. LH is disproportionately increased, presumably reflecting failure of the hypothalamus to respond to testosterone.

Individuals with androgen insensitivity may feminize but still show clitoral enlargement and labioscrotal fusion; the term incomplete or partial androgen insensitivity (PAI; incomplete testicular feminization) is applied. A milder end of the spectrum consists of males manifesting only gynecomastia or only oligospermia/azoospermia (mild androgen insensitivity, MAI). Complete, partial, and mild androgen insensitivity are all inherited in an X-linked recessive fashion. The different phenotypes reflect different mutations of the same androgen receptor gene, which is located on the X long arm (Xq11).

In CAI, breasts contain normal ductal and glandular tissue, but areolae are often pale and underdeveloped. Pubic hair and axillary hair are usually sparse (e.g. only vellus hair); scalp hair is normal. Limited pubic and axillary hair is not uncommon and should not dissuade one from the diagnosis of

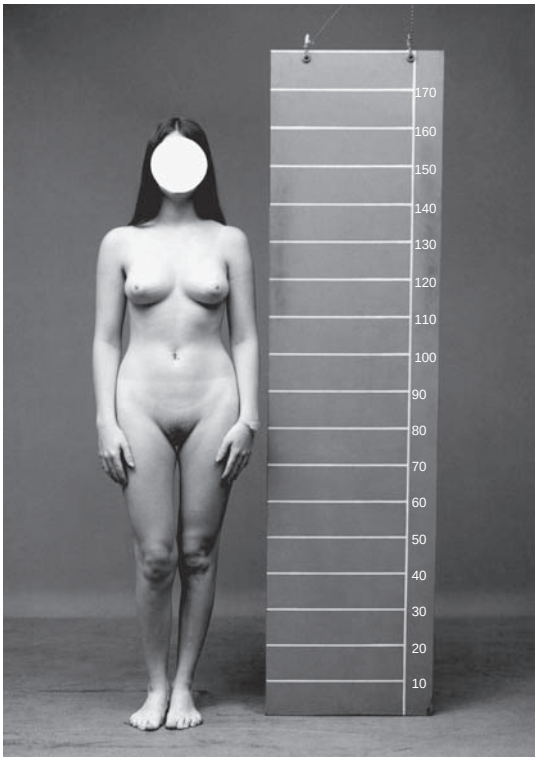


Figure 5.5 Photograph of a patient with complete androgen insensitivity syndrome. Reproduced with permission from Simpson JL: Disorders of Sexual Differentiation: Etiology and Clinical Delineation. New York: Academic Press, 1976.

CAI. The vagina terminates blindly, foreshortened but still adequate for coitus. Occasionally the vagina is only 1–2 cm long or represented merely by a dimple. Use of progressive dilators is usually effective to create a functional vagina, and only rarely is surgery considered necessary. Although neither uterus nor fallopian tubes are ordinarily present, fibromuscular remnants, rudimentary fallopian tubes, or rarely even a rudimentary uterus may persist.[149]

Testes are usually normal in size and located in the abdomen, inguinal canal, labia, or anywhere along the path of embryonic testicular descent. If present in the inguinal canal, testes may produce inguinal hernias. Height is slightly increased compared with normal women, but unremarkable compared to 46,XY males.

Gonadal neoplasia is increased in frequency, probably due only to intra-abdominal location. Before 25–30 years of age, the risk of malignancy is low. Benign tubular adenomas (Pick adenomas) are common in postpubertal patients, probably the result of increased LH secretion. Orchiectomy is eventually necessary, but not necessarily before spontaneous pubertal feminization. However, if herniorrhaphy is needed before puberty most surgeons perform orchiectomy simultaneously.

Molecular aspects

Perturbation of the androgen receptor gene on Xq11-12 is responsible for the full range of phenotypes. As this is a genetically lethal X-linked recessive condition, one-third of all cases are new

(sporadic) mutations. Heterozygous mothers may show decreased pubic hair and delayed puberty.

The CAI gene is 90 000 bp long, and has 8 exons. Exon 1 confers regulatory function; the DNA-binding domain (amino acids 552–616) is encoded by exon 2 and part of exon 3; the C-terminal region of 250 amino acids is encoded by exons 4–8 and constitutes the androgen-binding domain. Many different mutations have been reported.[150,151] Mutations most commonly involve exons 5–8, the androgen-binding domain. Large deletions and mutations resulting in premature termination (stop codon) cause complete androgen insensitivity. Most mutations are missense, resulting in PAI, CAI or MAI in almost unpredictable fashion. Exon 1 encompasses half of the AR gene, but has the fewest recognized mutations (10% of total). Mutations in either exon 2 or 3 can result in either CAI or PAI (see below). Some point mutations may produce limited quantities of functional androgen receptor, although the receptor may be unstable or display poor binding.

PARTIAL ANDROGEN SENSITIVITY (PAI) AND MILD ANDROGEN INSENSITIVITY (MAI)

At puberty certain 46,XY individuals feminize (i.e. breast development), but their external genitalia are characterized by phallic enlargement and partial labioscrotal fusion (Figure 5.6). Defined as partial or incomplete androgen insensitivity (or incomplete testicular feminization), the phenotype shares these features with CAI: bilateral testes with Leydig cell hyperplasia, absence of müllerian derivatives, pubertal breast development, lack of pubertal virilization, normal (male) plasma testosterone, and failure to respond to androgen. Cellular pathogenesis of PAI involves decreased numbers or qualitative defects of androgen receptors.

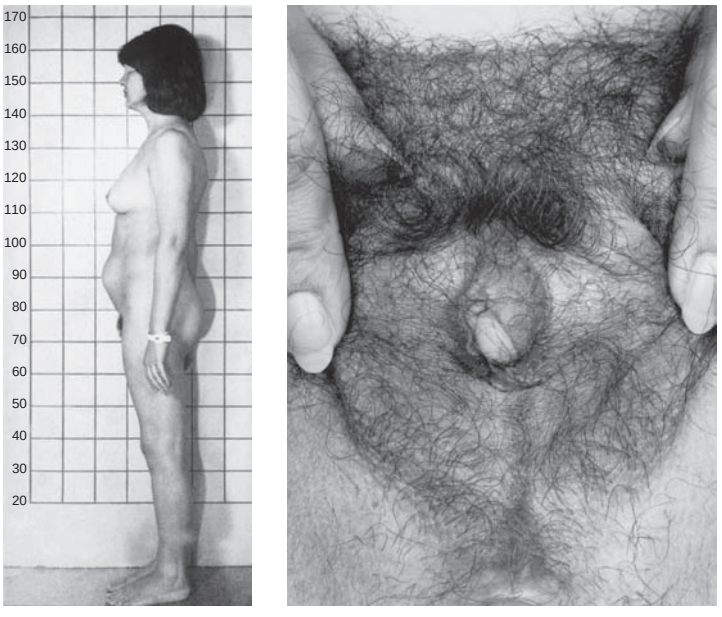


Figure 5.6 Photographs of a person with partial androgen insensitivity. Despite the enlarged phallus and labioscrotal fusion (A), breasts developed at puberty (B). Reproduced with permission from Park IL, Jones HW: Familial male hermaphroditism with ambiguous external genetalia. Am J Obstet Gynecol 1970; 108: 1197.

PAI must be excluded before assignment of a male sex of rearing. Response to exogenous androgens is necessary. Identifying or excluding a specific molecular perturbation can be useful if the molecular defect in an index case or relative is known. The same approach is applicable for prenatal genetic diagnosis.

In MAI phenotypic expression may be restricted to impaired spermatogenesis. Gynecomastia, impotence, and poor virilization may occur. Again, molecular/phenotypic correlation is imprecise, the same mutation being observed with either PAI or MAI.

LUTEINIZING HORMONE RECEPTOR DEFECT (LHR)

In the complete absence of Leydig cells, 46,XY individuals have female external genitalia, no uterus, and bilateral testes devoid of Leydig cells. Epididymides and vasa deferentia are present; serum LH is elevated.

Leydig cells presumably fail to develop because LH cannot exert its normal effect during embryogenesis. Embryonic testes still secrete AMH, thus explaining the absence of a uterus. Affected siblings have been reported and parental consanguinity observed. Thus, autosomal recessive inheritance has long been accepted.

Previously we discussed the consequence of LHR mutation in 46,XX women, who show premature ovarian failure due to failure of folliculogenesis. Located on chromosome 2, LHR consists of 11 exons and 699 amino acid residues. Many different LHR mutations have been found in 46,XY females with Leydig cell hypoplasia. These include missense mutations, deletions, and stop codons.[59,60,152]

Reported 46,XX LHR cases are typically sibs of 46,XY 'female' sibs, all of whom present also with primary amenorrhea. Thus, sibs of opposite sex chromosomal complements show the same phenotype.

5α-REDUCTASE DEFICIENCY AND SRD5A2

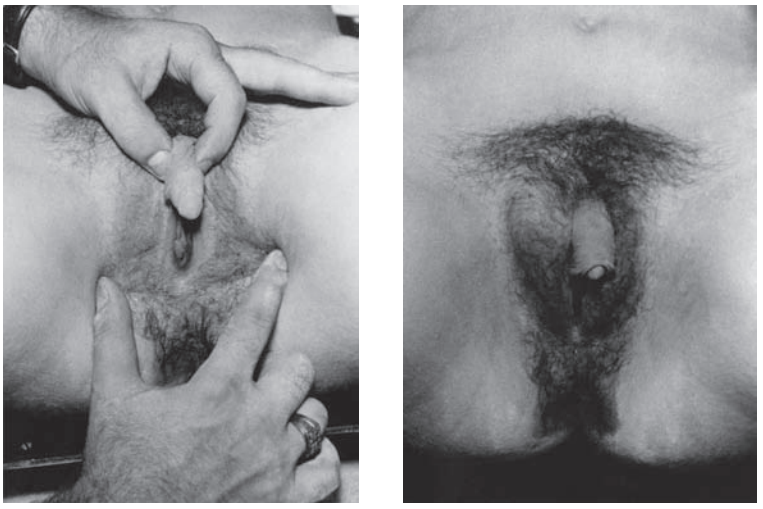
Some genetic males show ambiguous external genitalia at birth, but at puberty virilize like normal males. Phallic enlargement, increased facial hair, muscular hypertrophy, and voice deepening occur, but breast development does not. External genitalia consist of a phallus that resembles a clitoris more than a penis; a perineal urethral orifice is present. A separate, blindly ending perineal orifice resembles a vagina (pseudovagina) (Figure 5.7).

This disorder was initially called *pseudovaginal perineoscrotal hypospadias* (PPSH) and shown to be inherited in autosomal recessive fashion.[153,154] The responsible enzyme proved to be 5α-reductase,[155] the enzyme that converts testosterone (T) to dihydrotestosterone (DHT). That intracellular 5α-reductase deficiency results in the PPSH phenotype is consistent with virilization of the external genitalia during embryogenesis requiring only dihydrotestosterone. At puberty, virilization can be accomplished without dihydrotestosterone.

Diagnosis can be made on the basis of an elevated testosterone to DHT ratio following administration of hCG or testosterone propionate. The relative ratio of the urinary metabolites of testosterone and DHT (i.e. etiocholanolone and androsterone) can be determined. An elevated ratio of urinary tetrahydrocortisol to 5α-tetrahydrocortisol can be diagnostic. In infants, baseline levels of testosterone and DHT are low; thus, distinguishing normal from affected individuals may be difficult.[156]

Of the two 5α-reductase (SRD5) genes, only type II SRD5A2 is relevant here. Located on chromosome 2p23, type II is expressed in gonads and, hence, when deficient causes male pseudohermaphroditism. SRD5A2 consists of five exons.[157] Missense mutations are most common, but cases from Papua, New Guinea, are usually characterized by deletions. Different ethnic groups typically show different mutations, scattered among the five exons and presumably reflecting founder effects, because within a given ethnic group a sentinel mutation is usually observed. Affected cases are homozygous, presumably reflecting parental consanguinity.

46,XX females homozygous for 5α-reductase deficiencies are fertile and show normal ovarian function.[158] Their breast development is normal. Limb and pubic hair may be reduced, and menarche delayed.



(a) (b)

Figure 5.7 Photographs of the external genitalia of an individual with the phenotype of 5α-reductase deficiency. At puberty, phallic enlargement occurred and breast development did not. Reproduced with permission from Opitz JM, Simpson JL, Sarto GE et al: Pseudovaginal perineoscrotal hypospadias. Clin Genet 1972; 3: 1.

TRUE HERMAPHRODITISM

True hermaphrodites have both ovarian and testicular tissue. Gonads may consist of a separate ovary and a separate testis or, more often, one or more ovotestes. Most true hermaphrodites (70–80%) are 46,XX; however, 46,XX/46,XY, 46,XY, 46,XX/47,XXY, and other complements may exist. The phenotype logically should reflect chromosomal constitution, but this has actually never been proved. Thus, we shall generalize concerning phenotype.

CLINICAL FEATURES

Before the era of routine medical intervention, two-thirds of true hermaphrodites were raised as males.[159] Paradoxically, breast development usually occurred at puberty, even with predominantly male external genitalia. Gonadal tissue may be located in the ovarian, inguinal or labioscrotal regions. A testis or an ovotestis is more likely to be present on the right than on the left. Spermatozoa are rarely present; however, apparently normal oocytes may be observed even in ovotestes.

The greater the proportion of testicular tissue in an ovotestis, the greater the likelihood of gonadal descent. In most ovotestes, testicular and ovarian components are juxtaposed end to end[160] (Figure 5.8). An ovotestis may thus be detectable by inspection or palpation; testicular tissue is softer and darker than ovarian tissue. Imaging (magnetic resonance imaging (MRI) or ultrasound) may be helpful, and invaluable if the undesired portion of an ovotestis is to be extirpated. Gonadal neoplasia has been reported, probably reflecting the intra-abdominal location of testicular tissue. This is consistent with neoplasia arising in 25% of 46,XY cases but only 3% of 46,XX cases. Breast carcinomas may also occur.

A uterus is usually (90%) present, although sometimes bicornuate or unicornuate. Absence of a uterine horn is associated with ipsilateral testis or

Figure 5.8 A bisected ovotestis from a patient of Van Neikerk. The patient had a 46,XX complement. The ratio of ovarian to testicular tissue is about 1:4; ovarian tissue is present in the upper right. The testicular portion appears yellowish-brown, whereas the ovarian portion was white, although in this photograph, the color difference cannot be appreciated. The ovarian portion was firmer than the testicular portion. In 80% of ovotestes, just as in this particular case, ovarian and testicular tissues are arranged end to end. Reproduced with permission from Van Niekerk WA: True Hermaphroditism. New York: Harper & Row, 1974.

ovotestis. The fimbriated end of the fallopian tube is not infrequently occluded ipsilateral to an ovotestis. Squamous metaplasia of the endocervix may occur.[160] Menstruation is not uncommon and may be manifested in unusual fashion (e.g. cyclic hematuria). Presence of a uterus in true hermaphroditism is diagnostically useful, particularly in the rare 46,XY cases. If an individual with genital ambiguity has a Y chromosome, the only disorders in the differential diagnosis are 46,XY hermaphroditism and 45,X/46,XY mosaicism.

Approximately a dozen true hermaphrodites have become pregnant – usually, but not always – after removal of testicular tissue. Excluding one 46,XX/46,XY case,[161] pregnancies have all occurred in 46,XX true hermaphrodites. Offspring seem no more likely to be abnormal than in the general population, although Kuhnle et al[162] surprisingly reported that all offspring were male.

46,XX/46,XY AND 46,XY

46,XX/46,XY true hermaphroditism is usually caused by chimerism, the two cell lines by definition derived from different zygotes. 46,XX/47,XXY cases probably result from nondisjunction or anaphase lag. Actually, 46,XY cases may be unrecognized chimeras.

46,XX AND FAMILIAL AGGREGATES OF TRUE HERMAPHRODITISM

46,XX true hermaphrodites are most likely to have resulted from translocation during paternal meiosis of SRY from the Y to an X. Other mechanisms include translocation of SRY from the Y to an autosome, or autosomal sex-reversal genes.

46,XX true hermaphrodites do not usually show SRY sequences from their father's Y,[163] in marked contrast to the 80% of 46,XX males who do. A few XX true hermaphrodites have shown mutant SRY, and in a few others somatic mutation resulted in gonadal mosaicism.[164]

Given the above, autosomal factors are the more likely explanations for 46,XX true hermaphroditism. This thesis is supported by the existence of families characterized by either siblings with XX true hermaphroditism or sibships in which 46,XX males or 46,XX true hermaphrodites exist. In the latter families the 46,XX males atypically show genital ambiguity, unlike the more typical '46,XX male', who has normal male external genitalia.

An attractive hypothesis is that perturbation (derepression) of an ordinarily repressed autosomal gene induces inappropriate (testicular) gonadal development in 46,XX individuals. Consistent with this, many autosomal regions influence testicular differentiation.

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6. Adolescent nutrition

Kimberly McClanahan, Marlene Huff, and Hatim Omar

'Nutrition is a most important determinant of growth,'[1] and adolescence is a period of rapid growth exceeded only by that experienced in infancy,[2] leading to a greater need for adequate nutrition, including increased requirements for energy, protein, and many vitamins and minerals.[3] As adolescents go through this rapid period of physical growth in height, weight, and body components, changes also occur across cognitive, social, and emotional domains. Changes across these domains, with their concomitant increases in autonomy, individual identity, peer influence, gradual separation from family, and desire for experimentation, can all negatively affect the physical domain through food choices that leave the adolescent in a nutrient-deficient state at a crucial time of growth and development.

Although general developmental sequences of puberty remain constant for typical adolescents, there can be great variability in terms of age of onset, duration, and pace of the events; therefore, adolescents of the same age may look very different physically.[3] For females, the first signs of puberty generally occur between the ages of 8 and 13, with an average age at menarche of 12.4 in the United States. The most rapid spurt of linear growth occurs between 9.5 and 14.5 years of age, and it is estimated that 15–25% of final adult height is accomplished during this growth spurt of puberty. The linear growth spurt in females usually ends by the time they are 16.5 years of age. Additionally, by age 18, 90% of adult skeletal mass will have accrued.[3]

Nutritional intake affects age at menarche, height, weight, and bone mass and density, with the quality of nutrition playing a determining factor in whether adolescent females will be nutritionally sound and able to reach full growth potential. Given the large variability in growth among girls, the stage of their development will dictate their nutritional needs, and thus, nutritional recommendations need to be tailored to each girl.

HEALTHY NUTRITION FOR THE ADOLESCENT FEMALE

Prior to puberty, nutritional needs are similar for males and females. It is during puberty that biologic changes (e.g. menarche) and body composition (e.g. increased adiposity) affect gender-specific nutrient needs. Nutrient needs are the greatest at peak velocity of adolescent growth, and during that time, the nutritional requirements may be twice as high as those of the remaining period of adolescence.[4] Energy (i.e. caloric intake) requirements are determined by basal metabolism rate, growth needs, and level of activity. Energy is provided by fat (9 kcal/g), carbohydrates (4 kcal/g), and protein (4 kcal/g).[5]

The Food and Nutrition Board of the Institute of Medicine (IOM), in response to continued increased knowledge regarding the role of nutrition in health, has updated the recommended daily allowances (RDA) scheme for appropriate nutrient intake and has named the new approach dietary reference intakes (DRIs).[6] The DRIs contain four categories of recommendations for nutrient reference values, as follows.[4]

1. Recommended daily allowances (RDA): Average daily dietary intake level necessary to meet nutrient requirements of nearly all (97–98%) healthy individuals in an age- and gender-specific group.
2. Adequate intake (AI): Recommended intake value based on observed or experimentally

determined approximation of estimates of nutrient intake by a group of healthy people that are assumed to be adequate (used when RDA cannot be determined).

3. Tolerable upper intake level (UL): Highest level of daily nutrient intake likely to pose no risk of adverse health effects for almost all individuals in the general population.
4. Estimated average requirement (EAR): A daily nutrient value estimated to meet the requirement of half of healthy individuals in an age and gender group (used to determine dietary adequacy of populations but not individuals).

The DRIs provide RDA, AI, UL, and EAR values for vitamins and minerals across all age groups. The information is copyrighted by the National Academy of Sciences, so the tables are not reproduced herein, although they may be found at http://www.iom.edu/Object.File/Master/21/372/0.pdf. The tables provide extensive information on nutritional requirements for adolescent females. They are, however, based on chronological age categories, not individual biological development, so health-care professionals must use judgment in determining nutritional needs for a given adolescent female.

The latest edition of *The Dietary Guidelines*,[7] produced by the US Departments of Agriculture (USDA) and Health and Human Services (also found at http://www.healthierus.gov/dietaryguidelines), is based on the premise that food guidance should recommend diets that provide all nutrients needed for growth and health. Thus, *The Dietary Guidelines* are based upon DRIs, and the guidelines outline two diet schemas that provide good nutrition for adolescent females, one of which incorporates the recommendations from the 2005 update of the USDA food guide, now called MyPyramid. See Figure 6.1 for a visual representation of the personalization of the current food guide. It still has the same food groups (i.e. grains, vegetables, fruits, milk, meats, beans, and oils), but it now also includes a person walking up the pyramid to indicate exercise as an important component of healthy nutrition as well as moderation, personalization (one size does not fit all), proportional portions of each food group, variety, and gradual improvement. Also see http://www.usda.gov/cnpp/pyramid.html for additional information.

Table 6.1 shows the estimated calorie requirements for females aged 9–18 years based on activity level. IOM DRI macronutrients were used in calculating the calorie requirements.

Table 6.2 shows the suggested food intake patterns for the different food groups for adolescent females at different levels of activity and caloric need.

Table 6.1 shows that adolescent females' optimal caloric intake is based on their age and activity level, and Table 6.2 gives a breakdown of nutrients needed based upon the caloric need as determined by the USDA food guide.

NUTRITIONAL CONCERNS FOR ADOLESCENT FEMALES

While there are clear guidelines regarding the nutritional needs of typical adolescent females and what they should be ingesting, nutrient intake of youth in the US shows that they do not consume adequate amounts of vitamins and minerals.[8–11] Females exhibit this trend more than males.[4] It has been found that females are likely deficient in the following nutrients: folate, vitamin A, vitamin E, vitamin B6, calcium, iron, zinc, magnesium, and potassium; adequate amounts of fiber may also be lacking in the adolescent female diet.[7–11] According to the 1994–96 USDA Continuing Survey of Food Intake by Individuals (CSFII), 24-hour recall data using a 2-day average showed that among all age groups of children and adolescents, females aged 14–18 had the lowest mean intake of vitamins.[9–12] Also, adolescent females consume more than the recommended amounts of fat and sodium.[8–11]

Due to the substantial changes across all developmental domains during adolescence, as a group, adolescents tend toward lifestyle changes as they age. This has huge ramifications for nutrition in adolescence because adolescents snack more, skip

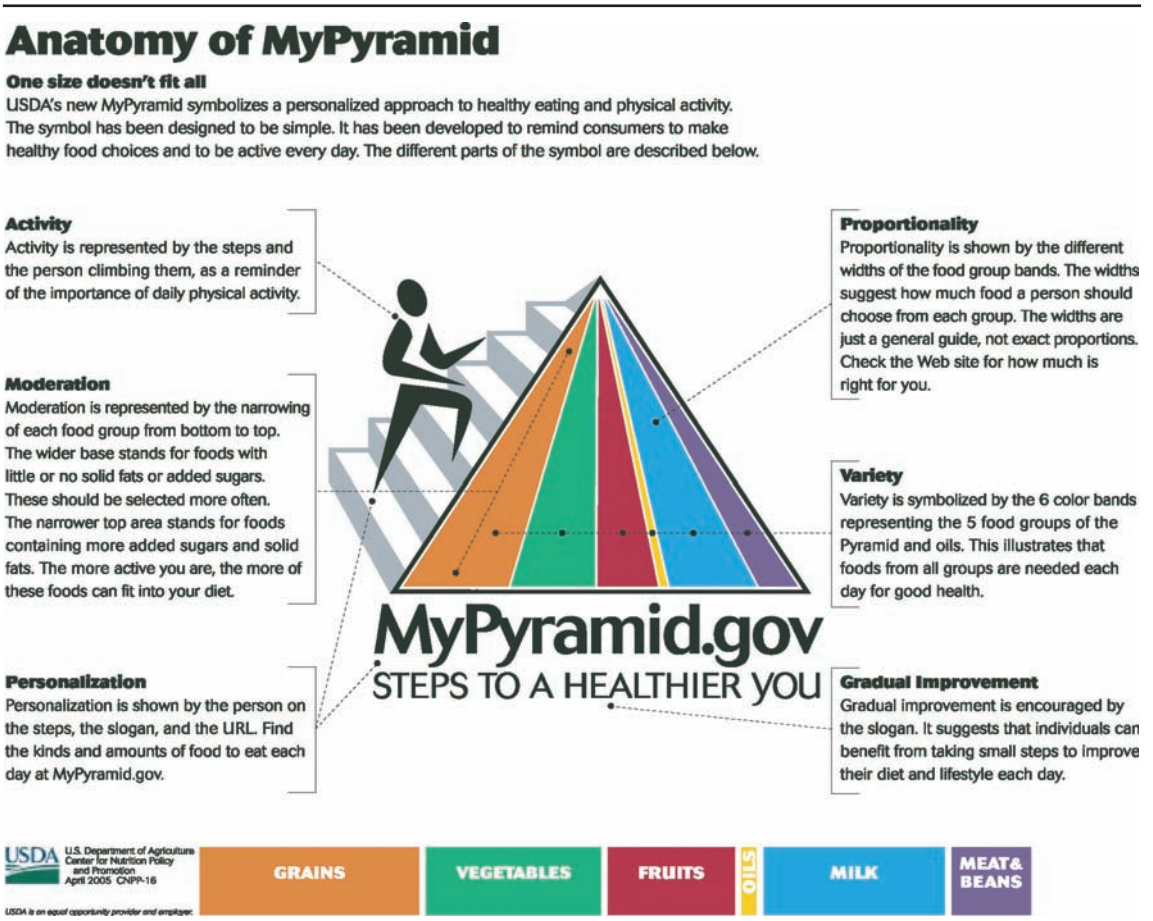

Figure 6.1 Anatomy of MyPyramid.

more meals, eat out more often, eat at home less often, and tend to worry about diet and weight.

Some 88% of adolescents eat at least one snack per day, with a range of one to seven snacks.[13,14] Snacks account for 25–33% of daily energy intake among adolescents.[15] According to CSFII data, the top 10 sources of energy among teens were milk, breads, cakes/cookies/donuts, beef, cereal, soft drinks, cheese, chips, sugar, and chicken.[16] In the third National Health and Nutrition Examination Survey (NHANES III), 21% of energy intake was provided by beverages, with soft drinks alone providing 8% of caloric intake among adolescents.[15] Soft drinks are the most commonly chosen snack for adolescent females and account for about 6% of total calorie intake.[16] One day dietary recall from the NHANES III showed a mean energy intake of 1793 calories per day for females aged 12–19,[17] fewer calories than needed except for the youngest age group (see Table 6.1), and when one considers the quality of the calories ingested, it seems clear that typical adolescent females do not get the nutrition they need.

Skipping meals is also common among adolescent females. Breakfast is the most commonly skipped meal, and the percentage of adolescents that skip

breakfast increases with age, especially among females. Survey data have shown that 24% of female adolescents skipped breakfast on the day of the survey.[18] In all, 34% of 14–18-year-old girls, as opposed to 15% of 9–13-year-old girls, skip breakfast.[9] Additionally, lunch is skipped by almost 25% of adolescents.[9]

Dinner is the meal most frequently eaten at home by adolescents,[19] although only about one-third of adolescents eat dinner with family every day.[20,21] Frequency of eating meals with the family decreases with age, although it has been found that adolescents who eat dinner more frequently with their families have better overall dietary quality.[20] As an added plus, recent data show that adolescents who eat dinner with family at least five nights a week are more likely to get better grades, less likely to smoke, use drugs, have sex at younger ages, or get into fights.[22,23]

One-third of all adolescent eating occasions occur outside the home.[24] The average adolescent eats fast food at least twice per week, and fast-food visits account for 31% of all food eaten away from home and make up 83% of adolescents' visits to restaurants.[24] In general, fast food is not a healthy choice for anyone, especially adolescents, since most fast foods are low in nutrients and high in fats, sugar, and salt. A recent study showed that even when adolescents are supplied nutritional information about fast-food choices, they do not tend to switch to healthier menu choices. For 106 adolescents enrolled, 75 (71%) did not change their choice of meal. Of the 27 adolescents who rated themselves as overweight, only 9 (33%) changed their choice of meal.[25]

Another reason for inadequate nutrition in adolescent females is their increased concern regarding diet and weight. In 2005, the Youth Risk Behavior Survey found that 38.1% of high school females

Table 6.1 Estimated calorie requirements (in kcal) for females aged 9–18 at three levels of physical activity

Age	Sedentary†	Moderately active‡	Active§
9–13	1600	1600–2000	1800–2200
14–18	1800	2000	2400

These levels are based on estimated energy requirements (EERs) from the Institute of Medicine (IOM) dietary reference intakes macronutrients report, 2002, calculated by age and activity level for reference-sized females. 'Reference size,' as determined by IOM, is based on median height and weight for ages up to age 18.
†Sedentary means a lifestyle that includes only light physical activity associated with day-to-day life.
‡Moderately active means a lifestyle that includes physical activity equivalent to walking about 1.5–3 miles per day at 3–4 miles per hour, in addition to light activity associated with day-to-day life.
§Active means a lifestyle that includes physical activity equivalent to walking more than 3 miles per day at 3–4 miles per hour, in addition to light physical activity associated with typical day-to-day life.
Adapted from: US Departments of Agriculture and Health and Human Services, Dietary Guidelines for Americans, 2005, Table 3, p. 12.

Table 6.2 Suggested food intake patterns for adolescent females with varying levels of calorie needs

	Daily amount of food from each group				
Calorie level	1600	1800	2000	2200	2400
Fruits	1.5 cups	1.5 cups	2 cups	2 cups	2 cups
Vegetables	2 cups	2.5 cups	2.5 cups	3 cups	3 cups
Grains	5 oz-eq	6 oz-eq	6 oz-eq	7 oz-eq	8 oz-eq
Meats/beans	5 oz-eq	5 oz-eq	5.5 oz-eq	6 oz-eq	6.5 oz-eq
Milk	3 cups	3 cups	3 cups	3 cups	3 cups
Oils	5 tsp	5 tsp	6 tsp	6 tsp	7 tsp
Discretionary calorie intake	132	195	267	290	362

oz-eq, ounce equivalent; tsp, teaspoon. Adapted from: US Departments of Agriculture and Health and Human Services, Dietary Guidelines for Americans, 2005: Appendix 2-A.

described themselves as overweight, and 61.7% of high school females were trying to lose weight. It was found that 17%, 8.1%, and 6.2% of high school females went without eating for more than 24 hours, took diet pills or powders, or vomited, respectively, in order to lose weight.[26] As eating disorders are complex psychiatric syndromes in which cognitive distortions related to food and body weight and image are of concern, they are beyond the scope of the current chapter. However, the above data suggest that adolescent females have distorted views of their weight and body image given that only 38% thought they were overweight while 62% were dieting.

Adolescent nutrition is also impacted negatively when adolescents choose to eat unhealthy foods despite having a significant amount of knowledge about nutrition.[27] Adolescents have reported that they lack time to eat healthily; they are too busy to worry about food. They also find healthy eating inconvenient eating. Adolescents believe that healthy foods are harder to prepare and often more difficult to find, especially at school. Many adolescents lack self-discipline; given the choice of healthy foods or 'junk foods,' many will choose the latter. Finally, in keeping with the adolescent developmental worldview, many believe that they can worry about nutrition tomorrow.[27,28]

OVER- AND UNDER-NUTRITION

OVERWEIGHT AND OBESITY

Overweight and obesity are usually defined as a body mass index (BMI) equal to or greater than the 95th percentile, compared with pediatric population reference data when plotted on the appropriate age and gender chart. Adolescents with a BMI between the 85th and 95th percentile are considered to be at risk for obesity.[29] Figure 2.2 on page 22 shows a representative growth chart for females aged 2–20 based on age and BMI.

Between 1980 and 2002, overweight prevalence tripled in children and adolescents aged 6–19 years.[30–32] Comparing results obtained from the 2003–2004 NHANES to results from the NHANES survey in 1999–2000, 17.1% vs 13.9%, respectively, of US children and adolescents were overweight. For female children and adolescents, the percentage overweight increased from 13.8% in 1999–2000 to 16.0% in 2003–2004.[31] According to the 2005 Youth Risk Behavior Survey, 15.5% of female high school students were at risk for overweight, and 10% were already obese.[26] A descriptive study of sixth and ninth grade girls compared their perceptions of their weight status in relation to objective BMI measurements. The data showed that while 50% of ninth grade girls and 31% of sixth grade girls were at-risk for being overweight or were overweight, only 23% and 1% of ninth and sixth graders, respectively, perceived themselves to be overweight.[33]

It is important to address obesity at the earliest age possible because at least 70% of obese adolescents will remain obese into adulthood, significantly increasing the chances of obesity-related disease in adulthood, if those diseases do not have childhood onset.[34] In retrospect, in the year 2000, it was estimated that obesity would soon surpass tobacco smoking as the leading cause of preventable death in the US.[35]

One of the most important issues noted in the recent past is that maintaining a positive energy balance, even if only to a minimal degree, in the long term, will lead to weight gain and obesity. If endogenous causes of childhood obesity are eliminated, lack of physical exercise, sedentary behavior, and poor dietary choices are the most common risk factors for weight gain, potentially contributing to obesity-related disease states. Pinhas-Hamiel and Zeitler[36] noted that 'lifestyle-related diseases are no longer the exclusive domain of adult medicine.' The yearly rate of deaths related to complications of obesity is rising, and young adults are in the highest risk group to develop obesity.

In attempting to address adolescents in the categories of overweight and obesity, girls should be encouraged to eat nutritiously and add athletic activity to decrease weight. The goals of adolescent overweight management are: (1) promotion of sustained healthy physical activity and eating patterns, (2) resolution of or improvement in medical

complications, if present, (3) weight loss to ultimately achieve BMI below the 85th percentile, and (4) psychosocial well-being.[37]

UNDERWEIGHT

While much emphasis is currently placed on overweight status in adolescents, some adolescents suffer from being underweight. The World Health Organization (WHO) defines underweight as a BMI below the 5th percentile for age and gender,[38] although teens may look very thin and have a low percentage of body fat with BMIs below the 15th percentile.[39]

Underweight status may contribute to higher rates of morbidity and mortality, and has been associated with higher rates of asthma, scoliosis, intestinal problems, and emotional disorders.[40] Abnormal menses and subfertility have been demonstrated in underweight females.[41] Amenorrhea may also occur as a result of low leptin levels, decreased body fat, emotional stress, or anxiety.[42] Underweight adolescents who become pregnant may be at increased risk for pregnancy complications and poor fetal outcomes, including prematurity and low birth weight.[39] Onset of puberty may be delayed in females with a low BMI,[43] and the risk of osteoporosis may be increased.

There are many etiologies for underweight status; it may be related to genetics, acute or chronic undernutrition, or illness.[39] After ruling out psychiatric disorders, disordered eating behaviors, and chronic illnesses associated with underweight status, it is necessary to intervene appropriately to the individual situation, since adequate nutrition is necessary for the adolescent to progress successfully through puberty and achieve full growth potential. Interventions will differ to some degree based upon etiology.

Nutrient-dense foods are critical for the underweight adolescent as they will increase energy intake. An additional 500 calories per day above usual energy needs for growth and activity will help promote weight gain at a rate of one pound per week.[39] Adolescent females may require 3000 calories per day to achieve a targeted goal weight. The added calories should not come from unhealthy dietary fats and/or sugars, but should be based on the same food groups as presented in Table 6.2. Increased servings are recommended; Luder and Alton[39] recommend that underweight female adolescents consume 11 servings of grain, 5 servings of vegetables, 4 servings of both fruits and dairy products, 3 servings of meats, 6 servings of oils, and 2 servings of sweets and desserts per day to obtain adequate nutrition. Additionally, working out to increase lean body mass is recommended, if there are no contraindications for exercise (e.g. eating disorder).

UNIQUE NUTRITIONAL CIRCUMSTANCES

Among those requiring unique nutritional plans to achieve maximum quality of life are: female adolescents with disabilities, pregnant adolescents, vegetarian adolescents, and adolescent athletes.

ADOLESCENT FEMALES WITH DISABILITIES

Approximately 6% of adolescents cannot complete all activities of daily living without assistance.[44] Even though not all of these individuals have special dietary requirements, it is estimated that nearly half have nutrition-related risk factors or health problems.[44,45] Typically, nutrition problems for children and adolescents with disabilities vary widely depending on the types of limitations caused by the condition, but several common ones should be noted.[46–48] They include:

- dental and gum disease
- appetite disturbances
- drug–nutrient interactions
- elimination problems
- delayed or stunted linear growth
- altered energy and nutrient needs.

When assessing female adolescents with special nutritional needs, a carefully selected set of criteria

for referral to a nutritionist should be considered for a more in-depth nutrition assessment. In addition to diet and feeding issues, the medical condition, associated biochemical interactions, and anthropometric characteristics should also be considered. See Table 6.3 for nutrition screening parameters.

GROWTH ASSESSMENT AND NUTRITIONAL INTAKE

It should be noted that adolescents with disabilities may not grow along the standard growth curves of the Centers for Disease Control and Prevention (CDC) growth charts. Standard pediatric charts can be used to track the growth and progress of adolescent females over time, but the disability, medical status, and genetic condition should be considered when interpreting the growth parameters.

If the disability stems from a genetic condition and/or disease process that causes variations or disturbances in adolescent growth, then an understanding of the factors that cause variations on the growth curve is essential. Growth rates vary based on the genetic condition and issues surrounding weight gain or loss, active infections, malabsorption, or disease processes and should be monitored closely.

Nutritional assessments for adolescents with disabilities should include an evaluation of the quality and quantity of diet. In order to complete such an assessment, there are four variables to consider. These include physical activity, elimination patterns, feeding skills, and the long-term use of medications. Interdisciplinary teams are often needed to assess the impact of the functional issues imposed by the disabling condition upon energy intake and to determine an appropriate intervention for diarrhea and constipation.[48]

PHYSICAL ACTIVITY

Disabilities that include motor impairment and physical limitations may limit the amount of exercise in which the adolescent female may engage. Excess weight gain can often become an issue. A careful balance of physical activity/exercise with energy intake is needed, along with periodic modifications as changes in functional aspects of the disability occur.

Table 6.3 Nutrition screening parameters and criteria for referral for adolescents with special health-care needs

Parameter	Screening data	Criteria for referral
Anthropometric	Weight Height Weight/height Body mass index	Weight/height < 5th percentile Weight/height > 95th percentile height/age < 5th percentile BMI > 85th percentile
Biochemical	Hemoglobin Hematocrit	Hemoglobin < 11 g/100 dl Hematocrit < 34%
Clinical/medical	Medical condition that affects nutrition (e.g. vomiting, reflux), medications, appetite or dental problems	Diagnoses such as cancer, diabetes, HIV/AIDS, renal failure, or spinal bifida
Diet/feeding	Feeding method, therapeutic diet, food aversions or allergies	Tube feeding or parenteral nutrition, therapeutic diet, inability to self-feed, limited diet due to food aversions/ allergies
Other	Parental/professional concerns	Unresolved concerns regarding diet, nutrition or growth

Adapted from: Willis JH. Adolescents with special health needs. In: Stang J, Story M, eds. Guidelines for Adolescent Nutrition Services. Minneapolis, MN: Center for Leadership, Education and Training in Maternal and Child Nutrition, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 2005: 219.

ELIMINATION PROBLEMS

Many female adolescents with disabilities have chronic elimination problems. Factors such as diet, hydration, mobility, activity level, muscle tone, medications, and health status all affect bowel function.

FEEDING SKILLS

If adolescents have a developmental delay and/or a neurological impairment that affects eating skills, they may require special feeding equipment to promote independent feeding. Some may require, for example, tube feedings to supplement their oral intake or to replace oral intake if feeding by mouth is not safe or efficient.[49] Again, interdisciplinary feeding teams are needed to manage complex feeding issues.

LONG-TERM MEDICATION USE

Many adolescents with disabilities take long-term medications to treat chronic medical conditions. Each medication should be evaluated in relation to appetite changes, nutrient digestion, absorption, and excretion. In addition, the use of vitamin and mineral supplements should be carefully assessed as they have the potential to interact with medication, and nutritional adequacy and safety should be considered carefully. Finally, dietary changes may be necessary to prevent or correct any unnecessary side effects from long-term medication usage.[47]

ATHLETES

Approximately 38 million children and adolescents participate in organized sports programs in the US each year.[50] The Surgeon General's Report on Physical Activity and Health clearly indicates that sports participation is a method of promoting good health and should be practiced throughout life.[51] The benefits of participating in sports activities are many[52] and include improved strength and endurance, healthier bones and muscles, weight control, reduced anxiety and stress, improved blood pressure, and healthier levels of cholesterol, and increased self-esteem.

At nearly all levels of competition, athletes search for various nutritional programs as a way to improve physical performance. Marketing advertisements, as well as misinformation from parents and professionals, can lead to unhealthy practices. For female athletes, the female athlete triad[53,54] is a particularly troubling phenomenon that links unhealthy eating behaviors, amenorrhea, and osteoporosis to yield an extremely dangerous constellation of factors that affect overall health.

When considering nutritional strategies for female athletes, physical growth (i.e. weight, height for age) and BMI should be assessed. Many factors affect female athletes' nutritional intake including socioeconomic status, the individual responsible for food purchase and preparation, access to sufficient calories, intentional weight loss and body image disturbance, peer pressure, and health problems.[55]

ENERGY

Athletes must have adequate caloric intake for growth and physical activity. Current research does not indicate the exact energy needs of adolescent female athletes but an average active teenager may require 1500–2000 kcal/day more energy than the RDA. To meet the nutritional needs for physical activity and health, the training diet should provide about 55% of total energy from carbohydrates, 12–15% from protein, and 25–30% from fat. Carbohydrates are the most efficient fuel for athletic performance. Carbohydrate needs are, in part, based on body weight and level of intensity of activity. Table 6.4 provides daily ranges for carbohydrates based on weight and level of intensity.

PRE-EVENT MEAL

The goal of the pre-event meal is to prevent the athlete from feeling hungry before or during the workout or competition as well as to maintain optimal blood sugar levels.[56] The primary nutritional

Table 6.4 Daily ranges for carbohydrate based on weight and level of intensity of activity

Intensity of activity	Carbohydrate (g/kg)
None/light training	3–5 g/kg
Moderate/heavy training	5–8 g/kg
Pre-event (24–28 hours)	8–9 g/kg
Post-event (within 2–3 hours)	1.7 g/kg

Source: Spear B. Sports nutrition. In: Stang J, Story M, eds. Guidelines for Adolescent Nutrition Services. Minneapolis, MN: Center for Leadership, Education and Training in Maternal and Child Nutrition, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 2005: 201.

Table 6.5 Pre-event meal/snack pattern for athletes

Meal/snack	Timing	Examples
Snack 15–20 g CHO < 5% fat	0.5–1 hour before	Pretzels/fluids
Light meal 30–40 g CHO 5–15% fat	2–4 hours before	Turkey sandwich, fruit, fluids
Heavy meal 50–60 g CHO 15–25% fat	4–5 hours (may need a snack later)	Baked chicken, potatoes, fruit, bread, lemonade

CHO, carbohydrates. Adapted from: Spear B. Sports nutrition. In: Stang J, Story M, eds. Guidelines for Adolescent Nutrition Services. Minneapolis, MN: Center for Leadership, Education and Training in Maternal and Child Nutrition, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 2005: 202.

goal for the pre-event meal is to provide high carbohydrate foods, especially complex carbohydrates, with moderate amounts of protein and small amounts of fat so as to achieve maximum performance within a given timeframe. Table 6.5 shows a sample meal/snack pattern.

POST-EVENT MEAL

Eating or drinking carbohydrates immediately after the exercise or competition and then again at 2-hour intervals may optimize the replenishment of glycogen in the muscles. It is recommended that the female athlete drink a high carbohydrate beverage immediately after the physical event and then eat a high carbohydrate meal within the next 2 hours.[57]

PROTEIN

Protein is an essential part of the nutritional intake of all adolescent females, including athletes. The purpose of adequate amounts of protein is to build, maintain, and repair muscle and other body tissue, produce hemoglobin, and form antibodies, enzymes, and hormones. It is a popular false belief among some young athletes that increased amounts of protein (beyond that needed by typical adolescents) will improve all of these functions. Current protein recommendations for adolescents are 0.9 g protein per kg of body weight per day. (Specific protein recommendations for female adolescent athletes are not available from scientific sources and are not included in this chapter.)

Protein supplements, although not proven as a muscle enhancer, are popular among young female adolescents. However, excess protein, either from food or nutritional supplements, will be stored as fat and can lead to dehydration, weight gain, and increased loss of calcium. Table 6.6 shows the potential adverse effects of excessive protein, vitamins, and minerals.

VEGETARIANISM AMONG ADOLESCENTS

Vegetarianism is a popular eating choice among adolescent females.[58] The adolescent vegetarian is

Table 6.6 Potential adverse effects of excessive protein, vitamins, and minerals

Nutrient	Adverse effect
Amino acid and protein supplements Excessive amounts (> 2 g/kg/day)	Dehydration, gout, gastrointestinal upset, hepatotoxicity, renal toxicity, hypercalciuria, impaired essential amino acid absorption
Vitamin A Excessive amounts (> 300% RDA)	Fatigue, irritability, increased cranial pressure, gastrointestinal upset, hepatocellular toxicity, bone and joint pain, hypercalcemia, skin and nail abnormalities
Niacin Excessive amounts (> 300% RDA)	Flushing, pruritis, gastrointestinal upset, skin abnormalities, glucose intolerance, hyperuricemia, hepatocellular toxicity
Vitamin B_6 Excessive amounts (> 300% RDA)	Headache, nausea, sensory neuropathy, hepatocellular toxicity
Vitamin C Excessive amounts (> 300% RDA)	Gastrointestinal upset, nephrolithiasis
Vitamin D Excessive amount (> 300% RDA)	Hypercalcemia and associated effects including: weakness, lethargy, anorexia, nausea, vomiting, constipation, polyuria, cardiac arrhythmia
Vitamin E Excessive amounts (> 300% RDA)	Gastrointestinal upset, fatigue, weakness, lipid abnormalities, inhibited absorption or action of vitamin K

Source: Spear B. Sports nutrition. In: Stang J, Story M, eds. Guidelines for Adolescent Nutrition Services. Minneapolis, MN: Center for Leadership, Education and Training in Maternal and Child Nutrition, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 2005: 199–205.

more likely to be female, not African-American, in middle school, conscious of her weight and body, dissatisfied with her body, involved in a variety of healthy and unhealthy weight control behaviors, previously diagnosed by her physician with an eating disorder, and more likely to have contemplated and attempted suicide.[59] The most common chosen vegetarian diets include semi-vegetarian or partial vegetarian, lacto-ovo-vegetarian (LOV), ovovegetarians, vegan, and macrobiotic. These diets are summarized in Table 6.7.

Table 6.7 Types of vegetarian diets and foods excluded

Vegetarian diet	Food excluded
Semivegetarian/partial vegetarian	Red meat
Lacto-ovo-vegetarian	Red meat, poultry, fish, seafood
Lacto-vegetarian	Red meat, poultry, fish, seafood, eggs
Ovovegetarians	Milk products, meat, fish, poultry
Vegan (total vegetarian)	Red meat, poultry, eggs, dairy products (may exclude honey)
Macrobiotic	Meat, poultry, eggs, dairy, seafood, fish, processed foods

Adapted from: Kong A, Stang J. Vegetarian eating patterns. In: Story M, Stang J, eds. Guidelines to Adolescent Nutrition Services. Minneapolis, MN: Center for Leadership, Education and Training in Maternal and Child Nutrition, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 2005, 209.

Although a vegetarian diet can contain adequate amounts of protein, fat, calcium, vitamin D, vitamin B_{12}, iron, and zinc, nutritional counseling is critical. Intake of zinc, iron, and calcium should be carefully monitored in *all* adolescent females. Research has found that a high intake of fiber and phytates can interfere with zinc and iron absorption, or the levels of zinc, iron, and calcium among female adolescent vegetarians may simply be too low to be considered adequate nutritionally.[58,60] The importance of including a variety of foods in the diet, nutrient-dense snack foods, avoiding skipping meals or consuming too many high fat snacks should be emphasized during the counseling process. Table 6.8 shows a vegetarian food guide for the adolescent.

Researchers have questioned whether a vegetarian diet eaten throughout adolescence would result in an alteration of the pubertal growth spurt and menarche compared to non-vegetarian peers.[61] Several studies have found that this may be the case, but by the end of adolescence, the vegetarian

Table 6.8 Vegetarian food guide for the adolescent

Food group	Servings per day	Comments
Bread, cereal, rice, pasta	6–7 or more	Choose wholewheat breads or cereals
Legumes, eggs, meat substitutes	2 or more	Provides iron, zinc and protein
Fruits and vegetables	5 or more	Include leafy greens Choose a variety Juices do not provide fiber as do whole foods
Nuts and seeds	1 or more	Flax seeds/walnuts provide essential fatty acids

Adapted from: Kong A, Stang J. Vegetarian eating patterns. In: Stang J, Story M, eds. Guidelines for Adolescent Nutrition Services. Minneapolis, MN: Center for Leadership, Education and Training in Maternal and Child Nutrition, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 2005: 213.

females were found to be as tall or taller than other non-vegetarian females.[62]

PREGNANCY

Adolescent pregnancy continues to be a significant concern because of documented higher rates of gestational hypertension, anemia, prematurity, low birth weight, and neonatal mortality observed among adolescents, particularly in those under 15 years of age, when compared with pregnancies among adults.[63] Other concerns for pregnant adolescents include the following.

- Both adolescence and pregnancy are periods of increased nutritional demand and risk. A mounting body of research indicates that the developing fetus and still-growing adolescent compete for nutrients that may be in inadequate supply.[64,65]
- Decreased placental blood flow and lower fetal micronutrient levels have been demonstrated in pregnancies of growing adolescents.[63]
- Research suggests that one-half of adolescents continue linear and pelvic growth for several years after menarche.[63]
- Young, growing adolescents appear to transfer less of their gestational weight gain to their developing fetuses than do older adolescents and adults even with adequate weight gain and body fat accumulation.[64,65]

DIETARY INTAKE

Nutritional intake has specific effects upon the body and the developing fetus. Infrequent eating and/or low dietary folate intake, for example, have been associated with higher risk of preterm delivery,[66,67] while higher intakes of energy, sucrose, and fat have recently been associated with higher rates of preeclampsia.[68]

WEIGHT GAIN

Gestational weight gain (both the total amount and the rate at which it is gained) are important influences on fetal growth, infant birth weight, and length of gestation.[69] The IOM recommendations for total weight gain and rate of gain, based on prepregnant BMI, are listed in Table 6.9.

Low birth weight (< 2500 g) and prematurity (< 36 weeks) are major determinants of perinatal mortality and morbidity.[69] Excessive gestational weight gain (> 40 lbs) does not enhance fetal growth

Table 6.9 Weight gain recommendations for pregnancy

Prepregnant BMI	Total (lbs)	Trimester 1 (lbs)	Trimesters 2 & 3 (lbs/weeks)
Underweight	28–40	5	1.0+
Normal weight	25–35	3	1.0+
Overweight	15–25	2	0.66+
Obese	< 15	1.5	0.5+

Source: Institute of Medicine. Nutrition during pregnancy: part I, weight gain: part II, nutrient supplements. Washington, DC: National Academy Press, 1990.

or length of gestation, but may increase the risk for postpartum weight retention and increased abdominal fat deposition, and may contribute to the development of obesity.[70]

CONCLUSIONS

Nutritional intake during adolescence is a complex component of many physical, cognitive, social, and emotional changes that are occurring within the same developmental phase. Yet, each female adolescent must be assessed individually within the context of specific living experiences. Although adolescents often find it difficult to focus on future negative long-term effects of poor nutrition that might be prevented with adequate nutrition, they are interested in more energy, feeling and looking well, and maximizing athletic performance. If nutrition can be presented in the context of *short-term* benefits to the adolescent, then they may be open to maximizing their nutritional intake, which will have long-term beneficial effects.

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Section II: Medical problems

7. The physical exam in the pediatric and adolescent patient

Eduardo Lara-Torre

As we become more familiar with the pathology encountered in the pediatric and adolescent patient with gynecological disease, knowledge of normal anatomy and proper technique for the performance of the physical exam becomes an essential part of patient evaluation. During the first visit it is appropriate to explain to the patient and parents that the examination of the external genitalia, although not always required, is an integral part of the routine physical examination. The pediatric assessment of the internal genitalia is indicated in cases of genitourinary complaints or suspected cases of genitourinary pathology (Table 7.1). Utilizing non-traumatizing techniques during an office examination of a child or adolescent affords the opportunity for the clinician to establish an adequate relationship with their patient, and allows for the early diagnosis of common conditions found in this age group. Key components of any examination should be covered to the extent allowed by the patient and in no way should the exam be forced by either the physician or the parent, as it may prevent successful future examinations in these patients.

THE PREPUBERTAL FEMALE

Before performing an examination in this age group, one should focus on obtaining the cooperation of the child. Explaining what the exam will entail and allowing the child to have a sense of control (e.g. allowing the child to choose which exam gown to wear) can be ways to enlist their cooperation and perform the examination with less difficulty. Preventing multiple examinations in a short period of time may also play a role in the cooperation of the patient.

OVERALL ASSESSMENT OF THE CHILD BEFORE INITIATING THE GENITALIA EXAMINATION

As with any other condition, a physical exam in the prepubertal patient should include a full assessment of other organ systems. Initiating the examination with an overall inspection will afford the opportunity to assess body habitus, hygiene, and presence of skin disorders while allowing the young patient to feel more comfortable in the exam room setting. It is also important to evaluate height and weight percentiles, carry out auscultation of heart and lung sounds, assess breast development, and perform an abdominal and inguinal examination as part of the comprehensive exam. Once the patient is comfortable with the examiner, the genitalia may be examined, and this should probably be done at the end of the examination.

PATIENT POSITIONING FOR THE EXAMINATION

As we attempt to achieve cooperation from our patients for an adequate examination, positioning becomes a key component to a successful pediatric

Table 7.1 Indications for genital examination in the pediatric patient

Signs of vaginal bleeding
Presence of vaginal discharge
History of vulvar trauma
Suspicion of solid masses or vulvovaginal cysts
Vulvovaginal ulcerative/inflammatory lesions
Congenital anomalies
Sexual abuse

Modified with permission from Bieber EJ, Sanfilippo JS, Horowitz IR. Clinical Gynecology, Chapter 32, Table 32-1. Philadelphia, PA: Churchill Livingstone 2006, p. 485.

gynecologic assesment. In some situations, more than one position may be required in order to have adequate visualization of the genitalia; the patient's age may also play a role in the exam position. A number of positions have been described to allow adequate visualization of the area, and the most useful will be the one that facilitates the goal at hand. The frog-leg position is the most commonly used position in the younger patient and allows the patient to have a direct view of the examiner and herself (Figure 7.1). Using stirrups and the lithotomy position may assist in better visualization of the perineal area as a child grows older. Asking for mother's assistance with the examination can prove useful and placing her daughter between her legs may be of assistance (Figure 7.2). Combining the use of low-power magnification as with an otoscope or ophthalmoscope with the knee-chest position, often allows visualization of the lower and upper vagina.[1] This position may be especially helpful in those patients where a vaginal discharge or a foreign body may be a complaint (Figures 7.3 and 7.4). Despite our best efforts, some patients may not cooperate during the exam and an optimal evaluation of the genitalia is not possible. In these patients,

Figure 7.2 Child in lithotomy position while in mother's lap. Reproduced with permission from Finkel MA, Giardino AP (eds). Medical Examination of Child Sexual Abuse: A Practical Guide, 2nd edn. Thousand Oaks, CA: Sage Publications, 2002: 46–64.

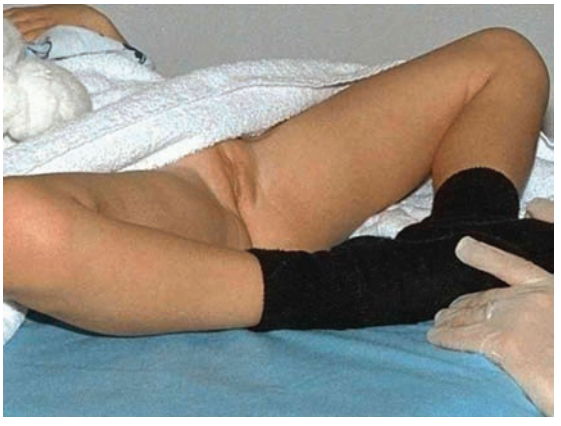


Figure 7.1 A 5-year-old demonstrating the supine 'frog-leg' position. Reproduced with permission from McCann JJ, Kerns DL. The Anatomy of Child and Adolescent Sexual Abuse: A CD-ROM Atlas/Reference. St Louis, MO: Intercort, Inc., 1999.

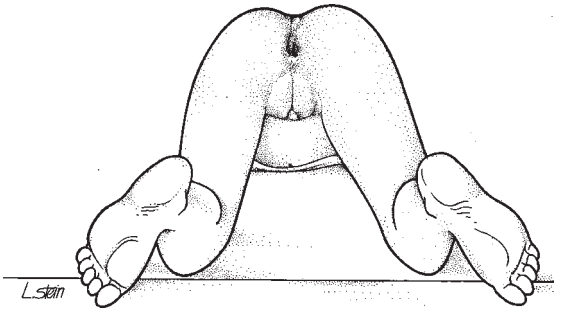


Figure 7.3 Child in knee-chest position for genital examination. Reproduced with permission from Finkel MA, Giardino AP (eds). Medical Evaluation of Child Sexual Abuse: A Practical Guide, 2nd edn. Thousand Oaks, CA: Sage Publications, 2002: 46–64.

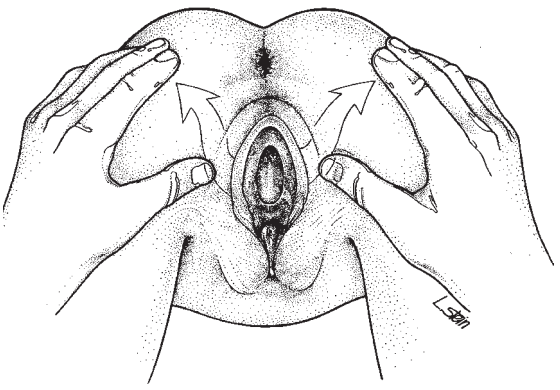


Figure 7.4 Technique for examination of female genitalia in prone knee-chest position. Reproduced with permission from Finkel MA, Giardino AP (eds). Medical Evaluation of Child Sexual Abuse: A Practical Guide, 2nd edn. Thousand Oaks, CA: Sage Publications, 2002: 46–64.

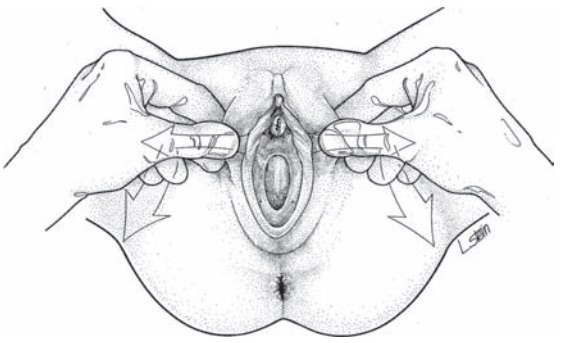


Figure 7.5 Examples of the techniques of labial separation and lateral traction for viewing the hymen of a prepubertal girl. Reproduced with permission from the North American Society for Pediatric and Adolescent Gynecology. The PediGYN Teaching Slide Set. Elaine E Yordan, MD ed.

it is important to consider the acuity of the complaint and the clinical consequence of the pathology. This will allow a decision regarding a multi-visit examination or if an exam under anesthesia is warranted.

When evaluating the newborn, attention must be paid to key characteristics of the external genitalia, which are a result of maternal estrogen stimulation. These findings should not be considered abnormal and tend to regress in 6–8 weeks. Becoming familiar with these characteristics is important for the practitioner when called upon to evaluate a newborn. The presence of vulvar edema, vaginal discharge, and breast enlargement are common in this age group; the hymen appears thick and may protrude to the introitus. This particular finding may persist for up to 2 years.[2] When evaluating newborns and prepubertal girls, the use of the colposcope for magnification may be of use, and may be considered.

In the prepubertal female, the non-estrogenized nature of the hymeneal and vulvar tissue makes it sensitive to touch and easily torn with examination. Care should be taken not to cause trauma or pain in the area, as this will promptly make the remainder of the examination difficult to complete. The use of gentle lateral and downward traction improves visualization and does not disrupt the integrity of the normal prepubertal genitalia (Figure 7.5). In young patients, care must be taken to describe the anatomy properly, and not confuse normal findings with signs of abuse. The presence of vaginal notches, ridges, anal erythema, and skin tags is common and should not be confused with prior sexual abuse. Location of hymeneal notches and ridges may be important, as those present between the 5 and 7 o'clock positions may be related to prior abuse and may require further questioning.[3]

In some patients, the presenting symptom requires an evaluation of the internal pelvic organs. The use of a recto-abdominal exam may assist in the palpation of the internal organs as well as possible pelvic masses. This part of the exam is particularly important in cases of suspected vaginal foreign body, abnormal pubertal development, or lower abdominal pain in which the differential diagnosis includes a pelvic mass. This task may prove difficult and should be attempted only in the cooperative patient to prevent trauma.

To provide an adequate and consistent description of the examination, proper nomenclature of the female genitalia should be used (Figure 7.6). A systematic approach describing each structure including

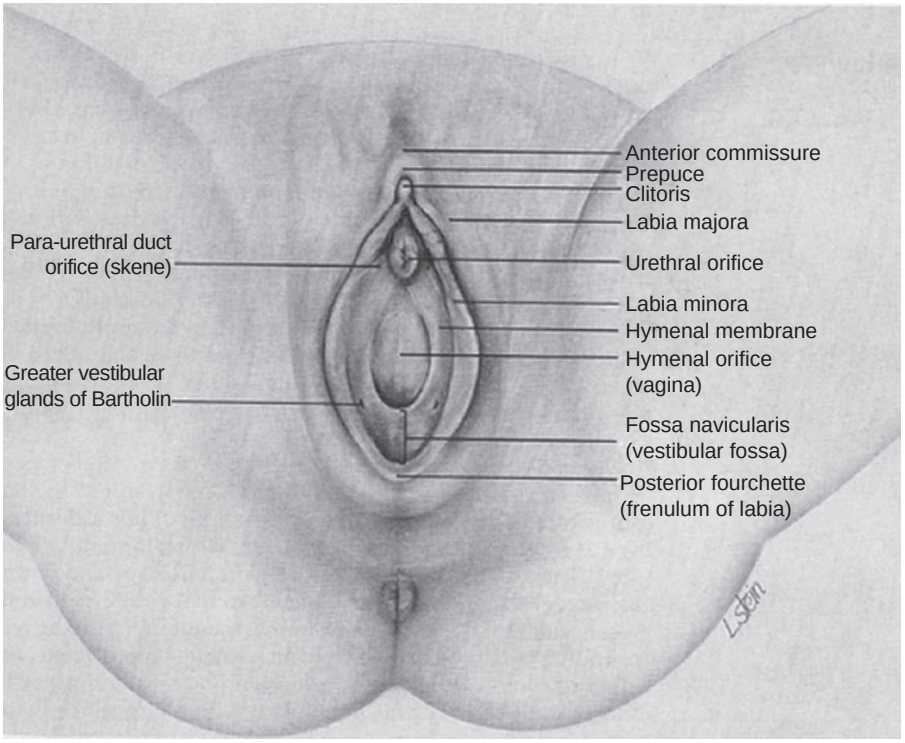


Figure 7.6 Proper nomenclature of the prepubertal external genitalia. Reproduced with permission from Finkel MA, Giardino AP (eds) Medical Evaluation of Child Sexual Abuse: A Practical Guide, 2nd edn. Thousand Oaks, CA: Sage Publications, 2002: 46–64.

inspection and palpation characteristics should be included. Components of such an examination include the assessment of pubertal development (Tanner stage), visualization and measurement of the clitoris, and description of the labia majora and minora including any discolorations, pigmentations or lesions. The urethra and the urethral meatus should also be reported. A proper description of the hymen, including type or shape, estrogen status, and abnormalities of configuration should be detailed. The prepubertal hymen is thin, red, and unestrogenized. At puberty, with estrogenization it thickens, becomes pale pink, and is often more redundant in its configuration. Common normal appearances and variants are shown in Figures 7.7 and 7.8. Other findings including presence of hemangiomas or other vulvo-vaginal lesions should also be described. The presence and appearance of the cervix, if visualized in the knee-chest position, is also important to document.

SPECIMEN COLLECTION

Certain patients will present with symptoms that require the collection of vaginal secretion samples. When cultures are indicated, moistened small male urethral Dacron swabs may be utilized (Figure 7.9). The hymeneal aperture is small in this age group and the use of traditional cotton swabs creates discomfort due to their larger size. It may also traumatize the surrounding tissue,

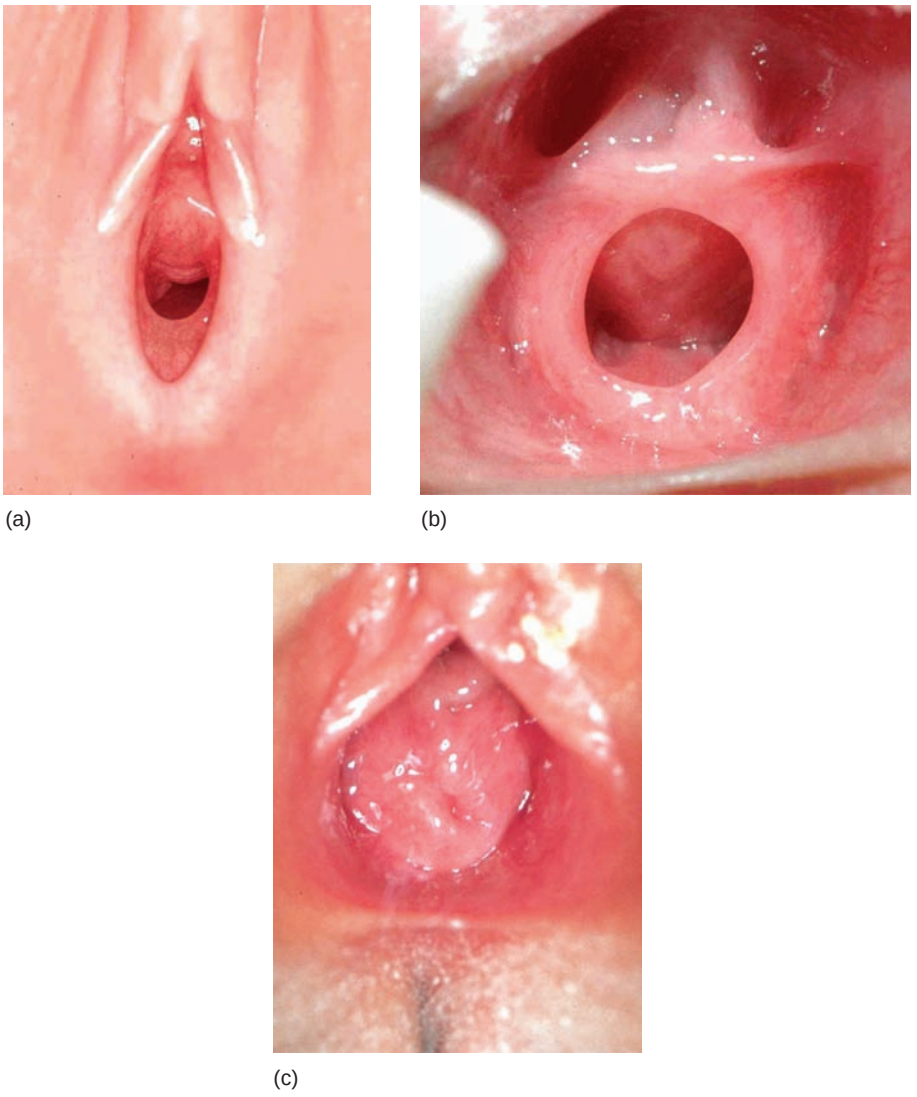
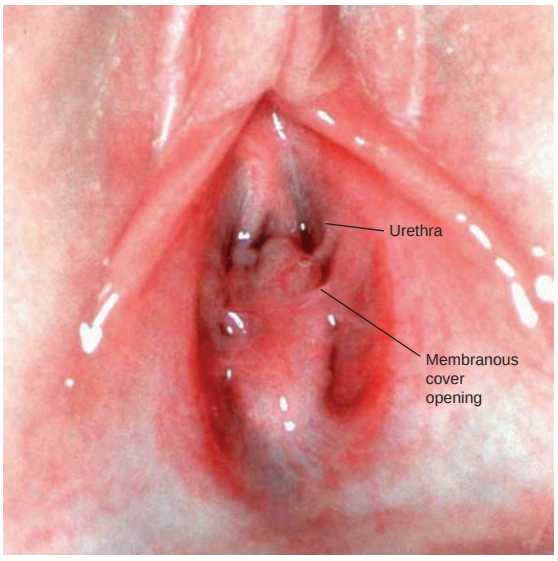


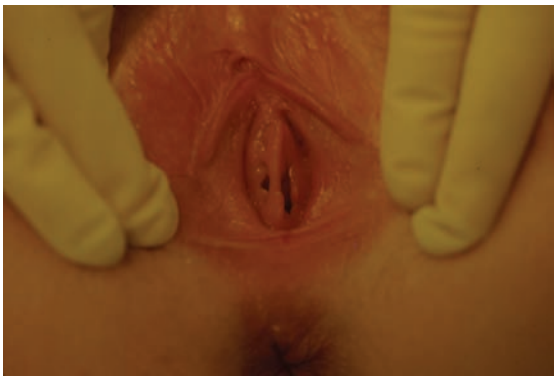
Figure 7.7 Types of hymens: crescentic (A), annular (B), redundant (C). Reproduced with permission from Perlman SE, Nakajima ST, Hertweck SP. Clinical Protocols in Pediatric and Adolescent Gynecology. London: Parthenon Publishing Group, 2004.

creating lesions that are not pathological in nature, but may confuse the examining practitioner. Another helpful method is a catheter-within-a-catheter technique in which a four-inch intravenous catheter is inserted into the proximal end of a no. 12 red rubber bladder catheter. This is then connected to a syringe with fluid and passed carefully into the vagina. The fluid is then inserted and aspirated multiple times to allow a good mixture of secretions (Figure 7.10).[4]

The presence of a foreign body in the vagina is a common presenting problem encountered in



(a)



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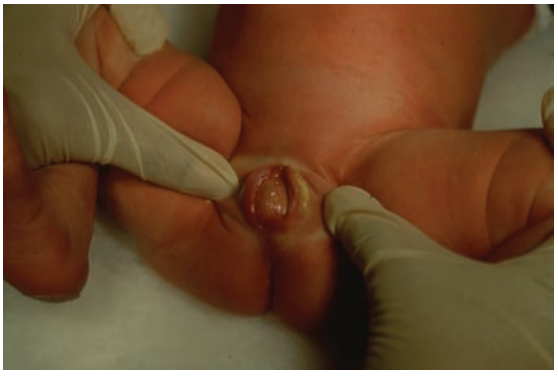

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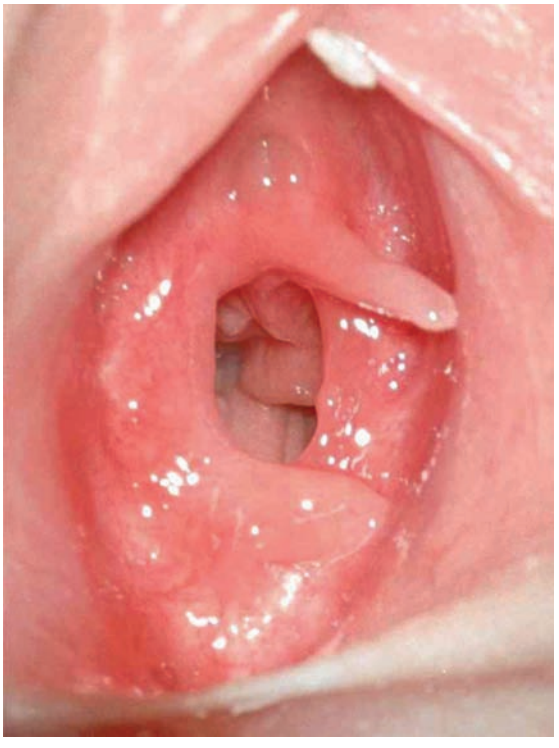

(d)

Figure 7.8 Variations in hymens: microperforate (A), septated (B), imperforate (C), and hymeneal tags (D). Reproduced with permission from Perlman SE, Nakajima ST, Hertweck SP. Clinical Protocols in Pediatric and Adolescent Gynecology, London: Parthenon Publishing Group, 2004 and McCann JJ, Kerns DL. The Anatomy of Child and Adolescent Sexual Abuse: A CD-ROM Atlas, Reference. St Louis, MO: InterCorp, Inc., 1999.

patients with a vaginal discharge. The use of a pediatric feeding tube connected to a 20 ml syringe may allow irrigation of the contents of the vagina and determine the nature of the foreign object, negating the use of speculums in these prepubertal patients in whom the small aperture of the hymen will not allow it, and where it would be injured with instrumentation by a speculum.

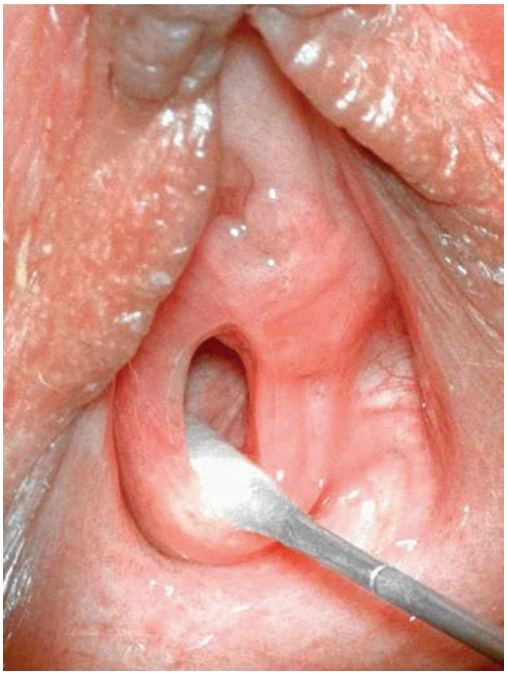

Figure 7.9 Use of small Dacron swabs to obtain vaginal swabs. Reproduced with permission from McCann JJ, Kerns DL. The Anatomy of Child and Adolescent Sexual Abuse: A CD-ROM Atlas, Reference. St Louis, MO: InterCorp, Inc., 1999.

DOCUMENTING THE EXAMINATION

When documenting genital exams of prepubertal girls, care should be taken to merely describe findings and variations, and not to make diagnostic descriptions in the recording of the exam. Conclusions such as 'an interrupted hymen suggestive of sexual abuse is seen' should be placed in the impression and plan portion of the documentation and not in the description of the findings. This will allow for a better interpersonal consistency when a second provider reviews and documents findings. The use of a clock-face method to delineate location of any abnormal findings may be the most helpful way of recording any abnormalities in the exam (Figure 7.11).

In some instances, the use of radiological studies is necessary to complete the evaluation of these patients. In order to be able to interpret the findings of such studies, knowledge of the normal appearance of the ovaries and uterus is important and may play a role in the evaluation. Ultrasound is by far the most utilized method of evaluation of the female genitalia, and is no different at this age. In 1984, Orsini and co-authors described the normal ultrasonographic appearance of the ovaries and uterus at different ages.[5] Their findings showed that before they reach puberty most patients will have an ovarian volume of 1 cm^3 or less and a uterine volume between 1 and 4 cm^3.

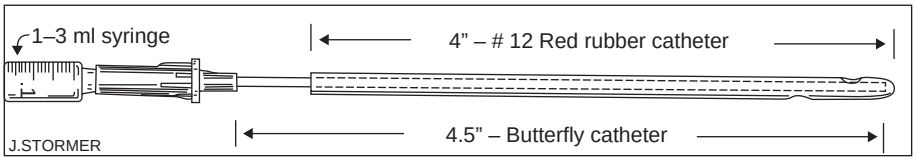

Figure 7.10 Assembled catheter-within-a-catheter aspirator, as used to obtain samples of vaginal secretions from prepubertal patients. Reproduced with permission from Pokorny SF, Stormer J. Atraumatic removal of secretions from the prepubertal vagina. Am J Obstet Gynecol 1987; 156: 581–2.

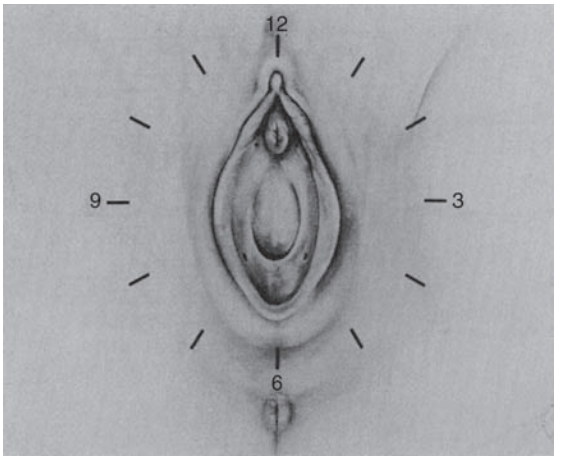

Figure 7.11 Clock-face orientation with patient in frog-leg supine position. Reproduced with permission from Finkel MA, Giardino AP (eds). Medical Evaluation of Child Sexual Abuse: A Practical Guide, 2nd edn. Thousand Oaks, CA: Sage Publications, 2002: 46–64.

ADOLESCENT GYNECOLOGIC EXAM

Although the peripubertal and adolescent patient may be older and able to understand the specifics of the examination, these patients present another challenge for the examining practitioner. In these patients, self-consciousness about their own body may make the exam even more difficult to perform. The extreme variation in their psychosocial and sexual development contributes to the challenge. Teens develop at varying rates; while some are menarcheal at 10, others may just be starting their pubertal development at 13, therefore careful interviewing and counseling should precede an examination. The use of educational videos that explain the examination process and the common reasons why they are done may be of benefit when interacting with the patient. Delaying the genital examination, even in some sexually active teens, may prevent the patient from having reservations about their examiner, and allow the rapport to be established more easily. While some teens may like to know and see everything that will happen, some would prefer not to look. These preferences should be taken into account to make the experience as minimally traumatizing as possible.

Table 7.2 Common indications for pelvic examination in the adolescent

Delayed puberty
Precocious puberty
Abnormal vaginal bleeding
Abdominal or pelvic pain
History of vaginal intercourse
Pathological vaginal discharge
Suspicion of intra-abdominal pathology

Modified with permission from Bieber EJ, Sanfilippo JS, Horowitz IR. Clinical Gynecology, Chapter 32, Table 32-2. Philadelphia, PA: Churchill Livingstone 2006, p. 485.

As in other patients, preventive health-care should be a part of the examination in this age group. As recommended by the American College of Obstetricians and Gynecologists (ACOG), the initial visit to the obstetrician gynecologist should occur between the ages of 13 and 15.[6] During this visit, important components of general health such as immunizations, risk prevention, screening for tobacco and substance abuse, as well as depression and eating disorders should be completed. As a quadrivalent HPV vaccine has been approved by the FDA, new challenging horizons await the health-care provider as a 'vaccinator.' Manufacturers' preliminary information on the effectiveness of these vaccines shows a prevention rate of more than 95% with HPV types 6, 11, 16, and 18 for patients not previously exposed to HPV.[7,8] The duration of protection appears to be more than 4 years but the exact duration is not known. Opportunities to interact with the adolescent will present during these vaccination visits, which allow the practitioner to improve his or her relationship with the parents and teen as other reproductive needs arise.

As discussed earlier, this examination does not necessarily need to include a pelvic examination. Table 7.2 lists indications for a pelvic examination in the adolescent. After the initial gynecologic visit in sexually active teens, semi-annual/annual visits should be scheduled thereafter. Sexually active teens should obtain sexually transmitted infections (STI) screening with each new sexual partner. With the development of urine and vaginal swab testing for

gonorrhea and chlamydia, STI screening has become easier, without the need for a pelvic exam. In those not sexually active, a visit in each stage of adolescence may be preferred (early adolescence ages 13–15 years, middle adolescence ages 15–17, late adolescence ages 17–19).[6,9,10]

Adolescents are primarily interested in confidentiality from a consistent provider who will ask the questions that they won't (e.g. STIs, contraception, acne, weight issues, menses, how their bodies work, and sexual behaviors like kissing, petting, and intercourse). To facilitate obtaining adequate screening for such issues as well as other risk-taking behaviors, ACOG developed the Tool Kit for Teen Care, which contains a confidential screening questionnaire to be used with each visit and an adolescent specific history and physical exam record (Figure 7.12).[11]

Whenever possible, it is important to meet initially with the teen and her parents/guardian together to explain the concept of confidentiality and privacy. After the initial history form is completed with both parent and teen together, the sensitive/confidential part of the history is taken with the teen without the presence of the parent (e.g. sexual history; dating; alcohol, drug, and substance use). It should be emphasized to the parents that information will be kept confidential and that open communication is encouraged between them. Review of local laws regarding the extent of available confidential services is necessary in order to not violate the parents' and teens' rights to information access and privacy. With sensitive questions, it may be helpful to give a wide range of acceptable answers. For example, 'Some teens can talk about sex with their parents; others cannot. How do you feel?' You may also create a context for questions as in 'A lot of girls your age … how do you feel about that?' Utilizing teen-friendly language and simple questions that are easy to understand may improve the collection of information.

When screening, remember to begin with less sensitive issues like safety (e.g. seat-belt use) before affect and sexuality issues. Do not assume that the patient understands the question and be specific when asking (i.e. instead of 'are you sexually active?' ask 'have you ever had sex?, do you know what sex is?, do you know there are different kinds of sex?'). An in-depth sexual history should be an important component of the initial gynecological visit. Tools for this purpose are available through a number of professional societies including ACOG, the North American Society for Pediatric Adolescent Gynecology (NASPAG), and the Society for Adolescent Medicine (SAM).

When indicated, before completing the initial gynecologic exam, take time to explain the process of the exam. In all patients, monitoring of height, weight, blood pressure, and body mass index (BMI) should be performed. Examination of the neck (including a thyroid and lymph node assessment) and evaluation of skin and breast development should precede the pelvic examination. The external genitalia should be visualized, if allowed, in all patients that present for preventive care. This will allow determination of any genital anomalies in this age group, as well as making it the first step towards a pelvic examination. Patients may choose to delay their pelvic examination up to 3 years after the initiation of intercourse, although care should be taken to counsel them about the consequences of non-detection of abnormalities in the female genitalia. Urine screening for STIs should be completed in sexually active teens who choose not to undergo a pelvic examination. Asymptomatic patients who are not sexually active may delay their initial pelvic exam up to the age of 21.[9] Pap testing is required within 3 years of the onset of sexual activity. Annual Pap testing should be considered, beginning with the initial visit in those patients with multiple partners or immunocompromised conditions and in whom follow-up is unlikely.

A thorough description of the external genitalia should be performed. Those adolescents that do require a pelvic examination, because of suspected pathology, or for annual screening, should be properly instructed in the methods used. Proper equipment for this age group should be available. A Huffman (1/2 inch wide × 4 inches long) or Pederson speculum (7/8 inch wide × 4 inches long) may be of help in young patients and those who are not sexually

CONDIDENTIAL FORM **DO NOT COPY** **NOT FOR RELEASE**

ADOLESCENT VISIT QUESTIONNAIRE

We strongly encourage you to discuss all issues of your life with your parent(s). However, unless it is a life threatening issue, the information you give us on this form is condidential between our doctors and nurses and you. It will not be released without your written consent. If you would like help filling out this form, please let the nurse know. IF YOU DON'T FEEL COMFORTABLE ANSWERING A QUESTION. LEAVE IT BLANK AND YOUR DOCTOR OR NURSE WILL TALK WITH YOU ABOUT IT.

Name _____ Age _____ Today's Date _____

Why did you come into our office today? _____

Please answer these general health questions. Ignore the last column. Your doctor or nurse will fill that out.

Friends and Family		**For doctor/nurse use**
Can you talk with your parent(s) or guardian(s) about personal things happening in your life?	❑ Yes ❑ No	
If no, is there another adult you trust and can talk to if you have a problem?	❑ Yes ❑ No Who?	
Who do you live with? (Please circle all that apply.)	Mother Father Guardian Sibling(s) Other:	
Do you think your family has lots of fun together?	❑ Yes ❑ No	
Do you think your Parents care about you?	❑ Yes ❑ No	
Do you have a best friend?	❑ Yes ❑ No	
School and Work		
Do you like school and do well in school?	❑ Yes ❑ No ❑ Not in school	
What grade are you in?	Grade: ❑ Not in school	
What school do you go to?	School: ❑ Not in school	
How often have you skipped school?	❑ Never ❑ Once or twice ❑ A lot	
Do you have any learning problems?	❑ Yes ❑ No	
Do you have a job?	❑ Yes ❑ No Doing what?	
Do you know what you want to be when you are older?	❑ Yes ❑ No What?	
Appearance and Fitness		
Do you have any concerns or questions about the shapte or size of your body or the way you look?	❑ Yes ❑ No ❑ Not sure	
Do you want to gain or lose weight?	❑ Gain ❑ Lose ❑ Neither	
Have you ever tried to lose weight or control your weight by throwing up, using diet pills or laxatives, or not eating for a day?	❑ Yes ❑ No	
Have you ever had your body pierced (other than ears) or gotten a tattoo?	❑ Yes ❑ No ❑ Considering	
Do you exercise or do a sport at least 5 times a week that makes you sweat or breathe hard for 30 minutes?	❑ Yes ❑ No	
How many fruits and vegetables do you eat each day?	❑ None ❑ 1–2 ❑ 3–4 ❑ 5–6 ❑ 7 or more	
How much milk, yogurt, ice cream do you eat each day?	❑ None ❑ 1–2 ❑ 3–4 ❑ 5–6 ❑ 7 or more	
Safety/Weapons/Violence		
Do you wear a seat belt when you ride in a car, truck, or van?	❑ Yes ❑ No	
Do you wear a helmet when you use a bike, motorcycle, all-terrain vehicle, mini-bike, skateboard, rollerblades, or scooter?	❑ Yes ❑ No	
Do you or does anyone you live with have a gun, rifle, or other firearm?	❑ Yes ❑ No ❑ Not sure	
Have you ever carried a gun or weapon?	❑ Yes ❑ No	
Have you ever been in trouble with the law?	❑ Yes ❑ No	
Has anyone touched you in a way that made you uncomfortable?	❑ Yes ❑ No ❑ Not sure	
Has anyone ever forced you to have sex?	❑ Yes ❑ No ❑ Not sure	
Has anyone ever hurt you physically or emotionally?	❑ Yes ❑ No ❑ Not sure	

Figure 7.12 ACOG Adolescent Visit Record and ACOG Adolescent Visit Questionnaire. Reproduced with permission from the American College of Obstetricians and Gynecologists. Tool Kit for Teen Care. Washington, DC. © ACOG, 2003.

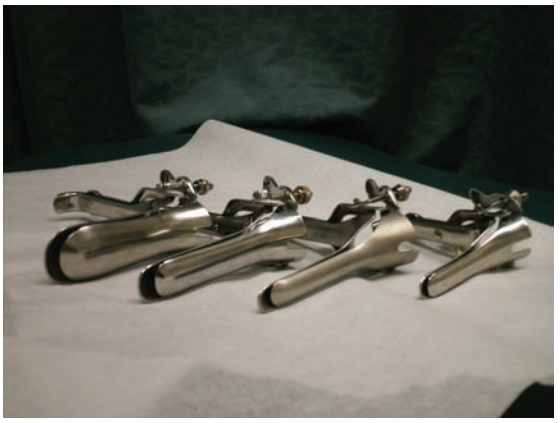

Figure 7.13 Types of specula (from left to right): infant, Huffman, Pederson, and Graves. Reproduced with permission from Emans SJ, Laufler MR, Goldstein DP. Pediatric and Adolescent Gynecology, 4th edn. Philadelphia: Lippincott, Williams & Wilkins, 1998.

active. The use of tampons before their examination and the presence of menses may facilitate the use of a speculum, as they may be more comfortable with vaginal manipulation (Figure 7.13).

The use of a finger applying pressure to the perineal area, away from the introitus, allows for lessening or diffusing of the sensation from the exam ('extinction of stimuli') and may be of benefit in those undergoing their first pelvic examination. Once a finger has been placed in this area, the insertion of a speculum may be easier. Adequate visualization of the cervix and vagina can be obtained in these patients using these techniques. Once access to the cervix is obtained, the collection of screening cervical cytology and cultures may be undertaken as indicated. When attempting to palpate the internal organs, the use of a single-digit bimanual or rectovaginal examination should be attempted. The approach used will depend on the patients' preference, tolerance, and sexual history, as well as the pathology suspected.

All adolescents should be reassured that the examination, while uncomfortable, is not painful, and will not alter their anatomy. This may reassure those who may believe that the exam will alter their 'virginity'.

After the examination, it is helpful to meet again with the family and the patient together to explain the exam findings and to plan further management. In the sexually active teen, if confidentiality is a concern, first discuss findings with the patient alone while in the exam room. Make a plan together about how to discuss with the parent/guardian before meeting with the family together. Ensure that the adolescent assumes the role of decision making and help to empower her to take charge of her own health-care with her parents and your guidance and assistance. Encourage the patient to allow you to be the liaison between her and the family, stressing the benefits of informing everyone of her health-care needs and the importance of communication; but overall, keep confidentiality consistent with your teen's desire.

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8. Human papillomavirus and abnormal cervical cytology in adolescents

Lea E Widdice and Anna-Barbara Moscicki

INTRODUCTION

Genital human papillomavirus (HPV) is a common infection among sexually active individuals, with lifetime risks rising to 80%. HPV infection can either be detected without disease or can result in a variety of clinical pictures including condyloma accuminatum, abnormal cytology and, rarely, malignancies of the cervix, anus, vagina, vulva, penis, and oropharynx. Of these malignancies, cervical cancer is the most common. Because it affects women during their economically productive and child-rearing years and because the majority of malignancies result in death in developing countries, cervical cancer has had the greatest economic impact in the developing world. Current prevention measures include both screening and vaccination.

The introduction of routine cytology screening in the 1970s in the United States led to a substantial decline in the rate of cervical cancer. Interestingly, cervical cancer screening based on the identification of cancer cell precursors was introduced before the etiology of cervical cancer was established. The field of cervical cancer research has rapidly expanded since the 1980s when new molecular techniques were introduced, allowing for widespread epidemiologic studies. These studies quickly reported disparate findings. Adolescents and young women under 25 years of age had the highest rates of infection and the lowest rates of cervical cancer. The high rates of HPV were initially interpreted to indicate that young women were at risk for cervical cancer but were not adequately screened. Consequently, aggressive cytology screening practices were rapidly introduced into this population. Despite broadened screening programs, cervical cancer remained virtually undetected among adolescents. In contrast, abnormal cytology was diagnosed at extremely high rates in younger women, which resulted in a substantial increase in colposcopy referral and treatment. Epidemiology studies began to clarify the natural history of cervical cancer by showing that acquisition of HPV alone is not a risk factor for cancer. Rather, HPV persistence is the key to cervical cancer development. This model quickly explained the high rates of HPV infection in adolescents and low rates of cervical cancer (i.e. this age group had high rates of acquisition but low rates of persistent infection). Consequently, these observations led to new guidelines for cervical cancer screening and triage of abnormal cytology in this young age group.

In addition to cytology screening, prevention measures for cervical cancer now include vaccination. The recent development and introduction of the first HPV vaccines has potential to change the epidemiology of HPV infection and abnormal cytology, as well as to prevent cervical cancer, specifically in countries where screening programs are difficult to coordinate.

This chapter will describe HPV virology and clinical manifestations of genital HPV infection. To provide a framework to understand current approaches to cytology screening, triage, and treatment, we will focus on the epidemiology of cervical HPV infections, abnormal cytology, and cervical cancer, including their prevalence and factors associated with the occurrence of each. The natural history of infection, abnormal cytology, and cancer as well as the factors associated with regression and

progression of each will be discussed. Understanding the epidemiology of HPV will help facilitate communication with and delivery of effective healthcare to adolescents.

HPV VIROLOGY

Human papillomavirus is a small virus with a double-stranded DNA genome surrounded by a protein capsid. HPVs are classified by genotypes (types). A unique HPV type is defined as a papillomavirus with greater than 10% difference in a defined region of the viral DNA. Over 100 different HPV types exist. Certain types tend to cause disease in either cutaneous (e.g. plantar warts) or mucosal epithelium (e.g. genital warts). Approximately 30 types have been identified as 'genital' HPV types, although many of these types can be seen in oral mucosa in addition to the genital mucosal epithelium. HPV types infecting genital mucosa are further grouped into high-risk and low-risk types based on epidemiological evidence for their role in cervical cancer (Table 8.1). Low-risk types infect mucosal epithelium and can result in disease, but are not implicated in cervical cancer.[1]

It is believed that HPV infection requires direct access to basal epithelial cells, often through a wound or inflammation. Infection occurs by attachment of the capsid proteins, L1 and L2, to host cell receptors. The viral genome is then released into the cell and makes its way to the nucleus.[2–4] Within the nucleus, the virus uses the host cell machinery to run its own replication process. Whether there is a latent phase and how long it exists prior to active replication remains controversial. What is known is that HPV requires cell differentiation for the replication process to be completed. Early in infection, two proteins, E (early) 6 and E7, are expressed at relatively low levels in the parabasalar cell layer of the epithelium. The functions of these proteins have been well described. For the high-risk HPV types, E6 and E7 proteins interfere with the keratinocyte's cell cycle control, resulting in abnormal cell proliferation. Both E6 and E7 have transformation properties *in vitro* and are termed oncoproteins (see below: Cancers). As the cell matures, other viral proteins are expressed, such as E4, which results in the characteristic perinuclear halo. Cytologically, these changes are referred to as squamous intraepithelial lesions (SIL). The two late proteins, L1 and L2, are responsible for virion assembly and make up the viral capsid. They are expressed late in the viral life cycle and only in the mature squamous cells. The final production of the infectious virion requires terminal differentiation of the infected epithelial cell.[5,6] Release of infectious virus occurs at the time of normal cell desquamation.

Table 8.1 Classification of genital HPV types based on epidemiological evidence of carcinogenesis

Epidemiological classification	HPV types
High-risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
Probable high-risk	26, 53, 66
Low-risk	6, 11, 40, 42, 43, 44, 81

From Munoz N, Bosch FX, de Sanjose S et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003; 348(6): 518–27.

CLINICAL MANIFESTATIONS

WARTS AND OTHER PAPILLOMAS

HPV causes a wide range of epithelial diseases including benign and malignant tumors. The most common benign disease is the disfiguring and sometimes uncomfortable genital wart. Types 6 and 11 cause the majority of genital warts.[7] Although genital warts do not have any malignant potential and are not a risk for cervical cancer, having a history of genital warts is a risk for vulvar cancer.[8]

Rarely, genital HPV types have been identified in papillomas of the conjunctivae and gingival and nasal mucosa. HPV 11 is also associated with recurrent laryngeal papillomatosis (RLP). Although the papillomas of RLP are benign, the disease can be

potentially fatal due to obstruction of the airway, specifically in infants and young children. Recurrent juvenile respiratory papillomatosis (RRP) is thought to be caused by vertical transmission of low-risk HPV types from mother to neonate during delivery. Some evidence suggests other routes of transmission including horizontal transmission from mother to child.[9]

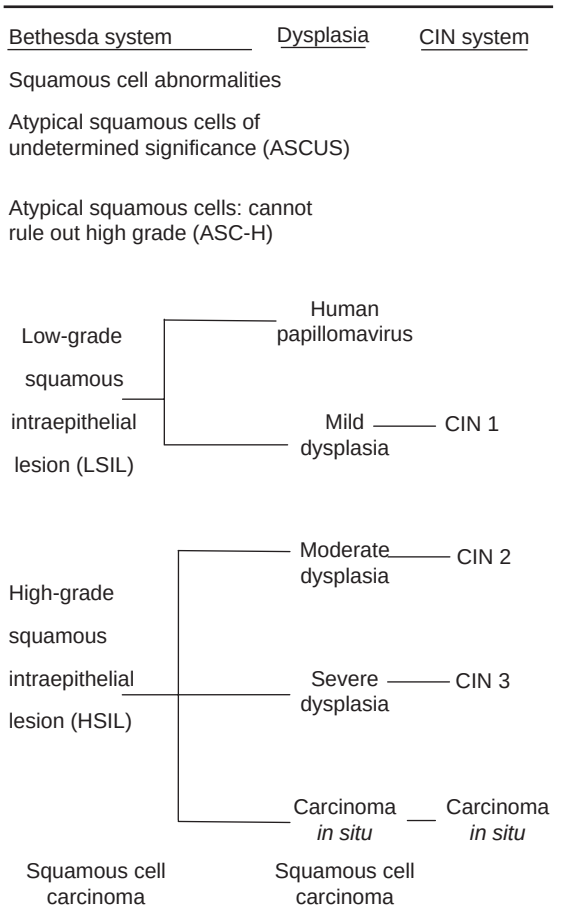

Figure 8.1 Comparison of descriptive systems for cervical squamous cell cytology and histology. From solomon D, Davey D, Kurman R et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002; 287(16): 2114–19. CIN, cervical intraepithelial neoplasia.

ABNORMAL CYTOLOGY AND HISTOLOGY

SIL is a cytologic term and diagnostic categories are used for triage for further testing to detect dysplasia or cancer with biopsy and histologic diagnosis (Figure 8.1). In general, histologic diagnosis of cervical intra-epithelial neoplasia (CIN) 1, 2, 3 and carcinoma *in situ* is used for treatment algorithms (see below: Treatment guidelines).

As described earlier, expression of viral proteins results in specific pathologic changes referred to as SIL. Early changes which include mild basal cell proliferation and perinuclear halos are considered benign and are termed low grade squamous intra-epithelial lesions (LSIL).[10,11] Changes that result in greater histological abnormalities are termed high grade squamous intra-epithelial lesions (HSIL). These changes include aneuploidy, altered chromatin texture, and increased nuclear volume. HSIL manifestations are predominantly due to expression of E6 and E7. As the histologic lesion progresses, L1 and L2 are rarely expressed, the reciprocal of E6 and E7 expression. Although HPV DNA detection in the face of normal cytology is far more common than HPV detection with SIL in epidemiology studies, many believe that all active HPV infections result in some form of histologic change. Since cytology is a relatively insensitive test to detect disease, this premise will be difficult to establish. However, most agree that whether HPV DNA is detected with or without LSIL, both infection and LSIL are usually benign and reversible (see below: Natural history). Some also contend that LSIL is not required for the development of cervical cancer; rather, HSIL is the only true precancerous lesion and may occur *de novo* (see below: Natural history). This hypothesis suggests that LSIL coexists with HSIL but that the lesion itself does not progress to cervical cancer. Unfortunately, cytology does not always detect HSIL or CIN 2/3 lesions. Most CIN 2/3 lesions are detected in women referred for LSIL, limiting studies that focus on cytology only.

CANCERS

Anogenital and oropharyngeal cancers are the rarest manifestation of HPV. Of the anogenital cancers, cervical cancer is the most common and the most comprehensively studied. Virtually 100% of squamous cell cervical cancers are due to HPV infections.[1] The development of cervical cancer is multifactorial, as is the case for most cancers. However, HPV persistence is thought to be critical in the development of cervical cancers. There is no standardized definition of persistence, although most agree that with each month of continued infection, the risk of developing significant disease, including cancer, rises. Persistence refers to detection of the same HPV type two or more times in a given time period. The time period is defined in the context of the study being reported. Although there are numerous cytopathologic events associated with HPV viral expression, hallmark oncogenic events include interference with cell cycle control through E6 and E7 viral proteins that include enhanced p53 degradation, disruption of the E2F/pRb complex resulting in activation of E2F (an important cellular transcription factor), blockade of apoptosis, and activation of telomerase (an enzyme responsible for telomere lengthening, resulting in prolonged life of epithelial cells).[12] The exact sequence and triggers of events remain elusive.

Compared with cervical cancers, only 50% of vulvar, vaginal, and penile cancers and 80% of anal cancers are associated with HPV.[13] Mechanisms of these cancers are much less understood, due mostly to the rarity of these cancers. Recent data also tie 20–50% of oropharyngeal cancers to high-risk HPV infections.[14]

EPIDEMIOLOGY OF HPV INFECTION, SIL, AND CANCER

PREVALENCE OF HPV DETECTION

HPV prevalence rates are usually based on detection of viral DNA from exfoliated samples taken from the anatomic site of interest, such as the cervix. Although assays have been developed to detect antibodies, they are not used clinically. There are no standard, reliable assays available, which makes interpretation of the data using these assays difficult.

Rates of cervical HPV DNA detection vary by age and geographic region. Women younger than 25 years old have been shown to have 2.5–4 times greater rates of infection than women over 35 years old. Rates in women less than 25 years old range from 15 to 54% and in women older than 35 years old they range from 5 to 28%.[15–19] In most regions, rates of HPV are shown to peak in women under 25 years, fall in women in the third and fourth decade of life, and then remain steady. Although some countries show a second rise in women over 60 years of age, the rates remain lower than those in younger women.[16,20]

Among women who have cervical HPV infection, high-risk types comprise a larger proportion of infections than low-risk types. In general, HPV 16 is the most commonly detected type.[21] This is true whether women have normal or abnormal cytology.

BEHAVIORS AND OTHER RISKS FOR HPV ACQUISITION

HPV is easily transmitted through skin-to-skin contact. Certainly, any skin-to-skin contact such as sexual intercourse, oral sex, hand–genital contact, and anal sex can result in transmission. Most information on acquisition of HPV was obtained from studies on cervical infections. Several studies have documented that most cervical infections are acquired shortly after the initiation of sexual intercourse, and reporting a recent new sexual partner is a strong risk for acquisition.[22–24] Both of these aspects underscore the common nature of transmission with any sexual intercourse. About 50% of young women appear to acquire HPV within 3 years of sexual debut.[22] Although sexual intercourse is the most common risk for cervical HPV infection, finger–vaginal sex is also a plausible mode of transmission. There are no good data to suggest that HPV can ascend from the vulva to

the cervix or whether vaginal infections lead to cervical infection. Results from studies are confusing, since sampling techniques alone may lead to contamination rather than detection of true compartmental (i.e. vulvar, vaginal, or cervical epithelium) infections.

Another risk associated with HPV infection includes early age of sexual debut.[25] In addition, sexually transmitted infections such as herpes simplex virus (HSV) or *Chlamydia trachomatis* are also associated with increased rates of HPV infection.[23] Inconsistent associations have been found with oral contraceptive use and smoking.[26] Condom use has been shown to decrease the risk of HPV infection.[27]

RISKS FOR HPV THAT INCREASE ADOLESCENTS' VULNERABILITY TO HPV INFECTION

Besides sexual behavior, the high rates of HPV seen in adolescents may also be explained by certain biologic factors unique to adolescence. The epithelial structure of the adolescent cervix and a naïve mucosal immune response may increase adolescents' vulnerability to HPV infection. Little is known about the immune response to HPV infection in either adults or adolescents. However, it is plausible to speculate that over time, women develop appropriate cell-mediated immune responses to HPV that result in rapid clearance of infections when re-exposed.

The structure of the adolescent cervix is quite different from most adult cervices in that the adolescent cervix is predominantly composed of fragile columnar and rapidly differentiating metaplastic epithelium compared with squamous epithelium that predominates in most adult cervices. The predominance of columnar and metaplastic epithelium is often referred to as ectopy or cervical immaturity and is likely related to the biologic vulnerability to HPV infection associated with adolescence. Changes to the cervical epithelium begin *in utero* when the columnar epithelium of the müllerian tract is replaced in part by urogenital squamous epithelium. The replacement is usually incomplete, resulting in an abrupt squamo-columnar junction present on the ectocervix.

Prior to puberty, the squamo-columnar junction is relatively quiescent. Most adolescents enter puberty with somewhere between 20 and 80% of the cervix portio covered by the single-layered columnar epithelium, giving the cervix its red hue (Figure 8.2). With the onset of puberty, the columnar epithelium is gradually transformed into squamous epithelium in a process referred to as squamous metaplasia; uncommitted generative cells of the columnar epithelium commit themselves to becoming squamous epithelium instead of columnar. This area of transition is referred to as the transformation zone. By adulthood, a new junction lies in the endocervical canal. Thus, the ectocervix and cervical os become covered by the thicker and more protective squamous epithelium, giving the cervix its pink hue (Figure 8.3). Most women have little to no ectopy visible by their twenties or thirties. The transformation zone is particularly vulnerable to HPV-related carcinogenesis since it is known to be the area where squamous cell cancers arise.

As mentioned earlier, HPV infection is thought to start with invasion of the exposed basal layer of the epithelium. The areas of metaplasia and ectopy may be more prone than squamous epithelium to damage and exposure of the basal layer arising from trauma, such as from intercourse or infection. Triggers of squamous metaplasia include increase

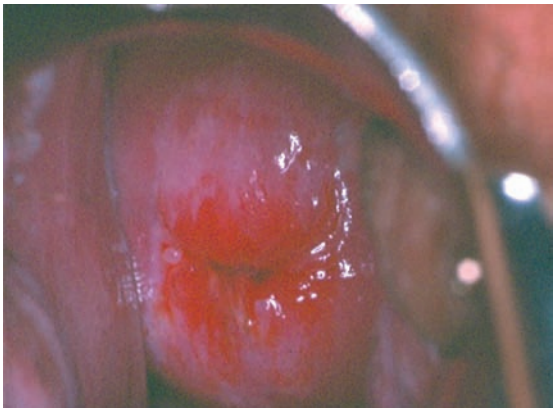

Figure 8.2 Colpophotograph of a cervix with ectopy.

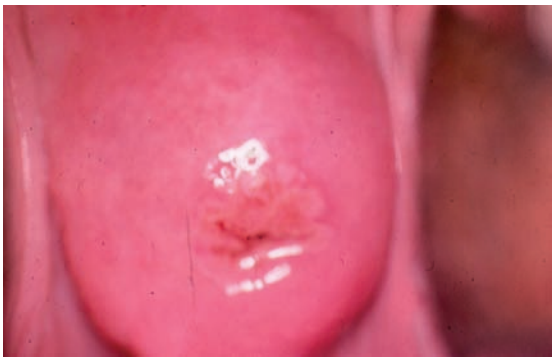

Figure 8.3 Colpophotograph of a mature cervix with no ectopy.

in estrogen levels, increased acidity of the vagina (both associated with puberty), trauma, and infection. Sexual activity appears to enhance the metaplastic process; cervices of adolescent women with multiple sex partners appear more adult-like, with smaller areas of ectopy.[28,29] Active, exposed areas of squamous metaplasia in the adolescent also increase the risk of cytologic abnormalities caused by HPV infection,[30] since HPV replication and transcription patterns that lead to cellular changes require rapidly differentiating keratinocytes, as occurs in squamous metaplasia.[31]

ROUTES OF TRANSMISSION IN CHILDREN

HPV can be transmitted perinatally to infants and children.[9] There is little evidence to suggest that this mode of transmission results in cervical infections in female infants. Certainly, external genital warts can be found in infants and toddlers and are often associated with a history of genital warts in the mother, suggesting perinatal transmission.

Another mode of transmission in children appears to occur from skin-to-skin contact from caregivers. In a study of 76 families, oral HPV in the father and oral or cervical infection in the mother was associated with an increased rate of HPV detected on the external genitalia of infants.[9] Although these studies did not correlate HPV DNA detection and appearance of genital warts, the appearance of genital warts in any child should not be casually dismissed as perinatally acquired.

As in adults, children can acquire HPV through sexual contact. Thus, appearance of genital warts in a child of any age warrants concern. However, the diagnosis of genital warts does not confirm that abuse has occurred.[32] An evaluation for sexual abuse by a specialist is appropriate when genital warts are diagnosed in a child.[33]

PREVALENCE OF ABNORMAL CYTOLOGY

Although biologically all HPV may result in SIL, the rates of SIL detection are lower than rates of HPV DNA detection.[34–36] Paralleling rates of HPV infection, SIL is more common in younger women than older women. Mount et al reviewed over 79 000 cytology slides and found that 3.9% of sexually active women aged 15–19 years had SIL compared with 1.3% of women aged 30–39 years.[35]

The majority of abnormal cytology in adolescents is classified as LSIL. Mount et al showed that among 15–19-year-olds, 2.5% were diagnosed as having LSIL and 0.7% as HSIL. None had carcinoma *in situ*. A population screening program of over 100 000 Norwegian women showed that in 15–19-year-olds, twice as many smears were LSIL compared with HSIL, and none were carcinoma.[34] As compared with older women, LSIL is usually four times more common in adolescents. Interestingly, although the proportion of HSIL to LSIL is greater in older women (usually around 1:1.1) than the adolescent (1:2.5), the overall rates of HSIL are similar (0.5% in older women and 0.7% in adolescents).[35]

As mentioned above, LSIL and HSIL are cytologic diagnoses that are used as triggers for colposcopy referral and histologic confirmation. Most CIN 2/3 lesions are diagnosed from referrals for LSIL, regardless of the patient's age. Consequently, the rate of CIN 2/3 in the general population is unknown, since known rates are based only on referral populations. Studies of referral groups show that a greater percentage of LSIL results in

diagnosis of CIN 2/3 in older women than in adolescents. In two studies including older women, 15–30% of women with LSIL on cytology screening had CIN 2 or 3 on biopsy.[37] In comparison, only 7% of adolescents will have CIN 2/3.[38] This concern over misclassification of LSIL on cytology screening has influenced guidelines to use LSIL as a threshold for referral to colposcopy for older women but not adolescents.

RISKS FOR DEVELOPMENT OF ABNORMAL CYTOLOGY

As discussed above, risks for LSIL are thought by some to be related to HPV acquisition alone. However, one study showed that LSIL had different risks than acquisition of HPV. In this study, smoking was a risk for LSIL but not HPV acquisition.[23]

Persistent HPV, especially of high-risk types, is the strongest risk factor associated with the development of HSIL.[24] One study showed an increased relative risk of 14 for developing HSIL after persistent infection.[39] In addition, risk factors associated with the development of high-grade lesions include tobacco use and possibly oral contraceptive use and *Chlamydia trachomatis* infection.[40,41] Condom use has been associated with a decreased risk of high grade lesions in HPV-positive women[42] and a randomized clinical study showed an increased rate of CIN regression in women who used condoms.[43]

RATES OF CERVICAL CANCER

Invasive cervical cancer is virtually undetected in adolescents. In the United States, the incidence of invasive cervical cancer from 2000 to 2004 was zero for those under 14 years old, 0.1 per 100 000 for 15–19-year-old women, 1.5 for 20–24-year-old women, 6.2 for 25–29-year-old women, and 11.5 for 30–34-year-old women[44] (Figure 8.4). Unfortunately, other factors possibly involved with the few cases of cervical cancer in adolescents, such as immunocompromised status, are unknown.

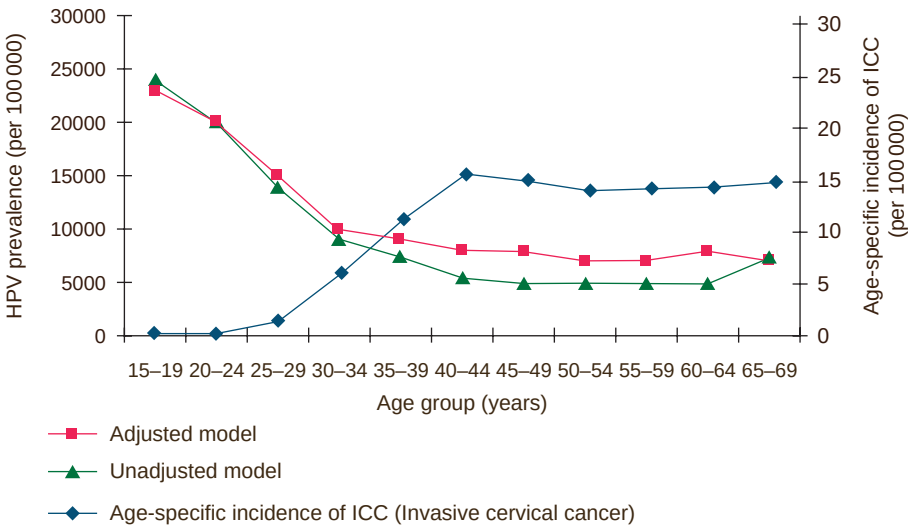

Figure 8.4 Comparison of the rate of HPV infection and invasive cervical cancer (ICC) in different age groups. HPV Infection Rates: age-specific prevalence in women with normal cytology. Data are based on the crude and adjusted estimates derived from a meta-analysis of 78 studies reported in Burchell AN, Winer RL, de Sanjose S, Franco EL. Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. Vaccine 2006;24 Suppl 3:S52–61. ICC Rate: data are from Ries L, Melbert D, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2004, National Cancer Institute. 2007. [Available from: http://seer.cancer.gov/csr/1975_2004/]

RISKS FOR CERVICAL CANCER

As previously stated, persistence of high-risk HPV infection is a necessary precursor to cervical cancer. HPV 16, in particular, is associated with carcinogenesis. Together, HPV 16 and 18 are responsible for almost 70% of cervical cancers[1,45] (Figure 8.5). Cervical cancer has long been known to be associated with sexual behaviors including multiple partners and young age at first intercourse. In contrast to tobacco's inconsistent association with HPV acquisition, tobacco use has consistently been shown to increase the risk of developing cervical cancer. Carcinogens from tobacco have been identified in cervical mucous of smokers and exposure to tobacco may decrease the local immune response, giving plausibility for this association.[46–48] Prolonged use of oral contraceptives and medroxyprogesterone, i.e. 5 or more years, is also associated with an increased risk of cervical cancer.[49] Although several biologic mechanisms have been postulated, the exact relationship remains unknown. High parity, often five or more pregnancies, is also associated with cervical cancer and thought to be either due to the chronically high progesterone levels or possible repeated cervical trauma.[46,47] Other factors possibly associated with development of cervical cancer include infection with *Chlamydia trachomatis* and dietary factors.[41,47]

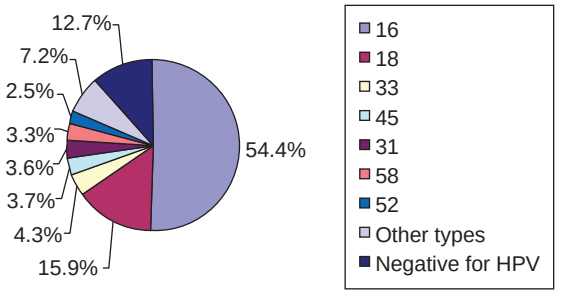

Figure 8.5 Prevalence of type-specific HPV among women with invasive cervical cancer. From: Smith JS, Lindsay L, Hoots B et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer 2007; 121(3): 621–32. The values include squamous cell carcinoma and adeno/adenosquamous carcinoma. The total adds up to > 100 because each type was considered separately.[44]

NATURAL HISTORY OF HPV INFECTION AND ABNORMAL CYTOLOGY

NATURAL HISTORY OF HPV INFECTION

Following the recognition of the high rates of HPV in young women, an important finding from natural history studies in the 1990s was that, once acquired, HPV is a transient infection in most adolescents and young women. This contrasts early assumptions that HPV would mimic other viral sexually transmitted infections such as HSV and cause lifelong infections. Among adolescents and young women, the average duration of infection has been reported to be between 7 and 10 months.[24] Within 3 years of observation, 70–93% of infections will become undetectable,[24,39,50] with 7–30% showing persistence. It is unknown whether the virus is truly cleared in those with negative HPV testing. Some researchers suggest that all women with a previous history of infection continue some form of infection including latency. During latency, the presence of HPV DNA is not detectable using current laboratory techniques. Clinically, whether the body completely clears the virus is irrelevant since most agree that only detectable persistence is a risk for cervical cancer.

If HPV persists, the time from HPV infection to the development of CIN 3 has never been directly determined but is estimated to be 7–15 years.[47] On the other hand, recent studies have shown that some women appear to develop CIN 3 within months of acquiring HPV.[51] The reason for these differences remains unclear.

FACTORS ASSOCIATED WITH HPV CLEARANCE AND PERSISTENCE

Clearance of HPV infection is most likely controlled by innate and adaptive immune responses.[48] Some have contended that infections with multiple HPV

types clear more slowly than those with a single type,[24] potentially due to defects in mucosal immune responses or to the multiple types working synergistically. Some studies have also shown that high-risk types clear more slowly than low-risk types. In 3 years of observation, 70% of infections with high-risk HPV types cleared and 90% of low-risk HPV types cleared.[39] Additionally, condom use has been shown to increase HPV clearance[43] and consistent condom use is associated with shorter duration of infection.[52,53] Other factors have also been inconsistently associated with the development of persistent infection. Increased persistence with high- and low-risk HPV has been linked to tobacco use[53,54] and *Chlamydia trachomatis* infection.[40]

NATURAL HISTORY AND REGRESSION OF SIL

Since LSIL is merely a manifestation of HPV replication, we would expect the majority of LSIL to revert to normal as HPV clears. In a study of women aged 13–22 with LSIL who had repeat cytology every 4 months, the probability of regression of LSIL to normal cytology was 61% by 1 year and 91% by 3 years.[55] The average time between LSIL detection and regression to normal was 8 months, similar to clearance of HPV. In studies including older women, LSIL generally regresses, albeit at lower rates (64–88%)[56,57] than in younger women. The lower rate of LSIL regression in older women is most likely an artifact of misclassification of HSIL as LSIL on older women's cytology or the detection of an already persistent lesion.

Difficulty arises in describing the regression of precancerous lesions (HSIL) because of a lack of uniformity in describing and classifying lesions. In the United States, HSIL constitutes the histological diagnosis of both CIN 2 and 3. Diagnosis of CIN 2 has low reproducibility, and is dependent on pathologists' training. This influences study findings, leading to disagreement about the nature of CIN 2 lesions. Some contend that CIN 2 is more like CIN 1, others liken its natural history to CIN 3, and still others claim that there is no CIN 2 state. Given this controversy, the US has moved towards using HSIL for cytology and uses both CIN 2 and 3 for histology. Unfortunately for those trying to determine the natural history of CIN 2 and 3, histology is often referred to as CIN 2/3 (or HSIL).

Nevertheless, HSIL is less likely to regress than LSIL. Older studies examining the natural history of CIN 2 and 3 separately suggest that the natural histories of CIN 2 and 3 are quite different. Syrjanen et al found that over half (53%) of CIN 2 and only 14% of CIN 3 lesions regressed. Of note, similar to CIN 2, 56% of CIN 1 lesions regressed.[56]

PROGRESSION OF SIL

Whether an LSIL progresses to HSIL and cancer or is associated with an adjacent HSIL that will progress independently from the LSIL remains a contentious issue. However, in studies that have followed women with LSIL on cytology or CIN 1 on histology, progression of these lesions appears to occur. Of note, clinically, HPV persistence is a better predictor of HSIL development than LSIL detection, probably due to the insensitivity of cytology. What is noted with most studies is that the rates of progression vary between adult and adolescent populations. In a study of adolescent women 13–22 years old with LSIL, 3% of LSIL progressed to HSIL.[55] By comparison, Schlecht et al reported that 20% of women 16–60 years old with persistent LSIL progressed to HSIL or cancer[57] and others have shown that the risk of CIN 2/3 within 2 years of LSIL detection is around 28%.[58]

In contrast to LSIL, HSIL (CIN 2/3 lesion) has a reasonable chance of progression to cancer. CIN 3 lesions are the most likely to progress and are considered true precancers. In the study by Syrjanen et al, 69% of CIN 3 progressed to cancer, compared with 21% of CIN 2 and 14% of CIN 1 after 72 months of follow up.[56] These studies cannot be repeated today because following CIN 3 to cancer would be of concern ethically. Since CIN 2 is much more common than CIN 3 in adolescents compared with older women,[34,36] HSIL detection is expected to have a distinct outcome depending on age.

Rates of progression are also dependent on time of follow-up. In a study with a mean follow-up of 78 months, Nasiell et al confirmed that the time for progression to severe dysplasia for women was longer in younger age groups.[59] Thus, when we pool findings, it is evident why CIS and invasive cancer are rare among adolescents despite the fact that adolescents and older women have similar rates of HSIL; among those young women with HSIL, CIN 2 is more common than CIN 3, and among those young women with CIN 2, regression is likely and if progression occurs, it is uncommon while an adolescent.

Time for CIN 3 lesions to progress to invasive cancer likely varies between women. Using historical data from over 30 years ago, Schiffman et al commented that between one- and two-thirds of women with CIN 3 will progress to invasive cancer in an unpredictable time-dependent fashion.[60] However, the overall lifetime risk for cervical cancer in developed countries is estimated at 1.5%.[61] Risk factors associated with progression from CIN 3 to invasive cervical cancer have not been determined.

SCREENING PRACTICES

The most recent screening, triage, and treatment guidelines for adolescents are based on a number of factors, which include recognition of the benign and transient nature of LSIL in adolescents and understanding that, usually, years pass between the time of HPV infection and the development of carcinoma *in situ,* the true precancer lesion. Because previous screening practices that extended screening to younger women led to a vast increase of referrals and treatment of benign lesions without a corollary increase in cancer detection, it was determined that the balance of risk favors avoiding excessive, unnecessary screening and diagnostic work-ups in healthy young women.[62]

In the United States, the guidelines[62–64] recommend that initiation of screening occurs within 3 years after the onset of sexual activity. Guidelines provide an age limit of 21 years to start screening if providers or patients do not discuss sexual activity. The 3-year delay allows for many of the benign infections and cytology abnormalities to regress before detection. Cancer within 3 years of exposure to HPV is thought to be non-existent or extremely rare. Because HPV DNA testing is not used in the triage of abnormal cytology in women under 21 years of age, reflex HPV DNA testing should not be obtained.

Once screening is initiated, the recommended screening interval varies based on whether the woman is older or younger than 30 years and whether conventional or liquid-based cytology is used. In women younger than 30 years of age, annual screening is recommended if conventional cytology smear is used.[62,64] Annual[64] or bi-annual[62] screening is recommended if liquid-based cytology is used. Since HPV DNA testing is not recommended as part of cervical cancer screening[62–64] in women younger than 30 years, the use of this test does not influence screening intervals as it does in older women. Screening guidelines do not address screening in vaccinated women and women who have sex with women. Women who have received partial or full HPV immunization should follow current guidelines regardless of immunization status given that the vaccines do not prevent disease from HPV infections acquired before vaccination or prevent infections from oncogenic types not included in the vaccine that are responsible for almost 30% of cancers. Women who have had sexual contact only with women are at risk for HPV infection and abnormal cytology, and therefore should be screened.[65]

When recommendations led to screening at younger ages, the Pap smear became a tangible marker for providers and patients to initiate discussions of gynecologic and reproductive health. Recent guideline changes that increase the age of initiation of screening will make it necessary to establish a new marker. Onset of puberty and menarche may be more appropriate markers to initiate discussions of reproductive health-care, including education about normal anatomy and function, access to birth control, prenatal services, and sexually transmitted infection screening as

recommended by the American College of Obstetricians and Gynecologists.[66]

TRIAGE OF ABNORMAL CYTOLOGY SCREENING

In adolescents less than 21 years old, whether pregnant or not, if atypical squamous cells of undetermined significance (ASCUS) or LSIL are detected on cytology screening, surveillance cytology should occur at 12 months and 24-months. On the 12-month repeat cytology, if HSIL or ASC suggestive of HSIL (ASC-H) are detected, referral to colposcopy is recommended. If LSIL or ASCUS are detected, continued surveillance is recommended. On the 24-month repeat cytology, if HSIL, ASC-H, ASCUS, or LSIL are detected, referral to colposcopy is recommended[67] (Figure 8.6). According to the current recommendations in the United States, in women 20 years or younger, care should be taken to avoid obtaining reflex testing for high-risk HPV. If it is inadvertently obtained in a woman under 21, the result should not be considered in the management of the abnormal cytology. Because of the high rates of HPV detection and clearance in young women, using HPV testing would needlessly lead to a large number of women at low risk of cancer being referred for colposcopy. However, in the triage of ASCUS for women 21 years and older, HPV DNA testing is cost-effective. Regardless of age, women with HSIL or ASC-H on cytology should be referred for colposcopy[67] (Figures 8.7 and 8.8).

TREATMENT GUIDELINES

Biopsy-confirmed CIN 1 is considered a benign lesion in all age groups. Biopsy-confirmed CIN 1 in satisfactory colposcopy incurs watchful waiting regardless of age.[68] It is currently recommended to follow CIN 1 in women less than 21 years old with cytology annually. If LSIL or ASCUS occur at the 12-month follow-up, no referral is necessary and annual cytology should continue. At 24 months, HSIL, ASC-H, ASCUS, or LSIL on repeat cytology should trigger re-referral for colposcopic evaluation. It is not recommended to treat CIN 1 at any time in adolescents, including adolescents with unsatisfactory colposcopy[68] (Figure 8.9).

CIN 2 can be followed in a compliant adolescent after discussion of possible risks. The follow-up is

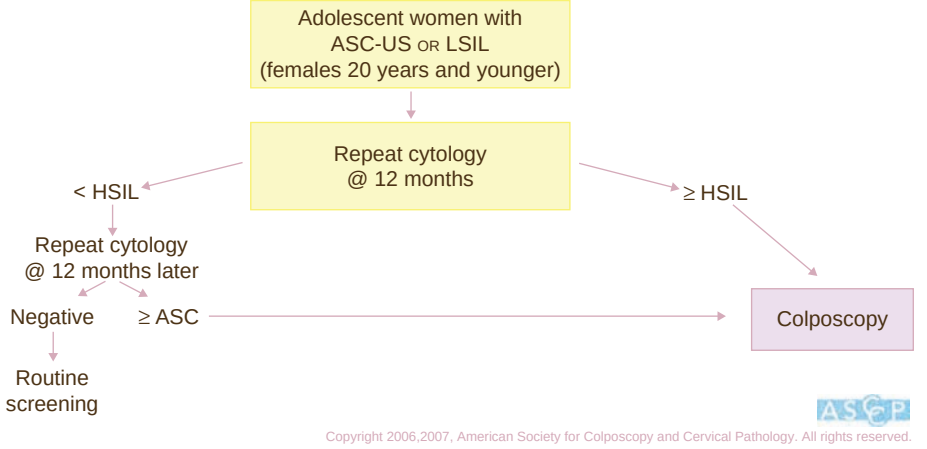

Figure 8.6 Algorithm for the management of adolescent women with either atypical squamous cells of undetermined origin (ASCUS) or low-grade squamous intra-epithelial lesion (LSIL). Reproduced with permission from www.asccp.org (accessed 10-29-2007).

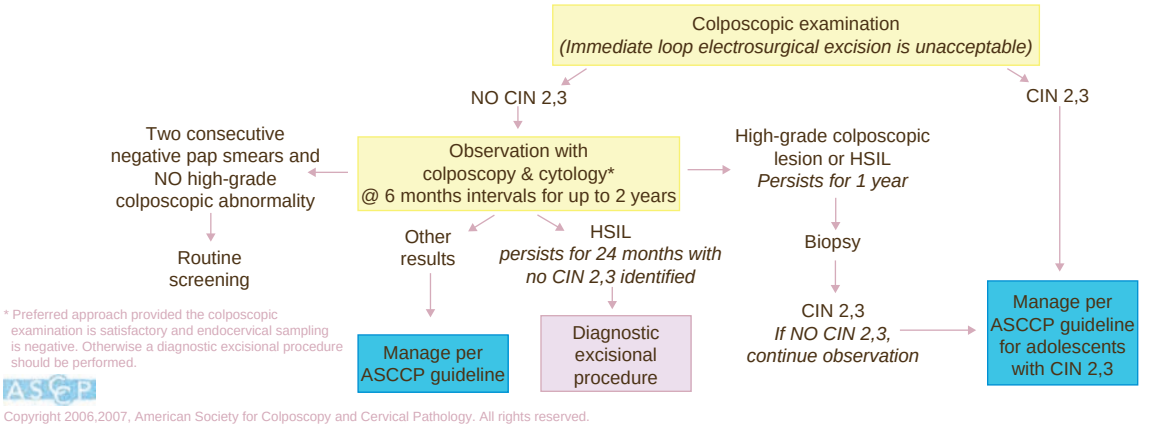

Figure 8.7 Algorithm for the management of adolescent women with high-grade squamous intra-epithelial lesion (HSIL). Reproduced with permission from www.asccp.org (accessed 10-29-2007).

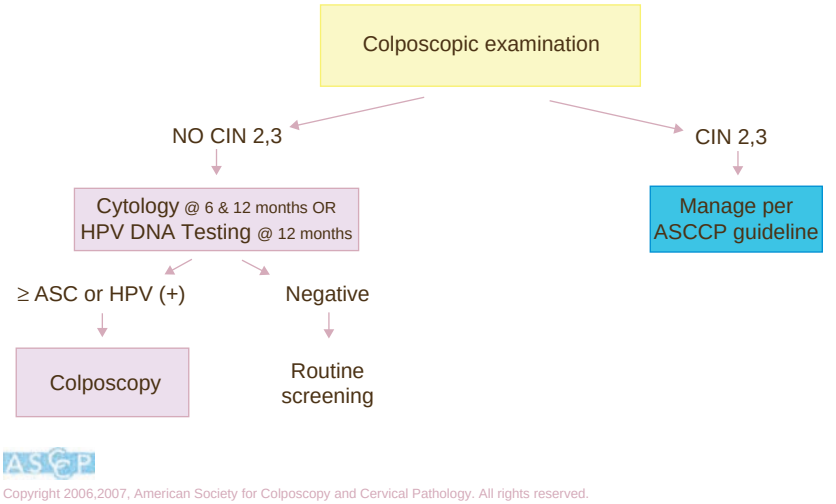

Figure 8.8 Algorithm for the management of adolescent women with atypical squamous cells: cannot exclude high-grade SIL (ASC-H). Reproduced with permission from www.asccp.org (accessed 10-29-2007).

repeated cytology and colposcopy every 6 months for up to 2 years. Repeat biopsy is recommended if cytology continues to detect HSIL for 1 year or if colposcopy shows a worsening lesion or a persistent high grade lesion for 1 year. Treatment of lesions is recommended if CIN 2/3 or HSIL persist for 2 years. CIN 3 is treated regardless of the woman's age. Diagnosis of CIN 2/3 can be managed similarly to CIN 2 in women less than 21 unless the diagnosis is considered to be carcinoma *in situ* or colposcopy is unsatisfactory. Treatment of HSIL on cytology without CIN 2/3 confirmation on initial evaluation is not appropriate in the adolescent age group[67,68] (Figures 8.7 and 8.10).

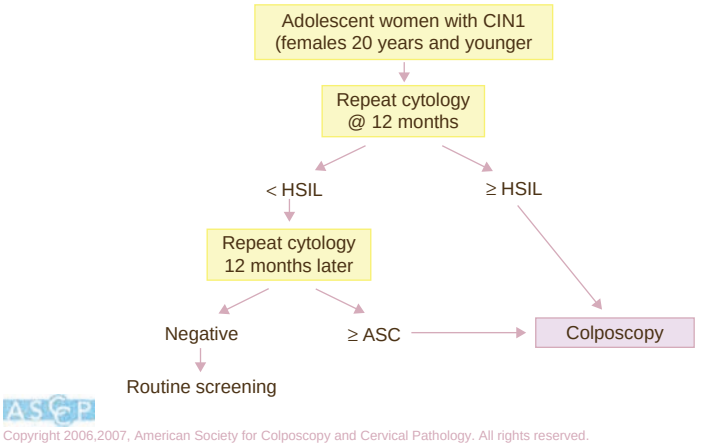

Figure 8.9 Algorithm for the management of adolescent women with a histological diagnosis of cervical intra-epithelial neoplasia – grade 1 (CIN 1). Reproduced with permission from www.asccp.org (accessed 10-29-2007).

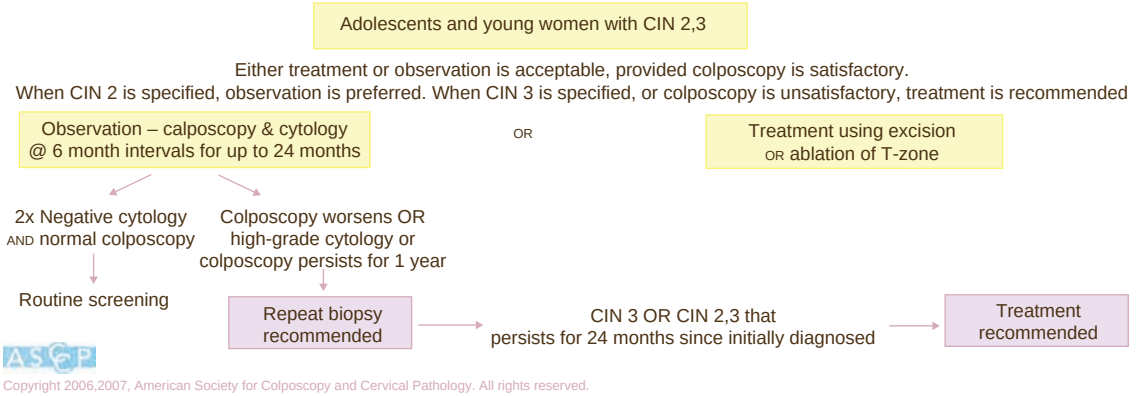

Figure 8.10 Algorithm for the management of adolescent and young women with a histological diagnosis of cervical intra-epithelial neoplasia – grade 2, 3 (CIN 2, 3). Reproduced with permission from www.asccp.org (accessed 10-29-2007).

HPV AND EDUCATION AND EFFECTIVE HEALTH-CARE DELIVERY TO ADOLESCENTS

A patient's understanding of cytology screening test results is not correlated with her age or educational background.[69] Providing results along with education in an individualized, accurate, and nonjudgmental manner has the potential to minimize patients' distress and encourage safe sexual behaviors and regular cytology screening.[70] Patient education should emphasize that HPV is a common and a self-limiting infection in most women. Cytology screening detects abnormalities caused by HPV, most of which will need to be followed over time. If abnormalities persist or worsen while being monitored, they must be tested further.

Colposcopists seeing adolescents should remain mindful that many adolescents may be unfamiliar with medical procedures and their own anatomy. Younger adolescents may be in a stage of development

characterized by heightened self-awareness and feelings of being different or abnormal. A preceding explanation of the indication for colposcopy and what to expect may reduce patient anxiety.

At this time, sexually transmitted infection screening and diagnosis should not include HPV DNA testing. HPV DNA results cannot assist clinicians or patients in determining the risk of developing warts or cancer, or risk of transmission to sexual partners, or provide guidance for treatment. Rather, clinical care can focus on the diagnosis of genital warts, appropriate cytology screening, and promotion of prevention measures. Future diagnostic tests may change these recommendations but none are in current clinical practice.

PREVENTION OF HPV INFECTION

Prevention measures should include counseling adolescents to abstain or postpone sexual intercourse, to use condoms consistently, and to limit the number of sexual partners. Condom use has been shown to decrease the risk of HPV infection.[27] In those who have acquired an infection, consistent condom use is associated with a shorter duration of infection[52,53] and a decreased risk of high grade lesions.[42] Additionally, CIN lesions regress more quickly in women who use condoms.[43]

In addition to counseling, prophylactic vaccines may be offered. Prophylactic vaccines against HPV induce antibodies to the L1 protein. A quadrivalent and a bivalent vaccine are commercially available. The quadrivalent vaccine protects against HPV types 16, 18, 6, and 11 and is given in a series of three intramuscular (i.m.) injections at 0, 2, and 6 months. It is licensed for use in the United States in women 9–26 years. The Advisory Committee on Immunization Practices (ACIP) currently recommends routine immunization of girls aged 11–12 years, with catch-up vaccination of girls aged 13–26 years. The bivalent vaccine protects against HPV types 16 and 18 and is given at 0, 1, and 6 months. It is being reviewed for licensure in the United States and is approved in some countries outside of the US. These vaccines are close to 100% effective in preventing CIN 2/3 associated with the vaccine HPV types when given before exposure and infection,[71,72] i.e. the vaccine does not promote clearance of an established infection or prevent progression of lesions. Thus immunization of girls before the onset of sexual activity should be a priority. Sexually active women may be vaccinated; although, they should be counseled that the vaccine offers no protection from a specific HPV type if they have already been exposed to that type.[72] Currently there is no role for HPV DNA testing to determine the eligibility of sexually active women for vaccination. As the vaccines are introduced to the general population, their impact on the epidemiology of HPV infection, LSIL, HSIL, carcinoma *in situ*, and invasive cancer will be determined. The vaccines' impact will depend on their availability, uptake by individuals and communities, and the interplay of immunology, virology, economics, and human behavior. Until the impact is determined, current cervical cancer screening guidelines apply to all women regardless of immunization status, specifically because the vaccines do not protect against infections from 13 additional carcinogenic HPV types.

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9. Vaginal discharge and genital bleeding in childhood

Mary Anne Jamieson

Vaginal discharge and genital irritation together comprise a significant portion of the gynecological complaints presenting in childhood. Many of the conditions that can cause these two symptoms can also cause genital bleeding, but in isolation, genital bleeding is fortunately far less common.[1]

This chapter will review the various causes of these problems. Key features of the history, physical examination, choice of investigations, and basic management will be outlined.

As regards terminology, vulvitis is a term that should be reserved for external genital irritation whether the patient describes pruritus, redness, burning, or soreness. Vaginitis implies vaginal discharge, usually with an odor, and occasionally with a blood tinge. When the symptom complex is combined, the term vulvovaginitis is used. It should be mentioned that because the genital tissues in childhood lack estrogen, they are particularly vulnerable and sensitive, and even vaginal discharge can cause secondary external burning or irritation. That is, even primary vaginitis can cause secondary vulvitis and therefore vulvovaginitis (Figure 9.1).

Table 9.1 outlines the common organisms isolated in cases of pediatric vaginitis along with other underlying etiologies that can cause vaginal discharge in the child.

Fortunately genital bleeding in childhood is relatively uncommon, but it should prompt a careful assessment. While vulvitis, vaginitis, and vulvovaginitis can cause bleeding, other possible underlying etiologies must be considered and these are listed in Table 9.2. While sexual abuse, deliberate genital trauma, and sexually transmitted infections are definitely to be considered in the differential diagnosis of either vaginal discharge or vaginal bleeding in childhood, these topics are covered in detail in Chapter 18. Similarly, dermopathies such as lichen sclerosis, eczema, and psoriasis can present with either symptom, and these are covered in detail in Chapter 10.

VAGINAL DISCHARGE AND VAGINAL FOREIGN BODY

When a child presents with vaginal discharge, health-care providers should at least explore with the parent and then with the child (if verbal) the

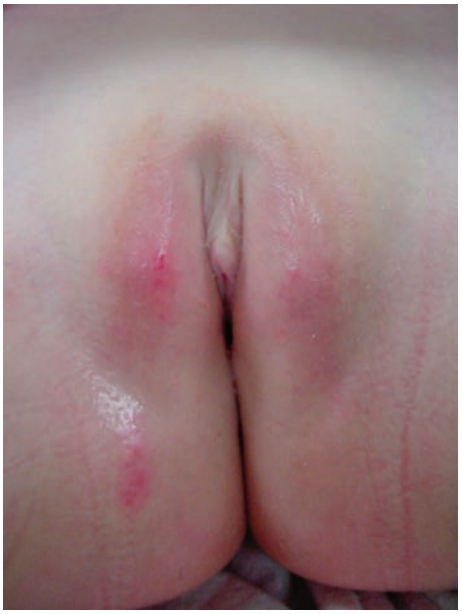

Figure 9.1 External vulvar excoriation from foreign body-related vaginal discharge.

Table 9.1 Vaginal discharge: organisms and etiologies[1,2,6,13–15,17]

Organisms	Sexually transmitted infections	Other etiologies for vaginal discharge
Group A β-hemolytic streptococci	*Chlamydia trachomatis*	Physiologic leukorrhea
Hemophilus influenzae	*Neisseria gonorrhoeae*	Vaginal foreign body
Staphylococcus aureus	*Trichomonas*	Ectopic ureter
Moraxella catarrhalis		Fistula
Streptococcus pneumoniae		
Neisseria meningitidis		
Shigella		
Yersinia enterocolitica		

Table 9.2 Other causes of genital bleeding in childhood

Vaginal foreign body
Genital trauma: inadvertent or deliberate
Neoplasm: polyp, hemangioma, sarcoma
Neonatal estrogen-withdrawal bleed
Premature menarche/precocious puberty
Urethral prolapse
Rectal or anal bleeding
Labial adhesions
Dermopathy: contact/allergic dermatitis, lichen sclerosis, eczema, psoriasis
Pinworms with excoriation from scratching

possibility of victimization (see Chapter 18). It is important, however, to realize that often the culprit organisms (Table 9.1) are those normally found in the lower gastrointestinal (GI) tract or in the upper respiratory tract and these organisms can be found in the vaginas of asymptomatic girls, making it hard sometimes to be certain of causation/etiology of the symptoms.[2–4] The close proximity of the anal verge to the vaginal introitus and the tendency for children to have some fecal residue left behind after wiping creates opportunity for colonization of the lower vagina. While the mechanism is not completely understood, anecdotally (and in this author's opinion) there is an association between constipation, straining with large stools, and recurrent vulvovaginitis.[5] Furthermore, without diligent guidance, many prepubertal girls will wipe from back to front, dragging bacteria toward the vaginal opening. Without good hand-washing and hygiene, the lower vagina can even become colonized with upper respiratory flora such as *Haemophilus influenzae*.[6,7] Even the household water supply used for bathing could be a source of bacteria.

While many care-givers assume that *Candida* spp. are the cause of discharge, pruritus, irritation, redness, etc., yeast infections are not nearly as common as they are during reproductive years.[1,2,7,8] Exceptions would include children who have been given recent antibiotics, children who are still in diapers, diabetics, and immunocompromised girls. With the best of intentions, parents or health-care providers who treat the child with topical antifungals may be exposing the child's genital skin to an irritant or allergen that can then worsen the external symptoms.

PHYSIOLOGIC LEUKORRHEA

Both the neonate and the peripubertal female who is just beginning to show signs of thelarche are estrogenized and thus can experience physiologic leukorrhea. This is typically a mucoid, clear or white vaginal discharge without odor, although some yellow staining can be present. When the health-care provider notes signs of secondary sexual development, reassurance and education may be all that is necessary, especially if the child is older than 7 years of age.

HISTORY AND EXAMINATION

When examining the child with a history of vaginal discharge, note should be made of the key features listed in Tables 9.3 and 9.4. If cultures are necessary, then it is important that they are representative of the vagina and not just the introitus or vulva. A fine 'calgiswab' wire swab (Figure 9.2) should be used to ensure that the sample can be taken without touching the hymeneal edges, which in childhood are exquisitely sensitive. To achieve this, two people may be necessary; one to perform gentle labial traction (Figure 9.3) and the other to pass the swab through the hymen after it gapes open (the technique is demonstrated on the vaginoscopy video on the CD). Alternatively, Pokorny describes a 'catheter-in-a-catheter' technique of acquiring vaginal irrigant aspirates without causing pain or discomfort to the child, who is probably already anxious.[9,10] The swab (or aspirate) is then placed in

Table 9.3 Vaginal discharge and foreign bodies: key elements of the history

- Duration
- Odor, color
- Associated symptoms: e.g. burning, itching
- Tendency to rhinitis or nose-picking
- Tendency to constipation, fecal straining
- History of foreign body insertion
- Direction or nature of wiping after toileting
- Diaper, antibiotics, diabetes, or other illness
- History of (or opportunity for) victimization
- Possible water supply contamination
- Signs of early puberty?

Table 9.4 Vaginal discharge and foreign bodies: key elements of the physical examination

- Frog-leg, straddle, or knee-chest position, labial separation and gentle traction (see Chapter 7)
- Presence of thelarche (or newborn) – i.e. suspect physiologic leukorrhea
- Nature of discharge
- Presence of visible erythema, excoriation, dermopathy
- Nature of hymen: size, shape, consistency of edge (see Chapters 7 and 18)
- Visualize at least the lower vagina for presence of foreign body
- Without touching hymeneal edges, swab *vagina* if required
- If hard foreign body is suspected, consider rectal exam
- If toilet paper fragment is suspected, consider vaginal irrigation
- If foreign body is strongly suspected, consider vaginoscopy (+/− EUA)

EUA, examination under anesthesia.

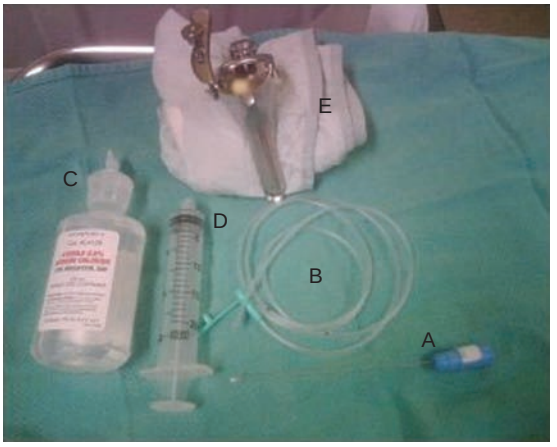

Figure 9.2 Narrow wire swab to sample vagina (A), pediatric feeding tube with sterile saline and syringe (B, C, D), and narrow, short pediatric speculum (E).

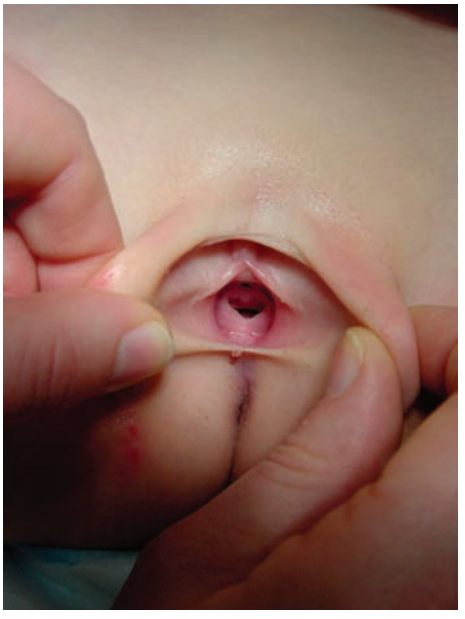

Figure 9.3 Technique of labial traction.

the usual vaginal culture media unless it is being sent for chlamydia or shigella testing, which requires distinct processing (contact the microbiology lab for instructions). Good communication with the microbiology lab is essential, otherwise they may just examine and plate the swab as if it were from a reproductive female; i.e. report only on the presence or absence of yeast, *Gardnerella* and *Trichomonas*. As already mentioned, there is a great deal of overlap in the flora found in asymptomatic versus symptomatic girls and infection with a single 'pathogen' is more likely when there is significant foul-smelling discharge and vulvar redness.[2] It is the opinion of the author that not all cases of first presentation of vaginal discharge require a culture swab but rather, organism identification is necessary when standard approaches to simple colonization vulvovaginitis (see treatment below) are unsuccessful or when a sexually transmitted infection is being considered. Similarly, when discharge fails to respond to treatment strategies, when it is blood-tinged or when it recurs despite diligent hygiene, a vaginal foreign body should be considered[11,12] and the physical examination should, as a minimum, include labial separation with visualization of the lower vagina, a rectal examination, and irrigation of the vagina (see also vaginoscopy under Management below).

The rectal examination can often be performed with the fifth or smallest finger or with the index finger properly lubricated and with explanation. Palpation anteriorly will usually identify the small firm cervix but also the presence of any rigid or hard foreign body. Fragments of toilet paper are common and sometimes can be flushed out of the vagina with a pediatric feeding tube hooked to a 20–30 ml syringe of *warm* sterile water or saline (Figure 9.2). The child should be shown that there are no needles and that this is just a 'squirt gun.' Again, the feeding tube (as with the swab or catheter described above), must be advanced through the hymen into the upper vagina without touching the edges and this often requires two people. When index of suspicion is high for vaginal foreign body, one may choose to proceed to vaginoscopy, which usually, but not always, will be done as part of examination under anesthesia (see below).

Table 9.5 Vaginal discharge and foreign bodies: key elements of management

- Daily tub soaks
- Treat constipation
- Strategic wiping after toileting
- Hand-washing before and after toileting
- Course of broad-spectrum antibiotic
- Vaginoscopy +/− EUA when indicated

EUA, examination under anesthesia.

MANAGEMENT (TABLE 9.5)

Because by far the most common cause of pediatric vaginal discharge is colonization of the lower vagina with fecal flora or upper respiratory flora, the initial approach is one of education and diligent hygiene. Daily tub soaks, strategic wiping (front to back or separately), hand-washing before and after toileting, with or without a 7-day course of a broad-spectrum antibiotic will usually suffice. Antibiotic choice will obviously depend on drug allergies but in the absence of such restrictions, amoxicillin or amoxicillin/clavulinic acid are good choices. They are dosed according to weight and come in flavored elixirs with various concentrations. Trimethoprim would be a good alternative in the case of penicillin allergy. If vaginal foreign body is still suspected despite the office/clinic strategies mentioned above, or if the child will not tolerate examination, then examination under anesthetic and vaginoscopy are indicated (Figures 9.4 and 9.5). The vaginoscopy may identify irregularities along the vaginal wall (local granular reddening or papillary reaction) suggestive of a recent foreign body that was spontaneously extruded.[11] (See the video of the vaginoscopy technique on the CD.)

OTHER VULVOVAGINAL PATHOGENS IN PEDIATRIC VULVITIS

Recurrent group A streptococci, shigella, and *Enterobius vermicularis* deserve special comment for their idiosyncrasies. Group A beta-hemolytic streptococcus can cause intense fiery red inflammation

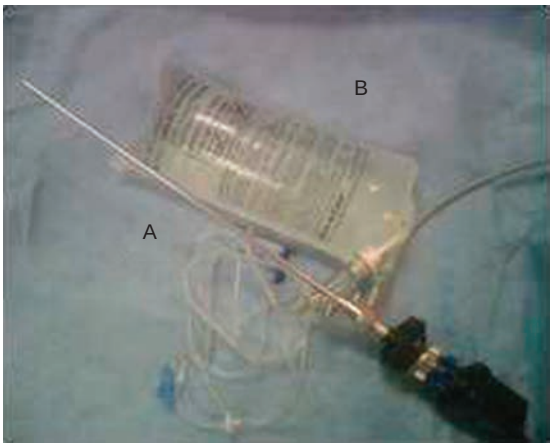

Figure 9.4 Vaginoscopy equipment: (A) ≤ 5 mm scope (hysteroscope, pediatric laparoscope or cystoscope), (B) normal saline or sterile water through IV tubing.

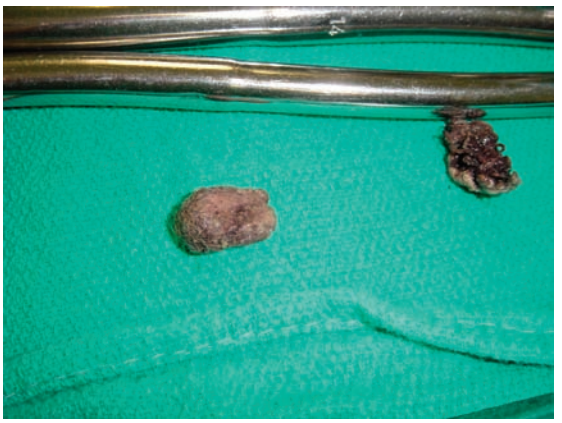

Figure 9.5 Vaginal foreign body (likely old toilet paper).

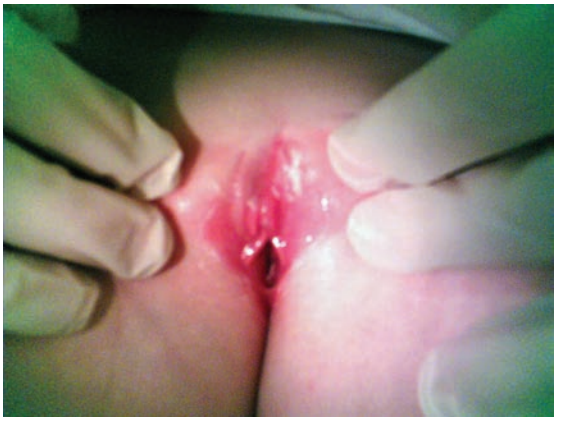

Figure 9.6 Intense erythema secondary to recurrent group A streptococcal vulvitis.

of the external vulva with or without vaginal discharge (Figure 9.6). The thin hypoestrogenic genital tissues can become so inflamed that surface bleeding can occur. Penicillin-based oral therapy usually suffices along with local care but azithromycin can be an alternative antibiotic when the child is allergic to penicillin. Coexistent or recent pharyngitis can be a clinical clue but is certainly not a prerequisite.[2,4,7,13–15]

While shigella can be a cause of bloody vaginal discharge, and while the child may also have bloody diarrhea, neither of these features are necessarily present. The astute clinician always considers shigella infection when standard routine approaches to presumed either nonspecific vulvovaginitis or hygiene-related 'colonization vaginitis' fail. As mentioned above, before acquiring a sample or swab, communication with the microbiology lab is recommended. Because shigella can be resistant to amoxicillin and trimethoprim-sulfamethoxazole (TMP-SMX), some are advocating quinolones or cefixime as first-line oral antibiotic therapy, but this is quite controversial and others argue that it should be reserved as second-line therapy for resistant organisms.[16–20]

Finally, *Enterobius vermicularis,* commonly known as pinworms, can be a cause of intense and extreme genital pruritus. Again, because the vulvar tissues in the hypoestrogenized child are very thin, scratching can create tissue breakdown and excoriation that leads to genital bleeding. Sometimes the worms are visible at the anal verge, but a 'tape test' is often used to make the diagnosis, whereby usually a pre-prepared commercially available sticky paddle is pressed against the anal verge early in the morning before the child awakens. The paddle is

then brought in for microscopy to see the ova. Treatment consists of washing all the linens in hot water, treating all household members with oral mebendazole (100 mg), and repeating the dose in 2 weeks.[21,22]

GENITAL TRAUMA (INADVERTENT/STRADDLE INJURY)

HISTORY AND EXAMINATION (TABLES 9.6 AND 9.7)

It is not uncommon for a child to fall and injure the vulva, labia, or introitus. Playground incidents (Figure 9.7),[23] cycling accidents, diving-board slips, and bath-tub falls are some of the well-recognized scenarios. The child falls with significant impact straddling a rigid object and traumatizes the genital tissues. Pain, swelling, and discomfort can be quite significant and the amount of bleeding can be minimal or quite impressive. Labia minora can be torn, there can be extensive bruising of the mons and vulva/labia majora (which may not appear until the following day), and the perineal body can be split (Figure 9.8). With very few exceptions,[10,24,25]

Table 9.6 Genital trauma: key elements of the history

- Take the history from adult and child separately
- Mechanism consistent with findings and plausible
- Other injuries possible?
- Loss of consciousness?
- Quantify blood loss/symptoms of blood loss
- Ongoing bleeding?
- Able to void? (Risk for bony pelvis fracture?)
- Degree of pain
- Any suggestion of penetration/violence/abuse (see Chapter 18)
- Anal sphincter at risk?

Table 9.7 Genital trauma: key elements of the physical examination

- Develop rapport, be gentle, be aware of significant anxiety of child and parent(s)
- Involve appropriate personnel if more global trauma or other injuries are suspected
- Vital signs – signs of volume depletion?
- Degree/pattern of bruising and swelling
- Ongoing bleeding?
- Expanding or large hematoma?
- Blood from upper vagina (or just pooling)?
- Urethral meatus spared
- Hymen/lower vagina spared?
- Anal verge torn/anal sphincter integrity?

Figure 9.7 Playground equipment with potential for straddle injury (chain-link tight-rope).

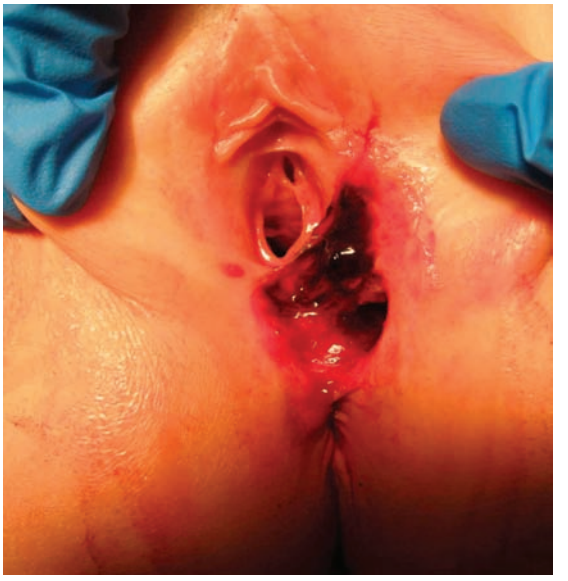

Figure 9.8 Straddle injury to the vulva. (Courtesy of Dr Diane Merritt, MD.)

the labial fat pads and the mons protect the hymen and vagina from injury and, thus, where tears of these tissues are found, consideration must be given to the possibility of a penetrating (and usually deliberate) injury. Similarly tearing of the anal verge should prompt assessment for abuse by an experienced and skilled care provider. The collection of forensic evidence may be necessary. On the other hand, where there has been significant bleeding while the child has been lying supine, blood can have pooled in the vagina giving the false impression of upper vaginal bleeding and injury. Health-care providers should try to create a non-threatening opportunity whereby the verbal child can recount the events, while parents or care-givers are offered the same opportunity but in isolation. The stories should be consistent and plausible. Chapter 18 addresses child sexual abuse. In terms of extent and severity of injury, the health-care provider should determine whether there was a loss of consciousness, whether any other injuries may have occurred, and whether there are any symptoms of significant blood loss. The ability to void is reassuring regarding urethral injury and integrity. In the female, the urethra is seldom seriously injured unless there are fractures of the anterior bony pelvis; however, swelling, stinging, and pain can preclude bladder emptying. Urinary retention may necessitate catheterization but may require some type of anesthesia or sedation to minimize the patient's trauma. Similarly, the anal sphincter integrity must be considered when taking the history and performing the physical examination. Simple inspection along with a reputable mechanism of injury will often be enough to reassure the health-care provider, but a digital rectal exam for anal sphincter tone can be helpful. Indications for examination under anesthetic are listed in Table 9.8. Obviously this section is not intended to discuss the approach to trauma as a whole but it should at least be mentioned that straddle injuries can occur as one small feature of a more major trauma such as a roadside accident, and the 'ABCs' take priority. Detailed expert reviews of genital trauma in the prepubertal female are provided in articles by Pokorny et al[10,25] and Merritt.[26]

Table 9.8 Genital trauma: indications for examination under anesthesia

1. Suspect penetrating genital injury:
   - for degree of injury and possible repair
   - for forensic/criminal processing/evidence collection (see Chapter 18)
2. Ongoing bleeding requiring hemostasis
3. Repair urethra or anus
4. Expanding hematoma
5. Child unable to tolerate exam or catheterization (when indicated)

Table 9.9 Genital trauma: key elements of management

- Reassurance
- Analgesics
- Ice packs
- Tub soaks or sitz baths
- Void in water if necessary (indwelling catheter if necessary)
- Reassure child and family
- Follow-up

MANAGEMENT OF GENITAL TRAUMA (TABLE 9.9)

The management of genital trauma, assuming inadvertent (usually straddle-type) injuries, involves an assessment of the various injuries and their nature and extent/severity as outlined above. The management of serious urethral injuries is described in the urological literature.[27–37]

In typical straddle injuries, analgesics are often indicated along with cold therapy to reduce swelling. Regular tub soaks and/or sitz baths several times per day are indicated and children will often be better able to void in the bath-tub where skin abrasions will not sting as much. Healing is usually quite impressive, leaving no sign of trauma except to the trained eye. Parents and children can therefore be reassured but follow-up is important. Often parents are concerned about their daughter's future reproductive and sexual function, but with very few exceptions, they can be fully reassured.

HYMENEAL OR VAGINAL POLYPS (FIGURE 9.9)

These benign 'skin tags' will usually be identified in the neonate or newborn. At birth, polyps tend to be

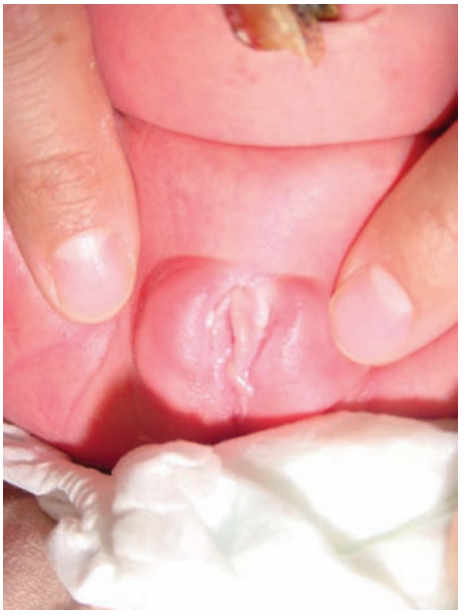

Figure 9.9 Regressing hymeneal polyp in 2-week-old newborn (now thinner than originally).

smooth and resilient from the recent maternal, placental, and even fetal ovarian estrogen exposure. It is not until the effects of estrogen regress that the polyp is left friable enough to be a cause of genital bleeding (1–2 months of life). Merely the contact with the diaper itself or urine and stool can lead to bleeding, which while usually scant, can be a source of great distress for parents. Reassurance and possibly a barrier type of cream or ointment can prevent further bleeding until the polyp atrophies and vanishes. The diagnosis is made on physical examination, with labial traction confirming the tag to arise from the lower vagina or the hymen. Follow-up will help to reassure the parents and to confirm the diagnosis, as regression will surely occur.

HEMANGIOMA OF THE VULVA/VAGINA

The most common type of hemangioma seen in the vagina or on the vulva is the cavernous hemangioma often referred to as a 'strawberry mark.' This benign cluster of vessels is often not visible at birth but rather enlarges over the first year of life. The natural history usually results in regression by the age of 10 (if not sooner), leaving either no residual marking or a bruise-like discoloration. The skin overlying the hemangioma can break down under tension and this can result in ulceration and/or bleeding as well as a vulnerability to infection. Barrier-style protective cream and reassurance are often all that is necessary, as major bleeding is rare. In cases of extreme symptoms, treatments tried have included corticosteroids, laser, embolization, and excision.[38–46]

RHABDOMYOSARCOMA OF THE LOWER GENITAL TRACT

Unfortunately malignancies do occur in the vagina of prepubertal girls and the most common is sarcoma botryoides or embryonal rhabdomyosarcoma. This tumor will often present with vaginal bleeding but can cause discharge, abdominal pain, or a prolapsing grape-like (multicystic) mass at the introitus (or urethra). Peak incidence is in childhood and in particular under the age of 5, although exceptions do occur. The diagnosis is made by examination under anesthesia and biopsy. Fortunately cure/survival has improved significantly over the past few decades (approximately 90% when disease is local). In addition, the morbidity from treatment has been reduced through combination therapy involving chemotherapy (e.g. vincristine, actinomycin D, and cyclophosphamide) and conservative surgery, followed by radiotherapy for residual disease.[47–50] Given the much subspecialized nature of these malignancies and the unique issues that they present, work-up and management should probably occur in a center with the appropriate expertise and resources.

NEONATAL ESTROGEN-WITHDRAWAL BLEEDING

The female fetus is exposed to maternal, placental, and even endogenous ovarian estrogen production

the hypothalamic-pituitary (ovarian (HPO) axis is active *in utero*) and as such, the uterine endometrium can proliferate enough to be a source of bleeding in the newborn as estrogen levels fall. This is often referred to as a 'mini-period' in an attempt to describe the mechanism. This diagnosis should only be made if the baby girl is 1–4 weeks of life, if the episode of bleeding is no more than a couple of days in duration, and if there is no recurrence thereafter. Other causes of genital bleeding must be considered if any of these criteria are not met. Reassurance is all that is necessary if the diagnosis is certain and the presentation is consistent.

URETHRAL PROLAPSE (TABLE 9.10)

A condition of the prepubertal child (or the postmenopausal woman), urethral prolapse tends to occur in hypoestrogenized females and more often in children of African descent.[51] Those who experience repeated valsalva such as would accompany chronic constipation, an upper respiratory infection or cough, and urinary tract infection are particularly at risk. The mucosa from the distal urethral lumen prolapses beyond the meatus, resulting in a beefy red ring of friable tissue that can bleed easily (Figure 9.10). Other than symptoms of the above-mentioned predisposing conditions, urethral prolapse itself can cause dysuria, hematuria, genital bleeding, and even urinary retention. The diagnosis is made on physical examination using labial traction and if necessary a moistened cotton swab to elevate the tissue and confirm that it is arising from the urethral meatus (as opposed to the vagina).

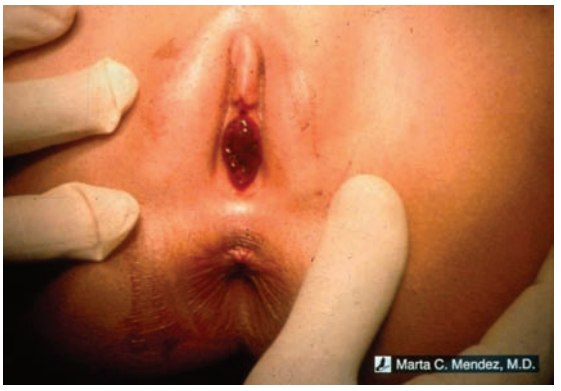

Figure 9.10 Urethral prolapse. Reproduced from the NASPAG teaching slide set, 1st edn, with permission.

Table 9.10 Urethral prolapse: key elements

History
• Recurrent valsalva: UTI, constipation, URTI/cough
• Blood staining in undergarments
• Dysuria, hematuria, urinary retention
Physical examination
• Ring or 'bud' of beefy friable red tissue
• Arising from urethra (moistened cotton swab to elevate)
Management
• Local care: tub soaks and sitz baths
• Eliminate need for valsalva
• Topical estrogen twice daily until regression
• Analgesics
• Surgical excision under anesthesia when conservative/medical therapy fails or when recurrent

UTI, urinary tract infection; URTI, upper respiratory tract infection.

Management is somewhat controversial, especially in children who experience recurrence(s) but first-line conservative therapy includes treating the cause of valsalva, local tub soaks or sitz baths, analgesics, and topical estrogen cream.[51–55] Some authors report also using hexachlorophene soap and topical proviodone.[55]

Surgical treatment should be considered for severe cases and cases of recurrence, and this involves excising the redundant prolapsing tissue and re-anastomosing the distal non-exposed urethral mucosa with the peri-meatus vestibular epithelium. Fine absorbable suture should be used followed by short-term indwelling catheterization. The procedure necessitates anesthesia and carries risks of bleeding, urethral stenosis, and recurrence.[56,57]

PREMATURE MENARCHE AND PRECOCIOUS PUBERTY

Vaginal bleeding in childhood should always prompt examination for signs of secondary sexual

characteristics. If present, puberty and menarche – whether precocious or just unexpected – are the likely cause. For a more detailed discussion of these entities, see Chapter 3.

LABIAL ADHESIONS (TABLE 9.11)

In the absence of estrogenization, the labia minora can become agglutinated either partially or completely. Symptoms include genital irritation and scant genital bleeding, post-void urinary dribbling, perceived or real urinary tract infections, and even urinary retention. While irritant exposure can be a causative factor, in some children the mere opportunity for the labia to lie in apposition for prolonged periods is enough to allow adhesions to form. Because urine is trapped in the vestibule allowing prolonged exposure of these vulnerable tissues, inflammation can result causing the irritation and blood staining. On physical examination there will be a fine and usually faint white, translucent or gray line representing the site of agglutination of the labia minora (Figure 9.11). As opposed to congenital fusion, the adhesions are not present at birth (estrogenization present), although many parents will believe that the 'labia/genitals have always looked like that'. Similarly, congenitally fused labia represent a spectrum of ambiguous genitalia (or cloacal defects) and with few exceptions there will be some degree of scrotalization of the 'vulva' or 'clitoromegaly' (Figure 9.12), which is not present

Table 9.11 Labial adhesions: key features

History
- Urinary symptoms: post-void dribbling, UTI symptoms, retention
- Genital irritation or scant bleeding
- Parents may have noticed 'no opening'

Physical examination
- White or gray vertical line
- No ambiguity to genitalia
- Excoriation or inflammation (causative vs secondary from urine exposure vs primary dermopathy)
- Labial traction to expose any gap in adhesions

Management
- Observation (prevent progression) if asymptomatic
- Topical estrogen cream with gentle traction if almost complete and/or symptomatic
- Manual separation
  - when urinary retention or
  - if symptomatic and topical estrogen fails

UTI, urinary tract infection.

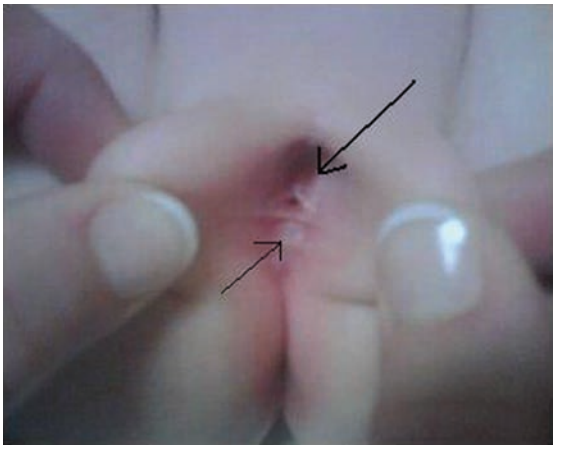

Figure 9.11 Labial adhesions/agglutination in an 11-month-old child (short arrow) with anterior small opening (long arrow) that allows urine to escape.

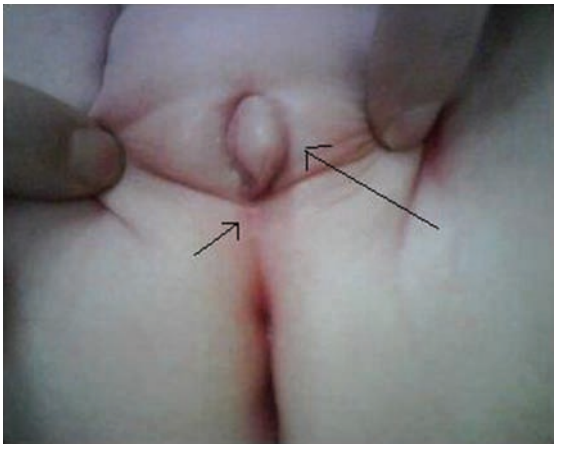

Figure 9.12 Congenital labial fusion (short arrow) in 2-month-old female with ambiguous genitalia secondary to partial 21-hydroxylase deficiency. Note clitoromegaly (long arrow).

with the acquired labial adhesions. Gentle labial traction will expose any defect where labia remain separate (Figure 9.11) but this is not the urethral meatus. Rather, this is the only point where the labia are not adherent and in behind lie the vestibule, hymen, urethra, and lower vagina. Again, as opposed to congenital ambiguous genitalia, the clitoris will be of normal small size. The outer vulva may show signs of inflammation, erythema, or excoriation because of repeated exposure to urine (post-void dribbling into undergarments). In cases where excoriation is marked, one should consider lichen sclerosis or irritant/contact dermatitis, which can result in secondary adhesions (Chapter 10).

When symptomatic, labial adhesions can be treated with topical estrogen cream nightly (or twice daily) along with gentle traction.[58] Parents should be shown the line of agglutination and instructed to apply a thin layer of the cream to that particular area to maximize efficacy and minimize systemic exposure. Prolonged topical and systemic exposure to estrogen can result in labial pigmentation and breast buds/tenderness. Betamethasone may be an alternative but a retrospective chart review included courses of treatment ranging from 4 to 6 weeks and did not include a no-treatment group.[59] It is generally accepted that some cases of labial adhesions will resolve spontaneously. It is important to try to identify any possible irritant or allergen exposures and eliminate them (see Table 9.12). It is also important to teach the child, and/or the parents, diligent surveillance with routine labial separation to avoid recurrence. Sometimes a bland barrier type of cream will reduce the likelihood of recurrence. When asymptomatic, parents need only be educated to routinely inspect the labia with gentle separation a couple of times per week to prevent progression and therefore reduce the likelihood of resultant symptoms. In the case of urinary retention, or when topical estrogen fails and the child is symptomatic, manual separation with some form of sedation or with some form of anesthesia should be performed.[60–63]

CONTACT/IRRITANT (OR ALLERGIC) VULVAR DERMATITIS (VULVITIS) (TABLE 9.12)

A prepubertal child's genital epithelium is particularly sensitive and vulnerable to inflammation/erythema and excoriation when it is exposed to chemical or synthetic agents. Even moisture, heat, and urine can result in symptoms such as burning, stinging, soreness, redness, or pruritus. With repeated exposure, skin can break down enough to cause scant bleeding. While other primary dermopathies such as lichen sclerosis, eczema, psoriasis, and lichen planus should be considered (see Chapter 10), a meticulous history will often reveal irritative contacts. Well-recognized contributors include: bath products, laundry products (residue in undergarments), urinary incontinence, nighttime incontinence products, chlorine, tight-fitting moisture-trapping athletic clothing, non-cotton undergarments (and in reproductive women, panty-liners and thongs).

The physical examination usually reveals a symmetrical bilateral vulvar erythema. There can be some lichenification from repeated rubbing or scratching and the skin can show microabrasions and cracking.

Management involves identifying and eliminating the 'culprit', daily tub soaks, and occasionally a low potency topical corticosteroid ointment once or twice daily short term.[64] Parents should be educated

Table 9.12 Contact or irritant vulvitis: key elements

History
- Exposure to urine or incontinence products, chlorine, moisture, heat, bath products, laundry products, etc.
- External vulvar burning, stinging, soreness, redness, pruritus
- Blood staining in undergarments
- Activities and clothing that trap heat, sweat, and moisture

Physical examination
- Usually symmetrical external vulvar erythema, excoriation +/– lichenification

Management
- Identify and eliminate irritant
- Local care: tub soaks and sitz baths
- Possible low potency corticosteroid ointment

with the following list of strategies for genital care in childhood:

- daily tub soaks without bath products
- no need for soap on genitalia
- shampoo in shower or standing up in tub at end of bath time
- cotton undergarments – double rinsed
- avoid remaining in wet bathing suits – rinse chlorine from genital skin.

EXAMINATION UNDER ANESTHESIA AND VAGINOSCOPY

While there are a number of causes of genital bleeding, as described above, it is this author's opinion that care providers should have a low threshold for performing examination under anesthesia and visualization of the entire vagina (vaginoscopy). Especially when the diagnosis is unclear or when bleeding recurs, it is important to eliminate the possibility of a foreign body or a lower genital tract lesion such as hemangioma, polyp, or the far more sinister rhabdomyosarcoma. While this latter malignancy is quite rare and while it is not discussed in detail in this chapter, it can present with genital bleeding and must be ruled out. To perform vaginoscopy, one can use an otoscope, a narrow but fairly long nasal speculum or a hysteroscope (Figures 9.2 and 9.4). The latter uses sterile saline and IV tubing as distension media and the labia are squeezed together around the shaft forming a seal. (See the video of vaginoscopy technique on the CD.)

SUMMARY

Vaginal discharge is quite common in childhood and is often the result of colonization of the lower vagina with fecal or upper respiratory tract flora. Diligent hygiene and local care strategies with or without a course of broad-spectrum oral antibiotics will often result in resolution of the symptoms. When these conservative strategies fail to treat the symptoms, one should consider: bacterial antibiotic drug resistance or an unusual organism (such as shigella), a sexually transmitted infection, or a vaginal foreign body. While the genital tissues in childhood are quite fragile and vulnerable to irritation, vaginal bleeding in childhood always warrants a careful assessment. While simple inflammation, vulvovaginitis, or a vaginal foreign body as described above can cause bleeding or bloody discharge, consideration must be given to: genital trauma (deliberate or accidental), neoplasms, premature menarche, dermopathies or excoriation from scratching, urethral prolapse, and labial adhesions with inflammation. Labial traction with the child in the frog-legged position will usually suffice, but when cultures are necessary they should be obtained with minimal discomfort and without touching the hymeneal edges. While most children can be assessed adequately in the clinic or office setting, some will require examination under anesthesia and some will require vaginocopy.

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10. Basic dermatology in children and adolescents

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Dermatologic conditions are commonly encountered in all areas of medicine. This chapter discusses the more frequent skin diseases that may be seen in the adolescent. When discussing clinical features of skin disease, it is important to accurately describe the lesion or rash; a brief overview of the descriptive terms used in dermatology is given in Table 10.1.

DIAPER DERMATITIS AND INFLAMMATORY DERMATOSES

Diaper (nappy) dermatitis can be a persistent and difficult problem in the pediatric outpatient setting; it is estimated that around 50% of infants will develop this condition. The more common causes of diaper dermatitis often have other associated clinical findings that may or may not be directly related to the inflammation in the diaper area; these other manifestations are also covered in the following section. Other common inflammatory dermatoses that may present in the groin or other areas of the skin are also discussed.

CONTACT DERMATITIS

Contact dermatitis can essentially be divided into two categories: allergic contact dermatitis and irritant contact dermatitis. These two entities and their distinctive characteristics are discussed in the following section.

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis (ACD) is an acute inflammatory skin reaction that can result from a number of different allergens. The exact incidence of allergic contact diaper dermatitis is unknown, but it is estimated that at any given time, between 7% and 35% of the infant population may be affected.[1] Numerous antigens may be implicated in causing ACD of the diaper area including: dyes, fragrance, rubber compounds, and barrier creams.[2,3]

ACD presents as acute onset of well-demarcated erythematous papules and plaques, often with the presence of small, clear fluid-filled vesicles. The vesicles may erode and ooze, eventually evolving into more eczematous plaques with lichenification. It is important to note that during the initial sensitization phase, the rash may not become apparent until 5–7 days after contact with the antigen. Upon re-exposure to the antigen, the rash will typically appear 12–24 hours after contact.[4]

ACD can occur in areas besides the groin, and distribution of the rash is a useful clue in diagnosing ACD. Rashes localized to specific parts of the body (i.e hands, feet, earlobes) or rashes that have discrete shapes (Figure 10.1) and sharply demarcated borders prompt a consideration of ACD.

Identification and removal of the inciting antigen is of paramount importance in treating ACD. For ACD in the diaper area, this can be done by changing diaper brands, wipes, and barrier creams to see if relief is obtained. Patch testing can be done in a dermatologist's office for severe cases where an etiologic agent cannot be easily identified. Although quite useful, this type of allergy testing may not be practical in the infant patient.

For symptomatic relief, topical low potency corticosteroids such as desonide 0.05% cream or ointment may be applied twice daily for 2–3 weeks. Of note, some patients may experience an allergic

Table 10.1 Descriptive terms used in dermatology

Configuration	
Annular or circinate	Ring-shaped, often with an area of central clearing
Confluent	Lesions that merge
Discrete	Lesions that remain distinct and separated
Clustered or herpetiform	Groupings of lesions that are similar in morphology
Guttate	Drop-like
Linear	Occurring in a line
Umbilicated	Lesions that have an area of central depression or a 'dell' in the central portion
Primary lesions	
Macule	A flat, nonpalpable area of less than 1 cm in diameter that appears different from the surrounding skin
Patch	A flat, nonpalpable area of greater than 1 cm in diameter that appears different from the surrounding skin
Papule	An elevated, palpable, circumscribed lesion that is less than 1 cm in diameter
Plaque	An elevated, palpable, broad lesion that is greater than 1 cm in diameter
Nodule	An elevated, palpable, solid lesion less than 2 cm wide with a deeper component that may extend into the dermis or subcutaneous tissues
Tumor	An elevated, palpable, solid lesion greater than 2 cm wide with a deeper component that may extend into the dermis or subcutaneous tissues
Wheal	A pink to red edematous, inflamed, elevated lesion, often with central clearing
Vesicle	An elevated lesion less than 1 cm in diameter that is fluid-filled
Pustule	An elevated lesion less than 1 cm in diameter that is pus-filled
Bulla	An elevated lesion greater than 1 cm in diameter that is fluid-filled
Abscess	An elevated lesion greater than 1 cm in diameter that is pus-filled
Secondary lesions	
Crust	Dried serum, blood, or exudative remains on the surface of a lesion
Scale	Desquamated corneocytes that have been shed onto the surface of a lesion
Fissure	A linear cleavage in the skin
Erosion	Superficial loss of the epidermis and/or portion of the dermis that leaves denuded skin
Ulcer	A deeper loss of the epidermis and dermis, and sometimes portions of the subcutaneous tissue
Excoriation	Superficial loss of skin, often due to scratching or trauma
Lichenification	Thickening of the epidermis with enhanced skin markings from chronic rubbing of the lesion
Color	
Erythematous	Red
Violaceous	Purple
Sclerotic	Scar-like, often having a shiny white to pink appearance

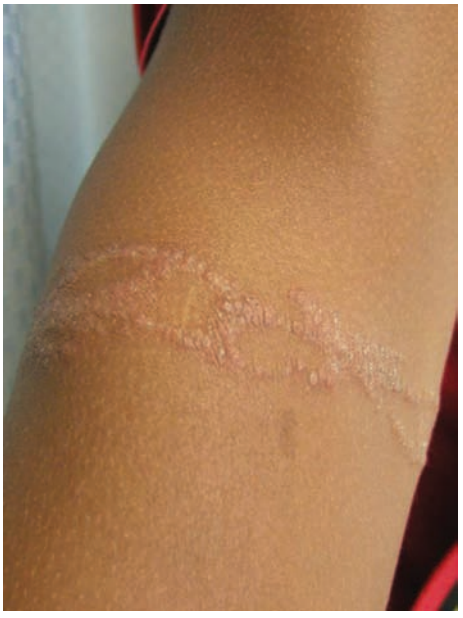

Figure 10.1 Allergic contact dermatitis to para-phenylenediamine, a dye component, in a henna tattoo manifests as a discrete shape.

reaction to certain components of the topical steroids; this is an important consideration if the expected relief is not obtained. Additionally, barrier/repair creams may be effective in expediting healing of affected areas.

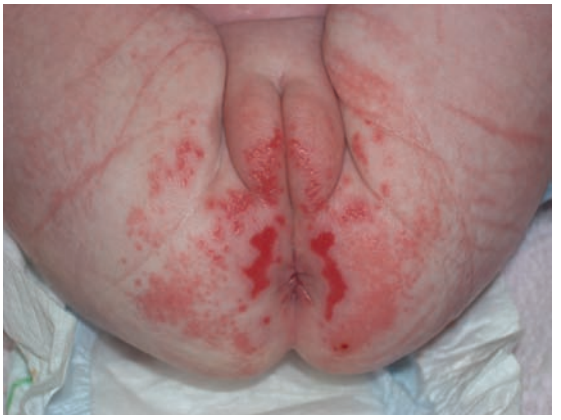

Figure 10.2 Irritant contact diaper dermatitis with erythematous plaques and erosions.

IRRITANT CONTACT DERMATITIS

Irritant contact dermatitis (ICD) of the diaper area is a non-immunologic reaction to various irritants in the diaper environment including urine, feces, and chemicals. As opposed to the immunologic basis of allergic contact dermatitis, ICD results from the direct toxic effect of these agents on the skin. ICD can be exacerbated by friction, occlusion, moisture, cracks or fissures in the skin, and cleansing wipes.[4]

ICD can be difficult to clinically distinguish from ACD. Typically, there are discrete areas of erythema that have a glazed appearance and may be surrounded by erythematous papules. ICD is most evident in the convex areas of skin that are exposed to the offending agent; the inguinal folds are usually spared. ICD can occur in areas other than the groin/genital area; for example, peri-oral ICD eruptions sometimes result from oral secretions (saliva or food).

The absence of clear, fluid-filled vesicles as seen in ACD steers the clinician towards a diagnosis of irritant dermatitis; however, blistering and erosions may be seen in severe cases (Figure 10.2). The presence of punched out erosions is characteristic of Jacquet's erosive diaper dermatitis (Figure 10.3). Granuloma gluteale infantum is another form of

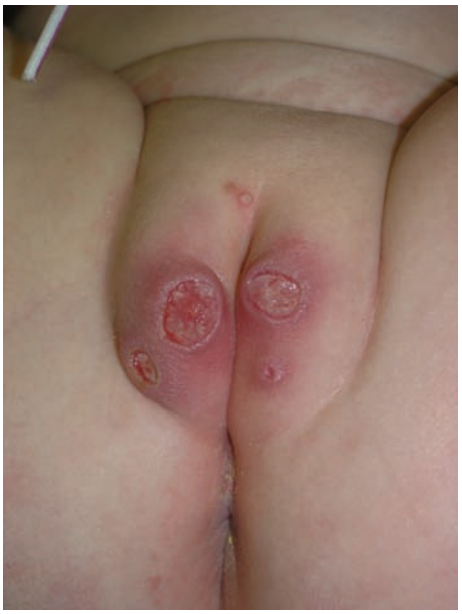

Figure 10.3 Jacquet's erosive diaper dermatitis presenting as characteristic erythema with punched out erosions.

severe ICD that usually presents in the first year of life[5] as oval reddish-brown or reddish-purple nodules or plaques varying from 0.5 to 3 cm.

As with ACD, the best treatment is prevention. Frequent diaper changes will minimize irritation from moisture and feces in the diaper area. The use of barrier creams with pure zinc oxide and no fragrances will help prevent recurrences.

INFLAMMATORY DERMATOSES WITH INFECTIOUS ETIOLOGIES

CANDIDIASIS

High levels of *Candida albicans*, a common yeast, may be found in skin with diaper dermatitis and may cause acute or chronic infection of the skin or the mucous membranes. *C. albicans* is not a normal cutaneous saprophyte but exists in the microflora of the vagina. Certain systemic medications (antibiotics, corticosteroids, immunosuppressives) as

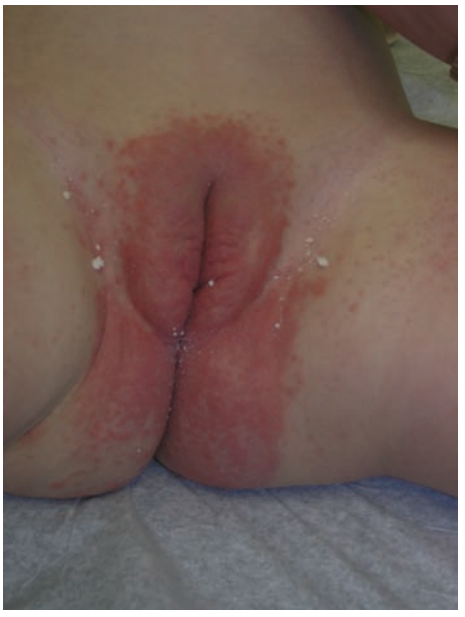

Figure 10.4 Candidal diaper dermatitis presents with bright red papules coalescing into plaques and satellite pustules at the periphery. Note the involvement of the intertriginous folds.

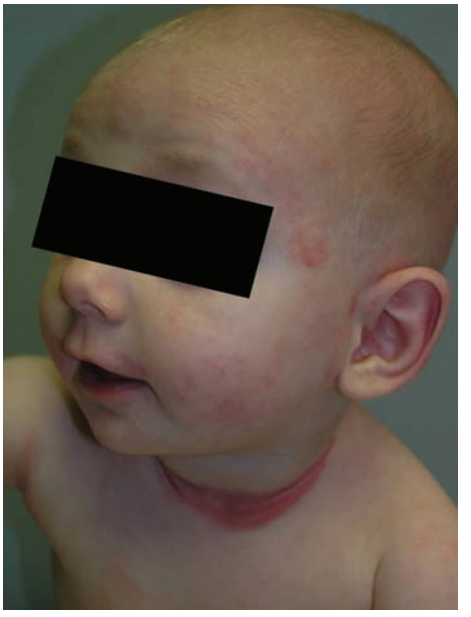

Figure 10.5 Intertrigo in the neck of an infant shows macerated erythematous plaques.

well as the moist and warm environment of the diaper area can alter the normal flora, making infants more susceptible to candidal overgrowth.

The presence of bright red papules, satellite pustules, beefy red plaques, and scales are characteristic of infection with *C. albicans* (Figure 10.4). As opposed to ACD and ICD, candidal infection will often involve the intertriginous folds. In children, other presentations of candidiasis include oral candidiasis, vulvovaginitis, angular chelitis (perleche), and paronychia (nail infection). A potassium hydroxide (KOH) wet-mount can confirm the presence of *Candida.*

Intertrigo refers to an inflammatory disorder of the skin that is often secondarily infected with *Candida*; this occurs in areas of skin-to-skin contact, known as the intertriginous areas, such as the neck in infants, axillae, and groin (Figure 10.5). The combination of friction in a moist and warm environment causes inflammation to occur, resulting in macerated erythematous plaques in these areas.

Candidal diaper dermatitis and intertrigo are most effectively treated with a topical antifungal cream such as spectazole, nystatin, or clotrimazole applied after diaper changes. Frequent changing of diapers and dusting powders such as Zeasorb will also aid in preventing excess moisture in the diaper area. For immunocompromised children or widespread infections, oral antifungals such as fluconazole may be needed. For cases with severe inflammation, a low potency topical corticosteroid is indicated. For candidal vulvovaginitis, antifungal vaginal tablets or creams such as clotrimazole or miconazole may be used daily for 3–7 days. Fluconazole 150 mg is also effective as an oral, single dose for adolescents.[6]

TINEA

Superficial fungal infections can occur anywhere on the skin, including the groin (tinea cruris). Tinea

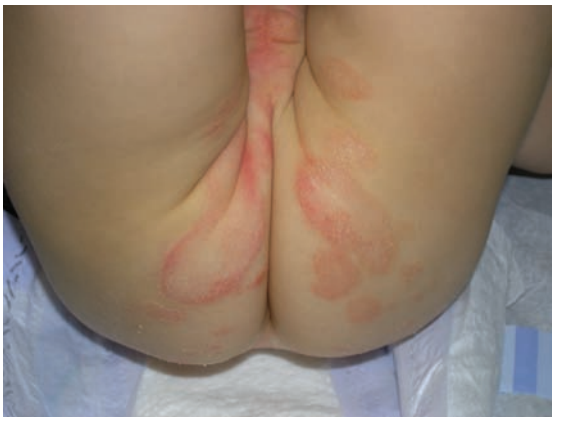

Figure 10.6 Tinea cruris demonstrating the classic findings of scaly erythematous plaques with central clearing.

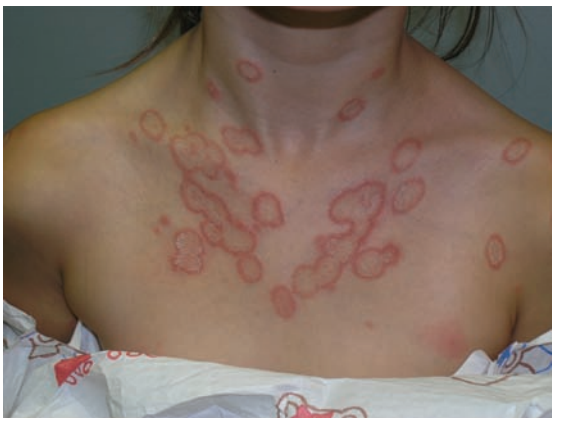

Figure 10.7 Tinea corporis with characteristic polycylic annular scaly erythematous plaques with central clearing.

can be caused by a number of different pathogens and presents with scaly erythematous plaques, often with central clearing (Figures 10.6 and 10.7). The plaques can vary in size from less than 1 cm to greater than 10 cm. They are often asymptomatic.

Most uncomplicated superficial fungal infections can be treated with a topical antifungal agent. For complicated or widespread infections, a systemic antifungal such as terbinafine, fluconazole, or

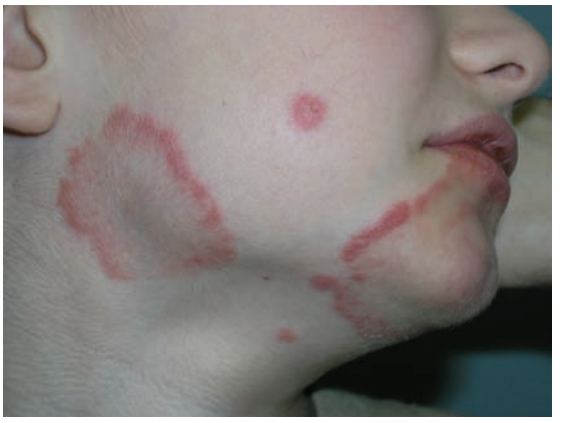

Figure 10.8 Majocchi granuloma (fungal infection of the hair follicles) following treatment of a superficial fungal infection with betamethasone, a topical steroid, for 1 year; note the degree of erythema and inflammation.

itraconazole may be indicated; however, these agents have not been extensively studied in the neonate and pediatric populations.[7] Topical or systemic corticosteroids should never be used either alone or in preparations with topical antifungal agents to treat superficial fungal infections, as these preparations can exacerbate the infection or result in fungal infection of the hair follicles (Figure 10.8).

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is an erythematous scaly eruption that typically occurs in the infant and adolescent age groups. The pathogenesis is likely related to increased sebum production and a hypersensitivity reaction to the presence of the *Malassezia* species of yeast.

In infancy, seborrheic dermatitis usually appears during the first month of life. Affected infants will have thin, scaly, yellow to erythematous, greasy plaques on the scalp, face, or diaper area. Adolescents with seborrheic dermatitis present with varying degrees of erythema and dry to greasy scale, classically involving the scalp, face, chest, or back. Many adolescent patients will complain of typical symptoms of dandruff: mild to moderate pruritus

and irritation of the scalp along with desquamation leading to flakes of skin in their hair and on their clothing. Diagnosis is made clinically and may be confirmed with a KOH scraping from the affected area.

Infantile seborrheic dermatitis often resolves spontaneously. For more persistent cases, topical antifungals are effective. If there is significant inflammation, a low potency corticosteroid such as hydrocortisone 1% may be used. Baby oil can be applied to help loosen any adherent scale before shampooing. Adolescents with seborrheic dermatitis are effectively managed with antiseborrheic shampoos or washes containing ingredients such as ketoconazole, zinc, sulfur, salicylic acid, or tea tree oil. If there is significant inflammation and pruritus, topical corticosteroids of low to mid potency may be added.

PERIANAL STREPTOCOCCAL DERMATITIS

Perianal streptococcal dermatitis (PSD) is an infection seen in the diaper area caused most commonly by group A beta-hemolytic streptococci (GABHS), Gram-positive bacteria. The mean age of onset is 4.25 years. The incidence of PSD ranges from 1 in 2000 to 1 in 218[8] of pediatric outpatient visits. Transmission among family members and in day-care settings has been reported.[9,10]

PSD presents as a well-defined plaque, which can vary in appearance from a dry pink plaque to a bright red moist erythema. Affected infants and children may have tenderness and sensitivity of the area, rectal pruritus and discomfort, blood-streaked stools, and constipation. Guttate psoriasis, classically associated with streptococcal pharyngitis, can be related to PSD, therefore, a thorough anogenital exam should be performed in infants and children presenting with skin findings of guttate psoriasis (discussed below). Diagnosis is made clinically, and a culture or rapid strep test can be used to confirm the diagnosis.

Oral penicillin V is the treatment of choice for PSD; erythromycin or other macrolides may be used in penicillin-allergic patients, but close attention to regional resistance patterns is recommended, since certain areas of the US have large percentages of streptococcal isolates that have become resistant to macrolide antibiotics. In these areas, clindamycin is a more appropriate second-line therapy for streptococcal disease. Cephalosporins are also effective in treating streptococcal infection.[11] Treatment duration should be at least 14 days.[9] Topical mupirocin may be used in conjunction with the oral antibiotics.

Patients with PSD should be monitored for signs and symptoms of post-streptococcoal glomerulonephritis, including edema, hypertension, and tea-colored urine. Medical history and physical exam should include thorough examination of the pharynx to identify possible coexisting pharyngitis.

OTHER INFLAMMATORY DERMATOSES OF THE GROIN

LICHEN SCLEROSUS

Lichen sclerosus (LS) is a T-lymphocyte-mediated chronic inflammatory condition that has bimodal peak incidence in female patients: prepubertal and postmenopausal. Of the prepubertal cases, most have an onset before age 7. Prevalence rates are estimated at 1:300 to 1:1000 based on referrals to dermatology.[12] The exact cause of LS is unknown; there is a noted association with autoimmune diseases such as alopecia areata, vitiligo, thyroid disease, and pernicious anemia. However, it is not recommended to screen for these disorders unless other clinical findings raise suspicion. Koebnerization occurs with friction or rubbing of the affected area.

On physical exam, white to pink, slightly elevated, flat-topped papules coalesce into plaques; scarring, atrophy, and follicular plugging can develop within the plaques. Telangiectasias, excoriations, and purpura may also be noted (Figure 10.9). LS is characterized by irritation, bleeding, pruritus, dyspareunia, and dysuria. The course waxes and wanes with episodic flares. It classically involves the genital area, although any area of the skin may

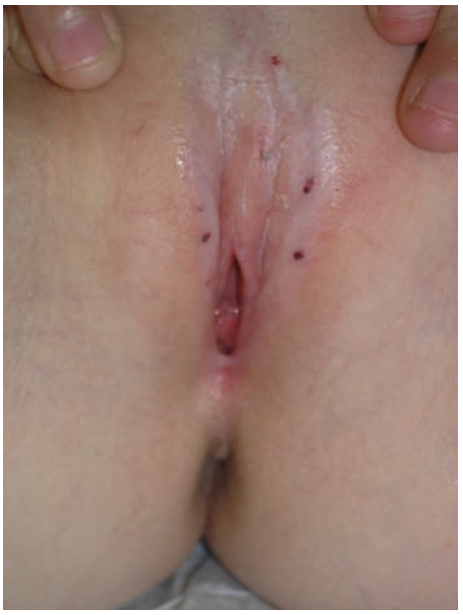

Figure 10.9 Hemorrhagic lichen sclerosus demonstrating the classic sclerotic and porcelain appearance along with telangiectasias and hemorrhage.

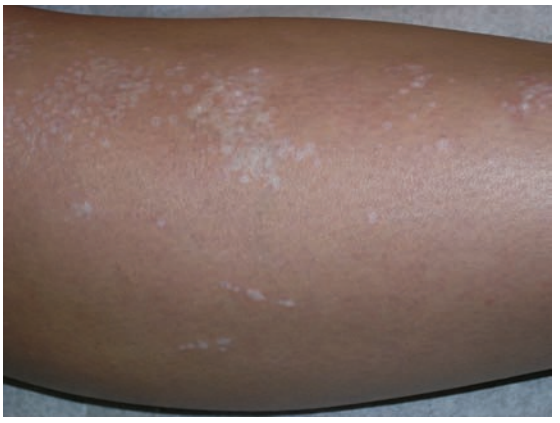

Figure 10.10 Lichen sclerosus of the leg.

be affected (Figure 10.10). Diagnosis is made clinically; however, a biopsy may be needed to confirm the diagnosis in some cases. Other diseases that present with similar symptoms include lichen planus, discoid lupus, morphea, vitiligo, and Bowen's disease.

The goals of therapy are alleviation of symptoms and prevention of complications such as scarring. LS in premenarchal and adolescent girls is effectively treated with ultrapotent steroids such as clobetasol propionate 0.05% cream or ointment[13] twice a day for 4–6 weeks. Pimecrolimus and tacrolimus ointments, both steroid-sparing agents, have also been effective in treating this process[14] but tend to be more effective maintenance agents once a higher potency topical steroid has been used to quiet the acute flare. Scarring may need to be corrected surgically if medical therapy fails. In adolescents (and adults) with chronic, long-standing LS, there is an association with squamous cell and verrucous carcinoma, and proper screening is of great importance. Children with LS who are properly treated have no similar predisposition towards neoplasia.

PSORIASIS

Psoriasis is a chronic papulosquamous disorder that can present in the diaper area as well as other areas of the skin. It is immune-mediated and is driven by both genetic and environmental factors. Koebnerization may be seen and is postulated in causing psoriasis to appear in the diaper area of infants. Other triggering factors can include friction, yeast overgrowth, surgical procedures, and sunburn, among others.

Lesions start as small red papules, which enlarge to form pink to erythematous thick plaques with silvery scale (Figure 10.11) ranging in size from less than 1 cm to greater than 10 cm. The classic distribution is on the extensor surfaces (as opposed to the flexural surfaces in atopic dermatitis); however, lesions can occur anywhere on the body including the genital region. Psoriatic lesions in the genital region of infants may lack the classic surface scale due to the moist nature of this area. Patients may also have symptoms of geographic tongue, nail pitting or dystrophy, or arthritis. Psoriasis is usually

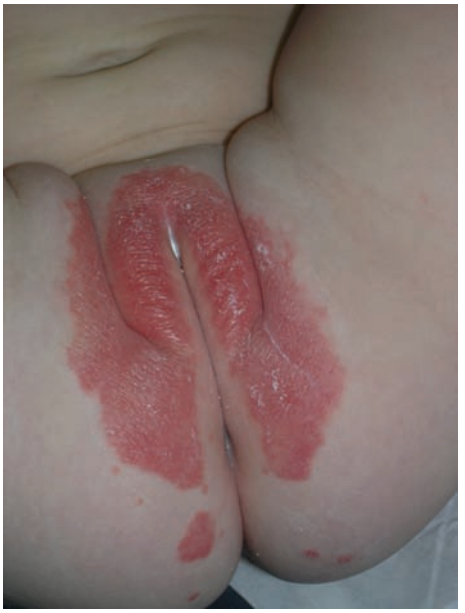

Figure 10.11 Psoriasis of the diaper area shows thick pink and erythematous plaques with scale.

not pruritic. Guttate psoriasis is a particular subtype that manifests as drop-like 1–2 cm scaly red plaques and often occurs after streptococcal infection of the oropharynx or perianal area. It is important to screen for asymptomatic streptococcal pharyngeal infection with culture and ASO titer, as many patients report no preceding sore throat.

Topical treatments are effective for limited disease and include corticosteroids (low to mid potency in infants and children), calcipotriene, tar, and anthralin. Keratolytic agents such as salicylic acid will help break down the scale and increase penetration of these topicals. Ultraviolet light, including narrowband ultraviolet B light, is also very effective in treating psoriasis. Exposure to natural sunlight will help with flares, although sunburn must be avoided as this can trigger the disease. For widespread involvement or psoriasis that is refractory to topical therapies and/or light, systemic treatment with methotrexate, cyclosporine, or biologic agents may be necessary. These medications require careful follow-up due to their side effect profiles and should be given only by a clinician well versed in their possible side effects and comfortable with monitoring guidelines. Systemic steroids should be avoided because of the risk of a rebound flare upon discontinuation.

ATOPIC DERMATITIS

Atopic dermatitis is a very common chronic inflammatory skin disorder of children that runs in families with seasonal allergies or asthma. The exact pathogenesis is poorly understood but is likely related to a complex relationship between interrupted epidermal barrier and immune dysregulation of the T cells and Langerhans cells of the skin.[15]

The clinical appearance of atopic dermatitis can vary significantly from patient to patient. Classic features include the presence of erythematous scaly or lichenified plaques with or without excoriation; vesicles may be present and can coalesce, leading to oozing and crusting. Atopic dermatitis may also present as hyperkeratotic, follicularly based papules and can be associated with keratosis pilaris (Figure 10.12). The cheeks are often involved as well as the flexural surfaces. Diffuse xerosis and pruritus may be present. Sparing of the diaper area is common and this helps to differentiate atopic dermatitis from other inflammatory dermatoses of the groin.

Because of the interrupted epidermal barrier as well as impaired local immunity, secondary infection of affected areas with *Staphylococcus aureus* or *Streptococcus pyogenes* is fairly common. Over 90% of eczema patients are colonized with *Staph. aureus* at the time of an acute flare; therefore topical or oral antibiotics are an essential component of treatment in these patients. Viral diseases such as herpes simplex or molluscum may also infect areas of atopic dermatitis.[15]

Affected individuals must be treated with regular moisturization using a thick emollient immediately after bathing. Mild, non-abrasive soaps and cleansers without fragrances should be used to wash the skin. Topical steroids are an essential tool in managing

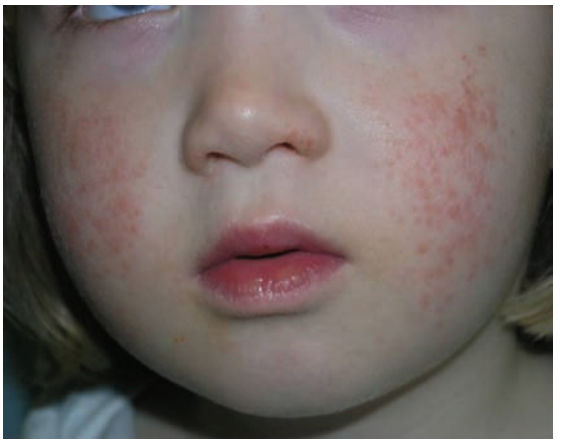

Figure 10.12 Keratosis pilaris presents as erythematous follicularly based hyperkeratotic papules.

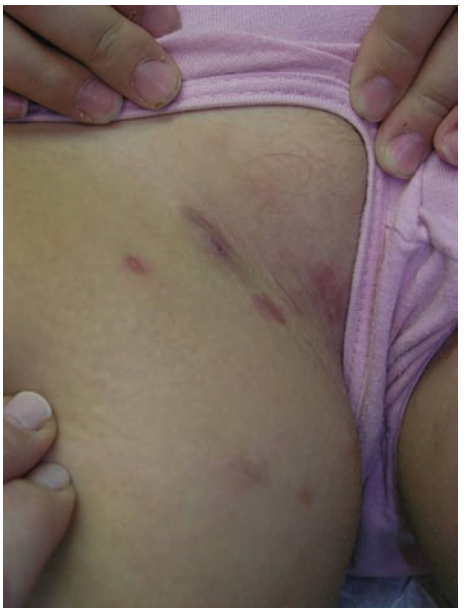

Figure 10.13 Mild early hidradenitis of the groin shows inflamed, draining papules and pustules.

moderate and severe cases; steroid selection is determined depending on location and severity of the disease. In general, low potency topical steroid should be used for the face and intertriginous areas or for milder disease. Mid to high potency topical steroids may be used on other areas of the body and for more severe symptoms. Steroid agents such as topical pimecrolimus and tacrolimus help control mild to moderate disease and are useful for maintenance therapy between flares. Side effects of topical steroids include: allergic contact dermatitis, acne, telangiectasias, erythema, tachyphylaxis, and atrophy. Antihistamines may be a helpful adjunctive treatment in children with severe pruritus. For severe cases of recalcitrant atopic dermatitis, treatment with systemic immunosuppression or ultraviolet light may be necessary. Triggering allergens should be avoided in sensitive individuals.

HIDRADENITIS SUPPURATIVA

Hidradenitis is an inflammatory disorder that commonly presents in the groin. This chronic condition occurs secondary to plugging of the apocrine ducts,[16] and usually develops after puberty. The etiology is poorly understood, but genetics, hormones, and obesity leading to occlusion of the follicular orifice may all play a role.

Patients complain of painful, inflamed, foul-smelling, draining pustules and abscesses which swell and enlarge (Figure 10.13). With further progression, sinus tracts will form, eventually resulting in extensive scarring.

Treatment of hidradenitis should be based on individual symptoms. Wound care with antibacterial soaps or washes is often helpful. Oral antibiotics, especially tetracyclines, help control the inflammatory component. Oral retinoids have variable results in treating this condition. There are emerging reports of the biologic agents (infliximab, etanercept, and adalimumab) being used for hidradenitis with positive results. For persistent cases, surgical excision may be necessary. Carbon dioxide laser treatment has also been effective.[17]

LICHEN PLANUS

Lichen planus is an inflammatory dermatosis of unknown etiology that classically presents as flat-topped, polymorphic, pink to violaceous papules that can vary in size from 0.2 to 1 cm or more. The lesions are usually pruritic and commonly occur on the flexural surfaces of the extremities, genitalia, or face; lichen planus can also present in the mucous membranes as a network of delicate white lines referred to as Wickham's striae. Koebnerization may be observed (Figure 10.14). Atypical presentations include bullous, annular, hypertrophic or vesicular lichen planus.

Lichen planus often responds to potent topical corticosteroids and oral antihistamines. For recalcitrant cases, a course of systemic corticosteroids may be indicated. Patients should be screened for hepatitis C, as this has been linked with lichen planus, especially in the adult population.

URTICARIA

Urticaria is an IgE-mediated type I hypersensitivity reaction that causes activation of mast cells. This fairly common condition can present anywhere on the skin and can be triggered by certain allergens or physical stimuli.

Urticaria presents with erythematous, edematous wheals, which are annular or serpiginous in configuration and often have areas of central clearing and no scale. The size of individual lesions can vary from less than 1 cm to greater than 10 cm, and they may be focal or widespread (Figure 10.15). Individual lesions rarely last longer than 12–24 hours, a quality that distinguishes them from lesions of erythema multiforme, which remain fixed in a given location for longer periods of time. Urticaria is usually very pruritic and patients often complain that the discomfort caused by the intractable itching interferes with their daily activities.

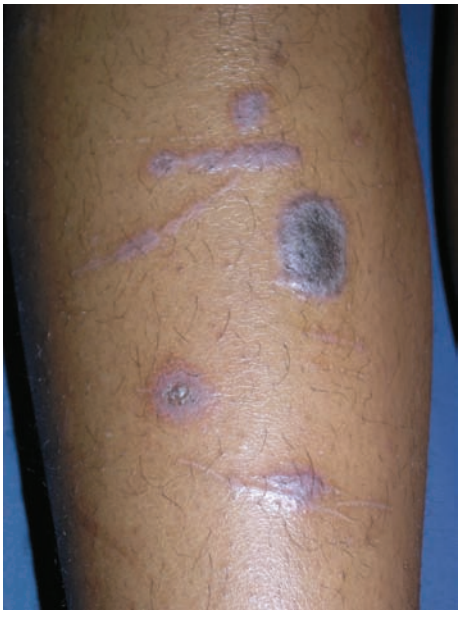

Figure 10.14 Hypertrophic lichen planus shows koebnerization due to trauma, most likely from scratching. The purple, lichenified flat-topped appearance of the lesions is classic.

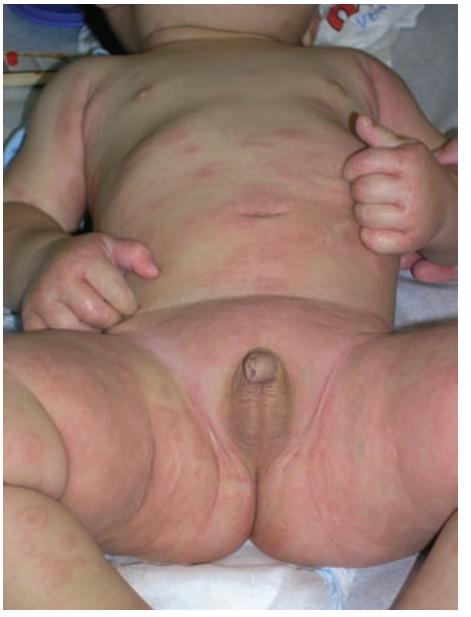

Figure 10.15 Widespread urticarial eruption due to a drug reaction. Edematous, erythematous wheals without scale are present diffusely.

The most effective treatment is identification and elimination of the inciting agent. Antihistamines are usually very helpful in controlling symptoms, and H1 blockers such as cetirizine are often used. Hydroxyzine or diphenhydramine may also be utilized, but these agents often cause sedation and should be administered before bedtime. Antihistamines should be continued through clearance of the urticaria and then gradually tapered. For severe cases, epinephrine or systemic steroids may be indicated.

OTHERS

Other, less common, conditions that should be considered in the differential diagnosis of inflammatory disorders of the groin include: Langerhans cell histiocytosis, acrodermatitis enteropathica, mastocytosis, erythema multiforme, and pityriasis rosea, among others. A full discussion of these entities is beyond the scope of this chapter. When these conditions are suspected, a skin biopsy is useful in making the proper diagnosis.

INFECTIOUS DISEASES

Infectious diseases are common in the pediatric and adolescent population because they are easily spread among individuals. Some of the more frequent infections are discussed in the following section.

HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV) is a highly transmissible inflammatory infection. There are two subtypes of HSV: HSV-1 has an affinity for oral and external nares areas while HSV-2 has a predilection for the genital, perineum, and perianal areas. The virus is spread by contact in tears, saliva, genital secretions, or skin-to-skin contact. Once an individual is infected with HSV, the virus remains latent in the spinal ganglia and can be reactivated by stress, infection, UV exposure, and menstruation.

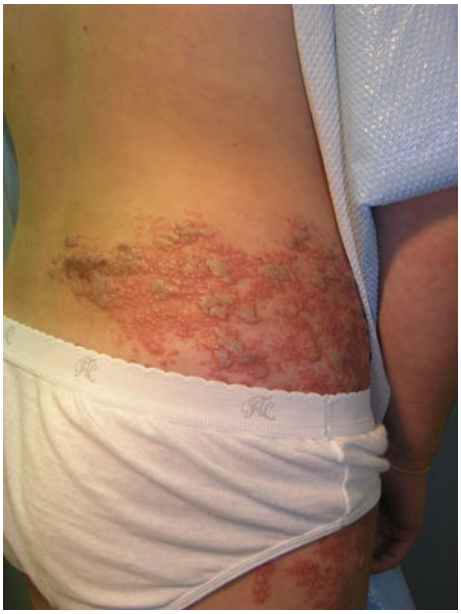

Figure 10.16 Herpes zoster due to reactivation of the varicella-zoster virus.

Clinical manifestations of genital herpes infection range from asymptomatic viral shedding to severe localized and systemic symptoms. During primary infection, patients may exhibit flu-like symptoms in addition to the neuropathic and cutaneous findings of burning, pruritic pain followed by an eruption of one or more groups of deep-seated serous vesicles on an erythematous plaque. After several days, the vesicles crust over and form punched-out ulcerations, which may coalesce into large erosions. Healing takes place over a couple of weeks. Associated symptoms include dysuria, vulvovaginitis, cervicitis, cystitis, and rarely urinary retention.[18]

Herpes simplex infection can look clinically similar to herpes zoster secondary to varicella-zoster virus (Figure 10.16). Other dermatologic diseases with vesicular or erosive skin eruptions should be considered in the differential diagnosis. Viral culture, real-time PCR, direct fluorescent antibody staining, Tzanck preparation, and type-specific serologic tests are used to confirm the diagnosis of HSV.

HSV infection is a chronic and recurrent condition for which there is no cure. Management of HSV is focused on reducing morbidity by shortening the length of and/or preventing outbreaks. Therapeutic options include valcyclovir, famcyclovir, or acyclovir. A patient may be a candidate for long-term suppressive therapy if she experiences more than five outbreaks a year. Pain control can be achieved by using analgesics.

Patients with HSV infection of the genital area should be screened for other sexually transmitted diseases, and patient education is essential to reduce the risk of infection. Patients with active genital herpes should abstain from intercourse. Condoms and suppressive therapy can be used to reduce the risk of HSV infection.

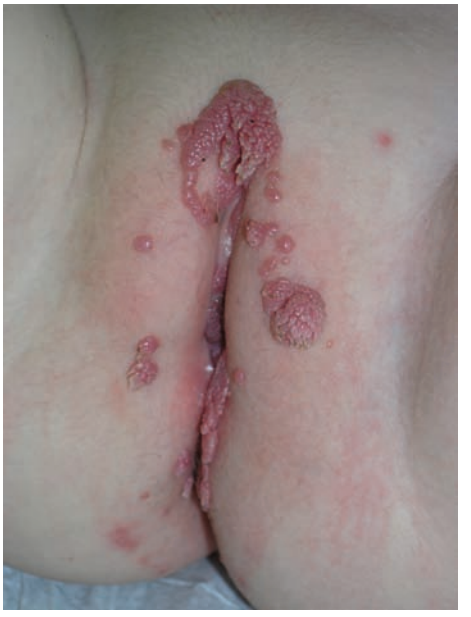

Figure 10.17 Genital warts demonstrate pinkish-brown papules with numerous narrow projections and a smooth, velvety surface.

HUMAN PAPILLOMA VIRUS

Genital warts, or condyloma acuminatum, are a common sexually transmitted infection caused by the human papilloma virus (HPV). Among sexually active females, about 40% of 14–19-year-olds and 50% of 20–24-year-olds are HPV-positive.[19] Genital warts in children can be due to vertical transmission,[20] autoinoculation, inoculation from another infected individual, and sexual abuse. The incubation period of warts can be many months to years.

Lesions are mainly found in the perianal and genital region and present as pink or brown discrete papules or nodules with narrow to wide projections and a smooth or velvety surface on a broad base (Figure 10.17). Lesions can range in size from a couple of millimeters to over a centimeter and may be solitary, multiple, scattered, or confluent. Condyloma accuminatum typically refers to clusters of warts that contain few to hundreds of projections. Warts can extend into the vaginal tract, urethra, and rectum; in these cases, a speculum or sigmoidoscope is essential to diagnose and properly treat the infection.

Diagnosis is usually made clinically; however, skin biopsy can be used for confirmation. Papillomavirus antigen can be detected by immunohistochemical stains, and PCR can identify the particular strain of HPV. The differential diagnosis includes condyloma lata (associated with secondary syphilis), pseudoverrucous papules, molluscum, and skin tags.

Spontaneous resolution occurs in 50% of cases over a few years. Patients seek treatment because of the cosmetic appearance and discomfort of the lesions. Therapeutic modalities include ablative therapy such as electrodesiccation, laser treatment, excision, and cryotherapy; these methods can be very uncomfortable for young children and therefore may require general anesthesia. Topical treatment with podophilox gel 5%, imiquimod 5% cream, or cidofovir gel are effective but often require several months of regular application. HPV strains 16 and 18 account for 70% of all cervical cancers, and recently, the HPV vaccine Gardasil has been FDA-approved for girls as young as 9 and up to age 26. This vaccine protects against HPV types 6, 11, 16, and 18.[21–23]

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a common cutaneous viral infection in children and a sexually transmitted infection of the genital region in adolescents and adults. In children, infection usually occurs between the ages of 2 and 5.[24,25]

The lesions of molluscum are discrete, dome-shaped, pearly umbilicated papules that vary in color from pink to flesh-colored or white. They have a tendency to look translucent. Molluscum lesions vary in size from 1 mm to 15 mm and can become inflamed and irritated. Any area of the body may be involved; however, in children, characteristic locations include the axilla, flanks, lower abdominals, inner thighs, and face. In adolescents and young adults, molluscum lesions often present in the external genital area.

Molluscum contagiosum cannot be cultured and the diagnosis is usually made on the basis of clinical appearance. Diagnosis is confirmed with biopsy, electron microscopy, or ELISA (enzyme-linked immunosorbent assay). Lesions that mimic molluscum include verrucae, varicella, folliculitis, juvenile xanthogranuloma, spitz nevi, and skin tags.

The infection is self-limiting and will resolve spontaneously after a few months without treatment in most patients. Genital lesions should be treated to prevent spread of infection to sexual partners. Medical or surgical management can be implemented if lesions last longer then expected or become irritated or bothersome. There are several modalities of destructive therapy including curettage, cryotherapy, or laser. Topical therapies include tretinoin cream, benzoyl peroxide, imiquimod, podophyllin resin in tincture of benzoin, cantharidin, and silver nitrate.

Children with active molluscum lesions should minimize time spent in contact sports, baths or swimming pools with other children to prevent the spread of infection. Adolescents with molluscum in the genital area should be screened for other sexually transmitted infections (STIs) and counseled regarding the risk of spread to their sexual partners.

SYPHILIS

Syphilis is a chronic infection caused by the spirochete *Treponema pallidum*. It is transmitted through sexual intercourse, blood transfusion, or maternal–fetal spread *in utero*. With increased awareness and effective treatment, the incidence of syphilis has decreased: 60 000 cases were reported in 2000 compared with 480 000 in 1941.[26]

Syphilis is termed 'the great masquerader' due to its wide array of clinical manifestations and is categorized into three phases of infection. Primary syphilis presents as an indurated, painless chancre at the site of infection (including the labia, cervix, perineum, or perianal region) accompanied by painless lymphadenopathy of the inguinal nodes. Around 50% of infected individuals who are untreated will go on to develop secondary syphilis, which is characterized by mucocutaneous lesions, systemic flu-like symptoms, hepatosplenomegaly, and generalized lymphadenopathy (pediderm). In the genital region, secondary syphilis can present as condyloma lata: hypertrophic, moist, wart-like papules and plaques. Tertiary syphilis develops in one out of six patients with untreated secondary syphilis, and symptoms include cardiovascular complications, central nervous system (CNS) lesions, and systemic granulomas.

Diagnosis can be made with laboratory tests, biopsy or darkfield microscopy. A presumptive diagnosis of syphilis is made when two of the following serologic tests are positive: venereal disease research laboratory test (VDRL) and rapid plasma regain (RPR) or fluorescent treponemal antibody test (FTA-ABS). Routine screening and testing should be performed for all pregnant women. Acute false positive serologies are seen with diphtheria and pertussis immunizations, infections with mycoplasma pneumonia, measles, mumps, and varicella pneumonia. Chronic false positives are seen in rheumatologic conditions such as systemic lupus, hepatitis B infection, and infection with *Borrelia burgdorferi*.

For uncomplicated infections and in pregnant women, the treatment of choice is penicillin G 2.4 million U given intramuscularly (IM) once. Titers should be measured at 3, 6, and 12 months following

treatment. If titers continue to be positive or clinical suspicion for continued disease persists, retreatment is recommended. Patients who are allergic to penicillin can be desensitized. Infants with congenital syphilis should be treated with benzathine penicillin G 50 000 units/kg/day IM as a single dose.[27]

IMPETIGO

Impetigo is a common superficial skin infection most commonly caused by *Staph. aureus*; however, *Strep. pyogenes* is cultured from 30% of all cases. Infection is highly contagious and lesions can easily be spread among family members, in schools, or in day-care settings.[27]

There are two subtypes of impetigo: bullous and non-bullous. Bullous impetigo is almost always caused by coagulase-positive *Staph. aureus* and presents as solitary or grouped flaccid bullae. The bullae collapse, leaving a rim of scale surrounding a shallow erythematous erosion. Non-bullous impetigo represents about 70% of all cases and often occurs after skin trauma such as insect bites, varicella lesions, abrasions, or atopic dermatitis exacerbations. Lesions begin as tiny vesicles or pustules that may rupture, revealing a red and moist base that may develop a whitish-brown or honey-colored adherent crust with surrounding erythema (Figure 10.18).

Diagnosis is made clinically but non-bullous impetigo can mimic many other cutaneous infections such as enteroviruses, varicella-zoster, and HSV. Bullous impetigo can look similar to non-accidental trauma (specificially cigarette burns), pemphigus folliaceus, erythema multiforme, thermal injury, or hypersensitivity response to insect bites. Cultures are diagnostic, but it can be difficult to identify the pathogenic bacteria from commensal skin organisms.

Most cases of impetigo will resolve spontaneously within 2 weeks. First-line treatment for uncomplicated infection is topical mupirocin applied three times daily for 7–10 days.[28] Oral erythromycin ethylsuccinate is also first-line therapy for more widespread infections; however, because of emerging resistance, azithromycin or cephalexin may be required.[29]

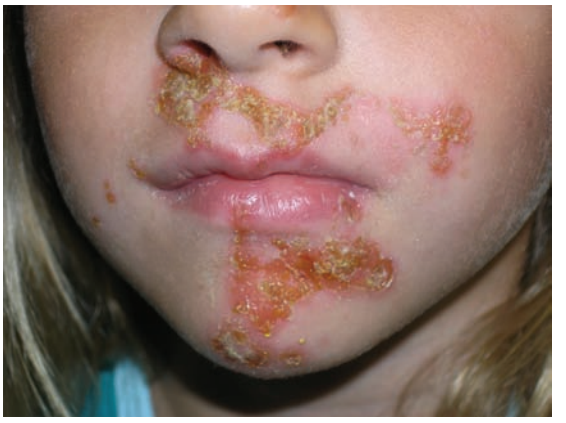

Figure 10.18 Non-bullous impetigo presents as erythematous papules and plaques with honey-colored crust and serous exudate.

Patients with recurrent impetigo should be screened for carrier status; colonizing strains are present in the nares 75% of the time as well as in the perianal region, umbilicus, and under the nails. Carriers of *Staph. aureus* may be treated with topical mupirocin ointment applied directly to these areas three times daily for 2–4 days; retreatment every few weeks to months may be required because of the risk of recolonization and recurrent impetigo.

SCABIES

Scabies is a highly contagious and intensely pruritic infection caused by the mite *Sarcoptes scabiei*. Infection is seen more commonly in settings of poverty or lower-income communities but can be seen in all ethnic groups and all socioeconomic levels. The female mite burrows into the skin, lays eggs, and causes the human host to become sensitized to its toxic secretions.

Patients present with small 1–2 mm erythematous papules and complain of intense itching (Figure 10.19). The presence of burrow tracts from the mite is very diagnostic. In women, itching is

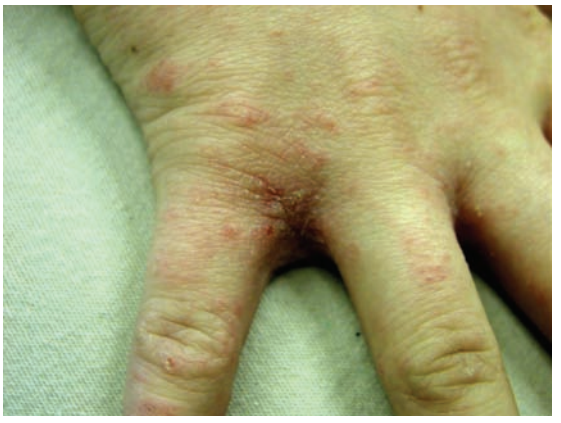

Figure 10.19 Scabies infestation of the hand shows erythematous papules that have been excoriated due to intense pruritis.

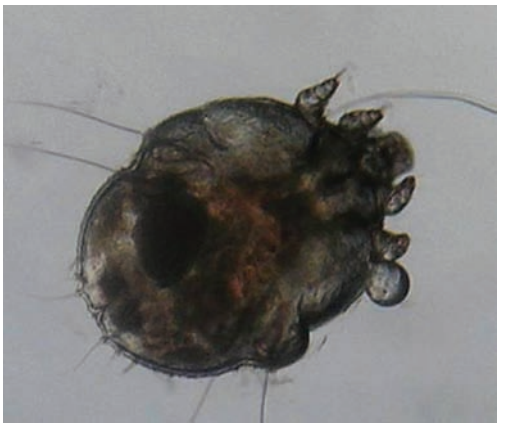

Figure 10.20 Scabies mite obtained from a skin scraping of an infected individual.

prominent around the nipples, wrists, finger webs, intergluteal cleft, and axillae. Infants and young children commonly develop lesions on the hands, feet, buttocks, and skinfolds around the neck; individual lesions may be vesiculopustular, especially on the palms and soles.[30] Pruritus may persist for up to 6 weeks following treatment.

Evidence of the mite, larvae, or eggs is diagnostic for scabies and can be obtained from skin scrapings or biopsy (Figure 10.20). Other diseases that can present with similar symptoms and clinical findings include follicular eczema, papular urticaria, and contact dermatitis.

Permethrin 5% cream is the first-line treatment for most patients and is safe to use in infants and pregnant women. The cream is applied to the entire body from the neck down and washed off in 8–14 hours. A second treatment 7 days later is crucial to kill the eggs that hatched into mites since the first treatment. Lindane cream is an alternative treatment for people unable to tolerate permethrin; however, its use is limited due to increasing resistance as well as potential side effects including neurotoxicity, especially in small children who are prone to increased systemic absorption due to their greater body surface area to weight ratio. Oral ivermectin is another option and is given as a single dose at 200 micrograms/kg; again, a second treatment 7 days later is essential. To symptomatically treat the pruritus, topical mid-potency corticosteroids may be used and are often required for several weeks following treatment.

For patients with severe infestations, all bed linens and clothing should be washed in hot water, as mites can live for 24–36 hours away from their host.[31,32] The risk of re-infestation from fomites is negligible in most scabies infections. Family members and all close contacts should also be treated.

CUTANEOUS TUMORS

HEMANGIOMA

Hemangiomas are the most common vascular tumors of infancy and comprise benign proliferations of capillaries. These tumors usually present within the first year of life and are not present at birth (with two exceptions, reviewed below); there is a slightly higher incidence in girls, whites, premature infants, and infants of multiple gestation.[33] Hemangiomas occur in 1–3% of all neonates and about 10% of all 1-year-old infants.[34]

Thirty to forty percent of hemangiomas appear as precursor lesions such as telangiectasias, macular erythematous stains, or bruises, which then enter

a proliferative phase and rapidly grow into hemangiomas over the first 6–12 months of life. After the first year of life, the proliferative phase terminates, there is a stage of stabilization, and then the involution phase begins: the hemangioma decreases in size by about 10% per year. There are two other distinct presentations of hemangioma that present at birth: noninvoluting congenital hemangiomas do not enlarge or regress, while rapidly involuting congenital hemangiomas tend to regress quickly.

Superficial hemangiomas have a predilection for the head and neck but can appear at any location, including the oral and genital mucosa. Hemangiomas can vary dramatically in size and depth of involvement. Superficial hemangiomas are located in the papillary dermis and will appear bright red clinically and grow into a firm, rubbery, lobular nodule or plaque. Deeper (formerly called cavernous) hemangiomas are located in the reticular dermis or subcutaneous fat and present as ill-defined, compressible, skin-colored or reddish-blue lesions. Hemangiomas are not painful unless they ulcerate (Figure 10.21); this occurs in approximately 10% of all hemangiomas.[35]

Hemangiomas of infancy are diagnosed by clinical appearance and natural history of the lesion. Deep hemangiomas can be hard to differentiate from soft tissue tumors such as fibrosarcoma or rhabdomyosarcoma, and may require MRI, CT scan, ultrasound or surgical pathology for definite diagnosis. Other vascular anomalies or tumors that should be differentiated include: lobular capillary hemangioma (pyogenic granuloma), tufted angioma, spindle cell hemangioendothelioma, Kaposi's sarcoma, and port-wine stain.

Hemangiomas follow a benign course; for uncomplicated lesions, observation is recommended. For hemangiomas that become ulcerated or start to compress vital structures, therapies such as corticosteroids (systemic, intralesional, and topical), pulsed dye laser (PDL), interferon α, and surgical excision should be considered. Systemic corticosteroids have been the mainstay of treatment, at a dose of 2–4 mg/kg per day for several months followed by a slow taper. Hemangiomas that occur in the lumbosacral region can potentially be associated with spinal, bony, and genitourinary abnormalities and should be investigated accordingly.

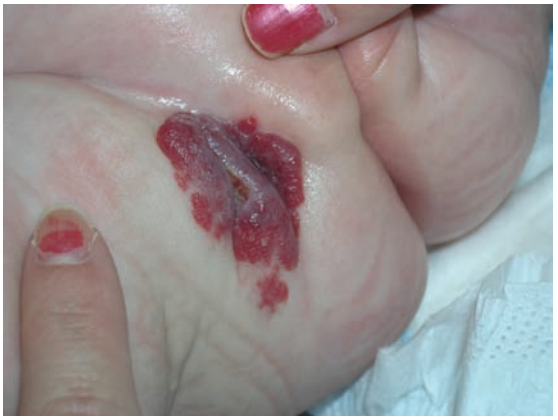

Figure 10.21 Ulcerated hemangioma of the groin.

LYMPHANGIOMA

Lymphangioma is a rare congenital malformation of the lymphatic system. These tumors can occur anywhere on the skin. Lymphangioma circumscriptum is one of the subtypes and presents at birth as asymptomatic discrete groups of 1–5 mm clear or blood-tinged papules that resemble vesicles (Figure 10.22).

A diagnosis of lymphangioma is usually made on clinical history and physical exam findings. MRI studies are helpful to identify the size of the lesion and any compression or involvement of underlying structures.

The preferred treatment of lymphangioma is complete surgical excision. Other modalities of treatment include cryotherapy, sclerotherapy, embolization and cautery.[36] Carbon dioxide laser treatment has also been successful.[37]

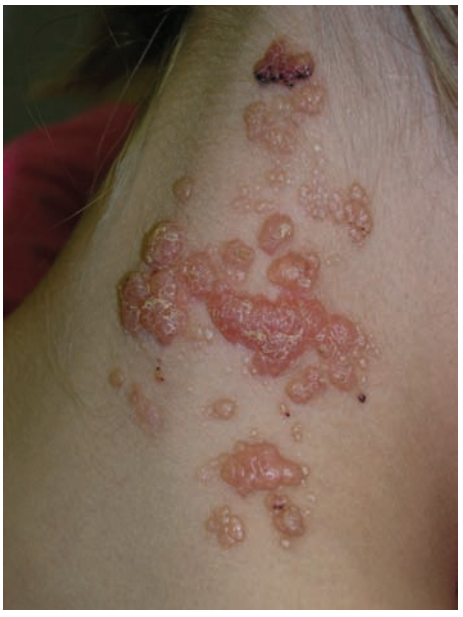

Figure 10.22 Lymphangioma circumscriptum presenting as groups of fluid-filled and blood-tinged papules that resemble vesicles.

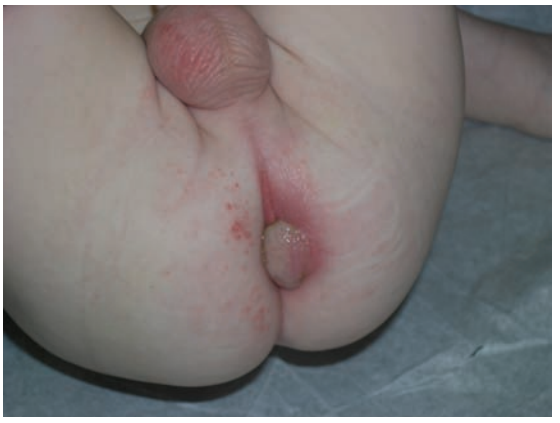

Figure 10.23 Perianal abscess due to infection with meticillin-resistant *Staph. aureus*; these abscesses must be differentiated from inflamed epidermal cysts.

CYST

Cutaneous cysts are common growths that can present anywhere on the body, including the genital area. There are many different types of cysts; however, this section will focus on one of the most common subtypes: epidermal inclusion cysts. Epidermal inclusion cysts are subcutaneous, firm nodules filled with keratin that arise from the infundibulum of the hair follicle.

Epidermal cysts present as firm dome-shaped intradermal or subcutaneous painless nodules that range from 0.5 to 5.0 cm. They are attached to the overlying skin and have a small punctum that looks like an open comedone. Cysts are usually asymptomatic but can become tender when inflamed and may be clinically confused with an abscess (Figure 10.23).

Epidermal cysts must be differentiated from other cutaneous tumors. Complete excision of the cyst may be performed under local anesthesia; care must be taken to remove the entire cyst wall to avoid recurrence.

PIGMENTED LESIONS

NEVI AND MELANOMA

Nevi, or moles, are very common skin neoplasms seen in the pediatric and adolescent population. The primary concern with nevi is their potential for malignant transformation. The likelihood of an individual mole transforming into melanoma is extremely low; however, all nevi should be monitored on a regular basis, and biopsy should be considered in nevi that are rapidly changing. Malignant melanoma is rare, but still does exist, in the pediatric and adolescent population; 1.3% of all melanomas occur in patients younger than 20 years.[38] The incidence of melanoma in patients younger than 20 years increased 2.9% per year from 1973 to 2001.[39]

Nevi can be congenital or acquired, and the tendency to develop nevi is likely multifactorial, with genetics, sun exposure, and skin type all playing a role. Congenital nevi have an increased risk for

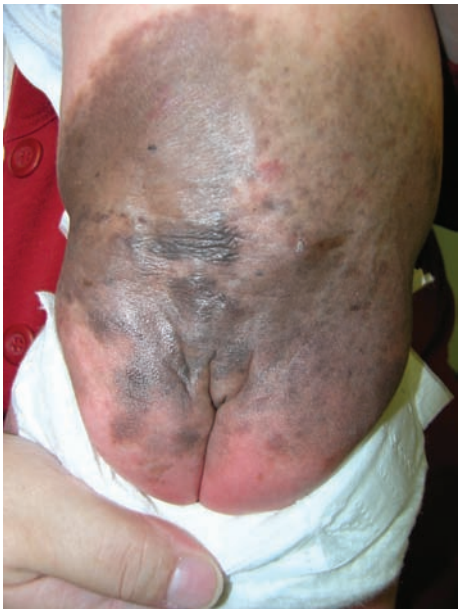

Figure 10.24 Giant congenital nevus in a 'bathing suit' distribution.

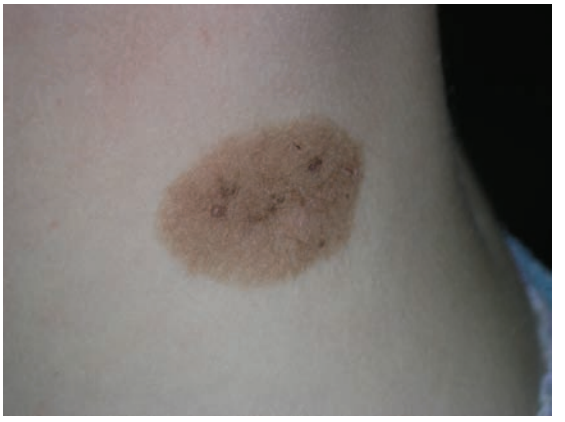

Figure 10.25 Benign-appearing congenital nevus.

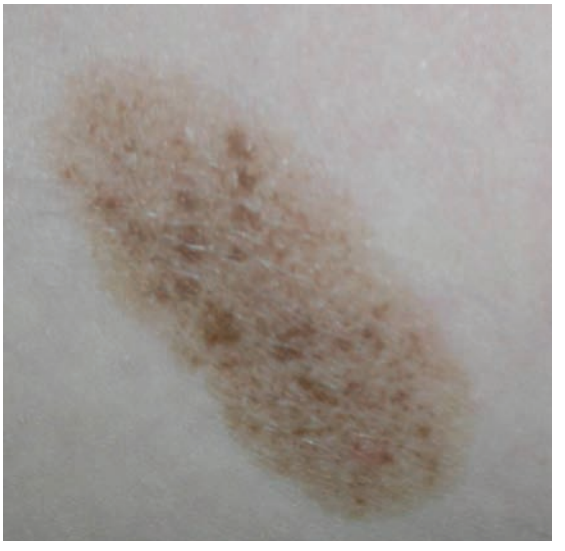

Figure 10.26 Nevus spilus shows a light brown patch with darker brown speckles within it.

malignant transformation compared with other types of nevi and therefore should be followed carefully. These lesions are usually present at birth, and are further subdivided depending on their size: small (< 1.5 cm), medium (1.5–19.9 cm), and large (> 20 cm). Small and medium-sized congenital nevi carry a risk of malignant transformation of approximately 1–4% over an individual's lifetime, whereas giant congenital nevi carry a much greater risk and can often transform well before puberty. Giant congenital nevi can occupy large segments of the body, sometimes involving most of the trunk in a 'bathing suit' distribution (Figure 10.24). Congenital nevi present as pink or light to dark brown patches and plaques; they may have some pigment variation, and there may be increased hair on the surface (Figure 10.25); they may become more elevated over time. Nevus spilus may be classified as a congenital nevus and often starts as a lightly pigmented patch resembling a café au lait macule, eventually developing darker brown pigmented 'speckles' within it (Figure 10.26). Nevus spilus is a low-risk lesion but should still be monitored over time.

Acquired nevi appear starting in infancy and will usually continue to emerge through the third and fourth decades, eventually involuting as patients

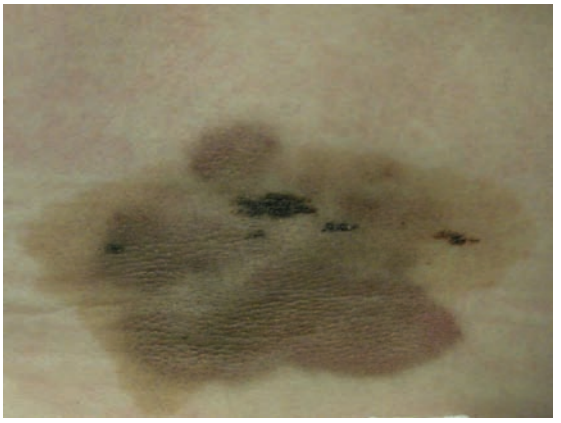

Figure 10.27 Dysplastic nevus displaying uneven color and irregular borders.

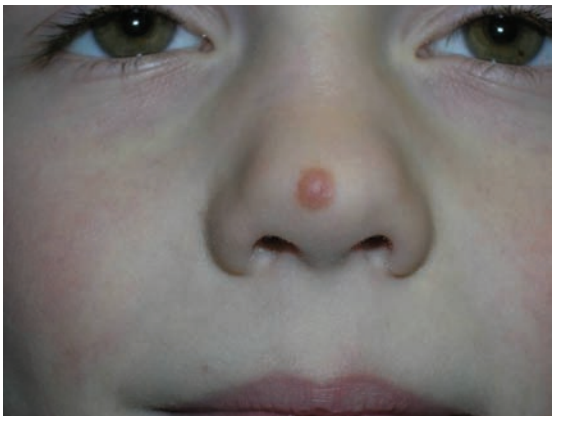

Figure 10.28 Spitz nevus presents as a smooth dome-shaped pink papule.

grow older. Acquired nevi can have a variety of clinical appearances but usually are well circumscribed and vary in color from tan to dark brown; they have an even pigmentation pattern and can vary from flat macules to fleshy, soft, sessile or pedunculated papules.

Dysplastic nevi have a distinct appearance. Clinically, these lesions will have one or more of the features described in monitoring for melanoma (discussed below) (Figure 10.27). The presence of one or more of these features does not ensure that the nevus is dysplastic; rather, they must be considered in the context of the individual patient and the particular lesion. A helpful rule of thumb for patients and parents is the 'ugly duckling' principle: atypical nevi often stand out from the patient's other moles as being unusual in morphology.

Spitz nevi are hairless, dome-shaped smooth papules that can range in color from yellowish-pink to red-brown to black and often present on the face (Figure 10.28). Halo nevi are brown or pink macules or papules that develop a peripheral rim of hypopigmentation. Blue nevi have characteristic features, presenting as blue to bluish-black macules or papules. Epidermal nevi are lightly to darkly pigmented soft to verrucous papules and plaques, often distributed in a linear or whorled

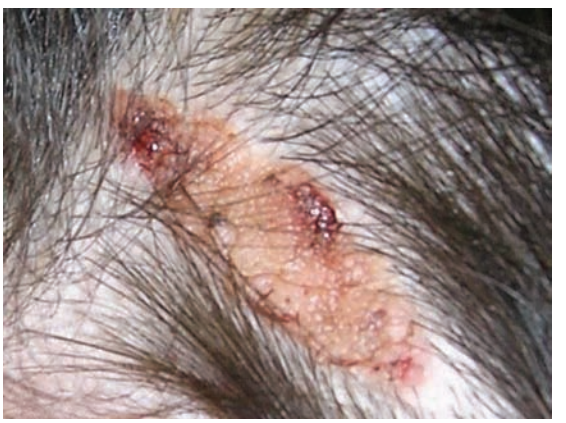

Figure 10.29 Nevus sebaceous at puberty displaying a verrucous surface.

configuration. Nevus sebaceous presents as a hairless yellow to tan soft plaque, which may have a pebbly or velvety surface that becomes more verrucous after puberty (Figure 10.29) and almost always occurs on the scalp or face.

Malignant melanoma usually has one or more of the following features: asymmetry, irregular border, dark color or variable pigment, large size, and elevation. These lesions often have a history of growing rapidly or changing features. Amelanotic melanomas

are one of the more common presentations, especially of pediatric melanoma, and can present as pink to red papules; they are difficult to distinguish from a number of other benign lesions including vascular tumors, Spitz nevi, and adnexal tumors. Risk factors for the development of melanoma in the pediatric and adolescent population include maternal transmission *in utero*, xeroderma pigmentosa, immunosuppression, familial history, nevus phenotype, and environmental factors such as ultraviolet radiation.[40] However, most pediatric patients with melanoma have no known risk factors.

Careful physical examination and history are important in diagnosing nevi and melanomas. Consultation with dermatology is often warranted in patients with congenital nevi or a history of dysplastic nevi or melanoma. Digital photography may be useful for following individual moles. An excisional biopsy should be performed whenever a nevus is changing, or when the diagnosis or behavior of a particular lesion is in question. This allows histologic evaluation of the entire lesion. The authors recommend sending specimens for histologic evaluation by a dermatopathologist experienced in pigmented lesions. Plastic surgery consultation may be necessary for large or giant congenital nevi and removal with tissue expanders, skin grafts, and/or cultured autologous skin substitutes might be indicated given the significant risk (4–10%) of malignant transformation of these lesions.[41] The management of biopsy-proven Spitz nevi remains controversial as their behavior is uncertain. Many advocate complete removal, while others recommend close surveillance for any changes.[42] Malignant melanoma must be excised with appropriate margins as indicated by the depth of the melanoma on initial biopsy. Sentinel lymph node biopsy may be warranted in certain cases; however, this is controversial.

Patients and parents should be counseled on the importance of periodic surveillance, sun protection, and characteristics of melanoma. They should also be instructed to have immediate evaluation of any rapidly changing nevi as this can be a warning sign of dysplasia or malignancy.

ACNE

Acne is a very common condition of the pilosebaceous unit of the skin, affecting over 80% of the population in the United States at some point, and usually peaking in the adolescent population. The single cause of acne remains unknown, however, numerous factors, including genetics and hormones, likely contribute. An increase in dehydroepiandrosterone sulfate (DHEAS) correlates with the onset of acne in prepubertal or pubescent females.[43] Increased androgen production leads to sebaceous gland enlargement and greater amounts of sebum production.[44] Additionally, *Propionibacterium acnes*, an anaerobic bacterium, and *Pityrosporum ovale*, a yeast, can contribute (Figure 10.30).

Stress and mechanical occlusion can exacerbate acne. The role of diet in acne pathogenesis remains controversial, and numerous controlled studies have failed to establish diet as a cause of acne.

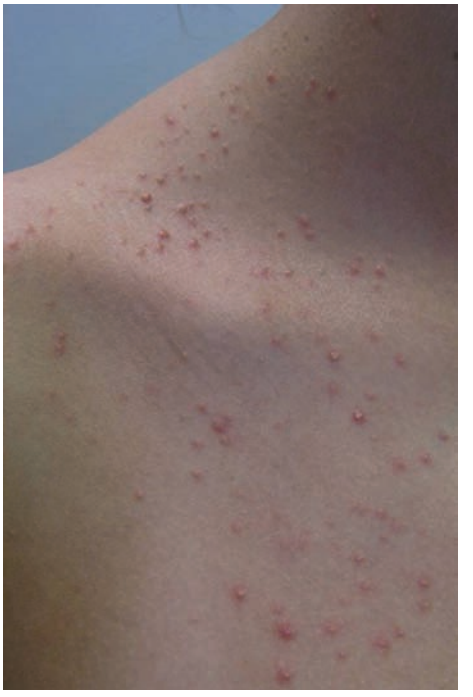

Figure 10.30 Acne caused by the yeast *Pityrosporum ovale*.

However, skim milk intake has been positively correlated with the development of acne, perhaps because of the presence of hormones and bioactives within milk.[45] Diet with a high glycemic index has also been correlated with acne in males. Certain medications including systemic steroids, anabolic steroids, lithium, phenytoin, isoniazid, and iodides, among others, can cause the sudden appearance of an acneiform eruption. Endocrinologic abnormalities are well-established causes of acne. A history of hirsutism, irregular menstrual periods, insulin resistance, or deepening of the voice should prompt a further investigation into possible endocrine disturbances such as polycystic ovary syndrome (PCOS). These patients should be screened with lab tests including serum free and total testosterone, DHEAS, 17-hydroxyprogesterone and, while not an integral part of the diagnostic criteria, leutinizing hormone/follicle stimulating hormone ratios of 2:1 or 3:1 support the diagnosis. (See PCOS in Chapter 12.)

Non-inflammatory acne, also referred to as comedonal acne, is characterized by open and closed follicularly based comedones. These may present as 1–2 mm red papules or pustules; open comedones appear clinically as blackheads. Inflammatory acne consists of comedones that expand to form papules, pustules, nodules, and cysts (Figures 10.31 and 10.32). These lesions have the potential for more serious scarring. Patients with acne often have post-inflammatory hyperpigmentation, which presents as pink to brown 1–3 mm macules.

When instituting new acne therapy, it is of utmost importance to counsel patients that 2–3 months of consistent use is necessary to determine the efficacy of any therapeutic regimen. Topical treatments are usually effective in patients with primarily comedonal acne. All patients with acne should be started on a topical retinoid such as tretinoin, adapalene, or tazarotene. Topical retinoids normalize the abnormal follicular keratinization that lies at the heart of acne and have anti-inflammatory properties. Patients should be warned of potential irritation as well as the possibility of a pustular flare during the first month of use. It is important to note that tazarotene is a topical medication that is pregnancy category X. Azelaic acid, a dicarboxylic acid that inhibits the growth of *P. acnes* and has comedolytic activity, is pregnancy category B, and is, therefore, the safest comedolytic to use during pregnancy. It is also helpful as an adjunct to acne therapy in darker-skinned individuals who exhibit post-inflammatory hyperpigmentation.

Topical antibiotics should be used in conjunction with topical retinoids because of their synergistic effects. The antibiotics target *P. acnes*, limiting the inflammatory component of acne. Effective topical antibiotics include clindamycin, erythromycin, and benzoyl peroxide. Resistance can occur with

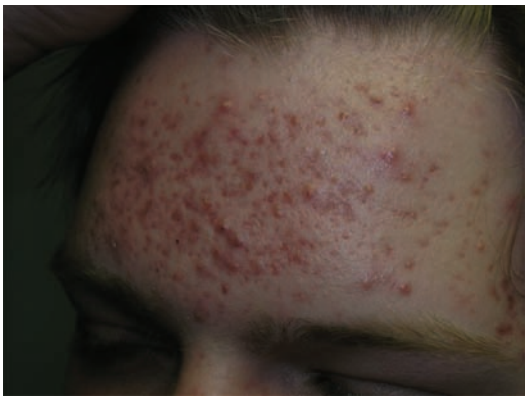

Figure 10.31 Inflammatory acne with numerous inflamed papules and pustules.

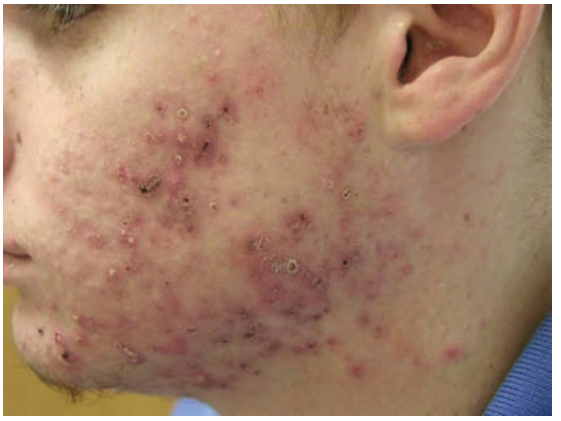

Figure 10.32 Cystic acne has a high potential for scarring.

prolonged use of any single agent, therefore, a combination of benzoyl peroxide with either clindamycin or erythromycin is often most effective in treating the acne and limiting resistance. Sodium sulfacetamide is another topical antibiotic with activity against *P. acnes*; it is available as a lotion or wash. This is a particularly helpful adjunct to treating acne in the athlete or patient with oily skin in whom the clinician suspects yeast overgrowth.

For patients with more severe acne or inflammatory cysts and nodules, an oral antibiotic may be indicated, as these have both an anti-inflammatory and an antibacterial mechanism in treating acne. Oral antibiotics should be used in conjunction with topical retinoids but should not be used with systemic retinoids. Tetracycline, or its derivatives, doxycycline or minocycline, are most commonly prescribed. Side effects of doxycycline include photosensitivity, gastrointestinal upset, esophageal erosions; side effects of minocycline include drug-induced lupus, and less commonly hypersensitivity reactions, hepatotoxicity, and interstitial nephritis.[46] Minocycline can also be associated with vestibular toxicity and a blue-black hyperpigmentation, especially within scars. Any of the tetracyclines can be associated with pseudotumor cerebri, especially in the setting of concomitant isotretinoin administration, and patients should be counseled appropriately. Tetracyclines should not be used in children younger than 10 years because of the potential for tooth discoloration. Erythromycin has also been used to treat acne; however, this is not first-line treatment as resistance to this medication is more common. Amoxicillin and trimethoprim-sulfamethoxazole are other antibiotics that may be used in resistant cases. The role of any of these antibiotics in decreasing the efficacy of oral contraceptives is controversial. The only antibiotic to reproducibly reduce oral contraceptive efficacy in well-performed studies is rifampin. The authors do recommend counseling acne patients on the possibility of decreased oral contraceptive efficacy just to be thorough.

Patients with acne thought to be secondary to hormonal disturbances should be managed appropriately. Oral contraceptives may be useful in this setting and several of these have been approved by the Food and Drug Administration (FDA) in treating acne (Ortho Tri-Cyclen, Estrostep, and Yasmin). Spironolactone can also be effective, as this drug acts as both an androgen receptor blocker and an inhibitor of 5 α-reductase. It is important to note that spironolactone is not recommended in pregnancy and can feminize a male fetus. Patients should be counseled accordingly.

For patients with severe, nodulocystic acne that does not respond to any of the above treatments, isotretinoin, an oral retinoid, may be indicated. Patients who are taking isotretinoin should discontinue all other acne medications, both systemic and topical. Isotretinoin acts upon the sebaceous glands, causing atrophy and reducing sebum production by up to 90%. *P. acnes* is unable to thrive, and follicular keratinization becomes normalized. Patients must be monitored carefully with monthly lab tests including a complete blood count, liver function test, fasting lipids, renal function, and pregnancy tests in women. The most common side effects of isotretinoin are dryness of the skin and mucous membranes. Less common side effects include visual disturbances, nausea, hepatitis, depression, myalgias, headache, pseudotumor cerebri, skeletal hyperostosis, osteoporosis, and premature closure of the epiphyseal plates. The teratogenicity of isotretinoin is well established and female patients must receive appropriate counseling and demonstrate appropriate contraceptive measures. The iPledge system is a national registry in the USA for patients taking isotretinoin, which aims to enforce appropriate follow-up, patient education, and pregnancy prevention while on this medicine. Pregnancy should not be attempted until 1 month after discontinuation of therapy.

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11. Menstrual disorders in adolescents

Claire Templeman

INTRODUCTION

Among 18–21-year-old females the most common reason for a physician visit is an obstetric or gynecologic complaint.[1] After pregnancy, concerns about menstrual cycle dysfunction including irregular or heavy menses are the most common dilemmas. As health-care providers it is important to assess these young girls to determine whether their complaint is a variant of normal development or a sign of underlying pathology. To this end, the American College of Obstetricians and Gynecologists (ACOG) Committee on adolescent health care[2] has suggested that the menstrual cycle be included as a vital sign when seeing adolescents at an office visit. Aberrations in the menstrual cycle can then be used as a screening tool to direct investigation further. Vital to this process is an understanding by both the physician and the patient of normal menstrual cycle parameters in this age group.

PATHOPHYSIOLOGY OF MENSTRUATION

In order to prepare for implantation, human endometrium undergoes distinct cycles of proliferation, differentiation, and shedding in response to ovarian steroid control.[3] Therefore regular menstruation is reflective of cyclic ovarian function and disruption of this produces menstrual cycle abnormalities.

Follicle-stimulating hormone (FSH) from the anterior pituitary stimulates estrogen production from the granulosa cells of the ovary. The endometrium is composed of two layers, the functionalis and the basalis, which are the target for estrogen and progesterone. Estrogen is responsible for the proliferative changes in the endometrium during the follicular phase of the cycle. Luteinizing hormone (LH), also from the anterior pituitary, stimulates ovulation on day 14 in a woman with a 28-day cycle. Following this the follicle from which ovulation occurred is transformed into the corpus luteum. This produces progesterone, which acts on the endometrium to prepare for possible implantation. If pregnancy does not occur, estrogen and progesterone levels decline and the functional layer of the endometrium is shed at menstruation. The basal layer is the source of endometrial regeneration.

MENARCHE AND NORMAL MENSTRUAL CYCLES

One study[4] investigated the average age at menarche in girls of different racial backgrounds in the US. Menstrual data from 2510 girls aged 8–20 years in the Third National Health and Nutrition Examination Survey were collected. The authors found that the median age at menarche was 12.43 years, with black, Hispanic and caucasian girls menstruating at a median of 12.06 years, 12.25 years, and 12.55 years, respectively. In addition, less than 10% of girls in the US menstruated before the age of 11 years and 90% of them were menstruating by 13.75 years of age. The interval between the development of breast buds (Tanner stage 2 breast development) and menarche was 2–3 years, however, this may be longer for girls with early onset breast development.

Worley et al[5] examined 207 children aged 3–18 years with cerebral palsy and moderate motor dysfunction. They compared the secondary sexual characteristics of this population with those from a

general population of children from the American Academy of Pediatrics Pediatric Research in Office Settings network and those of the National Center for Health Statistics National Health and Nutrition Examination Survey (NHANES III). They demonstrated that the median age of menarche for white girls with cerebral palsy was 14 years, 1.3 years later than their general population.

NORMAL CYCLE LENGTH AND OVULATION

Time to menstrual cycle regularity among adolescents has been investigated by the World Health Organization (WHO) Task Force on Adolescent Reproductive Health.[6] Girls aged 11–15 years from Sri Lanka and Hong Kong were recruited to keep menstrual diaries documenting length of menstruation and cycle length. The median length of the first cycle was 34 days, with 38.3% of cycles longer than 40 days. However, by the fifth cycle the median length was 31 days. Among girls who had recorded menstrual data from menarche, 19% achieved normal cycles (defined as at least three cycles not shorter than 20 days and not longer than 40 days) by the third cycle, and 67% by the end of the 2-year study period.

Time to regular ovulation may also be dependent upon the age at menarche, with 50% of girls with menarche at less than 12 years having ovulatory cycles in the first year post menarche. Treloar et al[7] examined menstrual cycle length and the time since menarche. These authors found that the 95th percentile was 90 days in the first 3 years post menarche, decreasing to 50 days by 4 years and 38 days by 7 years.

ABNORMAL MENSTRUAL CYCLES

The ACOG Committee for Adolescent Health Care[2] has published the following parameters for normal menstrual cycles in young girls: menstrual cycle interval of 21–45 days with a mean interval of 32.2 days in the first year post menarche, 7 days or less of menstrual flow and three to six pads or tampons per day. In an effort to determine whether a patient's description of her menstrual cycle is abnormal, having her keep a menstrual diary for several months can be very useful, since the complaint of more than one period in a month may still fall within a normal cycle interval. Similarly, this will also detail the number of bleeding days and if the periods are longer or more excessive than normal, further investigation for underlying pathology is warranted.

PROLONGED INTERVAL

From the data presented previously, girls with cycles of 90 days or more clearly require investigation and this becomes increasingly important as the time from menarche increases. Potential causes of cycle irregularity are detailed in Table 11.1. After excluding pregnancy, appropriate investigation to exclude thyroid dysfunction, hyperprolactinemia, and premature ovarian failure with TSH (thyroid-stimulating hormone), serum prolactin, and FSH, respectively, is important.

While polycystic ovarian syndrome (PCOS) is often not diagnosed until adulthood, careful questioning may uncover symptoms beginning in adolescence. A detailed history may reveal menstrual irregularity and hirsutism dating from puberty.

Table 11.1 Causes of menstrual cycle irregularity

Pregnancy complications
Benign and malignant neoplasms of the genital tract
Ovarian tumors such as granulosa cell tumors
Cervical polyps or malignancy
Endocrinopathy
Polycystic ovarian syndrome
Hyperprolactinemia
Thyroid disease
Diabetes (poorly controlled)
Exogenous drugs and hormones
Eating disorders
Excessive exercise

The classic syndrome as described by Stein and Leventhal in 1935 consists of amenorrhea, hirsutism, and obesity associated with polycystic ovaries. In 2003, the criteria for diagnosis were revised at the Rotterdam consensus meeting[8] to include two of the following three criteria after other causes of increased androgen have been ruled out: (1) oligo-amenorrhoea, (2) clinical or biochemical signs of androgen excess, (3) polycystic ovaries on ultrasound. More recently, the 2006 Androgen Excess Task Force[9] produced a definition that includes: clinical and/or biochemical androgen excess, functional or morphological evidence of ovarian dysfunction, and the exclusion of other causes of androgen excess such as tumors, congenital adrenal hyperplasia, and hyperprolactinemia.

In adolescence the presentation may be varied and may include menstrual irregularity, acne, obesity, and primary or secondary amenorrhea. Other characteristics of PCOS include hyperandrogenism and insulin resistance. Currently the hyperinsulinemia effect at the ovarian level is thought to be responsible for the metabolic aberration and increase in ovarian androstenedione and testosterone production. The long-term consequences of PCOS must be emphasized and include adult-onset (type 2) diabetes mellitus and an increased risk of cardiovascular disease.

Treatment for polycystic ovaries in adolescents should address menstrual cycle irregularity, hirsutism, and insulin resistance. Weight loss and exercise should be discussed and encouraged as the first line of intervention. For menstrual irregularity, oral contraceptives increase sex hormone binding globulin and thus lower the effects of free androgen, aiding menstrual cycle regulation and improvement in acne. Patients with hirsutism will benefit from oral contraceptives and antiandrogen medications such as 5 alpha reductase inhibitors and spironolactone. Metformin, an insulin sensitizer, originally used in the treatment of noninsulin-dependent diabetes mellitus, has also been used as therapy in the adolescent patient. Currently, metformin is approved by the Food and Drug Administration (FDA) only for type 2 diabetes, therefore the patient and parent should be informed accordingly. Metformin may be considered in selected adolescents with PCOS, particularly those with clinical or biochemical evidence of hyperinsulinemia or impaired glucose tolerance. While gastrointestinal side effects are not uncommon with metformin, the more profound but rarer problem is that of lactic acidosis.

AMENORRHEA

Primary amenorrhea has traditionally been defined as the absence of menarche and secondary sexual characteristics by 14 years of age or the absence of menarche by 16 years of age in a patient with secondary sexual characteristics.[10] Secondary amenorrhea is defined as three or more consecutive missed periods. Pregnancy must be excluded in all adolescents with amenorrhea at the initial visit.

A useful approach to determining the etiology of amenorrhea is a detailed history, physical examination, and assessment of the gonadotropin levels. Three major categories of etiology are produced with this classification: hypergonadotropic hypogonadism (with elevated FSH), hypogonadotropic hypogonadism (depressed FSH), and eugonadism (normal FSH) (Figure 11.1). Although there is overlap between the causes of primary and secondary amenorrhea, Reindollar et al[11] determined that the most common causes of primary amenorrhea are: ovarian failure (48.5%), müllerian agenesis (16.2%), gonadotropin deficiency (8.3%), and constitutional delay of puberty (6%).

A number of conditions shown in Figure 11.1 and Table 11.1 can cause secondary amenorrhea.[12] Excessive exercise and reduced caloric intake may cause disruption of gonadotropin release, in particular suppression of the pulsatile release of LH resulting in amenorrhea. Long-distance runners and those involved in esthetic sports like gymnastics, ballet, and figure skating are at particular risk for the female athletic triad, which comprises amenorrhea, disordered eating pattern, and osteoporosis. In one study, up to 65% of long-distance runners on a team reported secondary amenorrhea.[13] Girls with this triad typically have a deficit in available energy as assessed by dietary energy intake minus

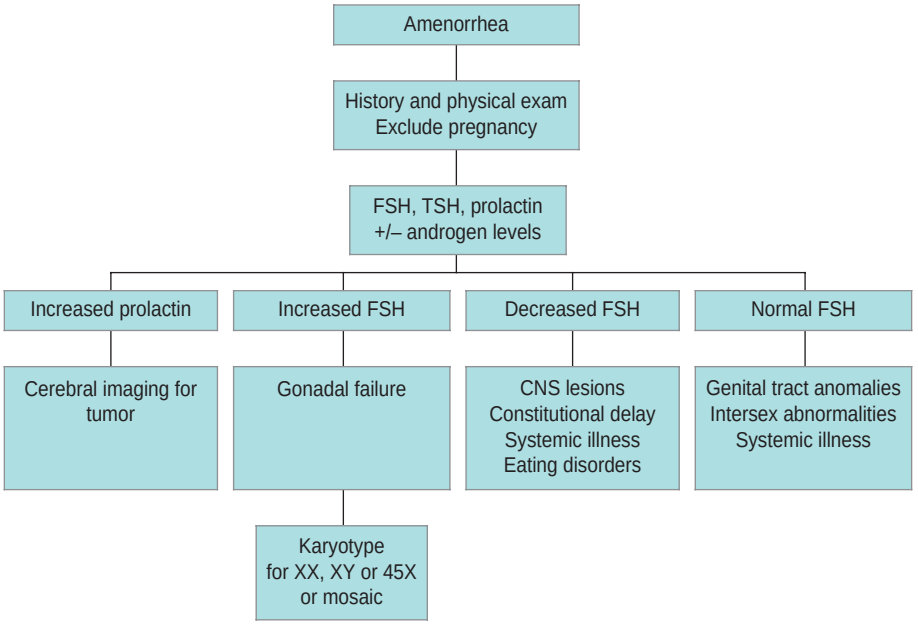

Figure 11.1 Investigation of amenorrhea.

exercise energy expenditure. Correction of the energy deficiency, either through exercise modification or increase in caloric intake, is required to restore menstruation. It is very important that athletes with secondary amenorrhea are questioned and screened for other aspects of the triad to aid appropriate treatment, since bone loss is proportional to the number of missed menstrual cycles.[13]

Secondary amenorrhea with low (or normal) gonadotropins may also be an early sign of anorexia nervosa. Significant weight loss, stress, and excessive exercise may contribute to the menstrual abnormalities associated with this condition. Bone loss accompanies the amenorrhea and therapy focused on restoring body image, accompanied by appropriate weight gain, usually restores menstruation.[14] Estrogen replacement may be indicated in selected patients.

Secondary amenorrhea with elevated gonadotropins is primarily indicative of gonadal failure, with Turner syndrome as the most common cause. With the latter, 45X karyotype or a mosaic is responsible. Perrault syndrome is characterized by 46XX gonadal failure and sensorineural deafness. XY gonadal dysgenesis and multiple X chromosomes are other related forms of hypergonadotropic hypogonadism.

Medications, in particular antipsychotics, may induce amenorrhea by competitive inhibition of the dopamine receptor resulting in elevated dopamine levels.[15] Metoclopramide, haloperidol, phenothiazine, risperidone, butyrophenones, and verapamil are all drugs that can act in this manner. Hormonal contraceptive use, common among teenagers, may be responsible for amenorrhea. This is particularly true of depot medroxyprogesterone acetate (DMPA); in addition, extended cycle oral contraceptive pills are specifically marketed for this purpose. However, pregnancy must be excluded in patients who are amenorrheic on contraceptive medications and testing is routinely performed prior to each 3-monthly DMPA injection. Chemotherapeutic agents may also be responsible for amenorrhea. Generally, pre- and post-pubertal ovaries are more resistant to cyclophosphamide than adult ovaries and there appears to be a dose-related response that

may be reversible. The addition of busulfan almost always results in ovarian failure. Radiotherapy can cause injury to the gonads and result in a hypergonadotropic amenorrhea.

EXCESSIVE MENSTRUATION

Menorrhagia is a subjective complaint and therefore quantification of blood loss can be unreliable. Warner et al found that using the definition of > 80 ml blood loss for more than two cycles did not predict iron status or clinical management.[16] Ferritin levels, clot size, and the number and frequency of sanitary protection change were found to be better predictors of the amount of blood loss.[17] Excessive, prolonged, or irregular bleeding from the uterine cavity is termed abnormal uterine bleeding (AUB); in the absence of anatomical causes, it is called dysfunctional uterine bleeding (DUB). In adolescents, immaturity of the hypothalamic-pituitary-ovarian (HPO) axis produces anovulation, which often results in excessive bleeding.

In adolescents who present with acute heavy vaginal bleeding, pregnancy and trauma should be excluded immediately. If, after careful questioning, the pattern of bleeding suggests menorrhagia, the exclusion of a coagulation disorder is important.

The incidence of an underlying bleeding disorder in an adolescent with menorrhagia varies widely in the literature from 2%[18] to 33%.[19] One of the reasons for this variation may be under-reporting of mild coagulation disorders, since the specific testing to make the diagnosis may not have been performed in all cases. Questioning regarding a history (personal or family) of nose bleeds, easy bruising or bleeding with surgical or dental procedures is helpful when assessing the patient for a bleeding disorder.

The most common genetic bleeding disorder encountered in clinical practice is von Willebrand disease, which occurs in the general population with a prevalence of 0.1–1%.[20] There are three subtypes of the disease, ranging from a mild functional deficit of von Willebrand factor (VWF) to more severe forms of the disease that produce a significant deficiency of VWF and resultant severe bleeding. Other clinically encountered bleeding disorders include factor X1 deficiency, which occurs more commonly in the Ashkenazi Jewish population and is suggested by a prolonged aPTT (activated partial thromboplastin time) and a normal PT (prothrombin time). It is confirmed by an assay specifically for the factor. Glanzmann's thrombasthenia is rare and is characterized by a failure of the platelets to undergo aggregation. Patients may have a history of mucocutaneous bleeding dating from childhood. Heavy bleeding may also be the result of drug treatment such as anticoagulants or chemotherapy but this should be evident from the patient history. Suggested evaluation for bleeding disorders will require referral to a hematologist. The likely work-up is shown in Tables 11.2 and 11.3.

Table 11.2 Recommended initial tests for the investigation of a suspected bleeding diathesis in adolescents with menorrhagia

Test	Abnormal result	Diagnosis
Platelet count	Decreased (< 150 000/ul)	Thrombocytopenia
Prothrombin time	Prolonged (> 17 s)	Clotting factor deficiency: factor VII, X, II, fibrinogen
Partial thromboplastin time	Prolonged (> 34 s)	Clotting factor deficiency: factor XI, X, IX, VIII, V, II, fibrinogen, von Willebrand factor
Bleeding time	Prolonged (> 9 min)	Vessel wall abnormalities Platelet dysfunction, e.g. Glanzmann's thrombasthenia; von Willebrand's disease

Reproduced with permission from Ellis MH, Beyth Y. Abnormal vaginal bleeding in adolescence as the presenting symptom of a bleeding diathesis. J Pediatr Adolesc Gynecol 1999; 12: 127–31.

Table 11.3 Confirmatory tests for selected bleeding disorders

Disease	Test	Result
von Willebrand disease	von Willebrand antigen level	Decreased
	Ristocetin cofactor	Decreased
	Factor VIII activity	Decreased
	Von Willebrand factor	Absent high molecular weight multimers
Factor XI deficiency	Factor XI activity assay	Decreased
Glanzmann's thrombasthenia	Platelet aggregometry	Decreased aggregation with collagen, thrombin, ADP epinephrine; normal aggregation with ristocetin

Reproduced with permission from Ellis MH, Beyth Y. Abnormal vaginal bleeding in adolescence as the presenting symptom of a bleeding diathesis. J Pediatr Adolesc Gynecol 1999; 12: 127–31.

The most commonly used treatments for menorrhagia in an outpatient setting are nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs act through inhibition of the cyclooxygenase enzyme pathway, which is responsible for the production of prostaglandins and leukotrienes. Some drugs in this family may also act through promotion of prostaglandin E2 (PGE2) a vasodilator. In placebo-controlled trials NSAIDs have been found to significantly decrease menstrual loss and improve dysmenorrhea.[21] Antifibrinolytics including tranexamic acid inhibit the conversion of plasminogen to plasmin and counteract fibrinolytic activity in the endometrium. Although not available in the United States, this medication is widely used in Europe and has also been shown to produce a significant reduction in menstrual blood loss in placebo-controlled trials.[21] The benefit of both the NSAIDs and tranexamic acid is that they only require use during the menstrual cycle.

Estrogens are also commonly used for the treatment of heavy vaginal bleeding. In patients with acute, severe dysfunctional uterine bleeding intravenous estrogens in a randomized controlled trial have been found to minimize blood loss.[22] The mechanism of action may result from an increase in clotting factor release from the liver and a direct stabilizing effect on the blood vessel wall.

The oral contraceptive pill (OCP) is commonly used for patients with menorrhagia and the potential for shortening or eliminating the pill-free interval is of benefit in these young women. Varying time intervals ranging from 63 to 84 days of active pills followed by 7 days of placebo have been used. One study[23] found that among gynecologists and pediatricians treating adolescents, 68% of the prescriptions for extended cycle OCPs were for menorrhagia.

Progestins have been used in the treatment of dysfunctional uterine bleeding since they stabilize the endometrium by inducing secretory change. Intramuscular DMPA at a dose of 150 mg every 12 weeks has been used in adolescents. Although this drug has been associated with irregular bleeding in the first few months of use, amenorrhea has been reported in more than 50% of users within 1 year of use and in 66% of users within 2 years.[24] The effectiveness must be balanced against the potential side effect of bone mineral density loss. A newer lower dose of DMPA formulated as 104 mg given subcutaneously every 12 weeks was approved by the FDA in 2004. This lower dose medication has also been found to suppress ovulation for up to 13 weeks and result in less irregular bleeding than the higher dose.[25] Progestins have been used to suppress menstruation in patients undergoing myelosuppressive therapy for cancer treatment. However, recently, gonadotropin-releasing hormone agonists (GnRH-a) administered 2 weeks prior to chemotherapy have been found to be superior to DMPA-150 for the suppression of menses in cancer patients.[26] A suggested approach to the management of dysfunctional bleeding is detailed in Table 11.4.

Table 11.4 Management of menorrhagia in adolescents

Hemoglobin value (g/100 ml)	Management
> 12	Reassurance Menstrual calendar Iron supplements Periodic re-evaluation
10–12	Reassurance and explanation Menstrual calendar Iron supplements Cyclic progestins or oral contraceptives Re-evaluate at 6 months
< 10, with no active bleeding	Evaluate for coagulation defect Transfuse, give iron supplements Oral contraceptives Re-evaluate in 3 months
Acute hemorrhage	Evaluation for a coagulation defect Transfuse Consider intravenous estrogens with progestin therapy Consider dilatation and curettage Oral contraceptive for 6–12 months

Adapted with permission from: Templeman C, Hertweck SP, Muram D, Sanfilippo J. Pediatric and Adolescent Gynecology, 2nd edn. Vaginal Bleeding in Childhood and Menstrual Disorders in Adolescence. Philadelphia, PA: WB Saunders, 2001: 237–47.

DYSMENORRHEA

Dysmenorrhea in adolescents may be primary or secondary. The true prevalence of primary dysmenorrhea is difficult to assess since many girls do not seek medical attention. One study revealed that 98% of adolescents used nonpharmacologic means to address their symptoms.[27] Dysmenorrhoea is reported to have a significant impact on school absenteeism and quality of life in caucasian adolescents, with recent reports confirming similar patterns among African-American and Hispanic girls.[27] The incidence of dysmenorrhea increases with the onset of ovulatory cycles and regular menstrual bleeding and is the result of excess prostaglandin production leading to uterine cramping and ischemia.[28]

There are serveral options for the treatment of primary dysmenorrhea and they include drug therapy, complementary medicine, and surgical nerve ablation techniques. There is a 35–40% placebo effect among treated patients with dysmenorrhea and this should always be considered when interpreting the results of treatment interventions. Table 11.5 summarizes possible treatment options for primary dysmenorrhea.[28]

After a careful history and physical examination to exclude an obvious cause for dysmenorrhea, a 3-month course of an NSAID at a therapeutic dose is useful: for example, ibuprofen 200–600 mg every 6 hours as needed, naproxen 440–550 mg followed by 220–275 mg 8-hourly as needed, or mefenamic acid 500 mg initially then 250 mg every 6 hours as needed.[27] Girls should also be advised to stop smoking and increase their intake of omega-3 fatty acids since these have been found to be associated with a reduction in dysmenorrhea symptoms.[27] If the symptoms persist, a 3-month trial of an OCP containing a potent progestin, e.g. levonorgestrel, may be helpful along with a pelvic ultrasound to exclude an occult uterine anomaly. If pain persists despite this, other causes, e.g. endometriosis, should be considered.

PREMENSTRUAL SYNDROME

Premenstrual symptoms are thought to occur in about 90% of women, with a smaller group being diagnosed with premenstrual syndrome (PMS). Only 10% of women fulfill criteria for premenstrual dysphoric disorder (PMDD). Although there is no universally accepted definition for PMS, in 2000, ACOG defined diagnostic criteria[29] (Table 11.6). Further, ACOG has placed the following stipulations: at least one affective and one somatic symptom must occur in the 5 days prior to menses in three prior menstrual cycles, all symptoms must resolve by day 4 of menses and not recur until after day 12. Symptoms must be present for at least two prospective cycles; symptoms must pose a disruption to social or work activities. There are also Diagnostic and Statistical Manual of Mental Health Disorders (DSM) criteria for PMDD and, despite overlap with PMS criteria, they differ by focusing more on problems with mood and mental

Table 11.5 Summary of treatment options for dysmenorrhea

Intervention	Mechanism of action in reducing dysmenorrhea	Effect on dysmenorrhea
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Inhibit endometrial prostaglandin production	More effective than placebo No significant difference between different NSAIDs in effectiveness
Oral contraceptive pills	Reduction in menstrual fluid prostaglandins Possible reduction in plasma vasopressin and uterine activity	More effective than placebo Monophasic, triphasic equally effective 20 μg ethinyl estradiol (EE2) pills effective
Injectable long-acting progestins	Suppression of ovulation	Insufficient data in studies with dysmenorrhea as primary outcome
Glyceryl trinitrate	Decreases nitric oxide levels in uterine muscle causing relaxation	More effective than placebo Limited by headaches as side effect
Vitamin E	Increase in prostacyclin (vasodilation) and PGE2	May be more effective than placebo, more trials are required
High frequency transcutaneous electrical nerve stimulation	Raises pain threshold, through afferent nerve stimulation	More effective than placebo in Cochrane Review More studies needed
Acupuncture		More effective than placebo in Cochrane Review More studies needed
Presacral neurectomy	Surgical division of presacral nerves	In patients with endometriosis Surgery in addition to nerve ablation more effective than surgery alone More studies required

Table 11.6 Diagnostic criteria for premenstrual syndrome

Affective symptoms	Somatic symptoms
Depression	Breast tenderness
Angry outbursts	Abdominal bloating
Irritability	Headache
Anxiety	Swelling of extremities
Confusion	
Social withdrawal	

1. Diagnosis made if there is a report of at least one of these affective and somatic symptoms in the three prior menstrual cycles during the 5 days prior to menses.
2. The symptoms must resolve within 4 days of onset of menses and not recur until day 12 of the cycle.
3. The symptoms must be present in at least two cycles during prospective recording.
4. The symptoms must adversely affect social or work-related activities.

health symptoms resulting in a greater degree of social disability.

The approach to the management of an adolescent with PMS symptoms includes attention to diet, regular exercise which combats stress, and adequate intake of calcium, which all appear to reduce physical and emotional symptoms.[30] If the patient has more pronounced physical symptoms, then the use of NSAIDs may be helpful. Suppression of ovulation with the OCP, especially with formulations that decrease the pill-free interval from 7 to 3–4 days and contain drospirenone, have been found to prospectively decrease both the mood and the somatic symptoms.[31] When mood symptoms are the primary complaint the selective serotonin reuptake inhibitors (SSRIs) are first-line therapy. Practitioners should be aware that the FDA issued a warning in 2004 regarding an increase in suicidal thinking and behavior in children on antidepressants. Placebo-controlled trials have found these drugs to be effective in both PMS and PMDD. Since fluoxetine is the only SSRI approved by the FDA for the treatment of depression in adolescents, a dose of 20 mg either daily or in the luteal phase of the menstrual cycle is used for PMS/PMDD. Whether other SSRIs may be equally effective has not been established.

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12. Polycystic ovary syndrome (PCOS) and hirsutism in adolescents

J Ricardo Loret de Mola

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most frequent cause of hyperandrogenism, irregular menses, and oligo-ovulation in adult women as well as among adolescents. It is estimated that 8% of the 18–25-year-old female population have the condition.[1] There is evidence to suggest that PCOS begins at puberty, when some of the clinical and metabolic abnormalities can be identified and usually progress into adulthood. However, the uniqueness of the adolescent and pediatric gynecological patient is that the PCOS features may be difficult to distinguish from symptoms of the end of puberty since they both overlap at times. The diagnosis of PCOS in an adolescent who shows signs and symptoms of hyperandrogenism and/or oligomenorrhea requires the same level of strict application of diagnostic criteria as is done for adults. The prompt diagnosis of PCOS is important, so we do not delay therapy to these young women given the limitations of our understanding of the disease and current diagnostic technology.

Given the strong association between PCOS and obesity, it is imperative that adolescent girls go through a work-up for the detection of the metabolic syndrome in order to allow for early intervention and the hopeful prevention of its complications over a lifetime. We cannot over-emphasize the importance of acknowledging that the rate of this condition is increasing in our pubertal and adolescent population, given the increased rates of obesity that are being detected throughout the United States and around the world.

Although the term PCOS is widely recognized, it may be more clinically useful to avoid the use of eponyms, particularly in the adolescent population, and instead to consider the spectrum of conditions and clinical manifestations that include persistent anovulation, acne, insulin resistance, and hyperinsulinemia, as well as hyperandrogenism. This is important to allow clinicians to focus on specific patient complaints so as to better address treatment strategies and individualize care.

INCIDENCE, DEFINITIONS, AND DIAGNOSTIC CRITERIA

The condition known as PCOS has been difficult to define over the past two decades. Given current criteria the prevalence of PCOS in the adolescent population is 8%. The uniqueness of adolescent and pediatric gynecological patients is that the clinical features of PCOS may be difficult to distinguish from symptoms of the end of puberty since they both overlap. Over half of the menstrual cycles are anovulatory even 3 years after menarche, and 88% of non-hirsute adolescent girls aged 12–18 with acne have elevated free testosterone and dehydroepiandrosterone (DHEAS) levels.[2] The first diagnostic criteria for PCOS were established by the consensus conference at the National Institutes of Health (NIH) in 1990, where it was defined as hyperandrogenism and chronic anovulation (with secondary causes of anovulation excluded, such as adult onset congenital adrenal hyperplasia (CAH), hypothyroidism, hyperprolactinemia, and androgen-secreting tumors).[3] Subsequently in 2003, a new consensus agreed at a meeting in Rotterdam by both the American Society for Reproductive Medicine (ASRM) and the European Society of Human

Table 12.1 Revised 2003 criteria for the diagnosis of PCOS from the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) 2003

- Oligo- and/or anovulation
- Clinical and/or biochemical evidence of hyperandrogenism
- Polycystic ovaries on transvaginal ultrasound:
  - Defined as the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increase in ovarian volume of greater than 10 ml

Reproduction and Embryology (ESHRE),[4,5] to revise these criteria and made recommendations for future research to be published under these new guidelines. The revised 2003 criteria are included in Table 12.1 with secondary causes of anovulation being excluded such as adult onset CAH, hypothyroidism, hyperprolactinemia, and androgen-secreting tumors, similar to the original 1990 NIH criteria.

There are few data on the use of the current diagnostic criteria as they relate to the adolescent population. It is clear that circulating androgen levels may represent an inherited marker for androgen excess,[5] therefore it is very difficult to have criteria by which the biochemical condition can be met. However, the use of free testosterone or the free testosterone index would probably be a more sensitive method in this patient population. Women with PCOS have lower SHBG (sex hormone-binding globulin) levels which increase the bioavailability of steroids, and this is commonly seen in girls with premature pubarche.[6] The likelihood of an androgen-secreting tumor in an adolescent is rare, and patients usually present with clear signs of virilization, and it is only in this patient population that total testosterone and DHEAS levels are of some value.[7] There is ample information on the routine use of 21-hydroxyprogesterone levels to rule out the possibility of adult onset adrenal hyperplasia in this population.

The clinical presence of hyperandrogenism is also more difficult to detect in the adolescent, but given the great concern adolescents have with excessive hair growth and acne, these symptoms usually bring them to medical attention. We also lack normative data in large adolescent populations regarding hirsutism, and its clinical assessment tends to be subjective. Hirsutism may be significantly less prevalent in the adolescent,[8] although PCOS is the leading cause of hirsutism in this age group and its presence should alert the clinician to the diagnosis. It is important to document the type, pattern, and extent of excess hair growth and score against a standardized method (Figure 12.1). This is particularly important in the adolescent to evaluate short-term therapies, as well as clinical studies and interventions as adults. A few terminal hairs on the face, areola, lower back, and lower abdomen may be normal, whereas terminal hairs on the upper back, shoulders, and upper abdomen usually result from hyperandrogenism. However, it should be kept in mind that ethnic and genetic differences are important in the amount and distribution of body hair. The fact that an adolescent complains of excessive hair does not mean that they have hirsutism, particularly among young women with ethnic/genetic predisposition (South European, Mediterranean, and Middle Eastern ancestry). It is also important to note that minor excessive hair among Asians and Orientals may trigger an investigation, given the rarity of idiopathic hirsutism in this ethnic group.

Over one-third of women presenting to a dermatologic clinic with acne were diagnosed with PCOS.[9] Acne has been used as a potential marker for hyperandrogenism, but its exact prevalence in the context of androgen excess is conflicting,[4] again, due to the lack of normative data given the significant overlap with patients with acne vulgaris, which is highly prevalent during adolescence and among patients with true hyperandrogenic disorders. Androgenic alopecia has also been used as a marker for hyperandrogenism in adults; however, it is unlikely that this will have a significant impact in the adolescent.

Some adolescents may present with acanthosis nigricans, a velvety hyperpigmented thickening of the skin particularly in the intertriginous areas such as the axilla and neck, which correlates with insulin sensitivity (Figure 12.2).[10] In adolescents the features can be variable, but its presence signals insulin resistance and an appropriate evaluation is recommended.

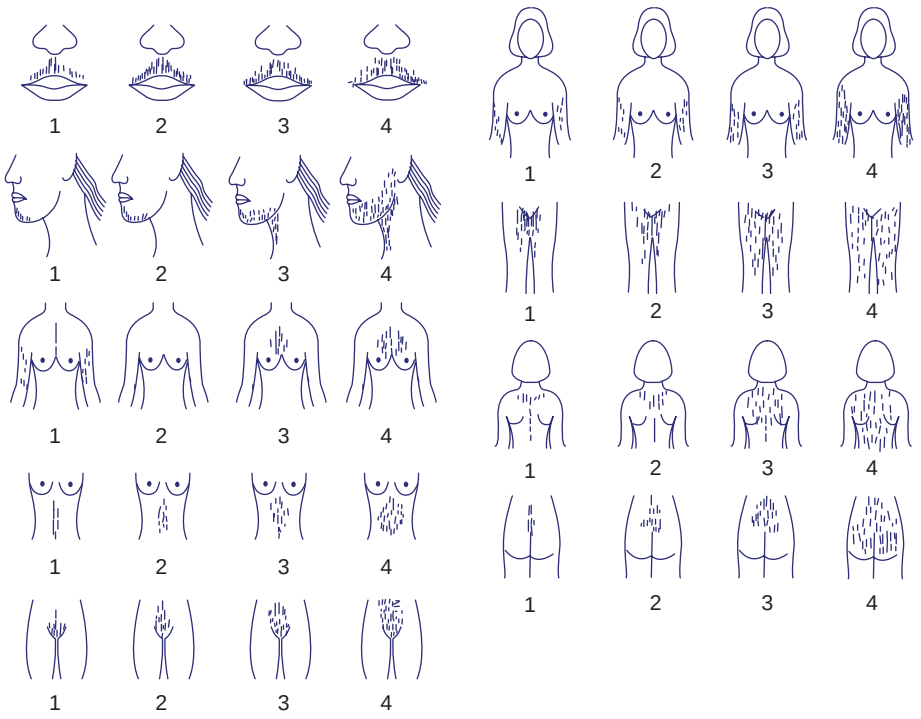

Figure 12.1 Modified Ferriman–Gallwey (F–G) hirsutism scoring system. Each of the nine body areas is rated from 0 (absence of terminal hairs) to 4 (extensive terminal hair growth), and the numbers in each area are added for a total score. A modified F–G score ≥ 6 generally defines hirsutism. Modified from Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: implications, etiology, and management. Am J Obstet Gynecol 1981; 140(7): 815–30. Image taken from Yildiz BO. Diagnosis of hyperandrogenism: clinical criteria. Best Pract Res Clin Endocrinol Metab 2006; 20: 167–76.

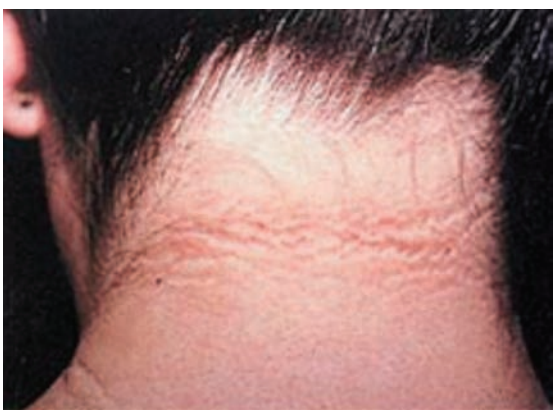

Figure 12.2 Acanthosis nigricans on the back of the neck.

Both the absolute level of circulating luteinizing hormone (LH) and its relationship to follicle-stimulating hormone (FSH) levels are significantly elevated in PCOS women as compared with controls.[11,12] This is due to the increased amplitude and frequency of LH pulses.[13] These elevations are observed in approximately 60% of women with PCOS,[14,15] whereas the LH/FSH ratio may be elevated in up to 95% of subjects.[16] Currently, we lack normative data on LH hypersecretion among adolescents and its role in the diagnosis and management is very limited, therefore serum LH levels should not be considered necessary for the clinical diagnosis of PCOS in the adolescent patient.

Polycystic-appearing ovaries are not uncommon among adolescents. The presence of PCOS-appearing ovaries is simply a signal for anovulation and, given the high prevalence of anovulatory cycles among adolescents, it is common to see this sign. In a cohort of 16–25-year-old females, PCOS-appearing ovaries were detected in 33% of the normal population.[1] Other studies have shown that the incidence of PCOS-appearing ovaries is five times higher in 16-year-old adolescents with oligomenorrhea, compared with girls with regular menstrual cycles.[17] In addition, offering a transvaginal ultrasound examination to an adolescent is frequently met with significant resistance, from both the patient and the parents. In trying to perform imaging via ultrasound transabdominally, it is usually technically difficult in this population and becomes an extraordinary inconvenience for these young women to fill their bladders and hold them for extended periods of time for completion of the studies. Moreover, all the criteria set up by the Rotterdam group were based on transvaginal and not transabdominal ultrasound, and we lack data with regard to the transferability of information from one mode to the other. Therefore, given the high prevalence of anovulation among adolescents, and the natural resistance from patients and parents to transvaginal ultrasound, PCOS-appearing ovaries should not be considered part of the diagnostic criteria.

Even with these limitations, the diagnosis of PCOS in a young adolescent who shows signs and symptoms of hyperandrogenism and/or oligomenorrhea requires the same level of strict application of these criteria as is done for adults. The strict application of the two clinical criteria is to be enforced, whereas pelvic ultrasound may be considered optional. Therefore, it is the author's recommendation that the 1990 NIH criteria be applied to adolescents prior to their becoming sexually active. A clinical diagnosis is important to prevent delaying therapy to these women, given the limitations of our understanding of the disease and current diagnostic technology. We must continue to acknowledge that the diagnosis of PCOS is primarily clinical and that hormonal assays only serve to exclude a differential diagnosis that includes potentially life-threatening conditions. Given the strong association between PCOS and obesity, it is imperative that adolescent girls undergo a thorough evaluation to detect the metabolic syndrome, to institute early intervention strategies, and to prevent its complications over a lifetime. We cannot over-emphasize the importance of acknowledging that the rate of this condition may be increasing in our pubertal and adolescent populations, given the increased rates of obesity that are being detected throughout the United States and around the world.

LONG-TERM HEALTH RISKS

Premature pubarche or the onset of pubic hair before age 8 may precede PCOS,[18] indicating early hyperandrogenism or premature andrenarche,[19] which is associated with a history of low birth weight. Premature pubarche is also a risk factor for hyperinsulinism and dyslipidemia among adolescents. The risk of premature adrenarche and PCOS appears to be higher among African-American and Caribbean-Hispanic girls, both of which appear to have an elevated androgen response. The mean adrenocorticotropic hormone (ACTH)-stimulated DHEAS/androstenedione ratio is significantly higher in this population than among normal girls in early puberty. This ACTH stimulation response pattern is similar to adult patients with PCOS, and young adolescent girls in these ethnic groups who show early signs of premature pubarche and/or obesity should be observed closely for the incidence of PCOS at a later age.

The mild hyperinsulinemia found among girls with precocious puberty increases markedly after the early stages of puberty, which is also associated with increased risk for gestational diabetes, abnormal glucose tolerance, and type II diabetes in first degree relatives of girls with precocious puberty. This suggests a genetic and/or environmental factor that contributes to the condition.[20] Several studies have documented the three- to seven-fold risk of developing type II diabetes in patients diagnosed with PCOS.[21,22] Although no cause and effect have been

reported, there is evidence to suggest that patients diagnosed with PCOS are at increased risk for cardiovascular disease,[23] as well as greater than normal susceptibility to coronary artery disease, dyslipidemia,[24,25] and markers of abnormal vascular function.[26] It is difficult to put into perspective the long-term detriment of these abnormalities in the adolescent population. However, it is reasonable to assume that the longer the condition has been present, particularly as patients enter adulthood, the risk will be magnified during their mature years. It is unlikely that adolescents with chronic anovulation and unopposed endometrial estrogen exposure will develop endometrial cancer, but the risk most certainly will increase in later years if left untreated.

There are many questions that remain to be answered regarding the effects of lifestyle changes and modification on the condition. Teenagers who suffer from chronic anovulation for at least 2 years after menarche are good candidates for hyperinsulinemia testing. During adolescence, insulin resistance develops probably from the increase in sex steroids and growth hormone resulting in a secondary increase in insulin and IGF-1, which subsequently leads to a decrease in SHBG, allowing for greater free sex steroid activity for pubertal development. Some teenagers fail to normalize the hyperinsulinemia associated with growth hormone increase in early puberty.[27] Anovulatory adolescents with PCOS, especially those who are overweight, should undergo periodic screening for abnormal glucose tolerance.[28] But the particular group that experiences premature andrenarche deserves special attention. Hyperinsulinemia can be a primary cause of premature andrenarche and can develop the full characteristics of anovulation, hyperandrogenism, and polycystic ovaries.[29] Low birth weight has been linked as a marker for this abnormality and its unique feature is that many of these individuals are not overweight, insulin resistance and dyslipidemia are present during childhood, indicating that the basic pathophysiology is hyperinsulinemia in early stages in fetal life, present in childhood that then worsens after puberty. Recent data suggest that treatment with metformin allows the metabolic parameters to normalize, which can then lead to normal ovulatory menstrual cycles.[30] It is unclear at this point whether long-term metformin treatment offers prevention of cardiovascular disease and early diabetes in this patient population.

Table 12.2 Criteria for the metabolic syndrome in women with PCOS

Risk factor	Cut-off value
1. Abdominal obesity (waist circumference)	> 88 cm (> 35 in)
2. Triglycerides	> 150 mg/dl
3. HDL-C	< 50 mg/dl
4. Blood pressure	> 130/> 85 mmHg
5. Fasting and 2-hour glucose from OGTT	Fasting 110 ± 126 mg/dl and/or 2-hour glucose 140 ± 199 mg/dl

Three out of five criteria qualify for the syndrome. HDL-C, high density lipoprotein-cholesterol; OGTT, oral glucose tolerance test. Reproduced with permission from: Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004; 19, 41–7.

The incidence of obesity in the adolescent population is increasing dramatically, and it is known as an independent predisposing factor for diabetes and PCOS; 10% of the prepubertal and pubertal population is obese.[10] Obesity is also associated with the metabolic syndrome (Table 12.2). A family history for PCOS is also an important risk factor, which appears to be more common in first degree relatives, mothers and sisters of women with the condition. These studies suggest that adolescents with a family history of PCOS deserve to be followed closely for evidence of oligo-ovulation and hirsutism.[4,5]

EVALUATION

PCOS should be considered in adolescent females with menstrual irregularities and signs or symptoms of androgen excess. The diagnosis can be made on clinical grounds alone; however, the laboratory evaluation of the adolescent patient should be

Table 12.3 Suggested laboratory evaluation of the adolescent with suspected PCOS

1. Testosterone, free or total testosterone and SHBG
2. 17-Hydroxyprogesterone, fasting 8–9 am in the follicular phase of the cycle. If abnormal proceed with an ACTH stimulation test
3. DHEAS
4. 24-hour urine for free cortisol if suspected Cushing syndrome, acanthosis nigricans or obesity
5. Thyroid-stimulating hormone (TSH)
6. Prolactin
7. 75 g 2-hour glucose tolerance test if evidence of family history, acanthosis nigricans or obesity
8. Fasting insulin if evidence of family history, acanthosis nigricans or obesity

Table 12.4 Clinical features of virilization

1. Hirsutism
2. Acne
3. Androgenic alopecia
4. Cliteromegaly
5. Deepening of the voice
6. Increased muscle mass
7. Decreased breast size
8. Amenorrhea

focused, with emphasis on excluding other more serious endocrinopathies and evaluating their metabolic status (Table 12.3). Elevated free testosterone levels are the biochemical confirmation of hyperandrogenism and consistent with a diagnosis of PCOS. In some symptomatic adolescents an elevated free testosterone level and/or decreased SHBG may be a better indicator of hyperandrogenism.[31] In a study of 588 patients evaluated for hirsutism, only 12 had elevated free testosterone in conjunction with normal levels of total testosterone and DHEAS.[32] Occasionally, an adolescent with evidence of hyperandrogenism will have an adrenal or ovarian tumor, non-classic CAH, or Cushing syndrome and therefore the practice is to obtain total testosterone, DHEAS, and 17-hydroxyprogesterone levels. A normal serum DHEAS essentially excludes the adrenal as a source of androgens, and elevated levels may be found in some cases of CAH, Cushing disease, and chronic hyperprolactinemia. If the levels exceed 700 μg/dl with or without testosterone elevation, the presence of an androgen-secreting adrenal tumor is strongly suggested.[33] In general, these tumors are associated with virilization (Table 12.4), and the diagnosis is based on the rapid progression of changes obtained as part of the history and physical exam.

Approximately 1–8% of hirsute women will have non-classic CAH. An elevated 17-hydroxyprogesterone level during the follicular phase will prompt an ACTH stimulation test to establish the diagnosis.[34] In addition, prolactin and thyroid-stimulating hormone (TSH) are recommended to exclude hyperprolactinemia and hypothyroidism, respectively. On occasions an FSH level is needed to exclude premature ovarian failure in the evaluation of an adolescent with primary or prolonged secondary amenorrhea, and minimal signs of androgen excess. Laboratory testing for glucose, insulin, and lipid profiles in adolescent patients should be based on the patient's family history, history of premature pubarche, presence of signs and symptoms of hyperinsulinemia (i.e. acanthosis nigricans), and/or obesity.[31] In adult women with PCOS, a fasting glucose to insulin ratio of < 4.5 has been shown to be an indicator of insulin resistance.[35] In young, obese adolescents with PCOS the mean glucose-to-insulin ratio was 1.9. Thus, it may be a useful indicator of insulin resistance and may help to identify the adolescent at risk for type II diabetes mellitus.[36] As previously discussed, ultrasonography is not particularly useful in the evaluation of the adolescent suspected of having PCOS, nor is it necessary to establish a diagnosis, but may be useful if a tumor is suspected.

MANAGEMENT

The focus of PCOS management in the adolescent is to treat the signs and symptoms of hyperandrogenism, regulate the menstrual cycle, identify more serious endocrinopathies, and treat glucose metabolism abnormalities as well as weight management. Combination oral contraceptives decrease testosterone levels, regulate the menstrual cycle, improve acne, and protect against endometrial hyperplasia, by decreasing ovarian steroid production and

increasing SHBG, which results in an overall decrease in free testosterone.[37] The decrease in free testosterone is so significant that it is unnecessary to monitor testosterone levels. Oral contraceptives are also an excellent pregnancy prevention measure for the sexually active adolescent and do not have an impact on the adolescent's weight.

The use of insulin-sensitizing agents, antiandrogens, topical treatments for acne and excess facial hair, and depilatories such as waxing, shaving, electrolysis, and laser treatments are dependent on the patient's symptoms and concerns and need to be individualized. Spironolactone blocks androgen synthesis and the androgen receptor in the hair follicle and is frequently used in combination with oral contraceptives to decrease hair growth. There is a slowing of hair growth at a dose as low as 100 mg/day.[38,39] Topical treatment with eflornithine cream is a non-hormonal alternative that is very efficacious, but has the disadvantages of its cost, frequent application, and return to baseline once it is discontinued.[40] With all medical treatments focused on decreasing hair growth, patients need to be counseled that it takes at least 6 months to notice any changes. Acne management can be a significant challenge that must be faced with the expert opinion of a dermatologist who can advise when to add other non-hormonal therapies such as antibiotics, topical preparations, and/or retinoic acid.

Consultation with a dietitian is helpful to encourage healthy eating habits. For the overweight adolescent, weight reduction is encouraged to reduce the risk of cardiovascular disease and type II diabetes mellitus. Numerous studies have shown that weight loss decreases androgen levels, improves insulin sensitivity, and leads to the spontaneous resumption of ovulation.[41] In addition, regular exercise is recommended. Studies have suggested that regular exercise decreases plasma insulin levels, and reduces development of type II diabetes, hyperlipidemia, and cardiovascular disease and the effects can be additive to weight reduction.[42] Insulin-sensitizing agents such as metformin improve ovulatory function and insulin sensitivity in adult women with PCOS; however, there is little information on its use among adolescents. Small initial studies suggest that it is well tolerated and effective.[43,44] Metformin may be particularly useful for treating the PCOS adolescent with insulin resistance and obesity, particularly if it is combined with dietary changes and exercise. It is expected that 39% of PCOS adolescents will regulate their cycles and ovulate on metformin, as well as improve their cholesterol levels.[43] However, use of metformin in adolescents with PCOS is still controversial and studies are needed to determine the long-term outcome in adolescent patients. Practitioners should pay special attention to sexually active adolescents on metformin, as ovulation may return and they will become vulnerable to pregnancy. In these patients combination therapy using contraception should be encouraged. As regards those patients transitioning from adolescence to adulthood in whom treatment of PCOS includes fertility management and ovulation induction, a Consensus workshop was held in 2007 and recommended clomiphene citrate as first-line treatment of PCOS. Should clomiphene fail to result in pregnancy, second-line treatment is either exogenous gonadotropins or laparoscopic ovarian surgery (drilling). The use of metformin is to be reserved for women with glucose intolerance.[45]

Finally, emotional support and psychological counseling may be beneficial for the adolescents with specific concerns about their appearance, future fertility, low self-esteem, and depression.[46] Management of the adolescent with PCOS is challenging and requires a supportive, multidisciplinary team approach, including a gynecologist, primary care provider, endocrinologist, dermatologist, psychiatrist or psychologist, and nutritionist, for optimal results.

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13. Breast disorders in children and adolescents

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Many congenital and neoplastic breast disorders present in childhood and adolescence. Although the vast majority are benign, any breast anomaly takes on major significance for young girls and their families. Breast development in adolescents is an important marker of transition to adulthood and alterations in normal development can have significant psychological effect.[1] Patients with breast disorders should be promptly diagnosed and counseled on the significance of the anomaly so that potential treatments can ensue in a timely manner. Such efforts permit minimal physical and/or emotional sequelae for the patient.[2]

NORMAL BREAST MATURATION

Development of the breast begins around 35 days of gestation, when the ectoderm on the anterior body wall thickens into a ridge known as the 'milk line,' 'milk ridge,' or 'Hughes lines.'[3] This ridge of tissue extends from the area of the developing axilla to the area of the developing inguinal canal. The milk line extends into the axilla and inferior to the inguinal area onto the medial thigh. The ridge above and below the area of the pectoralis muscle recedes while *in utero*, leaving the mammary primordium, which is the origin of the lactiferous ducts.[4,5] The initial lactiferous ducts form between weeks 10 and 20 and become interspersed through the developing mesenchyme, which becomes the fibrous and fatty portions of the breast.[5] The breast bud, under the stimulation of maternal estrogen, becomes palpable at 34 weeks of gestation.[5] This breast bud regresses within the first months of life, as the estrogen stimulation is no longer present. The nipple appears at 8 months gestation; it is initially a depression and later becomes elevated.[4]

Thelarche, or the onset of pubertal breast development, normally occurs between the ages of 8 and 13, with an average age of 10.3 years and is hormonally mediated.[6,7] The initiation of thelarche and progression in females is mediated by race. Research suggests that at all ages, normal thelarche is more advanced in African-American girls than in white girls. In a landmark study by Herman-Giddens et al they reported that approximately 15% of white girls have thelarche between the ages of 8 and 9 years whereas 48% of African-American children experience thelarche at this age. The mean age of onset of breast development for African-American girls was 8.9 years, while the average age of thelarche in white females was approximately 10 years.[8]

Once thelarche is initiated, adipose tissue and the lactiferous ducts grow in response to estrogen. Progesterone stimulation results in lobular growth and alveolar budding.[7,9] The normal development of the breast, which occurs over a period of 2–4 years, is classified by the Tanner system into five stages (Table 13.1). Maturation can sometimes occur asymmetrically due to fluctuation of the hormonal environments and end organ sensitivity.[10] Lack of development by age 13 is considered delayed and warrants endocrinological evaluation.[11] Menarche usually occurs approximately 2 years after initiation of breast development.[6]

BREAST EXAMINATION

A breast examination should be included in the annual examination of all children and adolescents.[1,7]

Table 13.1 Tanner staging of breast development[5,14]

Tanner stage	Comments
1 (preadolescent)	Elevation of the breast papilla only
2	Elevation of the breast bud and papillae as a small mound Enlargement of the areola diameter Areola becomes more pink
3	Further enlargement of the breast and areola with no separation of their contours Montgomery' s tubercules appear
4	Further enlargement with projection of the areola and papilla to form a secondary mound above the level of the breast
5 (mature stage)	Projection of the papilla only, resulting from recession of the areola to the general contour of the breast Erectile areolar tissue

Examination of the newborn includes assessment of breast size, nipple position, presence of accessory nipples, and nipple discharge.[1] Examination of the prepubertal female includes inspection and palpation of the chest wall for masses, pain, nipple discharge, and signs of premature thelarche.

Examination of the adolescent is performed with the patient in the supine position; the arm ipsilateral to the breast that is being examined should be placed over the patient's head.[1] The breast tissue is examined with the flat finger pads using the vertical strip method, concentric circular method, or in a clockwise fashion like the spokes on a wheel.[1] The Tanner stage should be noted (Table 13.1). A complete breast examination includes palpation for axillary, supraclavicular, and infraclavicular lymphadenopathy. In addition, the areola should be compressed to assess for nipple discharge.

SELF-EXAMINATION

There is lack of consensus among health-care providers regarding breast self-examination (BSE) and whether it should be recommended for adolescent patients.[12] The US Preventive Services Task Force concluded that the evidence was insufficient to recommend for or against teaching or performing routine BSE.[12] The impact of performing regular BSE on rates of breast cancer diagnosis, and breast cancer death, or tumor stage or size has not been proven.[12] In addition, BSE may increase the rate of breast biopsy for benign breast lumps.[13] However, advocates for BSE in adolescents suggest that it provides a mechanism to increase the adolescent' s understanding of the breast examination, enables the adolescent to contribute to her health care, helps the adolescent to accept her body, and provides an opportunity for discussion of issues related specifically to women's health.[1,7] In addition, BSE may be the primary mode by which adolescent breast masses are discovered.[14] Certainly, teenagers with a history of malignancy, radiation to the chest, or family history of BRCA1 or BRCA2 gene defects deserve early breast self-exam teaching in addition to the routine breast exams from their health-care provider.[2]

When teaching BSE to adolescents, it is important to stress the low prevalence of breast cancer within this age group.[15] Nonetheless, patients should be advised to seek medical attention if a breast mass persists beyond one menstrual cycle or is associated with erythema, pain, or fever. The following points should be emphasized when teaching BSE to adolescent patients[1] (Figure 13.1).

- Monthly BSE should be performed at the end of each menstrual cycle.
- The breast and armpit should be examined while standing and lying down. The patient should be taught to press gently with the middle three finger pads in one of the systemic approaches defined above.
- The nipple should be squeezed to assess for discharge.
- A health-care visit is recommended for nipple discharge or any unusual lumps in the breast or armpit.

When beginning to perform BSE, patients may have difficulty recognizing normal and possibly abnormal breast tissue. It is helpful for the adolescent to perform her first BSE on the same day that she had a normal examination in the office so that

How to Examine Your Breasts

Lie down and place your right arm behind your head. The exam is done while lying down, and not standing up. This is because when lying down the breast tissue spreads evenly over the chest wall and it is as thin as possible, making it much easier to feel all the breast tissue.

Use the finger pads of the three middle fingers on your left hand to feel for lumps in the right breast. Use overlapping dime-sized circular motions of the finger pads to feel the breast tissue.

Use 3 different levels of pressure to feel all the breast tissue. Light pressure is needed to feel the tissue closest to the skin; medium pressure to feel a little deeper; and firm pressure to feel the tissue closest to the chest and ribs. A firm ridge in the lower curve of each breast is normal. If you're not sure how hard to press, talk with your doctor or nurse. Use each pressure level to feel the breast tissue before moving on to the next spot.

Move around the breast in an up and down pattern starting at an imaginary line drawn straight down your side from the underarm and moving across the breast to the middle of the chest bone (sternum or breastbone). Be sure to check the entire breast area going down until you feel only ribs and up to the neck or collarbone (clavicle).

There is some evidence to suggest that the up and down pattern (sometimes called the vertical pattern) is the most effective pattern for covering the entire breast without missing any breast tissue.

Repeat the exam on your left breast, using the finger pads of the right hand.

While standing in front of a mirror with your hands pressing firmly down on your hips, look at your breast for any changes of size, shape, contour, dimpling, or redness or scaliness of the nipple or breast skin. (The pressing down on the hips position contracts the chest wall muscles and enhances any breast changes.)

Examine each underarm while sitting up or standing and with your arm only slightly raised so you can easily feel in this area. Raising your arm straight up tightens the tissue in this area and makes it difficult to examine.

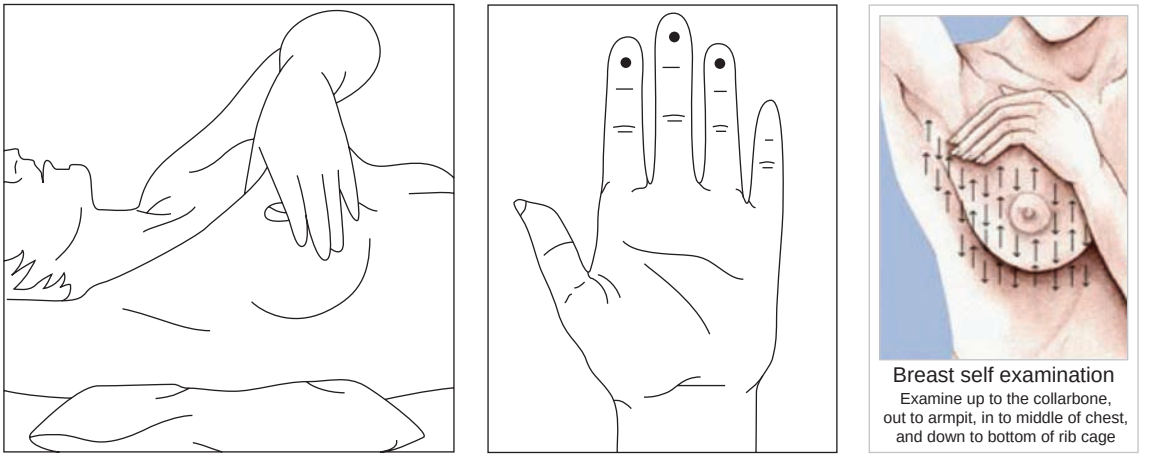

Figure 13.1 Self breast examination card.[73]

she has a baseline examination for comparison.[1] A guide to breast health for teenagers that includes information on self-examination of the breasts is available at www.youngwomenshealth.org/breast_health.html.

DISORDERS OF BREAST DEVELOPMENT

PREMATURE THELARCHE

Although normal thelarche occurs between 8 and 13 years of age, premature thelarche can occur as early as 1–3 years of age and, rarely, may even persist from birth.[16] Although the vast majority of patients with premature thelarche have no associated medical problems, hypothyroidism, which can be associated with premature thelarche, should be considered if other symptoms are present.[7] Premature thelarche is usually an isolated condition, but may be the first symptom of precocious puberty, particularly in girls older than 2 years of age.[16]

Precocious puberty occurs in up to 18% of girls with premature thelarche who are followed over time.[15] Serial examinations, with particular emphasis on growth velocity, secondary sexual characteristics such as pubic hair, pigmentation of the labia or areola, or vaginal bleeding are imperative to identify precocious puberty in girls with premature thelarche.[5,16] A complete evaluation is recommended in all cases of suspected premature thelarche to rule out precocious puberty.[10] Radiographs to estimate bone age may be appropriate for some patients if precocious puberty is suspected.[15]

Unless there are associated signs of precocious puberty, the parents should be reassured and the child followed.[9] Ninety percent of patients with isolated premature thelarche will have resolution of the breast enlargement 6 months to 6 years after diagnosis.[17] Long-term follow-up has shown that patients with isolated premature thelarche develop normal breasts at puberty and are at no increased risk for disorders or tumors of the breast.[17]

AMASTIA AND HYPOMASTIA

Lack of initiation of breast development by age 13 is considered delayed.[6] Complete absence of the breast, or amastia, is rare and is thought to occur from lack of formation or obliteration of the milk line.[4] Amastia can be associated with syndromes of more diffuse ectodermal anomalies such as congenital ectodermal dysplasia.[4,18] It can also be associated with anomalies of the underlying mesoderm, such as abnormal pectoralis muscle seen in Poland's syndrome.[4,19] Bilateral amastia is associated with other congenital anomalies in 40% of patients.[18] Such anomalies include systemic disorders (e.g. malnutrition, Crohn's disease) and/or endocrine disorders (e.g. congenital adrenal hyperplasia, gonadal dysgenesis, hypogonadotropic hypogonadism).[1,18] Amastia or hypomastia can also result from injuries sustained during thoracotomy, chest tube placement, inappropriate biopsy of the breast bud, radiotherapy, or severe burns.[5] Because the nipple complex does not normally develop until the 8th month of gestation, it can be quite hard to identify in the premature infant. As a result, placement of chest tubes or central lines can inadvertently injure the developing breast (Figure 13.2).

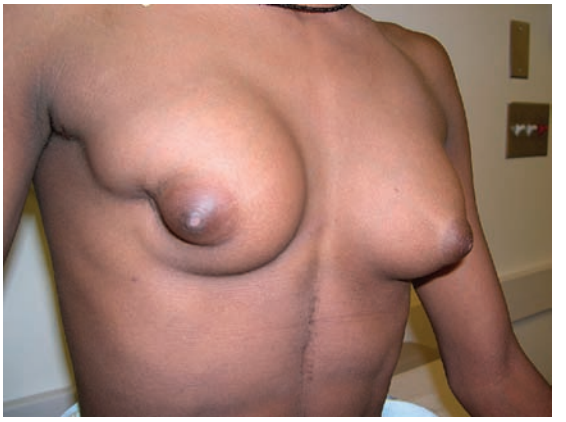

Figure 13.2 Breast deformity from placement of a neonatal chest tube.

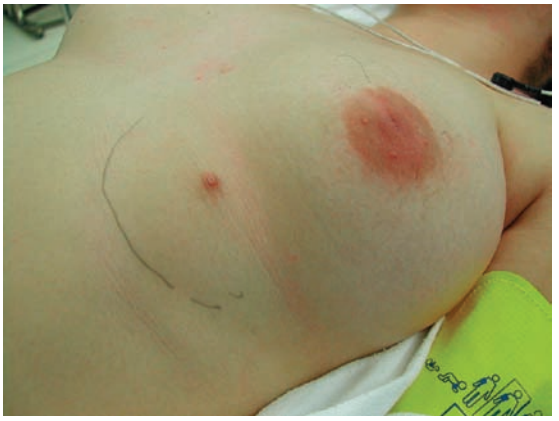

Figure 13.3 Polymastia. This complete breast, with nipple complex, is located in the most common position, just below the normal breast.

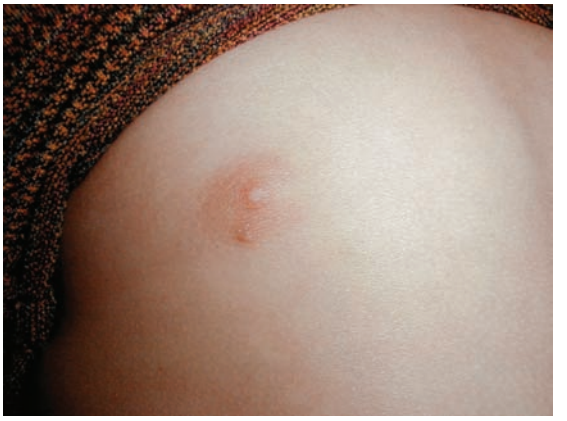

Figure 13.4 Intra-areolar polythelia, which is also called a dysplastic divided nipple.

POLYMASTIA AND POLYTHELIA

Supernumerary breast tissue, most commonly accessory nipples, occurs in approximately 1–2% of the population.[3,4,7] The abnormally placed tissue is almost universally located in the axilla or just inferior to the normally positioned breast along the embryonic milk line.[4] The normal axillary extension of breast tissue (the tail of Spence) should not be confused with supernumerary breast tissue. It has been found that 65% of children with supernumerary breast tissue have a single accessory nipple or breast, and 30–35% have two.[4] The largest number of reported supernumerary structures is 10.[4]

A complete accessory breast is termed polymastia (Figure 13.3). Supranumerary nipples are referred to as polythelia. Some studies have suggested the association of polythelia with abnormalities of the urinary tract and congenital heart disease, although this is debated by other authors.[3,5,18,20] True ectopic breast tissue, or breast tissue found outside the normal milk line, is exceedingly rare but has been reported on the face, back, perineum, and in the midline of the anterior torso.[4,21,22] Polymastia may warrant surgical excision in girls to prevent painful swelling during pregnancy. Resection of accessory nipples is occasionally warranted for cosmetic reasons.

CONGENITAL ANOMALIES OF THE NIPPLE

Athelia is defined as presence of breast tissue with absence of the nipple. This is not infrequent in accessory breasts, but is very rare in the normal location.[4]

Inverted nipples may predispose patients to infections, which can usually be prevented by careful attention to hygiene of the recessed area.[7] Surgical correction is possible, but elevation of the nipple inevitably divides the lactiferous ducts and makes future breastfeeding problematic if not impossible.[7] Other anomalies of the nipple that have been described include bifid nipples and intra-areolar polythelia, which is also called dysplastic divided nipples[7,18] (Figure 13.4).

BREAST ASYMMETRY AND HYPOMASTIA

Some degree of asymmetry is normal in women, and may be more pronounced during puberty while the breasts are developing.[7,15] Patients with mild asymmetry with no other associated pathology should be reassured. Significant hypomastia may be associated with connective tissue disorders or mitral valve prolapse[7] and is frequently familial.[5] Unilateral hypoplasia has been reported in association with a

Becker's nevus of the breast, which on examination will appear as a clear, brown stain.[5] This hamartoma has been reported to have increased androgenic receptors, which likely explains the hypomastia.[5] Bilateral breast hypoplasia may occur after chest wall irradiation or in the presence of ovarian dysfunction, hypothyroidism, or androgen-producing tumors.[7] Hypoplastic breast tissue can also be associated with a tuberous breast anomaly. In this condition, the base of the breast is limited and the hypoplastic breast tissue 'herniates' into the areolar complex.[7,15] Plastic surgery to correct the areolar complex and augment the hypoplastic breast may be indicated.

MACROMASTIA

Excessively large breasts are referred to as macromastia. The differential diagnosis of macromastia in the adolescent includes juvenile hypertrophy, pregnancy, tumors of the breast, and excessive endogenous or exogenous levels of estrogen and/or progesterone[23] (Table 13.2). D-Penicillamine and marijuana have also been reported as exogenous etiologies of macromastia.[23]

Table 13.2 Differential diagnosis of macromastia

Juvenile hypertrophy
Tumors of the breast
Giant fibroadenoma
Hamartoma[42]
Cystosarcoma phyllodes
Carcinoma
Hormonally active tumors
Ovarian granulosa cell tumor
Ovarian follicular cysts
Adrenal cortical tumors
Exogenous hormones
Estrogen
Testosterone
Gonadotropins
Corticosterone
Medications
D-Penicillamine
Marijuana

JUVENILE OR VIRGINAL HYPERTROPHY

Spontaneous massive growth of the breast in the adolescent, which may be unilateral or bilateral, is thought to be the result of excessive end-organ sensitivity to gonadal hormones.[23] The number of hormonal receptors in the hypertrophic breast tissue is normal, as are serum estradiol levels.[5,23] An autoimmune etiology has been suggested by some authors because of an occasional association with Hashimoto's thyroiditis, rheumatoid arthritis, and myasthenia gravis.[5]

Breast growth in patients with juvenile hypertrophy is rapid, begins shortly after thelarche, and can be dramatic, resulting in breasts that weigh up to 50 pounds each.[7,15] Spontaneous resolution is very rare.[23] Skin changes, such as peau d'orange and even necrosis may occur during phases of rapid growth.[23] The treatment depends on whether breast growth has been completed. If the patient is still growing, progesterone or antiestrogen medications can be used to control breast growth.[15] If this is unsuccessful, or if breast growth has been completed, breast reduction surgery is necessary.[23] Patients should be counseled that lactation may be affected by juvenile hypertrophy, particularly after breast reduction surgery, but that there is no increased risk of breast cancer.[23]

INFECTIONS OF THE BREAST

Mastitis is the most common infection of the breast. It is most common in lactating females. It can also occur in non-lactating females including young infants and adolescents, although it is rare. The prevalence of mastitis in these groups is not known and the etiology is unclear,[24] although some hypothesize that both populations have slightly enlarged breast tissue.[25]

Neonatal mastitis is an infection that usually occurs in term or near-term infants[26] within the first week of life.[25] It affects female infants twice as often as males and approximately 50% of infants with neonatal mastitis will develop a breast abscess.[26] Adolescents may develop non-puerperal mastitis or a breast abscess as a result of irritation of the skin (through shaving or nipple stimulation), a foreign body (e.g. piercing), or infection of an epidermal cyst.[15]

The initial therapy for all breast infections is antibiotics and analgesics.[26] One study suggests that infants need to be treated with parenteral antibiotics, while adolescents can be sufficiently treated with oral antibiotics.[24] Adolescent girls with mastitis may also achieve symptomatic relief with breast support.[15] Although *Staphylococcus aureus* is the offending organism in almost all cases, in infants, infections with *Shigella*, *Escherichia coli* and *Klebsiella* have been reported.[26] In most communities, the incidence of metacillin-resistant *Staphylococcus aureus* (MRSA) has become significant enough to warrant using antibiotics that have activity against MRSA such as clindamycin, sulfamethoxazole and trimethoprim, or vancomycin. Gram-negative coverage, particularly in newborns, may be indicated until culture results are obtained. Whether in an infant or an older child, small abscesses should initially be aspirated with a needle, using ultrasound guidance if necessary, and followed as antibiotic therapy is continued.[15]

Larger or persistent abscesses may need incision and drainage.[15] If incision and drainage are performed, a small, periareolar incision is indicated. In the prepubertal child, probing and disrupting the tissue should be kept to a minimum to avoid any injury to the underlying breast bud.

NIPPLE DISCHARGE

BLOODY DISCHARGE

The differential diagnosis of bloody discharge in children and adolescents includes mammary duct ectasia, chronic cystic mastitis, intraductal cysts, and intraductal papillomas. In adolescent athletes, bloody discharge may also be due to chronic nipple irritation (jogger's nipple) or cold trauma (cyclist's nipple).[27] Another important cause of bloody or brownish discharge in adolescents is discharge from the ducts of Montgomery (on the edge of the areola, not through the nipple). All children and adolescents with bloody discharge from the nipple should have the discharge cultured and appropriate antibiotics started.[9]

Mammary duct ectasia is a condition of benign dilatations of the subareolar ducts that results in inflammation and fibrosis. This is thought to be an anomaly of duct development that results in 'pleats' of obstructing epithelium in the lumen of the duct.[5,28] This obstruction can lead to bacterial overgrowth and abscess, most commonly with *Staphylococcus aureus*.[9] Other proposed etiologies include chronic inflammation of the periductal stroma with duct obliteration, trauma, and autoimmune reaction.[28] Infants with mammary duct ectasia typically present with a bloody discharge,[28] while adolescent patients usually present with a retroareolar mass, often bluish in color. Ductal ectasia often resolves spontaneously.[5,9,29] There may be recurrences but these usually respond to conservative therapy. Surgical excision may be indicated for persistent or recurrent symptoms or for an associated persistent cyst.[9] In girls, the excision should be limited to any identified cyst, with great care taken so as not to injure the underlying breast bud.

Intraductal papillomas are rare, subareolar lesions that are often difficult to palpate. They are bilateral in 25% of patients. Cytology of the bloody discharge shows ductal cells. Local excision, through a circumareolar incision, is curative.[7] In adolescents, cysts of Montgomery, which result from obstruction of the ducts of Montgomery, resolve spontaneously.

NIPPLE PIERCING

Body art, including piercings, is becoming increasingly popular among adolescents. Carroll et al found that 27% of surveyed participants in one adolescent clinic in 2000–2001 reported piercing.[30] Another

study of 12–22–year-old females in an adolescent clinic found that 36.7% of female adolescents had a piercing other than the earlobe.[31]

The most common reasons adolescents claim to get piercings include making a personal statement, reasons of fashion or self-acceptance, an improved perception of appearance and thus self-esteem, or as a rite of passage.[31–33] In some studies, adolescents with multiple piercings have been associated with high-risk behaviors or deviant activities.[33,34] Carroll et al documented an increase in drug use, distorted eating behaviors, and/or suicidal ideation, among adolescents with tattoo or body piercing compared with non-participants.[30] Suris et al noted that adolescent females with multiple piercings were more likely to have multiple sex partners, participate in higher-risk sex practices, be regular smokers, and use drugs more regularly.[35] Thus, piercing may be a warning sign to practitioners of adolescents with potential towards high-risk behaviors.

With the increase in nipple piercing is an increase in the risk of complications. The most common risks include infection, bleeding, pain, hematoma, cyst formation, allergic reactions, and/or keloid formation.[36] Infection is the most common health problem, with *Staphylococcus aureus* being the most reported causative organism.[31–33] Local infection is reported at rates of 10–30% and it can be treated with soap and warm compresses.[33] Topical ointment is not recommended as it is not considered effective and can delay healing and the piercing should not be removed. Oral antibiotics may be required depending on severity, and intravenous antibiotics may be required to treat systemic complications including endocarditis, toxic shock or septic arthritis.[31] Rarely abscess formation may occur and require antibiotics and/or incision and drainage.[36] In such cases, the piercing may have to be removed and a sterile replacement placed.

There is a potential transmission of viral hepatitis and human immunodeficiency virus (HIV) through body piercing.[32,33] Transmission can occur via use of contaminated needles or via sharing piercings with other persons with exposure to such infections. Accordingly, patients with post-piercing infections should also get screening for hepatitis B and C, and HIV. They should also have a glucose screen as diabetes mellitus can increase the risk of infection.[36]

Adolescents who plan to get a piercing should be given information regarding safe piercing strategies. Also, practitioners should ensure that they are up to date with immunizations (tetanus, hepatitis B) and are aware of the potential complications.[36] Lastly, patients should be aware that piercing should not affect subsequent breastfeeding.[33]

GALACTORRHEA

Milky discharge from the neonatal breast is a normal response to fetal prolactin levels, which peak at birth (Figure 13.5). In an adolescent, nonpuerperal lactation can be classified as neurogenic, hypothalamic, pituitary, endocrine, drug-induced, or idiopathic in origin.[37] Discharge from the areolar glands of Montgomery in the adolescent can be normal and should not be confused with galactorrhea.[7]

Neurogenic lactation occurs as a result of disorders of the chest wall, thorax or breast. Neurogenic lactation has been reported after thoracotomy, burns or injuries of the chest wall, herpes zoster, or chronic stimulation of the nipple.[37] Pituitary tumors, especially prolactinomas, are the most

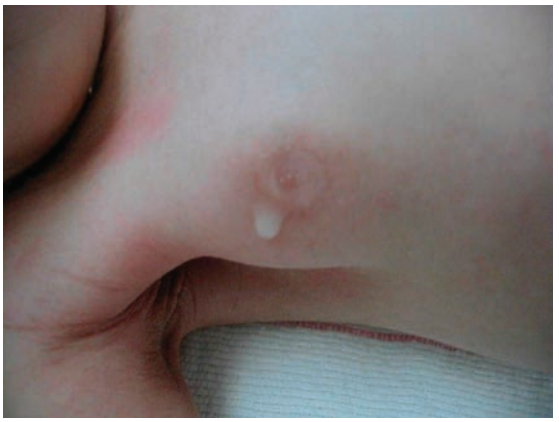

Figure 13.5 Normal breast bud and milky discharge in a neonate.

common hypothalamic or pituitary cause of galactorrhea, while the most common endocrine cause of galactorrhea in adolescents is hypothyroidism.[37] A wide variety of drugs have also been implicated in causing galactorrhea. The most common drugs are dopamine receptor blockers and catecholamine-depleting agents,[15,30] although oral contraceptive pills can cause this symptom as well.[38] Other common causes of galactorrhea in the adolescent including suckling or self-manipulation. Idiopathic or benign galactorrhea is a diagnosis of exclusion.

Patients with galactorrhea require a careful history and physical exam directed at the possible etiologies of galactorrhea. If there is a question as to whether the discharge is true galactorrhea, it should be sent for fat staining. Laboratory studies should include serum prolactin, follicle-stimulating hormone, luteinizing hormone, and thyroid function studies.[37]

Treatment includes instruction to avoid nipple stimulation or other behaviors that can promote the discharge. Treatment is directed by results of history, physical exam, and lab studies. If due to drugs the offending organism should be stopped, hypothyroidism treated, and/or prolactin tumors managed with appropriate medical or surgical care.[36]

BREAST MASSES

PREPUBERTAL BREAST MASSES

Neonatal breast hypertrophy is a normal response to maternal estrogen and occurs in both boys and girls in the first weeks of life.[7] Stimulation, such as attempting to squeeze the breast to promote the discharge, may result in persistence of the hypertrophied tissue. Neonatal breast hypertrophy resolves spontaneously and no treatment is necessary.

Initial breast development at the onset of thelarche starts with a firm, disc-like area of tissue under the areolar complex that can be mistaken for a 'mass.' This is often initially unilateral.[9] This is almost universally a normal, physiologic process but unilateral thelarche has been reported as a side effect of cimetidine, and is reversible with cessation of the drug.[39] Biopsy is contraindicated as this can result in injury to the developing breast.[11]

Hemangiomas and lymphangiomas can involve the developing breast (Figure 13.6). Although hemangiomas may involute after an initial growth spurt, compression of the breast bud during rapid growth can lead to injury and subsequent breast deformity. The diagnosis is usually made on physical examination, but can be confirmed with ultrasound or MRI. If there is doubt about the diagnosis a fine needle aspiration (FNA) biopsy may be indicated. Rapid growth of hemangiomas may require resection (if technically possible) or treatment with steroids to protect the developing breast bud from compression and injury.[9,40] In girls, the risk of injuring the breast bud by resection must be weighed against injury to the breast bud from the enlarging hemangioma or lymphangioma. MRI may aid in determining the resectability of the lesion and, hence, the risk to benefit ratio of surgical resection. Surgical resection of the lesion, with protection of the normal breast tissue, is indicated for complications of the lesion such as ulceration or hemorrhage.[9]

Other soft tissue or metastatic tumors of the breast are rare, but can present in the prepubertal child (Table 13.3). The majority of lesions will be benign but, if the diagnosis is uncertain, FNA or open biopsy may be indicated.[9]

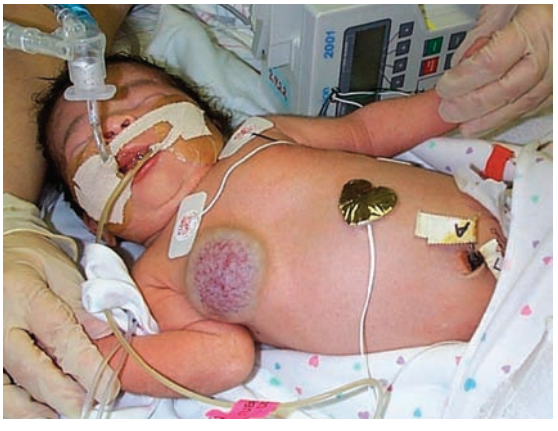

Figure 13.6 Hemangioma of the breast in a newborn infant.

Table 13.3 Differential diagnosis of the prepubertal breast mass

Unilateral breast bud development (premature thelarche)
Hemorrhagic cyst[8]
Abscess[8]
Lymphangioma[8]
Hemangioma[8]
Lipoma[8]
Metastatic tumor
Galactocele

BENIGN MASSES IN THE ADOLESCENT GIRL

Benign masses seen in post-pubertal girls include fibrocystic changes, fibroadenomas, phyllodes tumors, retroareolar cysts (or cyst of Montgomery), hamartomas, adenomas, papillomas, and trauma and other, very uncommon benign masses.

FIBROCYSTIC CHANGES

Fibrocystic changes in the breast can result in both localized masses and pain in the breast (also termed mastalgia). Patients should be reassured that this is a normal variant of female physiology, with these changes reported in 50% of women of reproductive age and 90% of women on autopsy.[15] Physical examination alone usually suffices to make this diagnosis since in most patients there is significant change with serial examinations done at different points in the menstrual cycle. Ultrasound may be helpful if the diagnosis is equivocal but mammography is not indicated. The treatment of mastalgia is a firm brassiere and NSAIDs.[7] Oral contraceptives have been reported to improve symptoms in 70–90% of women.[15] Treatments with vitamin E, evening primrose oil, and avoiding caffeine are unproven but popular.[7,15]

FIBROADENOMA

The most common mass seen in adolescent girls is the fibroadenoma. These masses usually occur in late adolescence, but can occur as early as 1–2 years before menarche.[7] Fibroadenomas are most often located in the upper outer quadrant of the breast and are more common in African-American patients.[9] The average size is 2–3 cm but they can become massive.[15] Fibroadenomas >5cm are referred to as giant fibroadenomas (Figure 13.7).

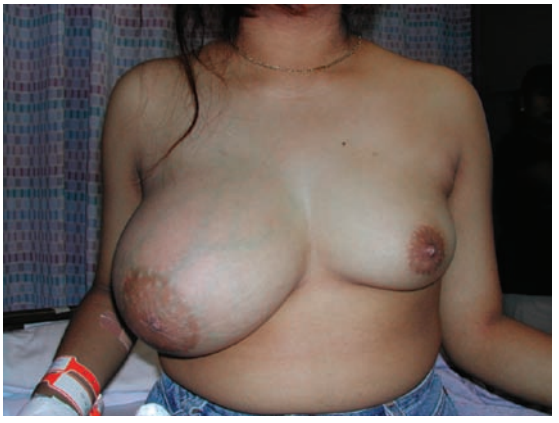

Figure 13.7 Giant fibroadenoma, mimicking juvenile hypertrophy, in an adolescent girl.

Ten percent of patients have bilateral lesions.[15] Up to 25% of girls will have multiple fibroadenomas, a condition that can be called fibroadenomatosis.[5,7] The lesions may enlarge slightly during the menstrual cycle.[9] The physical examination is usually diagnostic as these lesions are well circumscribed, 'rubbery,' mobile, and non-tender. In equivocal cases, an ultrasound may be helpful in making the diagnosis.[41] Mammography is not indicated in the adolescent patient.[9,10]

Fibroadenomas are believed to develop because of a local exaggerated response to estrogen stimulation.[9] The natural history of these lesions includes an initial period of growth, when the mass will double in size over 6–12 months, and then stabilization of the mass. Only 5% of fibroadenomas develop more rapid growth[42] and, in adults, many resolve spontaneously.[9,43] Because of the essentially non-existent risk of malignancy in adolescents, the low percentage of lesions with rapid growth, and the reports of spontaneous resolution, fibroadenomas

< 5 cm can be safely observed for at least one or two menstrual cycles.[44] If the lesion remains stable, then the practitioner and patient can decide between the options of serial observation versus excisional biopsy.

FNA, which is important in women old enough to be at risk for carcinoma of the breast, is not necessary or indicated in adolescent girls. Both observation and resection of persistent lesions can be justified in adolescence. The decision to proceed with excision is based on family anxiety, history of breast cancer, and the patient's age. As girls approach adulthood, and the risk of breast cancer therefore increases, most physicians recommend excision of persistent masses.[9] If there is growth of the lesion, excisional biopsy is warranted.[44] Families should be counseled that the biopsy or excision may result in cosmetic changes to the breast. Persistent local pain following removal of a fibroadenoma has also been reported.[45]

GIANT FIBROADENOMAS

Fibroadenomas > 5 cm are termed giant fibroadenomas. On examination, these may be softer than the typical fibroadenoma and may even resemble normal surrounding breast tissue.[15] There may be dilated veins over the surface and the skin overlying the mass may be warm to the touch[15] (Figure 13.7). Giant fibroadenomas should be excised, as they cannot be distinguished from cystosarcoma phyllodes by physical examination, mammography, or sonography.[46] In addition, these tumors have been reported to double in size in as little as 3 months in rare patients.[7] FNA and core needle biopsy can be helpful for planning the operative approach if the histology leads to a definitive diagnosis of cystosarcoma phylloides. However, it is very difficult to distinguish between a fibroadenoma and cystosarcoma phyllodes on aspiration or needle biopsy, so a negative result should not affect the decision to operate.[46]

Incisions for excision of a giant fibroadenoma can be problematic. Whenever possible, a periareolar incision should be used. Large lesions can be removed through a periareolar incision by placing them in a bag and then morcellating them before removal.[47] Excision of large fibroadenomas can result in significant deformity of the breast and patients should be counseled on this before removal of the tumor.

PHYLLODES TUMORS

Phyllodes tumors were first described by Johannes Müller in 1838, who coined the term 'cystosarcoma phylloides.' This term is misleading as these tumors are rarely cystic and do not have the malignant potential of most sarcomas.[44] For that reason, they are better termed 'phyllodes tumors.' Phyllodes tumors are stromal tumors that are histologically classified as benign, intermediate, or malignant.[9] The distinction is largely semantic as benign lesions can metastasize and may recur locally. The median age of presentation of phyllodes tumors is 45 years; however, they have been reported to occur in girls as young as 10 years of age.[44,48] These tumors occur more frequently in African-American adolescents.[7]

The diagnosis is difficult to make before biopsy, as the lesion may resemble a giant fibroadenoma. Large tumors may cause skin stretching, venous distention, and skin ulceration.[7] If the nipple complex is involved, there may be a bloody discharge.[7] Ultrasound findings which are suggestive, but not diagnostic, of cystosarcoma phyllodes include lobulations, a heterogeneous echo pattern, and an absence of microcalcifications.[46]

The treatment of benign cystosarcoma phyllodes is total surgical excision with a 1 cm margin of normal tissue.[49] Patients with histologically malignant cystosarcoma phyllodes traditionally have undergone mastectomy.[46] Some authors have reported, however, that adolescents with malignant phyllodes tumors have a more 'benign' course than adults and have suggested that the breast can be preserved in these patients.[44] Only clinically palpable nodes, which are present in approximately 20% of patients, should be resected.[49] The majority of these nodes will be enlarged in response to tumor necrosis and inflammation, since metastases occur

by hematogenous, not lymphatic dissemination.[7] Re-excision is indicated if adequate margins were not obtained at the first surgery.[49] If an adequate margin cannot be achieved on the chest wall, local radiation therapy should be considered.[49]

Local recurrence occurs in up to 20% of patients with phyllodes tumors and is treated with re-excision or mastectomy.[44] Systemic recurrence has been reported in 14–15% of patients.[49] Metastases can occur in lung, pleura, soft tissue, bone, pancreas, and the CNS and usually occur without lymph node involvement.[44,49] Isolated reports of palliation with single or multiple chemotherapeutic agents have been described, but in general, adjuvant therapy plays a limited role in successful treatment of phyllodes tumors.[44]

Overall, the 5-year survival rate for malignant phyllodes tumors in adults is approximately 80%. Because adolescents with phyllodes tumors may have a biologically less aggressive tumor than adults, their prognosis may be better, although these data are not known.[44]

RETROAREOLAR CYSTS

Montgomery's tubercles are the small papular projections on the edge of the areola and are related to the glands of Montgomery, which may serve a role during lactation.[15] In adolescents these glands can obstruct and present as either acute inflammation (62%) or an asymptomatic mass (38%).[50] The diagnosis of these retroareolar cysts, also referred to as cysts of Montgomery, is primarily clinical, but can be confirmed with ultrasound. Ultrasound will most commonly demonstrate a single cystic lesion, usually unilocular, in the expected retroareolar location.

The most common presentation of patients with retroareolar cysts is acute inflammation with localized tenderness, erythema, and swelling under the areola, extending into the breast tissue.[50] Conservative treatment with oral antibiotics directed at *Staphylococcus* and non-steroidal anti-inflammatory drugs (NSAIDs) usually results in resolution of the acute inflammation within 7 days.[50] Following this non-operative treatment, an asymptomatic mass is usually present. Patients with retroareolar cysts may describe a brownish discharge from one of Montgomery's tubercles, particularly with compression of the mass. In the absence of persistent infection or other complications, the treatment of retroareolar cysts is observation with serial physical examination and, if needed, repeat ultrasound examination. Over 80% of these cysts resolve spontaneously, although this may take up to 2 years.[50] Patients should be instructed not to compress the area as this may prevent resolution of the mass. Only rarely is drainage of a persistent abscess necessary. Resection may be indicated if the mass persists for more than 2 years or if the diagnosis is in question.[15]

OTHER BENIGN BREAST MASSES

A variety of rare benign tumors of the breast have been described in adolescents and young adults and include hamartomas, adenomas of the nipple, tubular adenomas, erosive adenomatosis, and juvenile papillomatosis (Table 13.4).

Hamartomas of the breast are a rare tumor composed of the normal components of the breast that can present as unilateral macromastia. They

Table 13.4 Differential diagnosis of the post-pubertal breast mass in girls

Fibroadenoma
Cyst of Montgomery
Duct ectasia
Fat necrosis
Vascular lipoma[8]
Subareolar neuroma[8]
Hamartoma[42]
Abscess[8]
Lymphangioma[8]
Hemangioma[8]
Lipoma[8]
Juvenile secretory carcinoma
Ductal carcinoma
Metastatic disease

have also been called lipofibromas, adenolipomas, and fibroadenolipomas.[51] Only eight cases have been reported in women under 20 years of age.[51] The treatment of hamartomas is total excision.

Adenomas of the nipple are very rare, but have been reported to occur in children and adolescents. They are treated by local excision.[52] Tubular adenomas cannot be distinguished from fibroadenomas by history or examination and the diagnosis is usually obtained on pathologic evaluation.[53] No further treatment is necessary after local excision. Erosive adenomatosis is a rare benign tumor that presents with erythema, erosion, and crusting of the nipple.[54] Serosanguinous discharge may occur and a nodule may or may not be palpable. Treatment is local excision of the lesion, which may be delayed until breast growth is complete. Successful treatment with cryosurgery has also been reported.[54]

Juvenile papillomatosis is a benign, localized, proliferative lesion usually seen in girls over 10 years of age.[55] Juvenile papillomatosis usually presents with a mass, similar to a fibroadenoma, in one breast. When resected, this is a well-demarcated mass with multiple cysts separated by fibrous stroma, giving it a 'Swiss cheese' appearance.[53] Juvenile papillomatosis is considered a marker for increased breast cancer risk in family members, but not necessarily in the patient, unless recurrent.[55] However, *in situ* and invasive carcinoma, which is usually juvenile secretory carcinoma, has been reported in up to 15% of cases of juvenile papillomatosis.[53] The treatment of juvenile papillomatosis is total resection, with preservation of the normal breast.[55]

Trauma can result in lesions that resemble either an infection or a mass in adolescents. In particular, fat necrosis that occurs after trauma can resemble a solid mass in the breast.[7] This has been reported following seat-belt injury as well as with other direct blows to the breast.[56]

PLASTIC SURGERY IN THE ADOLESCENT POPULATION

Cosmetic surgery performed in patients 18 years or younger has increased significantly over the last several years.[36] This can be attributed to our society's emphasis on beauty and self-improvement, as well as easy access to plastic surgery. The media and plastic surgery reality television shows have also exposed the adolescent population to esthetic surgery and altered patient's perceptions of such operations.[57,58]

The ultimate role of plastic surgery is to alter body image and thus improve a patient's quality of life. The teenage years are a time of sudden changes and in some patients newly unattractive features develop at an age where there is the greatest concern about being attractive. It has been shown that one's body image affects the amount of success that can be achieved. Thus it is not surprising that such invasive procedures to improve appearance, when condoned by parents, can be free of emotional turmoil and sequelae.[57]

The key to successful plastic surgery in the adolescent is based on appropriate patient selection. Proper patient management involves selecting mature candidates with clear and realistic expectations who are free of psychopathology. Appropriate candidates should be able to freely articulate what they are seeking via surgery, have realistic expectations, and clearly describe why they are motivated to have surgery. They must also be mature enough to tolerate the discomfort of surgery postoperatively. Finally, parents' expectations must be congruent.[57] Patients suspected of having body dysmorphic disorder, eating disorders or personality disorders should be evaluated to ensure that they are not requesting surgery for pathologic reasons.

One can argue that adolescents overestimate their deformities and thus are requesting surgery inappropriately. A study of English adolescents and their motivations for plastic surgery revealed that when adolescents request plastic surgery intervention, the adolescent does have realistic appearance perceptions and they are truly suffering appearance-related burden.[59] For instance, reduction mammoplasty can improve an adolescent's appearance and functional status for female adolescents with extremely large breasts. Plastic surgery surveys always show a very high degree of patient satisfaction with this procedure, with over 94% with evidence

that patients increase physical activity, fit into clothes better, and have improved self-esteem.[57] Proper selection is imperative, with the best time for surgery being after breast development has stabilized, and informed consent is necessary. Informed consent for reduction mammoplasty includes a possible inability for future breastfeeding, scarring, and/or nipple numbness.[60] Similarly, a patient with asymmetric breasts may require either unilateral breast reduction or augmentation, or both, and can have similar patient success with appropriate candidate selection. Informed consent includes awareness that breast implants are not typically associated with problems with future breastfeeding or with breast cancer; mammography may require additional views.[36]

One of the most commonly requested procedures in the adolescent population is breast augmentation. Teenage patients account for approximately 4% of breast augmentations.[61] When breast augmentation is done for purely esthetic reasons, it is discouraged before the age of 18 unless there is careful and thoughtful discussion with the patient and family. The American Society of Plastic Surgeons has adopted guidelines for appropriate selection of adolescents for esthetic breast surgery. They state that the adolescent candidate for purely esthetic breast augmentation should be at least 18 years of age. The Food and Drug Administration (FDA) considers the use of breast implants for esthetic augmentation in patients younger than 18 years to be off-label use.[62] Such guidelines are based on the hope that breast development will be finished and maturity of patients will be ensured, as not all teenagers who seek esthetic surgery are well suited for an operation.

MALIGNANT TUMORS OF THE BREAST

PRIMARY BREAST CANCER

The risk of primary breast cancer is small in the adolescent population. This risk is increased if there is a significant family history or mutations in the BRCA1 and BRCA2 genes, although most of these malignant tumors will not present until the patient is at least in her twenties. Mutations in these genes have been identified in 7–9% of all breast cancers.[15] Girls who have mutations in one of these genes have a 3.2% risk of breast cancer at age 30 and an 85% risk by age 70.[15]

Primary carcinoma of the breast has been reported in 39 children 3–19 years of age.[9,63] Over 80% of these patients were diagnosed with juvenile secretory carcinoma, with the remainder having intraductal carcinoma. Juvenile secretory carcinoma has been reported in association with juvenile papillomatosis.[9] Juvenile secretory carcinoma often has a thick-walled capsule, which may cause the lesion to appear cystic on ultrasound.[64]

Primary sarcoma of the breast is rare in all age groups and exceedingly rare in children. Rhabdomyosarcoma can occur as a primary tumor of the breast, usually in adolescent girls. Rhabdomyosarcomas are usually rapidly growing, mobile masses with no skin involvement. Histologically, these are usually alveolar rhabdomyosarcomas.[64] Liposarcoma has been reported within a phyllodes tumor of the breast in an adolescent patient.[65] These tumors may appear encapsulated but should be treated by wide local excision.[48] Fibrosarcoma and malignant fibrous histiocytoma may be the most common soft tissue sarcoma of the breast.[48] Other, rare primary sarcomas of the breast include fibrosarcoma, fibrous histiocytoma, leiomyosarcoma, and osteogenic sarcoma.[48]

Primary non-Hodgkin's lymphoma of the breast has also been reported in children.[66] Treatment of these rare primary malignancies of the breast is based on established protocols.

The treatment of these primary breast cancers in children is complete surgical excision, often by mastectomy.[9] Estrogen and progesterone receptors should be determined. Local recurrence is treated by re-excision, or complete mastectomy. Adjuvant therapy for juvenile secretory carcinoma is rarely used, and prognosis for these patients is excellent following local excision. Adjuvant therapy for intraductal carcinoma is based on the nodal status and hormone receptors, with most oncologists using modified adult protocols for the treatment of

children with this tumor. Before treatment with radiation or chemotherapy for breast cancer or other malignancies in an adolescent, the practitioner should consider options for fertility preservation if the patient desires. In single females, oocyte cryopreservation should be considered and can be carried out with the help of a reproductive medicine specialist.[67]

SECONDARY BREAST CANCER

Chest wall radiation, usually given to treat Hodgkin's lymphoma, increases the lifetime risk for breast cancer.[68] This is particularly true for girls who are 10–16 years of age at the time they receive radiation, as this is a period of rapid breast growth.[69] Girls with Hodgkin's disease who require radiotherapy of the chest have an 82-fold increased risk of breast cancer, with almost 40% of patients ultimately developing breast cancer.[69] The median time from radiation therapy to diagnosis of the breast cancer is 20 years. Angiosarcoma of the breast has also been reported in adult women following external beam radiation for breast conservation.[39] This exceedingly rare tumor has also been reported in adolescents. The treatment is mastectomy without routine axillary dissection.[70]

METASTASIS TO THE BREAST

Cancer metastatic to the breast has been reported in children with primary hepatocellular carcinoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, neuroblastoma, and rhabdomyosarcoma, particularly the alveolar variant.[9,66,71] Other, less common tumors that have been reported to metastasize to the breast in children include histiocytosis, medulloblastoma, renal carcinoma, and neuroblastoma.[71] Bilateral breast disease occurs in 30% of children with rhabdomyosarcoma metastatic to the breast.[71] Ultrasound is the diagnostic tool of choice as it can often differentiate these lesions from the more common benign lesions.[71]

OVERVIEW OF CLINICAL MANAGEMENT OF BREAST MASSES

Although breast malignancy is rare in children or adolescents, breast lesions in this population are quite common. Evaluation starts with a thorough history and physical exam. Ultrasound can be used as an adjunct when needed. Ultrasound is the technique of choice in adolescents. Mammography is not indicated in the adolescent patient as it is very hard to interpret owing to the large amount of fibroglandular tissue present[9] and because the developing breast tissue is more sensitive to radiation.[10]

Asymptomatic breast masses that are small and consistent with fibroadenoma on imaging can be observed. If the mass is cystic on examination and/or ultrasonography aspiration may be indicated. If the fluid obtained is clear, it may be discarded as the cytologic results have not been found to be clinically useful.[72] If the fluid is bloody it may be sent for cytologic examination.[73] If the mass collapses after aspiration, it may be assumed to be a cyst and can be re-evaluated in 3 months.[1]

When aspiration is not possible or nonproductive, or masses are hard, non-mobile, enlarging, or a source of anxiety, the patient should have the mass evaluated by biopsy or excision.[1] FNA is a relatively safe diagnostic procedure. Because malignancy is essentially non-existent in this population, excision of breast masses is performed through a periareolar incision for cosmetic reasons. FNA or excision is best done by a practitioner appropriately trained in surgical management of the breast.

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14. Adolescent sexuality

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INTRODUCTION

Adolescence is a time of self-discovery accompanied by psychological, cognitive, social–cultural, and physical changes.[1] Adolescent sexuality develops within the context of these changes. While much attention is given to sexual activity of adolescents – particularly to intercourse – it is important to understand the process of developing a healthy sexual identity.

Human sexuality encompasses sexual knowledge, beliefs, attitudes, values, and behaviors of individuals. Therefore, sexual development is a multidimensional process involving the basic human need of being liked and accepted, displaying and receiving affection, feeling valued and attractive, and sharing thoughts and feelings. This process takes place in adolescence and helps to complete a series of tasks such as developing a body capable of reproducing, learning how to maintain intimate relationships, managing a range of complex emotions, incorporating cultural–moral beliefs into behavior, and learning to think and problem-solve independently. This highly complex interaction of personal and social phenomena is known as sexuality.

Studies of the evolution of the menstrual cycle reveal that young women reach puberty and sexual maturity at younger ages compared to what was reported a century ago. This information combined with the frequency of sexual activity in the teen years, underscores the need for health-care providers to understand sexual development, in order to provide both anticipatory guidance and education for young people as they navigate their emerging sexuality.

Definitions to assist in the description of sexual development and expression are listed in Table 14.1.

SEXUAL DEVELOPMENT

Adolescent sexual development is a gradual process that begins during childhood. Genetic and biologic factors begin to shape sexual development even before birth. Specifically, chromosomal makeup will determine whether an individual is biologically male or female. The genetic imprint is set on the basis of one's chromosomal inheritance during embryonic development. However, one's genotypic expression is not always linked to the expression of phenotype. For example, enzymatic defects may prevent the development of specific reproductive hormones that would otherwise allow internal and/or external genital structures to fully or properly develop. The defects may be present at birth or may develop later. Timing of such enzymatic deficiencies may play a role in the development of the brain, and ultimately, in the development of one's relationships with others and one's sexual self.[2,3]

Genetic and biologic factors also influence sexual development by determining the levels of hormones and neurotransmitters that influence sexual response.[4] While children have lower levels of sex hormones than adults or adolescents, the same mechanisms of hormonal influences apply; there is a range of childhood responsiveness, with some children being much more sexually curious and attuned to their bodies. An outline of sexual development in females from infancy to puberty is provided in Table 14.2.[2,4,5–9]

Parents also play a role in the sexual identity process. The answer to the question, Am I a girl or a boy? is partly based on interaction between parent and child and interactions of parents or a parent with others. Children witness how people interact. Because children are impressionable, they learn by

Table 14.1 Definitions for the description of sexual development and expression

Anatomic sex	Assignment of male or female sex based on evaluation of external genitalia
Sexual identity	An early self-awareness as to one being male or female
Gender identity	Childhood development of the sense of oneself as a boy or girl in society
Gender roles	Characteristics, behaviors, and interests that are defined by cultures, which separate boys from girls (sometimes referred to as sexual roles)
Sexual orientation	A term used to describe an adolescent's underlying sexual preference – homosexual, heterosexual or bisexual; usually defined as a consistent pattern of erotic arousal toward persons of the same or opposite sex
Sexual self	An inclusive category referring to how an adolescent describes, feels or expresses his or her sexual self. This encompasses gender identity, sexual and gender roles, and sexual orientation

From: Ponton LE, Judice S. Typical adolescent sexual development. Child Adolesc Psychiatric Clin N Am 2004; 13: 497–511.

Table 14.2 Early sexual development in females

Age	Female behavior and feelings
9–11 months	Sporadic self-stimulation begins[7] May increase until 18 months or be absent
16–19 months	Early genital phase a. increased genital sensitivity b. masturbatory activity – repetitive direct (manual) or indirect (rocking, thigh pressure) accompanied by erotic arousal and facial expression[8,9] c. Curiosity with visual and tactile exploration of own and others' genitalia is common d. A pre-oedipal castration reaction with a turn from the mother to the father for affection demonstrated by an increased coyness, erotization toward the father e. With awareness of sexual difference from boys, direct masturbation decreases, indirect masturbation increases, greater attachment to dolls and doll play[10]
36 months	Phallic-oedipal phase a. Increase in masturbation/exhibitionism b. Preoccupation with own/others genitalia – may lead to mutual exploration with same- and opposite-sex peers as part of usual sexual play; heightened interest in father
Around 5–12 years	Latency phase a. Shift erotic trend from father to mother b. Begin interest in origin of babies Late latency a. Increased hormone levels with heightened bodily sensations/sexual excitations b. Increased sexual thoughts/feelings c. Masturbatory activity increases d. Some bisexual conflicts may occur

Modified from Sugar M. Female adolescent sexuality. J Pediatr Adolesc Gynecol 1996; 9: 175–83.

example. For instance, they may learn how a mother behaves as a woman or how a father behaves as a man, and how the two may interact with each other. Both positive and negative influences are possible during this period of time and these influences may shape one's sense of self and sexuality for the future. For example, an abusive relationship from either a man or woman may shape the ability to form a meaningful and appropriate relationship with men and/or women in the future.[3]

Society also affects one's sense of self and sexuality. Television, music, movies, magazines, and the internet provide portrayals of sexual behaviors and relationship norms that may affect adolescent sexual perception. In addition, culture assigns men and women specific roles. The roles may be clear or ambiguous. These roles shape gender identity as well. *Gender identity* is a personal or cultural construct that refers to an individual's innate sense of being male, female, or somewhere in between (Table 14.1). In contrast, *gender roles* refer to the outward expression of these feelings or how one's gender assignment affects interactions with society or one's culture. The beliefs of a cultural group or specific society can also shape one's beliefs and ultimately what is internalized as 'normal'[2,3] and the development of a child's sexual self. A child's parents and family's sexual attitudes, the roles genders play in a family, the ages and how a child learns about different aspects of sexuality, masturbation, intercourse, homosexuality, who teaches a child, and the attitudes used to teach children about sexual issues all play a role in sexual development. There is some research suggesting that healthy adult sex life is based on healthy sexual development

during childhood.[10,11] College students recalling early sexual experiences in a positive light report greater sexual satisfaction and sexual acceptance.[11]

SEXUAL DEVELOPMENT BY STAGES

EARLY ADOLESCENCE

Sexuality is affected by stage of development. Pubertal growth and development occur in early adolescence (ages 10–14). In this stage, adolescents are preoccupied with their own bodies. Adolescents in this age group are likely to ask questions about masturbation, develop crushes on the same or opposite sex based on idealized adults, and may initiate sexual activity as a means of experimentation. Menarche typically occurs during this phase and is an important marker of issues between mother and daughter and separation – individuation conflict begins.[12] Tampon use has been identified by some investigators as indicating a readiness or a growth toward fostering autonomy and individuation that accompanies learning to touch and explore one's external genitalia.[5,13]

Masturbation is also related to autonomy in adolescence and promotes females' sexual responsiveness and orgasmic capabilities.[10,14] Adolescent girls visually undress males and have many erotic thoughts and fantasies about them, just as males do about females.[15] However, research regarding adolescent masturbation reveals a difference in male and female responses. Of 400 high school students in Australia, almost 60% of boys reported at least one episode of masturbation compared with only 43% of girls. The frequency of masturbation was also different in boys vs girls, with almost 40% of boys masturbating three or more times a week compared with only about 10% of girls.[16] These differences extend into early adulthood and are supported by a study of university students, which revealed that twice as many boys as girls had tried masturbation; boys who masturbated showed a frequency three times higher than the girls.[17] Male college students also report higher frequency of sexual urges and masturbatory fantasies than college females. This may reflect physical and/or emotional differences or that perhaps that girls are more reluctant or even unable to identify their fantasies as masturbatory or sexual.[1] It may be that identifying fantasies as being designed for their own sexual pleasure may be too threatening for females and that female sexual development may delay that of males. In fact, some investigators believe that adolescent girls have not developed a strong awareness of their sexuality or the sense that their genitals are under their own power. The basis for this is research that notes a lack of the ability to name positively and understand that genitals are connected to the rest of the body. These studies indicated that girls were unable to do this and that the enrolled girls objectified their genitals and did not acknowledge that they were a part of their body.[18] Yates found that most adolescent girls were ashamed of their genitals and associated them with dirt and odor, and this finding did not seem to change with orgasmic activity.[19]

These differences in male and female sexual development have been hypothesized to be because strong gender roles are adopted in males during childhood but are developed in females during adolescence such that a more gradual self-awareness of sexuality happens in the female. Additional studies are needed to further define psychological aspects of adolescent sexual development investigating how adolescents report and feel about their sexuality. These types of studies are difficult to conduct because of requirements for parental permission, restriction about adolescent confidentiality, and society's reluctance to permit sexual studies on adolescents. Current research reflects the complexity of the development of a sexual self and the need for support of sexual development.[1]

MIDDLE ADOLESCENCE

In middle adolescence (ages 15–16), pubertal changes are reaching an end. Adolescents in this stage are becoming more independent. They may have conflict with parents since they are typically at the peak level of peer conformity. Often adolescents

in this stage make choices even when they do not fully understand the actions or the consequences. This group is most likely to experiment with risk behaviors such as alcohol or substance use, which is known to be associated with increased sexual activity.

For this middle adolescent group, romantic involvement is typically characterized by serial monogamy, or having several romantic partners in a relatively short period of time.

LATE ADOLESCENCE

In late adolescence (age 17 and older), the sense of responsibility and capacity for abstract thought are present. They have a more clearly defined body image and gender role. Many older adolescents have reaccepted some of their parents' values and become less concerned about peer influence. As a result of this process, older adolescents engage in fewer risk behaviors and have a more mature approach to relationships, both romantic and non-romantic.[2]

CULTURAL ASPECTS OF SEXUALITY

A major impact with respect to current adolescent sexuality and development is the increasing timespan reported between the onset of reproductive capability and the age of marriage. This span was about 2 gynecologic years in the 1850s, when the onset of puberty was 16 or 17 and the average age of marriage was 18 or 19. In 1950, this span was 7–8 gynecologic years and today the span is 11–14 gynecologic years. This increasing span of time from 2 to 11–14 years creates a gap of time in which premarital sexual relations are common and natural and creates a need for effective birth control and protection against sexually transmitted disease.[1]

In the United States, we have multiple cultural groups with varying issues and attitudes about adolescent sexual functioning. This is apparent when comparing Hispanic Americans to white Anglo-Saxon Americans and/or to African-Americans. For instance, Latin American women value chastity (marianismo) and consider it shameful to know about sexuality. Female Hispanic adolescents have been noted to have the lowest knowledge scores regarding body parts, function, and contraceptive options when compared with Anglo-Saxon or African-Americans.[1,20]

In many worldwide cultures, premarital sex is common and not considered a serious matter.[21] When compared to national approaches to adolescent sexuality in Germany, The Netherlands, and France, the United States has less sex education. In Europe, sex education is integrated into many school subjects, discussed at all grade levels and is supported by the media and free, convenient access to contraception through a national health service. European countries view adolescent sexual behavior as a normal part of development, not as a moral failing, political issue or a private family matter. Interestingly, teens in the US experience first intercourse at an average age of 15.8 years compared with 16.2 years in Germany, 16.8 years in France, and 17.7 years in The Netherlands. Furthermore, approximately 67% of adolescent girls in The Netherlands and 63% of adolescent girls in Germany reported using oral contraceptives in contrast with 20% of adolescent girls in the United States.[22]

SEXUAL DESIRE AND INITIATION OF SEXUAL ACTIVITY

The antecedents for adolescent initiation of sexual intercourse are presented in Table 14.3.[23]

The primary motivation for adolescent girls aged 12–15 to initiate sexual intercourse has been associated with their friends' sexual behavior and social processes.[24,25] Having a boyfriend at any age is associated with an increased likelihood of sexual initiation. According to the National Longitudinal Study of Adolescent Health, the most important predictor of sexual experience among participants in grades 7–12 was having been in a romantic relationship during the previous 18 months.[26]

Table 14.3 Antecedents of initiation of sex

Environment/context	Individual	Individual (continued)
Community +/– Higher % black or Hispanic vs white + Higher % with college education – Higher divorce rates – Higher rate of residential turnover – Higher unemployment rate + Higher family income – Higher crime rate + Greater neighborhood monitoring by adults in the community	**Biological** – Being male – Older age – Higher testosterone levels in both genders + Older pubertal development and timing + Older age of menarche – Greater physical maturity	**Healthy behaviors** + Greater participation in sports + Greater involvement in other healthy behaviors
School + Parochial school	**Race/ethnicity** – Race (black vs white) – Ethnicity (Hispanic vs white)	**Problem or risk-taking behaviors** – Greater impulsivity – Tobacco use – Substance abuse – Greater involvement in delinquent behaviors – Running away from home – Greater involvement in general unconventional behaviors
Family + Higher parental education + Two (vs one) parents – Divorce or change to single-parent household – Working mother during ages 5–15 + Higher income level + Health insurance – Greater number of siblings – Being a younger sibling + Greater family religiousity + Older mother's age at first sex + Older mother's age at first birth – Single mother's cohabitation – An older sibling who had sex – An older sister who gave birth as an adolescent + Conservative parental attitudes	**Relationship with family** + Higher quality of family interactions, child-bearing practices, support of parents, connectedness + More appropriate parental supervision and monitoring +/– Greater parental/child communication about sex and birth control	**Other behaviors** – Paid work more than 20 hours/week
	Attachment to and success in school + Greater school attendance + Better educational performance + Greater connectedness to school + Plans to attend college +/– Received sex education	**Emotional well-being and distress** + Higher self-esteem – Greater perceived risk of untimely death – Higher level of depression or stress
Peer – Older age of peer group and close friends – Peers with poor grades and high non-normative behavior – Peers with lower achievement orientation + Close friends' closeness to parents – Deviant life trajectories of peers – Peers who drink alcohol – Peers with permissive attitudes toward premarital sex – Sexually active peers	**Attachment to faith communities** + Greater religiosity + Having a conservative religious affiliation + More frequent attendance	**Sexual beliefs, attitudes, skills, and behaviors** – Viewing of TV shows with sexual content – More stereotypical gender roles – More permissive attitudes toward premarital sex and abstinence – More perceived personal and social benefits to sex + More perceived personal and social costs to sex + Greater desire to have friends believe youth is a virgin + Greater feelings of guilt if were sexually active + Greater perceived costs of pregnancy + Greater perceived risk of concern about STDs or AIDS + Greater self-efficacy to refrain from sex + Same-sex attraction or behavior – Dating at an early age or frequent dating – Ever kissed or necked – Greater intention to have sex + Pledge of virginity
	Relationship with peers – Being popular with peers – Engaging in physical fights	
	Relationship with romantic partners – Dating alone – Having a romantic relationship, going steady with boy/girlfriend – Having a relationship with an older romantic partner	**Sexual abuse** – Sexual pressure, coercion, and abuse

+, a protective factor; –, a risk factor; +/–, a protective factor in some studies and a risk factor in others. Reproduced with permission from Kirby D et al. Antecedents of adolescent initiation of sex, contraceptive use and pregnancy. Am J Health Behav 2002; 26: 473–485.[23]

Breast and pubic hair development have also been noted to be contributors toward sexual motivation. One investigator noted that the best indicator for sexual debut is the type of friends with whom the adolescent associates.[27] There is some evidence that hormonal levels affect female sexual practice. For example, women aged 18–34 have been noted to experience greater sexual arousal and pleasure as they progressed from the onset of menses to the late luteal phase. While sexuality has been theorized to be hormonally related, no hormonal levels were assayed in this research study. The study focused on

basal body temperature records and self-reports.[28] There are no such studies in younger adolescents relating hormonal levels to sexual debut or activity.

Nonsexual romantic relationships in the seventh grade (age 12–13 years) independently contribute to the onset of sexual intercourse by the ninth grade (age 14–15) for both males and females. Among females, 12–13-year-olds in serious relationships with older teens (2 or more years older), have an increased likelihood of sex at age 14–15. Further, both male and female 12–13-year-olds who had serious romantic relationships were already different in sixth grade from those who were not: they had peers who were more accepting of sexual activity, had experienced more unwanted sexual advances that could lead to sex (i.e. limited parental monitoring), and the females had undergone earlier menarche.[29]

For 11- and 12-year-olds whose mothers gave birth to them at young ages, and who have older adolescent friends, this is a powerful predictor of sexual initiation between the ages of 13–14 and 15–16. This should be viewed as a red flag for early sexual activity and a risk factor for teenage pregnancy.[30]

Many factors delay the initiation of adolescent sexual activity. Parental influence is very important. Parents who communicate about sex, who are emotionally close to their adolescents, express reasonable values, and are moderately strict, have daughters who are less likely to engage in sex before the age of 16.[31–33] A longitudinal study of psychosexual adolescent development in girls from an urban adolescent medical clinic confirmed these findings. Girls who described their families as being expressive, having a moral–religious emphasis, providing supervision, having greater maternal education, and who experienced menarche at an older age were older at the time of sexual initiation.[34] Finally, parent–child connectedness and clear communication of disapproval about sexual activity have been associated with a delay in sexual initiation.[35]

This has been confirmed among adolescent Mexican-American women in the US. Strong family expectations regarding educational attainment, negative parental messages about premarital sex and pregnancy, resistance to the influence of peers and partners, greater sense of personal control over sexual behaviors, preference for speaking Spanish, and a small age difference between the young woman and her first partner were all positively associated with later age of sexual initiation.[36]

In contrast, parents with extreme parenting styles, either authoritarian-controlling or permissive styles of parenting, are associated with earlier sexual debut.[37] Growing up in a single-parent household[38,39] or in households with significant levels of family conflict is also associated with earlier initiation of sexual activity.[40] Longitudinal data from community samples of girls followed prospectively from age 5 years to age 18 reveal that the absence of a father was strongly associated with early sexual activity as well as adolescent pregnancy.[41]

Longitudinal data also reveal that girls who are younger at first intercourse are less likely to report attraction or love with first intercourse and more likely to report peers having sex as a reason for sexual intercourse initiation. These girls are more likely to report curiosity, a grown-up feeling, partner pressure, and friends having sexual intercourse as reasons for intercourse. Younger girls are more likely to describe partner pressure as a reason for having sexual intercourse.[34] Girls 13 years or younger are more likely to report intercourse as non-voluntary and even those that characterize intercourse as voluntary may describe it as not being particularly desired.[42] When a male partner is 2 or more years older than the girl, intercourse tends to take place earlier in the relationship.[43] Girls with older age at first intercourse are more likely to report a feeling of being in love, physical attraction, too excited to stop, drunk or high partner, and feeling romantic as reasons for having sexual intercourse.[34]

Attendance at religious services and a person's religious affiliation have little impact on sexual behaviors once intercourse occurs. An evaluation of nationally representative data from the 1995 National Survey of Family Growth, suggests that

both affiliation and attendance are associated with age at first sex. Multivariant analysis shows that religious affiliation shares few associations with sexual behaviors, although frequent attendance at religious services at age 14 years continues to have a strong delaying effect on the timing of first intercourse.[44]

PRECOITAL BEHAVIOR

Girls' sexual lives begin long before first intercourse. The first intimate heterosexual interactions help to expand and clarify girls' sexual self-views. Smith and Udry noted that white adolescents engage in a series of non-coital, predictable behaviors that continue for a period of time before first intercourse, whereas black teenagers were less predictable and often involved only necking.[45] Among 90% of white adolescents, necking was noted as the most frequent sexual behavior, followed by feeling breasts clothed, then feeling breasts directly, etc. Intercourse was the least frequent sexual behavior among white adolescents. Among black adolescents, the most frequent sexual behavior (40%) was necking, feeling breasts clothed, and then intercourse.

A prospective cohort study of a small sample of 12–15-year-old girls interviewed at baseline and again at 1 year charting first participation in three milestone sexual behaviors and changes in their attitudes, expectations, beliefs, and values framing their sexual experiences (arousability, abstinence attitudes, perceived parental and peer approval, and sexual self-esteem) revealed that percentages of behaviors (breast fondling, sexual interactions involving genital contact, and sexual intercourse) 18%, 4%, and 6% increased significantly over the year to 42%, 44%, and 19%, respectively. Girls with no breast-fondling experience at either time point had stronger abstinence values, and lower arousability, peer approval, and sexual self-esteem scores compared with girls who initiated breast fondling over the year ('transitioners'). These 'transitioners' had similar sexual cognition to girls who had experience at baseline, a finding that suggests that changes in sexual cognitions precede actual sexual experience.[46]

NON-COITAL BEHAVIOR

The prevalence of non-coital behaviors – mutual masturbation, oral sex, and anal intercourse – among adolescence is unknown as there is a paucity of research data regarding such behaviors. A limited data set from 1982 from a marketing research firm database from households in 49 states revealed that 20% of the 1067 13–18-year-olds had ever had oral sex and 16% of young women who had performed fellatio had never had vaginal intercourse.[47] Data from approximately 2000 Los Angeles ninth to twelfth graders (aged 14–18 years) indicated that 29–31% of virgins had engaged in masturbation with a partner and 9–10% of those who had not yet had coitus had had oral sex. Very few (< 1% of non-coitally experienced students) revealed that they had ever engaged in anal intercourse.[48]

Adolescents do not perceive oral sex as sex. Although there are limited medical research data, survey data from pop-culture magazines are available. Approximately 50% of 15–19-year-old males and females (n = 723) approached in malls considered oral sex to 'not be as big a deal as sexual intercourse' and 40% said it did not count as 'sex'.[49] Another survey conducted by an online magazine received 10 000 responses from 13–19-year-old girls of whom 18% said that oral sex was something you did with your boyfriend before you were ready to have sex and the same proportion said that oral sex was a substitute for intercourse.[50]

ADOLESCENT SEXUAL BEHAVIOR

Several surveys are available to monitor trends in female adolescent sexual behavior. Both the National Survey of Family Growth (NSFG) and the Youth Risk Behavior Survey (YRBS) collect information about adolescent sexual behavior but differ in their purpose, design, and implementation strategies.

The NSFG collected detailed information on fertility-related behavior among a nationally representative household sample of women aged 15–44.

The YRBS used school-based samples and measured a broader range of adolescent health behaviors. The YRBS was designed to produce a nationally representative sample of both male and female students in public and private schools aged 14–18, primarily to monitor levels of adolescent risk behaviors. The Youth Risk Behavior Surveillance System (YRBSS) monitors six categories of priority health-risk behaviors among youth and young adults, including behaviors that contribute to unintentional injuries and violence; tobacco use; alcohol and other drug use; sexual behaviors that contribute to unintended pregnancy and sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV) infections; unhealthy dietary behaviors; and physical inactivity.

The most recent NSFG data are from 2002[51] and note that 46% of females aged 15–19 have had intercourse. Also, 30% of 15–17-year-olds have had intercourse at least once, which is a decline from prior data in 1995 (38%). The number of 18–19-year-olds who have had intercourse at least once remains stable at approximately 80%. Teenagers in 2002 were delaying sexual debut, with 13% of females having intercourse earlier than age 15 versus 19% in 1995 (Tables 14.4–14.6).

During the year 2001, 29% of teen females had sex with only one partner with only 4% having four or more partners. Older age was associated with more sexual partners. Many teens have had multiple partners over a lifetime. Twenty-eight percent of females had had more than one partner at the time of the survey. Younger age at first intercourse is associated with more partners than first intercourse at age 17–19, thus demonstrating the significant risk for those teens engaging in early first intercourse.

Table 14.4 Cumulative percent of never-married males and females 15–19 years of age who have ever had sexual intercourse before reaching selected ages, by new race and age and Hispanic origin classification: United States, 2002

Characteristic	Female	Male
All never-married[a]	45.5	45.7
Race and age		
White, single race, Not Hispanic or Latino:		
14 years	4.2	4.3
15 years	11.8	8.9
16 years	37.6	16.5
17 years	41.1	30.8
18 years	70.1	50.5
19 years	68.7	61.7
Black or African-American, single race, Not Hispanic or Latino:		
14 years	13.4	17.8
15 years	22.3	29.0
16 years	26.3	47.1
17 years	61.5	68.3
18 years[b]	55.4	71.6

[a]Includes persons of other, unknown, or multiple race and origin groups, not shown separately.
[b]Figures not shown for Not Hispanic black or African-American, single race, '19 years' due to inadequate sample size.

Notes: Numbers and percents reflect heterosexual vaginal sexual intercourse only, not other types of sexual activity. The denominator for each percent includes only those having reached the specified age to which the percent pertains. Reproduced with permission from reference 51.

The most recent data from the YRBS are from a nationally representative sample of students aged 14–18 years who attended public and private schools during October 2004–January 2006. During 2005, a total of 46.8% of high school students had ever had sexual intercourse; 37.2% of sexually active high school students had not used a condom at last sexual intercourse. Overall, the prevalence of having had sexual intercourse was higher among black (67.6%) than white (43.0%) and Hispanic (51.0%) students. The prevalence of having had sexual intercourse was 42.8% among those aged 14–16 years, 51.4% for those aged 16–17, and 63.1% in 17–18-years-olds, compared with 34.3% in 14–15-years-olds. Furthermore, the rate of sexual debut for girls was higher among these aged 14–16 years (44.0%), 16–17 years (52.1%), and 17–18 years (62.4%) compared with those aged 14–15 (29.3%).

Additional YRBS data reveal that nationwide, 6.2% of students had sexual intercourse for the first

Table 14.5 Number of males and females 15–19 years of age and percent who have ever had sexual intercourse, by new Hispanic origin and race classification: United States, 2002

Characteristic	Female		Male	
	Number in thousands	Percent	Number in thousands	Percent
All teenagers[a]	9834	46.8	10 208	46.0
Age, Hispanic origin, and race				
15–17 years	5819	30.3	5748	31.6
Hispanic or Latino	912	25.1	852	42.6
Not Hispanic or Latino:				
White, single race	3563	30.4	3584	26.0
Black or African-American, single race	852	41.8	813	51.6
18–19 years	4016	70.6	4460	64.7
Hispanic or Latino	608	63.5	775	69.6
Not Hispanic or Latino:				
White, single race	2507	69.1	2740	61.6
Black or African-American, single race	558	80.0	539	78.0
Hispanic origin and race				
Hispanic or Latino	1521	40.4	1628	55.5
Not Hispanic or Latino:				
White, single race	6069	46.4	6324	40.9
Black or African-American, single race	1409	56.9	1352	62.1

[a]Includes persons of other, unknown, or multiple race and origin groups, not shown separately.

Note: Numbers and percents reflect heterosexual vaginal sexual intercourse only, not other types of sexual activity. Reproduced with permission from reference 51.

time before age 13 years (Table 14.7). This was higher among black female (7.1%) than white female (2.9%) and Hispanic female (3.6%) students.

The 2005 YRBS data denote that 14.3% of students had sexual intercourse with more than four persons during their life. Overall, the prevalence of having had sexual intercourse with more than four persons was higher among 11th graders (16–17 years, 16.2%) and 12th graders (17–18 years, 21.4%) than 9th graders (14–15, 9.4%) and 10th graders (14–16, 11.5%); higher among 10th grade females (14–16, 9.7%), 11th grade females (16–17, 14.2%), and 12th grade females (17–18, 20.2%) than 9th graders (14–15, 5.7%). Nationwide, 33.9% of students had sexual intercourse with more than one person during the 3 months preceding the survey (i.e. currently sexually active). Overall, the prevalence of being currently sexually active was higher among black (47.4%) than white (32.0%) and Hispanic (35.0%) students; higher among black female (43.8%) than white female (33.5%) and Hispanic female (33.7%) students. The prevalence of being currently sexually active was higher among 10th grade (14–16 years, 29.2%), 11th grade (16–17, 39.4%), and 12th grade (17–18, 49.4%) than 9th grade (14–15, 21.9%) students. In addition, the rates were higher among 10th grade (14–16, 31.1%), 11th grade (16–17, 40.8%), and 12th grade females (17–18, 51.7%) compared with 9th graders (14–15, 19.5%).

Table 14.6 Number of never-married males and females 15–19 years of age and percent who have ever had sexual intercourse, by new Hispanic origin and race classification: United States, 2002

Characteristic	Female		Male	
	Number in thousands	Percent	Number in thousands	Percent
All never-married[a]	9598	45.5	10 139	45.7
Age, Hispanic origin, and race				
15–17 years	5815	30.3	5726	31.3
Hispanic or Latino	909	24.8	852	42.6
Not Hispanic or Latino				
White, single race	3563	30.4	3562	24.6
Black or African-American, single race	852	41.8	813	51.6
18–19 years	3783	68.8	4413	64.3
Hispanic or Latino	539	58.7	750	68.6
Not Hispanic or Latino:				
White, single race	2367	67.3	2724	61.4
Black or African-American, single race	555	79.9	534	77.8
Hispanic origin and race				
Hispanic or Latino	1447	37.4	1603	54.8
Not Hispanic or Latino:				
White, single race	5930	45.1	6286	40.5
Black or African-American, single race	1407	56.8	1347	61.9

[a]Includes persons of other, unknown, or multiple race and origin groups, not shown separately.

Note: Numbers and percents reflect heterosexual vaginal sexual intercourse only, not other types of sexual activity. Reproduced with permission from reference 51.

Among the 33.9% of currently sexually active students nationwide, 62.8% reported that either they or their partner had used a condom during last sexual intercourse (Table 14.8).

Overall, the prevalence of having used a condom during last sexual intercourse was higher among 9th grade (14–15 years, 74.5%) than 10th grade (14–16, 65.3%), 11th grade (16–17, 61.7%), and 12th grade (17–18, 55.4%); higher among 9th grade females (14–15, 71.5%) than 10th grade (14–16, 57.1%), 11th grade (16–17, 57.8%), and 12th grade female (17–18, 46.1%) students.[52]

A prospective longitudinal study demonstrated that having a higher number of lifetime sexual partners by age 19 was associated with earlier initiation of romantic relationships, which were indirectly associated with more frequent alcohol use in middle adolescence. The timing of first romantic relationship and alcohol use at age 16 were the result of complicated paths including sociability, and impulsivity at age 30 months, early physical maturation, physical attractiveness at age 13 for girls, and higher quality friendships and increased peer acceptance in early adolescence. This would imply that young people who are sociable, have a more mature appearance, and date early in adolescence would benefit from learning to responsibly manage their relationships in the midst of their emerging sexuality.[53]

Latest YRBS data from 2005 indicate that among the 33.9% of currently sexually active students nationwide, 23.3% had drunk alcohol or used drugs before last sexual intercourse (Table 14.9).

Table 14.7 Percentage of high school students who engaged in sexual behaviors, by sex, race/ethnicity, and grade – United States, Youth Risk Behavior Survey, 2005

Category	Ever had sexual intercourse						Had first sexual intercourse before age 13 years						Had sexual intercourse with ≥ 4 persons during their life					
	Female		Male		Total		Female		Male		Total		Female		Male		Total	
	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)
Race/ethnicity																		
White*	43.7	4.6	42.2	4.4	43.0	4.1	2.9	0.8	5.0	1.0	4.0	0.8	11.1	2.2	11.6	2.1	11.4	1.8
Black*	61.2	4.6	74.6	3.7	67.6	3.1	7.1	2.0	26.8	3.5	16.5	2.4	18.6	3.3	38.7	4.2	28.2	2.6
Hispanic	44.4	5.0	57.6	4.4	51.0	4.3	3.6	1.2	11.1	3.2	7.3	1.9	10.4	2.1	21.7	3.6	15.9	2.4
Grade																		
9 (age 14–15)	29.3	3.5	39.3	4.6	34.3	3.5	5.4	1.5	12.0	2.1	8.7	1.5	5.7	1.9	13.2	2.7	9.4	1.5
10 (age 14–16)	44.0	4.5	41.5	4.4	42.8	3.9	4.1	1.0	7.7	1.9	5.9	1.2	9.7	2.4	13.2	2.3	11.5	2.0
11 (age 16–17)	52.1	6.5	50.6	4.8	51.4	5.2	2.6	1.3	8.0	1.7	5.2	1.3	14.2	3.1	18.1	2.6	16.2	2.4
12 (age 17–18)	62.4	4.7	63.8	5.0	63.1	4.1	2.0	1.0	6.2	1.6	4.1	1.0	20.2	3.2	22.6	3.3	21.4	2.8
Total	45.7	3.6	47.9	3.4	46.8	3.3	3.7	0.7	8.8	1.1	6.2	0.8	12.0	1.6	16.5	1.8	14.3	1.5

CI, 95% confidence interval. *Non-Hispanic. Reproduced with permission from reference 52.

Table 14.8 Percentage of high school students who were currently sexually active*, who used a condom during last sexual intercourse,[†] and who used birth control pills before last sexual intercourse,[†§] by sex, race/ethnicity and grade – United States, Youth Risk Behavior Survey, 2005

Category	Currently sexually active						Condom use						Birth control pill use					
	Female		Male		Total		Female		Male		Total		Female		Male		Total	
	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)
Race/ethnicity																		
White**	33.5	4.2	30.6	3.4	32.0	3.3	55.6	3.2	70.1	3.7	62.6	2.5	27.1	5.8	17.2	3.6	22.3	3.7
Black**	43.8	3.1	51.3	4.5	47.4	2.6	62.1	6.1	75.5	4.4	68.9	3.6	10.7	3.4	8.4	4.0	10.0	2.7
Hispanic	33.7	4.2	36.3	4.0	35.0	3.9	49.8	4.3	65.3	7.3	57.7	4.1	9.4	3.8	10.3	4.2	9.8	2.7
Grade																		
9 (age 14–15)	19.5	2.8	24.5	3.4	21.9	2.4	71.5	5.7	77.1	6.5	74.5	5.1	8.8	5.1	6.4	3.7	7.5	3.0
10 (age 14–16)	31.1	3.3	27.2	3.6	29.2	2.9	57.1	6.1	74.4	6.0	65.3	3.9	18.0	4.8	10.3	3.6	14.3	3.4
11 (age 16–17)	40.8	5.4	37.9	4.4	39.4	4.3	57.8	5.6	66.0	5.7	61.7	3.8	20.2	4.8	16.6	4.3	18.5	3.7
12 (age 17–18)	51.7	5.1	47.0	4.0	49.4	3.8	46.1	3.8	65.8	5.4	55.4	3.5	28.9	6.5	21.9	4.6	25.6	4.6
Total	34.6	3.0	33.3	2.6	33.9	2.5	55.9	2.8	70.0	3.1	62.8	2.1	20.6	3.7	14.6	2.5	17.6	2.6

CI, 95% confidence interval.
*Had sexual intercourse with one or more persons during the 3 months preceding the survey.
[†]Among the 33.9% of students nationwide who were currently sexually active.
[§]To prevent pregnancy.
**Non-Hispanic. Reproduced with permission from reference 52.

Table 14.9 Percentage of high school students who drank alcohol or used drugs before last sexual intercourse*, were ever taught in school about acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection, and who were tested for HIV, by sex, race/ethnicity, and grade – United States, Youth Risk Behavior Survey, 2005

Category	Alcohol or drug use before last sexual intercourse						Taught in school about AIDS or HIV infection						Tested for HIV					
	Female		Male		Total		Female		Male		Total		Female		Male		Total	
	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)	%	CI (±)
Race/ethnicity																		
White†	20.5	2.6	29.9	4.3	25.0	2.8	90.1	2.3	88.7	2.5	89.4	2.2	11.6	1.8	8.8	1.2	10.2	1.1
Black†	12.8	3.8	15.4	3.7	14.1	3.1	87.2	3.3	85.4	3.9	86.3	3.2	24.1	3.6	17.9	3.2	21.0	2.4
Hispanic	18.7	3.8	32.2	7.3	25.6	4.7	85.8	3.0	83.6	2.6	84.7	2.5	11.2	2.0	12.7	1.8	12.0	1.4
Grade																		
9 (age 14–15)	22.7	5.7	29.0	8.5	26.2	6.0	85.5	3.3	84.4	3.5	85.0	2.9	7.9	1.6	9.8	2.1	8.9	1.4
10 (age 14–16)	18.9	5.4	23.6	5.2	21.1	4.5	89.4	2.3	87.3	3.5	88.4	2.6	13.2	2.4	10.2	1.6	11.6	1.5
11 (age 16–17)	16.8	3.4	29.0	4.4	22.5	3.0	89.7	3.0	89.5	2.1	89.6	2.3	14.1	2.4	10.2	2.3	12.2	1.5
12 (age 17–18)	19.2	3.5	27.6	3.8	23.1	2.0	90.1	2.4	88.7	2.2	89.4	2.0	19.3	3.5	12.3	2.0	15.8	2.0
Total	19.0	2.0	27.6	3.2	23.3	2.2	88.5	1.9	87.2	2.0	87.9	1.9	13.2	1.3	10.6	1.1	11.9	0.9

CI, 95% confidence interval. *Among the 33.9% of students nationwide who were currently sexually active.
†Non-Hispanic. Reproduced with permission from reference 52.

SPECIAL ISSUES AND SEXUALITY

Regardless of the era or stage of development, youth continue to engage in risk behaviors that may compromise their health and well-being. As health-care providers, it is important to review the risk factors associated with the most common health-related issues facing adolescents today.[54]

DISABILITIES

It is estimated that approximately 17% of youth have developmental disabilities. Like all adolescents, teens with disabilities have the desire for love, friendships, marriage, children, and normal adult sex lives. Teens with disabilities face the same issues that non-disabled teens face: pubertal development and risk behaviors. Puberty for disabled teens often begins earlier and ends later in males and females. For instance, precocious puberty occurs with an incidence of 20% among females with spina bifida. Such early development can affect these youth who already face difficulties with body image, self-esteem, and hygiene, and increase the risk of sexual victimization. The US Department of Justice has reported that 68–83% of women with developmental disabilities will be sexually assaulted.[55]

The range of impairment for disabled youth varies from social to motor. Adolescents with disabilities may not only be hindered by physical limitations but also by societal barriers. For example, some disabled youth may have difficulty in overcoming certain tasks due to over-protection during adolescence, making individuation difficult. Furthermore, youth with cognitive deficits may be more easily manipulated, therefore placing them at risk for being in a compromising situation.

Children with disabilities may be more vulnerable to sexual abuse because of their daily dependence on others for intimate care, increased exposure to a large number of caregivers and settings, inappropriate social skills and poor judgment, inability to seek help or report abuse, and a lack of strategies to defend themselves from abuse. Available evidence suggests that when sexual questions and behaviors are freely discussed within a family, the likelihood of abuse can be reduced or eliminated.[56,57]

Expressions of sexuality among adolescents with disabilities are similar to typically developing peers. Of 460 students with cerebral palsy, muscular dystrophy, or arthritis aged 12–18 (mean age 15 years 1 month), age at first intercourse for females was 14 years 2 months and did not differ from that of the control population.[58] This has also been noted from data in the US National Longitudinal Study of Adolescent Health.[59] Unfortunately, these adolescents additionally seem to lack proper knowledge of risk factors. Most adolescents with physical disabilities report that they have not been provided with adequate information on parenthood, birth control, and STDs.[60,61] Furthermore, the presence of a disability may affect the development of sexual identity, confidence, desire, function, and the ability to find a partner. Physical arousal and sexual function may be impaired in the presence of neurological conditions, even when sexual feelings and needs are intact. Waiting for adolescents with disabilities to ask explicit questions about their bodies and developing sexuality may allow learning opportunities to be overlooked. Sexual development, STDs, contraception, and sexual abuse should be discussed with all teens with disabilities. An interval comprehensive examination regarding physical, social, emotional, and cognitive development is important. Discussing sexuality, providing a venue for confidentiality, and risks of sexual misuse will allow disabled youth to function as healthy adults who make better decisions despite their disadvantages.[62] Health-care providers should take the lead in advocating independence for these teens, discussing these issues in private while informing parents of the general topics of discussion as appropriate.

GAY, LESBIAN, BISEXUAL, TRANSGENDER

Gender differences have existed for hundreds of years and across many civilizations, but societal disapproval has negatively influenced recognition. Many theories on gender now support the proposition that

genes shape the nervous system's development and environmental factors may shape genetic expression. Adolescents who are gay, lesbian, transgender or bisexual have a psychosocial developmental process similar to their heterosexual peers. It is estimated that 5–8% of adolescent youth are gay, lesbian or bisexual. With these teens, eventual integration of their sexual identity is often preceded by an arduous process. Many adolescents feel isolated as they attempt to explore their sexuality. They may initially explore heterosexual relationships before homosexual relationships. As a result, many gay, lesbian, transgender or bisexual adolescents are predisposed to violence, depression, suicide, difficulties in school, substance abuse, eating disorders, risky sexual behavior, and illegal conduct.[63] It is important for health-care providers to educate teens who may be struggling with gender identity about prevention of STDs. The rates of several STDs are in fact higher in lesbians compared with heterosexual youth. In addition, gay, lesbian, bisexual or transgender youth are more likely than their heterosexual counterparts to be homeless, have a history of abuse, have a history of substance abuse, and struggle in school, and more likely to experience depression and suicidal ideation. Furthermore, because these youth struggle with their sexual identity, they have had more sexual partners and they are more likely to have had sex for money and to be at an overall increased risk for all STDs.

Like all adolescents who engage in risky behaviors, gay, lesbian, bisexual, and transgender teens are at risk for STDs. The risks in this group are even higher as there is a paucity of consistent and uniform methods of helpful research to assist caregivers regarding this group of teens. As a result, disease transmission rates between same-sex couples, transgender couples, or bisexual couples are difficult to assess.[64]

EDUCATIONAL PROGRAMS

Adolescents are an actively evolving group who require education for intervention. Several interventions that promote the sexual health of youth are broad-based sexual education programs. These programs have been developed as strategies to decrease teen pregnancy, STDs, and early sexual activity. Abstinence from sexual intercourse is an important behavioral strategy to decrease early unwanted pregnancies and STD transmission. However, abstinence-only programs have also proven that many teens eventually become sexually active and this may in fact lead to early pregnancy or STD transmission due to lack of knowledge or proper understanding of sexual practices and their consequences.

Virginity pledges have demonstrated higher rates of delayed sexual activity but have not shown decreased STD rates. Among adolescents across all age and gender groups, those with dual-parent families, higher socioeconomic status, residing in rural areas, higher school performance, more religious, and high parental expectations had later onset of sexual activity or risk-taking behaviors.[65] Increased parental monitoring even within high-poverty urban settings was associated with improved adolescent decision-making regarding sexual initiation and STDs. Educating on all STDs is important for adolescents who are sexually active, since knowledge of symptoms or signs of disease may prompt them to receive earlier care.[66]

Effective communication was also important toward enhancing compliance for contraceptive use among teens. Contraceptive availability should additionally be stressed for pregnancy prevention in addition to proper condom use for STD prevention. Discussing all contraceptive options may allow adolescents to make better contraceptive choices to enhance their compliance.

Communication with a health-care provider was positively associated with an improvement in overall sexual health and decision-making capability.[67] Most adolescents have difficulty discussing sexuality issues in front of parents or friends. Therefore, it is critical to maintain confidentiality with adolescents except in cases of life-threatening emergency.

The discussions regarding risk-taking behaviors and sex should be routine. No assumptions should be made regarding the adolescent's specific gender

assignment as this can be viewed as threatening. However, it is important to ask questions regarding sexual practice; for example, 'Are you attracted to boys or girls or both sexes?' It is also important to inquire about vaginal, anal, and/or oral sexual practices as well as screening for early sexual contact such as breast fondling, mutual masturbation, and genital touching. This will allow appropriate counseling for the patient's stage of sexual development.

SUMMARY

Sexuality is a developmental process from birth, progressing through various stages before reaching full maturity in meaning and expression. It includes physical as well as cognitive and psychosocial processes. The capacity to communicate, develop mutual respect, experience intimacy, and assume responsibility is necessary for a full and healthy sexual life. To support healthy sexual functioning in the female adolescent, health-care providers need to identify early risk markers, whether biological, psychological or sociocultural. Recognizing and addressing such risk factors will lead to healthy sexual development.

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15. Adolescent contraception

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INTRODUCTION

Contraception is a crucially important adolescent health issue. Despite recent slight decreases in adolescent pregnancy rates and slight increases in the age of first sexual intercourse across North America, 2003 data still indicate that 33% of US ninth graders (i.e. aged 14–15 years) and 62% of twelfth graders (aged 17–18 years), have had sexual intercourse.[1,2] The median age at first intercourse for American males is 16.9 and for females is 17.4.[1] Use of contraception with first intercourse has also increased over recent years; in 2002 75% of adolescent women and 82% of adolescent men indicated having used protection with first intercourse. Oral contraceptive pills and condoms were the most common choices.[1,2] Nonetheless, 17% of adolescent women and 9% of adolescent men reported having used no method of birth control at last episode of intercourse.[1] In addition, 18% of adolescent males in the US and 11% of adolescent females report at least four previous sexual partners, highlighting the role of contraception not only for protection from pregnancy but also in prevention of sexually transmitted infections (STIs). Canadian data are similar, with the average age at first intercourse reported to be 16.5 in a 2005 survey; 41% of adolescent males and 29% of adolescent females reported more than one partner in the preceding year and 29% of males and 51% of females report not using condoms.[3]

An estimated 34% of American women under the age of 20 will experience a pregnancy.[4] Approximately 20% of all adolescent pregnancies will occur within the first month of coitus, and 50% within the first 6 months. Many adolescents will delay seeking contraception for as long as 12 months or more following sexual debut. Reasons include anxiety that their parents will find out, their sense of invincibility or misconceptions about contraception methods, and the extent of evaluation they anticipate before initiating contraception.[5,6] Dialogue and education around contraception should therefore become part of the routine health exchange with the adolescent before the initiation of sexual activity to promote healthy decision-making on the part of the adolescent.[5] The discussion should also include screening for medical and psychosocial concerns and ruling out coercive sexual activity. The adolescents' thoughts in regards to contraception should be explored and any misconceptions should be dispelled.[6] Despite initiating contraception, continuation rates for shorter-term methods such as the oral contraceptive pill over 1 or 2 years has been described to be as low as 12% and 2%, respectively. The reasons most commonly cited for discontinuation are running out of pills or forgetting to take them. Close follow-up with the adolescent after the initiation of contraception is therefore crucial to adherence.[6]

Discussing contraception with adolescents and educating them in these topics can often be problematic. The medical team and adolescent need to engage in a partnership and work together to find a method that will be successful. Ideally the medical professional should be skilled in interactions with the adolescent age group.[6] Programs and interactions need to be age-appropriate and tailored to the concrete thought processes of the adolescent. Encounters should be kept interactive and should encourage dialogue, such that the adolescent must participate in the exchange and demonstrate their cognitive abilities in selecting their contraceptive.[7]

Merely handing out contraception to adolescents and not educating them around contraception use and pregnancy prevention has been shown to be insufficient for improving compliance in this age group.[2] Risk-taking behaviors in regards to sexual activity may be linked to other risk-taking behaviors and the contraception encounter should screen for these issues as well.[8,9] It is further clearly shown that education and discussion around sexual activity do not increase the rates of sexual activity amongst adolescents.[2] More comprehensive youth development programs, which also provide information and counseling around life goals, career planning, and self-esteem, may be successful in reducing teen pregnancy rates.[2]

Confidentiality is an extremely important factor in communicating with adolescents; 25% of adolescents have indicated that they would avoid contacting a health-care provider about a sensitive topic if they felt that their parents would find out. Therefore, health care around contraception should be provided in a confidential and nonjudgmental environment.[7] Nevertheless, physicians are far from the only participants in the arena of adolescents and contraception. Adolescents who are able to experience conversations around these topics with their parents and families are less likely to engage in unprotected intercourse or become pregnant.[10] Greater parental supervision is further associated with increased used of contraceptives. In addition, greater warmth in parental relationships leads to increased likelihood of young women discussing contraception with their male partners.[10] The relationship between the adolescent and parent should be assessed, and the adolescent should be encouraged to openly involve their parents in their health concerns. Further, the attitudes of the partner and the greater social and cultural context should also be part of the information gathered around the contraception encounter, to ensure choice of a successful method and successful adherence to it.[10]

Despite the similar characteristics of the youth in the United States and the European Union (EU), significant differences in pregnancy rates are seen. Data suggest that neither the initiation nor frequency of sexual activity but rather the level of utilization of contraception is the reason for the increase in pregnancy rates in the US. In the EU, not only is there a higher use of contraception, but the reasons for prescribing are different. While in the US many prescriptions are given for the non-contraceptive benefits of the pill, in the EU most prescriptions are given during routine preventive visits, emphasizing the importance of preventive visits and the education given to the patients when started on the method. Education and awareness of teenagers in the US as well as availability of the contraceptive services most likely contribute to the differences from the EU and should be taken into consideration when developing comprehensive programs for contraception in teens.[11,12]

ABSTINENCE

While options for all forms of contraception should be discussed with an adolescent, abstinence should be encouraged as the healthiest method of preventing both pregnancy and STIs. Abstinence after a previous experience of sexual activity (secondary abstinence) should also be encouraged as an acceptable choice.[5,13] Adolescents selecting abstinence should be given considerable reassurance and encouragement with regards to their choice being a healthy choice also selected by many of their peers. They should have the opportunity to discuss what behaviors are and are not safe and how to communicate effectively with their partners around which sexual activities they do and do not wish to engage in.[13] Abstinence-only programs have specifically not been shown to reduce age at first intercourse and therefore any counseling or program on abstinence should also provide education around various other methods of contraception in the event that the adolescent later chooses to become sexually active.[2,5]

MALE BARRIER METHOD – THE MALE CONDOM

Barrier methods as a whole represent the oldest form of contraception, dating back to the ancient

era; male condoms and coverings of the penis are depicted in Ancient Egyptian art, for example. With the advent of newer forms of contraception, their use as a primary method of birth control has declined.[14] As a group, their use poses a challenge in that they are all coitus dependent; however, they can be used selectively and have minimal or no side effects in comparison with other forms of contraception.[14]

The word condom is thought to originate from the Latin word *condus*, meaning receptacle. Condoms were originally made of animal skins but have been manufactured from rubber since the late 1800s.[14] They have become a vitally important tool in public health, in the fight against the spread of human immunodeficiency virus (HIV).[14] Condom use has therefore increased since the advent of the HIV epidemic in the 1980s and the related public health campaigns; data indicate an overall increase in condom use in the US from 12% in 1982 to 20% in 1995, with the largest increases in singles and African-American adolescents.[6]

Male condoms are the second most popular form of contraception (next to the oral contraceptive pill, (OCP)) and the one most commonly used at first intercourse, likely due to the lack of need for a visit to a health-care provider.[2] School condom distribution programs have been associated with equal rates of sexual activity and small but significantly increased rates in condom use. In general, adolescents are about as consistent with condom use as their older counterparts, in the range of 65%.[2] Perfect condom use is associated with an efficacy rate of approximately 97%, although typical use is associated with an 86% efficacy rate over 1 year of use.[13,14] Spermicide is recommended in addition to any barrier method to improve contraceptive efficacy.[5]

Condoms require compliance on the part of the male partner and must be used with each and every act of intercourse. Correct use includes leaving a reservoir in the tip of the condom during application, holding the condom during withdrawal of the penis and removing the condom from the erect penis, as well as avoiding the use of an expired condom.[6,14,15] Importantly, condoms are inexpensive and available over-the-counter and are therefore an easily accessible form of contraception.[6] Patients can further be advised to obtain condoms ahead of time and keep them in a convenient location in the event that they are needed, but they should be kept out of direct light and extreme heat.[15]

Latex condoms are best for STI protection in comparison with natural materials (such as lamb cecum) and should be recommended for all penetrative sexual activity (i.e. vaginal, anal, oral) in addition to any other forms of contraception that are used; dental dams should be advised for STI protection in female receptive oral intercourse.[6] For individuals who are allergic to latex, polyurethane condoms are now available, and while they are stronger and thinner than their latex counterparts and safe to use with oil-based lubricants, they are unfortunately considerably more expensive.[5,14] Polyurethane condoms may be associated with improved sensation for the male partner as well.[14]

FEMALE BARRIER METHODS

Female vaginal barriers are also described in ancient texts, when various caustic materials were placed in the vagina to prevent conception.[14] Currently available female barrier methods include the diaphragm, diverse cervical caps and shields, the sponge, and the female condom.[14] In general, adolescents are uncomfortable with the idea of placing barrier methods in the vagina and these methods are therefore unpopular in this age group. Typically, adolescents are inconsistent users of female barrier methods and discontinuation rates average 55% over 1 year.[6] The highly motivated adolescent, however, may find significant success with these methods.[13] Individuals choosing a female barrier method are more likely to be in monogamous relationships and have to be motivated to use a method that must be contemplated with each act of intercourse.[16,17] There have been associations of barrier methods with toxic shock syndrome with prolonged placement and patients should be counseled with regards to symptoms. Barrier methods are also associated with higher rates of urinary tract

infections (UTIs), possibly related to higher rates of *E. coli* colonization and pressure on the urethra preventing complete bladder emptying.[14] They can, however, be complicated to use and are less effective than hormonal contraceptives, and these reasons are felt to be associated with their decreased rates of use.[17]

The diaphragm was the first widely available barrier method. In 1918, Margaret Sanger was arrested for distributing them. At one time it was used by one-third of women seeking contraception but its popularity has declined since the advent of hormonal contraception in the 1960s.[14] The diaphragm, which has an efficacy of 60–88%, is a rubber cup with a flat or coil spring rim or wide seal and is designed to fit in the vagina and cover the cervix. It must be fitted by a health-care provider, who measures the distance between the posterior vaginal fornix and the pubic symphysis. It is used in conjunction with spermicide, which should be placed in the cup of the diaphragm before intercourse; additional spermicide should be placed in the vagina with each additional act of intercourse. A 60–80 mm diaphragm will suit most adolescent women well. The diaphragm should be refitted after any pregnancy or pregnancy termination, if the user was virginal at first fitting, after a 10 lb or more weight change, if vaginismus is experienced, and on an annual basis. The diaphragm can be placed up to 6 hours before intercourse and must remain in place for up to 6 hours after intercourse but should not remain in the vagina for over 24 hours in total.[14,17] Efficacy is decreased with frequent coitus, numerous partners, younger age, use of oil-based lubricants, poor instructions for use, prior failure of contraceptive, and ambivalence about pregnancy.[13] Some studies have indicated that diaphragms are associated with a decreased risk of STIs. However, this may not be due to the method itself, but may be more related to the facts that it is often used in association with spermicide and that many diaphragm users are older, well educated, and in monogamous relationships.[14]

The cervical cap dates back to the late 1800s. It is smaller than a diaphragm and fits over the cervix, staying in place by suction. The Prentif brand cervical cap was approved for use in the USA but it was removed from the market in 2005. It comes in four different sizes and can also be fitted for size. The cervical cap, like the diaphragm, should also be used in conjunction with spermicide and can stay *in situ* for up to 48 hours.[14] Efficacy rates are again variable and similar to those found with use of the diaphragm, but are noted in particular to be decreased in parous women. For reasons that are unclear, there has been an association with the cervical cap and new Pap smear abnormalities; patients are therefore advised to have a Pap smear at the time of cervical cap initiation and again 3 months later.[13]

Lea's Shield® (Yama, Inc., Union, NJ, USA), approved for use in 2002, is a silicone vaginal barrier contraceptive that comes in one size and therefore does not need to be fitted by a health-care professional. It has a reservoir for spermicide, a central valve that relieves positive pressure and allows for drainage of cervical secretions, and a loop to aid in removal.[17] Being silicone, it is a suitable barrier method for individuals who are allergic to latex. Efficacy rates are similar to those seen with the diaphragm and may also be lower in parous women.[14,17] The FemCap® (Femcap Del Mar, CA, USA) is also a silicone barrier method; shaped like a sailor's cap with a strap for removal and such that spermicide can be put on the anticervical side. It comes in three sizes, fitted on the basis of the patient's obstetrical history. It can be left in place for up to 48 hours and is associated with less UTIs. It was found to be more problematic in regards to dislodgement, insertion, and removal in trials than were other barrier methods. Based on one trial, its efficacy seemed significantly less than that of the diaphragm.[14,17]

The Today® (Allendale Pharmaceuticals, New York, NY, USA) sponge is a disposable, single-use polyurethane sponge 3 inches in diameter and 1.5 inches thick, which contains 1 g of nonoxynol-9 and is inserted vaginally and does not need to be fitted.[13,17] It is moistened before insertion to activate the spermicide (125–150 mg is released over 24 hours) and has a dimple on one side which sits against the cervix and a strap on the other side for

removal. The sponge acts as a physical barrier, releases spermicide, and absorbs sperm; all of these methods decrease the exposure of sperm to the cervix. It can be placed up to 24 hours before intercourse, can be used for multiple acts of intercourse, and should stay *in situ* for 6 hours after intercourse, for a total of 30 hours *in situ*. To decrease rates of toxic shock syndrome, it is also recommended that the sponge is not used during menstruation, postpartum or after an abortion.[17] It has similar efficacy to the diaphragm although, like the cervical cap, decreased efficacy is noted in parous women. After being taken off the market in 1995, it has now been available again since 2005.[13,14,17]

The female condom was approved for use in the USA in 1993, and is marketed under the name FC Female condom® (formerly the Reality condom®) (The Female Health Company, Chicago, IL, USA). It is a female-initiated method of both contraception and STI prevention. The female condom is a single-use polyurethane sheath, 78 mm wide and 170 mm long, with a ring at either end. It is prelubricated on the inside with a spermicidal lubricant and one ring is placed in the vagina before intercourse and the other open ring sits outside the vagina to allow for intercourse. It can be placed in the vagina up to 8 hours before intercourse.[14] It has been shown to reduce rates of STI transmission in women whose partners refuse to use a male condom.[13] Importantly, however, it should not be used in conjunction with a male condom as the two can adhere to each other and become displaced.[14] While clinical evidence is limited, the polyurethane sheath as well as the small amount of protection provided over the perineum should provide STI protection similar to those observed with the male condom. Efficacy rates are also estimated to be similar to those observed with the male condom. Slippage is a problem noted specifically with the female condom and cost can be prohibitive to use.[14]

VAGINAL SPERMICIDES

Descriptions of vaginal spermicidal concoctions date back to Greek writings of the early common era. These agents, manufactured commercially since the 1930s, consist of a spermicidal agent (most commonly nonoxynol-9) with a carrier method such as a cream, foam, tablet, jelly or film and can be purchased without a prescription. Patients should be advised to allow the film or tablet to dissolve before intercourse and should also be reminded to use a fresh dose of spermicide before each act of intercourse. These vaginal suppositories can be used alone, with failure rates of 5–50% in the first year of use.[6,14] They are more often used in conjunction with other male and female barrier methods. *In vivo* and *in vitro* efficacy against STIs has been demonstrated. Vaginal spermicides used alone do not decrease rates of HIV transmission. Vaginal odor, irritation, yeast infections, UTIs, and allergic reactions are the primary side effects. In addition, the spermicide may leak out of the vagina after intercourse, which may be distasteful.[6,13,14] Nonoxynol-9 has also been associated with increased rates of HIV transmission in Kenyan sex trade workers, indicating that it is not necessarily effective as a microbicide but rather can increase irritation and abrasion to the vagina.[14]

HORMONAL CONTRACEPTIVES

COMBINED ORAL CONTRACEPTIVE PILL

The first oral contraceptive pill (OCP), Enovid-10, debuted in the 1960s. It was developed with money raised by Margaret Sanger and was designed for continuous use. It contained 9.85 mg of norprogestin and 150 μg of mestranol, an approximately 10-fold increase in the amount of progestin and 4-fold increase in the amount of estrogen compared with modern OCPs.[18] Over the more than four decades that OCPs have been in use, the hormonal doses have decreased and newer, less androgenic progestins have been developed. OCPs contain a combination of ethinyl estradiol and progestin and are packaged to be taken daily for 21 days followed by either 7 days of no pills (21-day packs) or placebo pills (28-day packs), during which time a withdrawal bleed occurs. OCPs can be classified as either

monophasic, which contain the same dose of hormones daily, or triphasic, in which the amount of progestin varies over the 21 days.[5,13]

OCPs work in a variety of ways to prevent conception. They exert a negative feedback on gonadotropin-releasing hormone (GnRH), thus preventing ovulation via inhibition of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In addition, cervical mucus is thickened, the endometrium is thinned, and tubal transport is delayed, all of which further decrease the probability of conception.[5,13]

Adolescents with medical conditions need to be assessed as to whether there are increased risks to their medical health from the combined OCP. Absolute contraindications would include a personal history of thromboembolic disease, known hypercoagulability, pregnancy, severe hypertension, active breast cancer, migraine with focal neurological symptomatology, active liver disease, cerebrovascular disease, diabetes with end-organ damage, congenital heart disease complicated by structural lesions with turbulent flow or cardiac stents, and cerebrovascular disease. The World Health Organization (WHO) has developed four categories of safety for use of combined OCPs (Table 15.1).[5]

Serious adverse reactions to the combined OCP are rare and are fewer in the adolescent population than in older adults.[5] Common adverse reactions include nausea, which typically subsides within the first one or two cycles. Candida vaginitis is also more common in users of the OCP; it can be treated without discontinuing the OCPs. Despite the concerns of adolescents, the current formulations of the OCP are not associated with inherent weight gain but patients must be advised to monitor their food consumption and exercise regimes.[13,19] The risk of a venous thromboembolic (VTE) event has decreased with the development of lower dose OCPs. It is still increased in users of the OCP compared with the general population, with a relative risk of between 3 and 6 according to a 1998 WHO study, with the highest risk in the first year of use.[20] The absolute risk in the healthy adolescent population is still extremely low, in the range of 1.6–5.0 events per 10 000 women, with a slightly increased risk with third-generation progestins. The risk of mortality from arterial or venous events attributable to the OCP, for women aged 20–24, is 1 in 370 000 users.[20] There is no significant concern for increase in myocardial infarction (MI) or stroke in nonsmokers under age 35 using the OCP.[21] There are a few drug interactions that may alter the efficacy of the OCP, specifically those that induce the hepatic cytochrome P450 enzyme system; examples include phenytoin, phenobarbital, and primidone. Rifampin and griseofulvin decrease the effectiveness of the OCP. Numerous other antiepileptic medications are associated with increased breakthrough bleeding but do not decrease OCP efficacy.[9]

In addition, there are many non-contraceptive benefits to use of the OCP. These include predictable menses, lighter menses, decreased rates of dysmenorrhea, decreased formation of ovarian cysts, decreased rates of pelvic inflammatory disease (PID), decreased ectopic pregnancy rate, a protective effect for endometriosis, improved acne, and reduction in lifetime rates of fibrocystic breast disease.[5,13,21]

Newer information on these non-contraceptive benefits of the pill may allow the practitioner to target certain populations with certain formulations. Newer indications such as premenstrual dysphoric disorder (PMDD) with a low-dose (20 μg ethinyl estradiol) formulation containing drospirenone (3 mg), which has both antiandrogenic and antimineralocorticoid properties, in a 24/4 regimen (24 days active/4 days placebo), has proven to be efficacious in reducing symptoms of PMDD.[22] By the same token this formulation has proven to be efficacious in the treatment of acne.[23] Information on the efficacy of some other formulations in reducing acne that include cyproterone, levonorgestrel or desogestrel may also favor the use of some combinations and allow the patient to obtain multiple benefits with one drug.[24] With respect to malignancy, OCP users have significantly decreased rates of endometrial and ovarian cancers, a possibly reduced risk of colorectal cancer, and increased rates of hepatobiliary and cervical cancer.[21] While there may be a small increased risk of breast cancer

Table 15.1 The World Health Organization (WHO) categories of safety for use of contraceptive methods

Low-dose combined oral contraceptives (COCs) < 35 μg of ethinylestradiol	**COCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV**	
Condition	**Category** **I = Initiation** **C = Continuation**	**Clarifications/evidence**
PERSONAL CHARACTERISTICS AND REPRODUCTIVE HISTORY		
Pregnancy	NA	**Clarification**: Use of COCs is not required. There is no known harm to the woman, the course of her pregnancy, or the fetus if COCs are accidentally used during pregnancy
Age		
a) Menarche to < 40 years	1	
b) > 40 years	2	
Parity		
a) Nulliparous	1	
b) Parous	1	
Breastfeeding		
a) < 6 weeks postpartum	4	
b) > 6 weeks to < 6 months postpartum (primarily breastfeeding)	3	
c) > 6 months postpartum	2	
Postpartum (in non-breastfeeding women)		
a) < 21 days	3	
b) > 21 days	1	
Post-abortion		
a) First trimester	1	**Clarification**: COCs may be started immediately post-abortion
b) Second trimester	1	
c) Immediate post-septic abortion	1	
Past ectopic pregnancy	1	
History of pelvic surgery	1	
Smoking		
a) Age < 35 years	2	**Evidence**: COC users who smoked were at increased risk of cardiovascular diseases, especially myocardial infarction, compared with those who did not smoke. Studies also showed an increased risk of myocardial infarction with increasing number of cigarettes smoked per day
b) Age > 35 years		
(i) < 15 cigarettes/day	3	
(ii) > 15 cigarettes/day	4	
Obesity > 30 kg/m^2 body mass index (BMI)	2	**Evidence**: Obese women who used COCs were at increased risk of VTE compared with non-users. The absolute risk of VTE remained small. Data are limited regarding the impact of obesity on COC effectiveness

(*Continued*)

Table 15.1 (*Continued*)

Blood pressure measurement unavailable	NA	**Clarification**: It is desirable to have blood pressure measurements taken before initiation of COC use. However, in some settings blood pressure measurements are unavailable. In many of these settings pregnancy morbidity and mortality risks are high, and COCs are one of the few methods widely available. In such settings, women should not be denied use of COCs simply because their blood pressure cannot be measured
CARDIOVASCULAR DISEASE		
Multiple risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes and hypertension)	3/4	**Clarification**: When a woman has multiple major risk factors, any of which alone would substantially increase the risk of cardiovascular disease, use of COCs may increase her risk to an unacceptable level. However, a simple addition of categories for multiple risk factors is not intended; for example, a combination of two risk factors assigned a category 2 may not necessarily warrant a higher category
Hypertension		
For all categories of hypertension, classifications are based on the assumption that no other risk factors for cardiovascular disease exist. When multiple risk factors do exist, risk of cardiovascular disease may increase substantially. A single reading of blood pressure level is not sufficient to classify a woman as hypertensive		
a) History of hypertension, where blood pressure CANNOT be evaluated (including hypertension in pregnancy)	3	**Clarification**: Evaluation of cause and level of hypertension is recommended, as soon as feasible **Evidence**: Women who did not have a blood pressure check before COC use had an increased risk of acute myocardial infarction and stroke
b) Adequately controlled hypertension, where blood pressure CAN be evaluated	3	**Clarification**: Women adequately treated for hypertension are at reduced risk of acute myocardial infarction and stroke as compared with untreated women. Although there are no data, COC users with adequately controlled and monitored hypertension should be at reduced risk of acute myocardial infarction and stroke compared with untreated hypertensive COC users
c) Elevated blood pressure levels (properly taken measurements)		
(i) systolic 140–159 or diastolic 90–99	3	**Evidence**: Among women with hypertension, COC users were at increased risk of stroke, acute myocardial infarction, and peripheral arterial disease compared with non-users
(ii) systolic > 160 or diastolic > 100	4	
d) Vascular disease	4	
History of high blood pressure during pregnancy (where current blood pressure is measurable and normal)	2	**Evidence**: Women who had a history of high blood pressure in pregnancy, who also used COCs, had an increased risk of myocardial infarction and venous thromboembolism, compared with COC users who did not have a history of high blood pressure during pregnancy. The absolute risks of acute myocardial infarction and venous thromboembolism in this population remained small
Deep venous thrombosis (DVT)/pulmonary embolism (PE)		
a) History of DVT/PE	4	
b) Current DVT/PE	4	
c) Family history of DVT/PE (first-degree relatives)	2	
d) Major surgery		
(i) with prolonged immobilization	4	
(ii) without prolonged immobilization	2	

(*Continued*)

Table 15.1 (*Continued*)

e) Minor surgery without immobilization	1		
Known thrombogenic mutations (e.g., Factor V Leiden; prothrombin mutation; protein S, protein C, and antithrombin deficiencies)	4		**Clarification**: Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening **Evidence**: Among women with thrombogenic mutations, COC users had a 2–20-fold higher risk of thrombosis than non-users
Superficial venous thrombosis			
a) Varicose veins	1		
b) Superficial thrombophlebitis	2		
Current and history of ischemic heart disease	4		
Stroke (history of cerebrovascular accident)	4		
Known hyperlipidemias	2/3		**Clarification**: Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening. While some types of hyperlipidemias are risk factors for vascular disease, the category should be assessed according to the type, its severity, and the presence of other cardiovascular risk factors
Valvular heart disease			
a) Uncomplicated	2		
b) Complicated (pulmonary hypertension, risk of atrial fibrillation, history of subacute bacterial endocarditis)	4		
NEUROLOGIC CONDITIONS			
Headaches	I	C	
a) Non-migrainous (mild or severe)	1	2	**Clarification**: Classification depends on accurate diagnosis of those severe headaches that are migrainous and those that are not. Any new headaches or marked changes in headaches should be evaluated. Classification is for women without any other risk factors for stroke. Risk of stroke increases with age, hypertension, and smoking
b) Migraine			**Evidence**: Among women with migraine, women who also had aura had a higher risk of stroke than those without aura. Among women with migraine, those who used COCs had a two to four-fold increased risk of stroke compared with women who did not use COCs
(i) without aura			
Age < 35	2	3	
Age > 35	3	4	
(ii) with aura, at any age	4	4	
Epilepsy	1		**Clarification**: If a woman is taking anticonvulsants, refer to the section on drug interactions. Certain anticonvulsants lower COC effectiveness
DEPRESSIVE DISORDERS			
Depressive disorders	1		**Clarification**: The classification is based on data for women with selected depressive disorders. No data on bipolar disorder or postpartum depression were available. There is a potential for drug interactions between certain antidepressant medications and hormonal contraceptives **Evidence**: COC use did not increase depressive symptoms in women with depression compared to baseline or to non-users with depression

(*Continued*)

Table 15.1 (*Continued*)

REPRODUCTIVE TRACT INFECTIONS AND DISORDERS		
Vaginal bleeding patterns		
a) Irregular pattern *without* heavy bleeding	1	
b) Heavy or prolonged bleeding (includes regular and irregular patterns)	1	**Clarification**: Unusually heavy bleeding should raise the suspicion of a serious underlying condition
Unexplained vaginal bleeding (suspicious for serious condition)		
Before evaluation	2	**Clarification**: If pregnancy or an underlying pathological condition (such as pelvic malignancy) is suspected, it must be evaluated and the category adjusted after evaluation
Endometriosis	1	
Benign ovarian tumors (including cysts)	1	
Severe dysmenorrhea	1	**Evidence**: There was no increased risk of side effects with COC use among women with dysmenorrhea compared to women not using COCs. Some COC users had a reduction in pain and bleeding
Trophoblast disease	1	
a) Benign gestational trophoblastic disease	1	**Evidence**: Among women with benign or malignant gestational trophoblastic disease, there was no difference in mean times to hCG normalization or incidence of postmolar trophoblastic disease for COC users compared to non-hormonal users
b) Malignant gestational trophoblastic disease	1	
Cervical ectropion	1	
Cervical intra-epithelial neoplasia (CIN)	2	**Evidence**: Among women with persistent HPV infection, long-term COC use (≥ 5 years) may increase the risk of carcinoma *in situ* and invasive carcinoma
Cervical cancer (awaiting treatment)	2	
Breast disease		
a) Undiagnosed mass	2	**Clarification**: Evaluation should be pursued as early as possible
b) Benign breast disease	1	
c) Family history of cancer	1	**Evidence**: Among COC users with a family history of breast cancer, there was no increased risk of breast cancer compared with non-COC users with a family history of breast cancer. Among women with BRCA1 mutations, COC users may have a small increased risk of breast cancer compared with non-users
d) Breast cancer		
(i) current	4	
(ii) past and no evidence of current disease for 5 years	3	
Endometrial cancer	1	
Ovarian cancer	1	
Uterine fibroids		
a) Without distortion of the uterine cavity	1	
b) With distortion of the uterine cavity	1	

(*Continued*)

Table 15.1 (*Continued*)

Pelvic inflammatory disease (PID)		
a) Past PID (assuming no current risk factors for STIs)		
(i) with subsequent pregnancy	1	
(ii) without subsequent pregnancy	1	
b) PID – current	1	
STIs		
a) Current purulent cervicitis or chlamydial infection or gonorrhea	1	
b) Other STIs (excluding HIV and hepatitis)	1	
c) Vaginitis (including *Trichomonas vaginalis* and bacterial vaginosis)	1	
d) Increased risk of STIs	1	**Evidence**: Evidence suggests that there may be an increased risk of chlamydial cervicitis among COC users at high risk of STIs. For other STIs, there is either evidence of no association between COC use and STI acquisition or limited evidence to draw any conclusions
HIV/AIDS		
High risk of HIV	1	**Evidence**: Overall, evidence is inconsistent regarding whether there is any increased risk of HIV acquisition among COC users compared with non-users
HIV-infected	1	**Evidence**: Limited evidence suggests no association between COC use and changes in RNA levels or CD4 counts among HIV-infected women. There is also limited evidence showing no association between COC use and female to male HIV transmission, and mixed results regarding increased risk of HIV and herpes simplex virus (HSV) shedding among HIV-infected women using hormonal contraception
AIDS	1	
On ARV therapy	2	**Clarification**: If a woman is taking antiretroviral (ARV) therapy, refer to the section on drug interactions. Because there may be drug interactions between hormonal contraceptives and ARVs, AIDS with ARV therapy is classified as Category 2
OTHER INFECTIONS		
Schistosomiasis		
a) Uncomplicated	1	
b) Fibrosis of liver (if severe, see cirrhosis)	1	
Tuberculosis	1	
a) Non-pelvic	1	**Clarification**: If a woman is taking rifampicin, refer to the section on drug interactions. Rifampicin is likely to decrease COC effectiveness
b) Known pelvic	1	
Malaria	1	

(*Continued*)

Table 15.1 (*Continued*)

ENDOCRINE CONDITIONS		
Diabetes		
a) History of gestational disease	1	
b) Non-vascular disease		
(i) non-insulin-dependent	2	
(ii) insulin-dependent	2	
c) Nephropathy/retinopathy/ neuropathy	3/4	**Clarification**: The category should be assessed according to the severity of the condition
d) Other vascular disease or diabetes of > 20 years' duration	3/4	**Clarification**: The category should be assessed according to the severity of the condition
Thyroid disorders		
a) Simple goiter	1	
b) Hyperthyroid	1	
c) Hypothyroid	1	
GASTROINTESTINAL CONDITIONS		
Gall-bladder disease		
a) Symptomatic		
(i) treated by cholecystectomy	2	
(ii) medically treated	3	
(iii) current	3	
b) Asymptomatic	2	
Viral hepatitis		
a) Active	4	
b) Carrier	1	
Cirrhosis		
a) Mild (compensated)	3	
b) Severe (decompensated)	4	
ANEMIAS		
Thalassemia	1	
Sickle cell disease	2	
Iron-deficiency anemia	1	
DRUG INTERACTIONS		
Drugs which affect liver enzymes		
a) Rifampicin	3	**Clarification**: Although the interaction of rifampicin or certain anticonvulsants with COCs is not harmful to women, it is likely to reduce the effectiveness of COCs. Use of other contraceptives should be encouraged for women who are long-term users of any of these drugs. Whether increasing the hormone dose of COCs is of benefit remains unclear

(*Continued*)

Table 15.1 (*Continued*)

b) Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)	3	**Evidence**: Use of rifampicin and certain anticonvulsants decreased the contraceptive effectiveness of COCs
Antibiotics (excluding rifampicin)		
a) Griseofulvin	2	
b) Other antibiotics	3	**Evidence**: The contraceptive effectiveness of COCs was not affected by coadministration of most broad-spectrum antibiotics
Antiretroviral therapy	2	**Clarification**: It is important to note that antiretroviral drugs (ARVs) have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. The limited data available suggest that potential drug interactions between many ARVs (particularly some non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs)) and hormonal contraceptives may alter safety and effectiveness of both the hormonal contraceptives and the ARVs. It is not known whether the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot medroxyprogesterone acetate and norethisterone enantate) would be compromised, as these methods provide higher blood hormone levels than other progestogen-only hormonal contraceptives, as well as than combined oral contraceptives. Studies are under way to evaluate potential interactions between depot medroxyprogesterone acetate and selected PI and NNRTI drugs. Thus, if a woman on ARV treatment decides to initiate or continue hormonal contraceptive use, the consistent use of condoms is recommended for preventing HIV transmission and may also compensate for any possible reduction in the effectiveness of the hormonal contraceptive

From Medical Eligibility Criteria for Contraceptive Use 3rd edn, 2004 with permission. 1. A condition for which there is no restriction for the use of the contraceptive method. 2. A condition where the advantages of using the method generally outweigh the theoretical or proven risks. 3. A condition where the theoretical or proven risks usually outweigh the advantages of using the method. 4. A condition which represents an unacceptable health risk if the contraceptive method is used. Also: 1 Use method in any circumstances; 2 Generally use the method; 3 Use of method not usually recommended unless other more appropriate methods are not available or not acceptable; 4 Method not to be used.

Table 15.2 Effectiveness of family planning methods

	Pregnancy per 100 women in first 12 months of use	
Family planning method	**Effectiveness with common use**	**Effectiveness with consistent use**
Male condom	14	3
Female condom	21	5
Diaphragm	12–40	6
Cervical cap	12–40	9
Spermicide	26–50	5
Combined OCP	3–7	0.1
DMPA	0.3	0.3
Progestin-only pill	1–5	0.5
Copper IUD	1.26	1.26
LNG-IUS	0.09	0.09

OCP, oral contraceptive pill; DMPA, depot medroxyprogesterone acetate; IUD, intrauterine device; LNG-IUS, levonorgestrel intrauterine system.

in young female OCP users, the absolute risk is very small and may be due to delay of the first full-term pregnancy rather than OCP use itself.[25] The significant decreases in endometrial and ovarian cancers, however, ultimately lead to 5.6 fewer cancers per 1000 Caucasian women who used the OCP.[21] While studies are equivocal as to whether OCPs exert a positive effect on bone mineral density (BMD), there are no studies indicating a detrimental effect. Some studies do indicate less increase in BMD in adolescents using 20 μg ethinyl estradiol OCPs compared with adolescent nonusers of the OCP.[21,26] OCPs are further shown to decrease rates of affective symptomatology of premenstrual syndrome (PMS), a disorder that affects 14–88% of adolescent girls, and PMDD, which affects 3–5% of reproductive-aged women. Effective PMDD treatment has recently been shown with the novel progestin, drospirenone.[27]

Despite many misconceptions on the part of adolescents, there are no routine laboratory tests required before initiation of the combined OCP; screening for thrombophilias in a healthy patient without significant family history is not cost-effective.[5] In addition, a pelvic examination is not required before initiation of the combined OCP. In an adolescent who is not yet sexually active, the OCP can be used for an indefinite period of time without pelvic examination; in a sexually active teen, the method can be initiated and the pelvic exam should be encouraged for routine STI screening but can be deferred. This allows for the establishment of a successful relationship with the adolescent and has been shown to increase the likelihood of successful follow-up. Many centers will defer the pelvic examination for up to 1 year after initiation of contraception in a sexually active teen.[5]

With ideal use, the combined OCP is 99.9% effective at pregnancy prevention over the course of a year; with typical use the efficacy is 97%. Adolescent users of the combined OCP have failure rates of up to 15% in the first year of use due to missed pills; 28% of 15–17-year-old users of the combined OCP report missing two or more pills in their most recent cycle (compared with 13% of those 18 and older).[2,5] Patients should therefore be advised how to manage missed pills, how to access and use emergency contraception, and to use condoms.[5] If one pill is missed, it should be taken immediately. If two or more pills are missed in the first 2 weeks of the pack, then two pills should be taken daily for the next 2 days and back-up contraception should be used for the following week; if necessary, emergency contraception should also be used. If two or more pills are missed in the third week of the pack or three or more pills are missed at all, the remainder of the pack should be discarded and a new pack started; again back-up methods and emergency contraception should be used as required.[28] On average, 45–66% of adolescent users will discontinue the OCP during the first year. Younger adolescent age is associated with poorer adherence. Many adolescents will identify the immediate consequence of a minor side effect while ignoring the long-term benefit of contraception. Careful education, dispelling myths about the OCP, and close follow-up are therefore important components of counseling and treatment initiation.[13,29] The 'quick start' method, in which the pill is actually initiated in the office in the presence of the health-care provider (rather than waiting for a Sunday start or starting with menses) is associated with better adherence over time.[29] Some small studies have found success with daily electronic reminders to adolescents.[4] New formulations of the OCP that are designed to enhance adherence include formulations containing iron, those with drospirenone (a spironolactone-like progestin), those that have just a 4-day placebo regimen and chewable, flavored pills.[30]

TRANSDERMAL COMBINED HORMONAL CONTRACEPTION

Recognizing the difficulties associated with daily adherence to a pill, development efforts have been aimed at contraceptive methods that are equally safe and effective but require less vigilance. A weekly contraceptive patch, named Evra®, has been available in North America since 2001 (Ortho-McNeil

Pharmaceutical, Inc., Titusville, NJ, USA). The patch is 20 mm^2 and contains ethinyl estradiol and norelgestromin, with daily absorption equivalent to 20 μg ethinyl estradiol and 150 μg norelgestromin.[31,32] Steady drug concentrations have been shown through the 1-week period of wear.[33]

The patch is typically placed weekly for 3 weeks then left off for 1 week, during which a withdrawal bleed occurs. It can be placed anywhere on the torso excluding the breasts, such as the lower abdomen, buttock or upper outer arm; sites should be rotated to avoid skin irritation.[16,31–33] In studies using over 70 000 patches, only 4.7% required replacement due to partial or complete detachment. In an adolescent study, 21% experienced a patch coming off completely and 32% experienced a patch peeling partially in the corner.[31] Women can maintain all normal activities, including all forms of bathing and water sports and the patch has also been shown to maintain adhesion in various weather conditions.[18,32–34] While the patch is designed to last for 7 days, if forgotten there is sufficient medication that it can be left in place for up to 9 days. If a patch is detached for less than 24 hours, it can be replaced in the same location or replaced with a new patch if the adhesive no longer works. If the patch is removed for more than 24 hours, contraceptive efficacy may be lost [5,31–33]

Contraindications, side effects profile, and noncontraceptive benefits are similar to those of the combined OCP; there are noted increased rates of breast discomfort and breakthrough bleeding during the first two cycles of use as well as local skin irritation. There are no noted effects on weight.[31,35,36] In 2005 and 2006, the Food and Drug Administration (FDA) issued warnings in regards to the contraceptive patch, indicating 60% increased estrogen exposure and a possible twofold increase in VTE in users of this product as compared with the OCP. Subsequently the manufacturer published two epidemiological studies looking at the rates of this event and had a small increase of events in one study, and the study failed to demonstrate the same effect.[30] Women over 90 kg in weight were shown to have increased pregnancy rates compared with thinner women and thus are thought to be poorer candidates for this method of contraception.[5,36]

As the patch is replaced weekly, it has particular appeal in the adolescent population over the OCP, which must be remembered daily. Studies in this population indicate good acceptance of the method, excellent cycle control, and adherence rates greater than those observed with the OCP.[18,31,32,37] In all, 97% of adolescents were either very or somewhat satisfied with the patch and 93% would recommend it to a friend.[31]

VAGINAL COMBINED HORMONAL RING

The use of the vaginal mucosa as an absorptive surface for hormonal contraceptives dates back to the 1960s; however, various problems in development slowed the process and the first flexible vaginal ring, NuvaRing® (Organon USA Inc., Roseland, NJ, USA), was approved for use in North America in 2001. Other longer-term rings remain in development.[38]

The contraceptive ring is an ethylene-vinyl-acetate copolymer that offers sustained, slow release of 15 μg ethinyl estradiol and 120 μg etonorgestrel daily over 3 weeks. The ring has an outer diameter of 54 mm and cross-sectional diameter of 4 mm.[39,40] The advantages of the method include the rapid absorption of steroid through the vaginal mucosa, the constant release rate of the medication, and the privacy of the method.[38] The ring is placed vaginally, starting on days 1–5 of the cycle, for 3 weeks and then removed for 1 week, during which a withdrawal bleed occurs.[39] There are no contraindications or difficulties in use of the device in conjunction with tampons or with barrier or spermicidal contraceptives.[39,41,42] If the ring is dislodged for less than 3 hours, it can be replaced without any interruption in contraceptive efficacy. If it is removed for more than 3 hours, contraceptive efficacy may be lost and a back-up method of contraception should be used for 7 days.[28]

The mechanism of action is identical to that of the OCP and studies have indicated complete suppression of ovulation in study patients as

assessed on ultrasound as well as measurements of serum FSH and LH.[39] Efficacy, side effect profile, and contraindications are again similar to those of the combined OCP and there is no effect on patient weight.[5,43,44] Rates of irregular bleeding (< 5%) are also lower than those noted with the OCPs and significantly more patients experience regular withdrawal bleeds than with OCPs.[18,39,40,45] Some increased leukorrhea and vaginal irritation have been reported, although there have been no noted changes to the vaginal flora.[5,39] The method has been well accepted by users in clinical trials, with 53% switching to the NuvaRing from another method and 90% indicating that they would recommend it to others.[39]

Adolescents have indicated, in relation to barrier methods of contraception, that they are typically uncomfortable with inserting contraceptive methods into the vagina and therefore the NuvaRing may have poor uptake in the adolescent population. An empty tampon applicator can be used to insert the NuvaRing for those who are uncomfortable about using their fingers to do so.[18] While the ring can remain *in situ* safely during intercourse and is only felt (but not thought to be bothersome) by 15% of women and 30% of partners, it can also be removed for up to 3 hours around intercourse and then be reinserted and can also be safely rinsed with water.[38–40]

CONTINUOUS COMBINED HORMONAL CONTRACEPTION

In the past few years there has been increased interest in the use of combined hormonal contraception in an extended or continuous regimen in which hormones are taken for longer than 21 days. The traditional regimen of 21 hormonally active days followed by 7 hormonally free days was developed to mimic the natural 'lunar' cycle and to be morally permissible.[46] The 7-day pill-free interval is not necessary for contraceptive efficacy or physiologic purposes. It simply produces scheduled monthly bleeding in most users by withdrawing the hormones. This monthly or periodic withdrawal bleed is not the same as menstruation. The doctrine that women using contraception need a menstrual cycle for health-related reasons is changing and reversible amenorrhea is becoming more acceptable to most women.[47,48] Physician views on prescribing extended cycles of combined hormonal contraceptives are also shifting to accommodate patients' requests and to treat gynecologic conditions exacerbated during the hormone-free interval.[49] Gynecologists more routinely recommend and prescribe extended regimens as compared with pediatricians, internists, and family physicians.[49]

Common gynecologic conditions including dysmenorrhea, endometriosis, menstrual migraines, and menorrhagia can easily be treated with an extended or continuous hormonal regimen. Continuous combined hormonal regimens are also effective methods of menstrual suppression in the special needs population. Shortening or completely eliminating the hormone-free interval has been shown to reduce the severity of symptoms during that week.[50] In addition to the medical benefits of reversible amenorrhea, many patients are interested in altering the menstrual cycle simply to have fewer menses. In recent studies of adolescents, conducted in both the USA and Europe, there was a clear preference demonstrated to menstruate less frequently than monthly or never again.[51–53]

No consensus exists on the optimal length for extending the pill-free interval. Sequences of 63 days on and 7 hormone-free days (63/7) and 84 days on and 7 hormone-free days (84/7) are common regimens described in the literature, along with continuous 365-day regimens. At present it is up to the prescribing physician to select the optimal regimen for the given patient. In the United States there are dedicated products for extended contraception including Seasonale® and Seasonique® (Barr Pharmaceuticals, Inc., Pomona, NY, USA), which are 63/7 regimens and Lybrel® (Wyeth, Madison, NJ, USA), which is a 365-day regimen. However, any cyclic product can be used in an extended or continuous regimen. More frequently a monophsic

pill is selected but triphasic pills have been used successfully in a continuous fashion with few adverse side effects.[54] Extending or continuous cycling with the transdermal patch and vaginal ring have also been shown to be effective alternatives to cyclical use with similar side effects.[55,56]

Breakthrough bleeding is often the most common reason for discontinuing an extended or continuous regimen. In a recent Cochrane review most bleeding outcomes showed either no major difference between groups or less bleeding and/or spotting with continuous dosing.[57] Overall, a continuous or extended regimen results in less scheduled bleeding days but bleeding/spotting appears to be very similar to a cyclic regimen.[58–62] Institution of a 3-day hormone-free interval has been found to be an effective treatment for breakthrough bleeding in patients specifically on a continuous regimen.[63]

Participant adherence and contraceptive efficacy appear to be very similar with both cyclic and continuous regimens.[57] Nevertheless, the most frequently forgotten pills are the first few days of the new pack and the last few days of the previous pack. An extended or continuous regimen decreases the total number of hormone-free intervals and is associated with less ovulation and greater sustained ovarian suppression.[64] This favorable effect would potentially decrease the number of high-risk days.[49]

One frequent patient and physician concern about a continuous or extended regimen is the possibility of endometrial 'build-up' with an extended administration of both estrogen and progestin on the endometrium. However, continuous pill administration maintains a progestin-dominant effect, resulting in a thin and decidualized endometrium. A recent study confirmed this progestin effect, as all subjects had endometrial stripe measurements less than 5 mm.[62]

Short-term adverse events are similar to conventional 21/7 cyclical regimens.[57] Long-term data on the safety of an extended regimen are not available. Safety data on use of a cyclic regimen, however, have been clearly demonstrated and continuous pill use appears to be a reasonable alternative approach.

DEPOT MEDROXYPROGESTERONE ACETATE

Depot medroxyprogesterone acetate (DMPA) is a progestin-only intramuscular injectable contraceptive administered every 11–14 weeks. A dose of 150 mg is initiated during the first 5 days of the woman's menstrual cycle and is repeated every 3 months. It has been available in many countries since the 1980s. It is a highly effective (failure rate less than 0.3% per year), safe, convenient, and reversible method of contraception.[65–71] The mechanism of action is primarily the prevention of ovulation, but decidualization of the endometrium and thickening of cervical mucus also provide supplemental action.[72] Effective plasma concentrations of DMPA are sustained for at least 14 weeks and ovulation is suppressed for an average of 18 weeks.[73] Fertility can be delayed for up to 9 months following discontinuation due to DMPA's very effective suppression of the hypothalamic-pituitary axis

Same day injection or 'quick start'[74] of DMPA has been reported as a safe and effective alternative to the standard prescribing practice of restricting initiation of DMPA to menstruation.[75] Although unproven, the effects of DMPA on a potential developing fetus should be discussed[76] with all patients before 'quick start'. Pregnancy testing is performed on the day of injection and repeated 2–3 weeks following injection. This method of administration is felt to enhance access to contraception without putting the patient at increased risk for pregnancy while she is waiting for her next menstrual cycle.[75]

DMPA is also useful in treating adolescents with medical conditions where estrogen would be contraindicated. DMPA has very few contraindications and most fortunately do not apply to the adolescent population. Absolute contraindications to DMPA are rare but include pregnancy (known or suspected), unexplained vaginal bleeding, and current diagnosis of breast cancer. Relative contraindications include severe liver cirrhosis, acute viral hepatitis, and benign hepatic adenoma.[71]

Side effects attributed to DMPA include weight gain, breakthrough bleeding, and potential bone loss.

Published studies on weight changes have been inconsistent. Some studies report weight gain changes as high as 9 kg in 2 years or less.[65,77–80] The product monograph indicates average weight gains of 2.5 kg after the first year of use, 3.7 kg after the second year of use, and 6.3 kg after the fourth year of use.[28] More recently, a prospective study demonstrated that this substantial increase in weight is composed entirely of increases in fat mass and not lean mass.[81,82] The mechanisms by which DMPA increases weight are unknown but are felt to be secondary to appetite stimulation.[82] Regardless, informed counseling about the potential weight changes must be included when prescribing DMPA to the adolescent population.

Breakthrough bleeding may be the most common reason for discontinuation of DMPA, particularly in the adolescent. Irregular bleeding may occur in as many as 25–50% of users in the first 6–12 months of dosing. Treatments that have been suggested include increasing the DMPA dose, shortening the interval between doses, adding supplemental estrogen such as 0.625 mg of conjugated equine estrogen (CEE) for 28 days, administration of a nonsteroidal anti-inflammatory drug (NSAID) twice daily for 10 days or adding an oral contraceptive pill for 1–3 months.[83] Unfortunately none of these methods is completely satisfactory. Fortunately amenorrhea occurs in 55–60% of DMPA users at 12 months[65,69,84–86] and up to 68% of DMPA users at greater than 1 year. Many teenagers perceive this as an appealing feature of the medication, which may contribute to their compliance.

Continuation rates of DMPA, despite its ease of administration, are similar to those of the OCP and range from 63 to 70% at 6 months.[84,87] 'Quick start' administration of DMPA has shown similar continuation rates at both 6 months and 1 year.[75,88]

DMPA received a black box warning from the FDA in 2004 regarding its potential negative effect on BMD. The adult literature does suggest that DMPA is associated with a reduction in BMD. Overall, DMPA users have lower mean BMD than nonusers. Studies specifically in adolescents also confirm these findings.[89–92] This difference in BMD in DMPA users is felt to be a loss in BMD in adolescent users compared with gains in adolescent nonusers and ranges from 2 to 3% for the first year of DMPA use. One study found that new adolescent users in fact lose more BMD than continuing users and the adjusted mean change in BMD decreases with increasing DMPA use.[92] In addition, in this same study, mean BMD levels reached the levels of nonusers by 12 months after discontinuation of DMPA. It is unknown, however, if adolescents ultimately achieved similar peak bone mass to that they would have achieved if they had avoided DMPA. Two studies have examined whether administering estrogen (0.625 mg CEE) would prevent further bone loss. Both studies showed an improvement in BMD in DMPA users who had already lost 1% bone mass in the first year of use or had a low spinal BMD and were currently on DMPA.[93,94] Although these studies are reassuring, the likelihood of the adolescent being compliant on both estrogen replacement and DMPA is highly improbable. Importantly, the clinical significance of reduction in BMD is unknown. It is unclear if this decrease in BMD is a good surrogate marker for subsequent fracture risk, particularly among the adolescent population. In addition, the loss of BMD use is analogous to changes in BMD that occur during both pregnancy and lactation, which are effectively prevented by use of DMPA in the sexually active adolescent.[95] The Society for Adolescent Medicine continues to endorse the use of DMPA with the following provisions: explain the benefits and potential risks, inform patients of the possible risk for bone loss, understand individual risk profile for osteopenia, consider the inclusion of bone density monitoring, recommend 1300 mg calcium carbonate plus 400 IU vitamin D and daily weight-bearing exercise, consider estrogen supplementation in those girls with osteopenia who are otherwise doing well on DMPA, and finally do not restrict DMPA use to 2 years.[96] The WHO also suggests that the advantages of using DMPA generally outweigh the theoretical safety concerns regarding fracture risk in the adolescent population (under 18 years of age).[97]

Non-contraceptive clinical benefits of DMPA include management of dysmenorrhea, endometriosis, protection against endometrial cancer, and a

reduction in sickle cell crisis and seizures.[98] DMPA has been shown to raise the seizure threshold and thus to lower seizure frequency in epileptic patients.[99] DMPA also offers a unique advantage to the adolescent with special needs who requires menstrual suppression.

PROGESTIN-ONLY PILL

The progestin-only pill (POP) consists of a daily pill containing 0.35 mg of norethindrone or 0.075 mg of norgestrel. The pill is taken daily and there are no placebo pills. The POP works as a contraceptive primarily by thickening cervical mucus. It also creates a hostile endometrial environment, decreasing the chance of pregnancy implantation.[13] Importantly, it does not reliably prevent ovulation. It is less efficacious than the combined OCP, with 1–3 pregnancies per 100 woman-years compared with the OCP with < 1; the failure rate with typical use is 5%.[5,9] The half-life of the pill is also short, requiring not only that it be taken on a daily basis, but that it be taken regularly exactly every 24 hours (efficacy can be lost if the pill is missed by more than 3 hours). This lower efficacy and requirement for very strict adherence make this a poor choice of contraceptive for most adolescents; however, it is an option for those with medical contraindications to estrogen.[5] It also has a role in the breastfeeding population, as it does not exert a detrimental effect on milk supply.[9] As with any progesterone-only method, the most common side effect is menstrual irregularities.[9]

INTRAUTERINE DEVICE CONTRACEPTION

Two intrauterine contraceptives are currently available in the US and Canada: the copper T intrauterine device (IUD) and the levonorgestrel-releasing intrauterine system (LNG-IUS). Both devices are approved for 5 years of use. Both are highly effective and reversible methods of contraception. Contraceptive efficacy is reported to be 1.26 per 100 women-years for the copper IUD and 0.09 per 100 woman-years for the LNG-IUS.[100] The mechanism of action for both IUDs includes prevention of fertilization and potential inhibition of implantation.[67,101] The copper IUD also affects sperm transport and sperm motility so that fertility rarely occurs.[102–104] The LNG-IUS causes endometrial decidualization and glandular atrophy,[105] and thickening of cervical mucus, which may create a barrier to sperm penetration.[106] Ovulation may also be suppressed.[107,108]

The use of the IUD as a method of contraception has decreased significantly following the highly flawed Dalkon shield. Only 2.1% of Americans and 2.6% of Canadians use this effective method of contraception.[109,110] Both devices today are distinctly different in design and delivery and do not pose the same risk of PID.

Although physicians have traditionally been reluctant to prescribe an IUD to the adolescent population, age alone is not an absolute contraindication to the IUD. In fact the WHO categorizes the IUD as class 2 for individuals less than or equal to age 20. The WHO states that IUDs do not protect against STIs including HIV. For those at risk for STIs, the correct and consistent use of condoms is recommended.[71]

Absolute contraindications to the IUD include pregnancy; current, recurrent or recent (within the past 3 months) PID or STI; severely distorted cavity; unexplained vaginal bleeding; copper allergy (for copper IUDs); and breast cancer (for LNG-IUS).[71]

The increased risk of upper tract disease is predominantly limited to the 20 days following insertion of the IUD according to the WHO.[106] After insertion, the risk of infection is related to exposure to STIs and not to the device itself.[111] Some studies suggest the LNG-IUS may actually protect against PID.[99,112] This protection is felt to be secondary to the progestin effect on the cervical mucus but still has to be further corroborated. Use of the IUD in the adolescent population should always include pre-insertion cervical cultures to rule out the possibility of subclinical infection.

Other risks following IUD insertion include perforation, which is a rare complication occurring at a rate of 0.6 per 1000 insertions.[113,114] Expulsion

can also occur and appears to occur more frequently in the nulliparous population.[115] Insertion may also be more difficult in the nulliparous patient and adolescent. Misoprostol can be used to soften the cervix before insertion and pre-insertion anti-inflammatories can be provided for analgesia. A para-cervical block can also be considered.

The LNG-IUS has a high rate of reduction of bleeding and 16–35% of recipients will become amennorrheic after 1 year of use.[100,116,117] Adolescents often respond favorably to this reduction in menstrual loss and possible amenorrhea. Adolescents must also be counseled about the nuisance, irregular bleeding that occurs most frequently in the first month following insertion. The copper IUD, in contrast, can increase menstrual loss[118,119] as well as both bleeding and spotting. This IUD may therefore be less acceptable to the adolescent. Discontinuation of the IUD due to pain or bleeding is higher in a younger population.[100,117,120]

The IUD should be considered in the adolescent, in particular those adolescents most at risk for unplanned pregnancy, including those who are already parents or have failed or refused other methods of birth control. Up to one-third of postpartum mothers will become pregnant again in the first 2 years postpartum.[121–123] The IUD offers a long-acting method of contraception with the advantage of improved compliance in the properly selected adolescent.

IMPLANTABLE CONTRACEPTIVES

Norplant® (off the market in US), a six-rod implantable progesterone contraceptive allowing slow release of levonorgestrel, was discontinued from the market in 2002. Despite disparaging reports about Norplant® and its ultimate removal from the market, it remained relatively well accepted and extremely effective at pregnancy prevention. Contraceptive continuation rates among adolescent mothers indicated a 12-month continuation rate of 91% among users of Norplant® as compared with 34% among users of the OCP; pregnancy rates in the study were 2% and 25%, respectively.[2] In the same group, Norplant® users had significantly more menstrual irregularities (73% compared with 5%) and an increased weight gain (8.7 lbs compared with 4.2 lbs).[2]

Implanon® (Organon USA Inc., Roseland, NJ, USA) is a single 4 mm by 2 mm rod, 68 mg etonorgestrel implant, which is placed discretely under the skin on the inner upper arm during a small procedure in the physician's office and releases 40 μg of etonorgestrel daily. It has been used worldwide since 1998 and was approved for use in the US in July 2006. Implanon® can be used for up to 3 years. Pearl index was 0.07 pregnancies per 100 woman-years provided that insertion was on days 1–5 of the menstrual cycle. Similar to other implantable progestin devices, menstrual irregularities are the most common side effect. Other side effects include headache, emotional lability, acne, and dysmenorrhea. Studies also indicated a 3.6% rate of complications associated with the site of Implanon insertion such as erythema, swelling, hematoma, and pain. Removal complications were only 1.7% and included problems of fibrosis, broken implant, and difficulty finding the implant.[124]

MISCELLANEOUS METHODS

The rhythm method, Billings method, and calculations of basal body temperature can all be used by the highly motivated adolescent to identify their body's physiologic changes and thus the most fertile period of their cycle. They can then avoid sexual activity during these times. Due to the high degree of motivation required, this method is not applicable to most adolescents and failure rates of these methods over time are quite high (6–38%). Lactational amenorrhea is not a reliable method, especially if the infant is over 6 months of age or if breastfeeding is not exclusive. Coitus interruptus or withdrawal is a technique that is also unreliable and relies on the male partner's ability and willingness to withdraw before ejaculation; these concepts are not realistic for most adolescent males. Furthermore, there is no protection against STI with any of these methods.[13]

EMERGENCY CONTRACEPTION

Emergency contraception is an option that all too few adolescents are aware of and which is advocated by all too few providers of contraception. In one survey of providers specifically trained in the care of adolescents, only 80% provided the emergency contraceptive pill (ECP) when prescribing contraception. Of those who did, many were misguided or misinformed in its use, such as not providing it to teens who would choose to keep a pregnancy or providing it only within 48 hours of unprotected intercourse.[2] In one study, 7% of ECP users went on to have subsequent pregnancies, indicating that those who use ECP should be identified as being at increased risk for pregnancy in the future.[2] Provision of emergency contraception should also involve discussion and provision of a longer-term method of contraception, if one is not already in use, or re-evaluation of a method that has failed.[125]

ECPs are designed to be used after an act of unprotected intercourse or when a chosen method of contraception fails (e.g. a broken condom) to prevent pregnancy from that act of intercourse. The mechanism of action of ECPs has not clearly been established, although it is felt likely that they inhibit or delay ovulation and may also prevent implantation or fertilization.[5,13] They do not disrupt an established pregnancy and do not increase the risk of an ectopic pregnancy. In general, ECPs are 75% effective at preventing pregnancy from that specific act of intercourse if taken within 5 days.[5,18] The only contraindication to the use of any method of emergency contraception is a known previously established pregnancy.[125] The patient should also be advised that their subsequent menstrual cycle can be altered, starting either earlier or later than usual.[13] Despite the large number of users of ECP, there are no reports of major adverse outcomes.[125] Increased provision of ECPs has not been shown to reduce adherence to longer-term contraceptive methods.[126]

ECPs have been used off-label since the 1960s and have been approved for use since 1998.[125] There are currently two FDA-approved versions of ECP. The Preven Emergency Contraceptive Kit® (off the market in the US) contains four pills of 50 μg ethinyl estradiol and 0.25 mg levonorgestrel as well as a pregnancy test and information booklet. Two pills each are taken 12 hours apart.[5] Preven® represents an example of the Yuzpe method, named after the Canadian physician who established the practice, in which any combination of OCPs totaling 100 μg ethinyl estradiol and containing levonorgestrel or norgestrel (recipes are published for at least 21 different brands of OCPs on the market) are taken twice, 12 hours apart.[2,18,126,127] The most common side effects are nausea (50%) and emesis (20%). For these reasons, many clinicians will provide an antiemetic along with the ECP; a repeat dose should be taken if there is emesis within 2 hours of taking either dose.[13]

The other available ECP is Plan B® (Barr Pharmaceuticals, Inc., Pomona, NY, USA), which consists of two pills of 0.75 mg levonorgestrel. Each pill is taken 12 hours apart, although recent data indicate the method to be equally effective if both tablets (totaling 1.5 mg) are taken together.[5,126] In randomized trials, Plan B® was shown to be slightly more effective than the estrogen-containing methods. Plan B® is 95% effective if used within 24 hours and 85% if used between 24 and 48 hours as compared with the Yuzpe method at 77% and 36%, respectively.[3,5,83] Because Plan B® contains no estrogen, nausea is also less common.[13] For these reasons, Plan B® is the preferred method of ECP where the choice is available. Since August 2006, Plan B® has been available at pharmacies in the US without prescription to women over the age of 18 with photo ID.[125] The progesterone-only pill containing 0.075 mg norgestrel can also be used; this requires taking two sets of 20 pills 12 hours apart or 40 pills simultaneously.[126,127]

In addition to the ECP, insertion of a copper IUD up to 7 days after ovulation (generally accepted as up to 5 days after unprotected intercourse to avoid calculation difficulties) is also a highly effective method of emergency contraception. It has been estimated to have an efficacy in the range of 99%. Unlike Preven® and Plan B®, the IUD is not cost-effective when used only for emergency

contraception but can, of course, thereafter be used for long-term contraception for up to 5 years.[125,127] The IUD is obviously a poor choice if there is concern about exposure to STIs due to the risk of ascending infection associated with insertion.[126] Side effects are the same as those associated with an IUD inserted at any other time and include abdominal cramping and pain, vaginal bleeding, and spotting.[127] The LNG-IUS is not presently licensed for use for emergency contraception.[126]

FUTURE DIRECTIONS

Contraception development persists with an emphasis on manufacturing novel formulations that will provide safe and effective contraceptive options that are increasingly convenient to use, thus enhancing adherence. Products currently under development include continuous use packaging of OCPs, a progesterone-only pill with a longer half-life that is capable of suppressing ovulation, a vaginal ring that can be used for an entire year (replaced after a monthly withdrawal bleed), and biodegradable implants that would not require removal, as well as new female barrier methods.[18,30]

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16. Adolescent pregnancy

Tia Melton

Every minute of every day one or two adolescents in the United States become pregnant. Of these 750 000 adolescent pregnancies: 30–35% end in elective abortions, 15% end in spontaneous abortions (including ectopic pregnancies and molar pregnancies), and the remainder result in live births.[1–3] The majority of these pregnancies are unplanned and occur in single adolescents aged 15–19 years, although pregnancies do occur in younger adolescents aged 10–14.[1,4] Fortunately, the number of pregnancies to these younger adolescents has decreased by 38% from an estimated 12 901 in 1994 to 7315 in 2004 (per 100 000).[5] This decline has occurred in spite of a 16% increase in the US population of adolescents aged 10–14 years. A general decline in adolescent pregnancy of 30% over the last two decades has occurred in all regions and among all racial groups in the US. African-American teens have the highest teen pregnancy rates (134/1000 teens aged 15–19). The Latina teen pregnancy rate is 131/1000 and for non-Latina whites in the US the pregnancy rate is 48/1000.[1] African-American teens aged 15–19 years have experienced the steepest decline in birth rates, although the overall birth rate for African-American and Latina adolescents continues to be the highest among all ethnic groups. The US adolescent birth rate has decreased from 61.8/1000 in 1991 to 41.2/1000 in 2004.[6] The current decreases in the US adolescent pregnancy, birth, and abortion rates are believed to be secondary to several factors, but primarily to teens' increased use of more effective forms of contraception. Some studies suggest that only 25% of the decline in the adolescent pregnancy rate could be attributed to abstinence/delayed sexual activity.[7]

In spite of the current declines, the US continues to have the highest rate of teen pregnancy in the developed world.[8] Data suggest that the current US rate is approximately two times the rate in Europe and Canada and eight times the rate in the Netherlands and Japan.[1] The reason for these regional variations is the subject of much research and debate. Strict moral and traditional values have been suggested as the reason for low teen pregnancy rates in areas like Japan and Singapore. Some suggest that the large minority population of the US is the etiology of its higher teen pregnancy rate. Although the minority population in the US has higher rates of teen pregnancy, non-Latina whites represent a larger proportion of the adolescent population and therefore have a greater absolute number of births.[8–10] Rates and age of first sexual intercourse are similar across the developed world and therefore cannot account for variations in pregnancy rates across countries.[11] Furthermore, the misconception that teens in the United States view pregnancy as a means of obtaining public assistance benefits is inconsistent with the lower pregnancy rates observed in some European countries that provide greater access and excellent public assistance benefits to pregnant teens.[9] The major difference between the US and the rest of the developed world is in policy related to teenage pregnancy, sexual education, adolescent sexuality, contraception, and reproductive health services. Access to comprehensive reproductive health services is a problem for many teens around the globe. Worldwide, 13–14 million children are born to women less than 20 years old;[12] 90% of these births occur to adolescents living in the developing world.[13,14] The adolescent pregnancy rate ranges from a high of 143/1000 in sub-Saharan Africa to 4–8/1000 in Singapore.[13,14]

For many teens in the US and across the globe, pregnancy and childbirth have long-term consequences that last well beyond the expected 40-week

Table 16.1 Key issues to end the cycle of poverty and prevent adolescent pregnancy

Recognize the possible causes of adolescent pregnancy
Identify any complications that are unique to the pregnant adolescent
Be aware of the outcomes of teen pregnancy
Identify barriers that exist to adolescents' access to reproductive health services
Identify key components important to adolescent obstetric care

gestational period. Pregnant teens around the world face similar challenges of poverty and decreased educational and employment opportunities. Lack of access to confidential care, abortion services, and contraception are major obstacles. These challenges are not insurmountable. Adolescent pregnancy remains an important issue because of the medical, financial, psychosocial, and political impact that it has on the teen, her child, and society. A comprehensive care plan to end the cycle of poverty, decreased opportunities, poor maternal and fetal outcomes, and repeated pregnancies involves several key issues (Table 16.1).

BASIC DEFINITION

The term adolescent pregnancy generally refers to pregnancies in girls less than 20 years of age. Much of the available research involves teens aged 15–19 years, with limited data about teens aged 10–14. Some differences in outcomes have been seen between the very young adolescent (10–14 years of age) and the older adolescent. Most data suggest that teens in the younger age group have poorer outcomes compared with older adolescents. The pregnancy rate is defined as the number of pregnancies per 1000 adolescents. The abortion rate represents the number of abortions per 1000 pregnancies; the abortion ratio is the number of abortions divided by the number of births plus abortions. Some studies suggest increased risk of poor outcomes (i.e. preterm delivery, obstructed labor, increased fistula formation, etc.) in adolescents with a low gynecologic age. Gynecologic age is equal to the chronologic age minus the age of menarche (i.e. the interval between menarche and first pregnancy).[15]

DIAGNOSIS

The diagnosis of adolescent pregnancy is no different from diagnosis of pregnancy in adults. A higher index of suspicion is sometimes necessary in the younger adolescent with an immature hypothalamic-pituitary-ovarian-uterine axis. Irregular menstrual cycles may lead to a delay in diagnosis. In 2008 the Center for Disease Control reported that 25% of teens in the United States had a sexually transmitted infection (STI). STIs can lead to fallopian tube damage. Therefore, the possibility of ectopic pregnancy must be considered in the pregnant adolescent. Serial quantitative human chorionic gonadotropin levels and ultrasound can assist in the exclusion of ectopic pregnancy and in following pregnancies complicated by gestational trophoblastic disease. The classic signs of the enlarging uterus and Chadwick and Hegar sign coupled with the usual symptoms (breast tenderness, change in diet, etc.) always require a pregnancy test in teenagers.

CAUSES OF TEEN PREGNANCY

A simple explanation for adolescent pregnancy is that it represents not utilizing contraceptives, failure of a contraceptive, or restricted access to contraception. Current research indicates that teen pregnancy is a far more complex issue. It is influenced by the society, environment, and circumstances into which the teen is born and lives. Several risk factors for adolescent pregnancy have been identified and are listed in Table 16.2.[16] Race and poverty are linked to adolescent pregnancy and it can be difficult for teens to break the familiar cycle of adolescent pregnancy.

Case 1 is a 15-year-old African-American female. She presented to the Emergency Department 2 days after her first act of sexual intercourse with peritoneal signs. A vaginal exam reveals a 2 cm vaginal

Table 16.2 Risk factors for adolescent pregnancy

Minority race
Poverty/living in disadvantage/impoverished conditions
History of abuse
Single-parent household
Lack of parental involvement
Early dating
Use of alcohol or drugs
Child of an adolescent pregnancy
Little perceived opportunity for success
School drop-out
Lack of support

From the Alan Guttmacher Institute, 2004 – U.S. Teenage Pregnancy Statistics: Overall Trends by Race, Ethnicity and State-by-State Information and references 9 and 19.

vault laceration that communicates with the abdominal cavity. She receives IV antibiotic therapy and has the laceration repaired in the operating room. During a confidential history and exam, the patient relays that the sexual experience was consensual. She reports a family history 'of having babies early' and chronic hypertension. She was brought to the Emergency Department by her 34-year-old mother. Over the next 4 years this patient conceives and delivers two children.

The interaction between race, social deprivation, and fertility is strong.[15] Thirty-eight percent of teens in the United States live in poor or low-income families; yet 73% of adolescents who give birth and 61% of teens who have elective terminations are from poor or low-income families.[2] European studies confirm these findings. Seventy-eight percent of Dutch teen mothers live in households with incomes in the lowest 20% compared with 26% of women who had their children in their 20s.[14] Around the world it is clear that minority race and disadvantage contribute to high adolescent pregnancy rates.[8,17] The United States has a greater population of teens living in such conditions compared with other industrialized countries, which may help to explain its higher rate of adolescent pregnancy.[18] Teens that grow up in such conditions are more likely to engage in risky behavior and to have children during their adolescence. In 1992, of the 14.6 million US teens who lived in poverty, 17% were white, 47% were African-American, and 49% were Latino (a category encompassing multiple races).[15] Daughters of single mothers are also at an increased risk for adolescent pregnancy.[19]

Case 2 is a 17-year-old obese white female who presents with 8 weeks of amenorrhea after her first act of intercourse. Her single employed mother accompanies the patient. Pregnancy is confirmed and during a subsequent visit to review her prenatal laboratory results she is informed that, not only has she conceived during her first act of intercourse, but she has contracted *Chlamydia trachomatis* and genital herpes simplex. It takes a great deal of encouragement and support to get her to stop repeating the phrase 'I am such a loser' at every visit. Fortunately with the support of her mother, her obstetrician, and her social worker she is able to improve her self-image. She had a normal spontaneous vaginal delivery at term and was able to delay her next pregnancy until age 21 when she had a job and was working to complete her education.

Research suggests that having a two-parent family decreases the risk of adolescent pregnancy. Furthermore, compared with two-parent families, children of single-parent families have greater reported difficulties (i.e. poverty, greater high school drop-out rates, etc.).[20] Past or current abuse has been suggested as another risk factor for adolescent pregnancy. In all, 40–60% of adolescents who become pregnant have a history of childhood physical or sexual abuse, which is frequently underreported or not reported at all.[9,10]

Case 3 is an 18-year-old African-American female. She was admitted to the gynecology service with bilateral tubo-ovarian abscess. She has been with her current sexual partner for the last 4 years. A detailed history reveals that her current sexual partner is the father of all of her pregnancies. He is also her abuser. He will not allow her to use contraception. The abuse typically escalates during her pregnancies and has been implicated in two of her second trimester losses. She is trapped. The patient finally relayed this abuse history on the second day of admission.

As many as 50–80% of teen mothers are in violent, abusive, or coercive relationships at some time during their pregnancy.[21]

Case 4 is a 22-year-old woman. She has had eight elective abortions and two spontaneous abortions. She states that she has not used contraception in the past for a variety of reasons, including fear of needles and inability to swallow pills. The patient was raped by her mother's boyfriend from age 11 to 15 years old until he was finally prosecuted and incarcerated. The patient's mother has maintained a relationship with the patient's abuser and plans to marry him when he is released from prison. The patient was also raped by her older sister's husband at age 13. She has been diagnosed with post-traumatic stress disorder. She is excited about her current pregnancy.

The majority of first intercourse experiences prior to age 15 are non-voluntary.[19] Younger teens are vulnerable to coercive and non-consensual sex. Involuntary sexual activity is reported by 74% of adolescents aged less than 14 and 60% of adolescents less than 15 years old.[9] In the United States and in countries around the world, teens who are in abusive relationships are believed to be at greater risk of pregnancy secondary to emotional damage, birth control sabotage, self-medication with alcohol or drugs, and increased sexual contact. Victims of abuse are at increased risk of being involved with violent or coercive partners. Their use of drugs or alcohol to blunt emotions may expose them to unprotected sexual activity.[21] In the developing world, forced prostitution is another form of violence that places adolescents at great risk. Sex workers are exposed to STIs and pregnancy and often have limited access to reproductive health care.[22] There are limited data available about the effect of emotional abuse and neglect on adolescent pregnancy rates.[23] A direct cause and effect between abuse and teenage pregnancy is still being debated and explored. However, many studies suggest a link. Fear of infertility or a desire to be loved and give love is sometimes the motivation for adolescents who plan a pregnancy. Some victims of violence plan a pregnancy to prove their fertility after long periods of unprotected sexual intercourse without pregnancy.

Susan Davis at the University of Alabama at Birmingham's School of Public Health questioned 455 low income African-American adolescents. Twenty-three percent of teens in her study expressed a desire to become pregnant in the near future.[24] Some teens see little difference in becoming a parent as an adolescent vs waiting until their 20s. Such teens believe that as an adolescent, not having a child will do little to change or improve their current situation. For some teens, the decision to become pregnant is the only area of their lives in which they have control.[25]

Finally, for some adolescents pregnancy is simply the result of immaturity and inexperience. They may not have the negotiating skills to say 'no' when pressured by a partner to have sex.[26] Limited skills coupled with lack of knowledge about and inexperience with using a particular contraceptive and/or limited access to contraceptive options make a teen vulnerable to pregnancy.[27]

ABORTION

Once an intrauterine pregnancy has been confirmed the pregnant teen must decide if she will continue the pregnancy or have an elective abortion.[10] Very few teens give their babies up for adoption.[5] More than 70% of adolescent pregnancies in the United States are unintended and approximately 50% of unintended teen pregnancies end in elective abortion versus 35% of adolescent pregnancies overall.[1,4] Low income teens account for approximately 60% of elective abortions, yet make up approximately 40% of the population. Teens from more affluent areas select abortion more often than teens from disadvantaged areas.[7] In the United States, teens account for approximately 20% of all the elective abortions that are performed each year.[2,4,20] Since the 1980s the proportion of adolescent pregnancies ending in elective terminations has been declining.[2] A number of rationales for this decline have been reported (Table 16.3).[8]

Adolescents in the United States and in many countries may have difficulty obtaining an abortion. Forty-three states in the US require parental

Table 16.3 Possible reasons for the decrease in adolescent elective terminations

Increased adolescent use of long-acting contraceptives leading to decreased pregnancy rates
Increased anti-abortion sentiment in the United States
Increased acceptance of non-marital childbirth in the general US population
Decreased accessibility of abortive services in the US
Increased state requirement of parental notification and/or consent
Long waiting periods
Unaccounted medical abortions that are the result of the use of mifeprogesterone
Delayed sexual activity

Adapted from Family Planning Perspectives 2000 – Adolescent Pregnancy and Childbearing: Levels and Trends in Developed Countries.

consent or notification before an elective abortion if the patient is less than 18 years of age.[4,28] Policies that stipulate/mandate parental involvement for either contraceptive or abortive services can potentially be harmful. They do not facilitate parent–child communication about sex, contraception, or related matters.[29] In the developing world, adolescents are at risk for unsafe abortions. It is estimated that worldwide 20 million of the 50 million elective abortions that occur each year are unsafe and that approximately 14% of all unsafe abortions are to women less than 20 years old.[4,22] An unsafe abortion is any abortion that is performed by someone who lacks the skills to perform the procedure with safe techniques in sanitary conditions. Teens who seek unsafe abortion, may be more at risk than their adult counterparts. They may delay seeking an abortion, which leads to greater gestation age at the time of procedure and thus increased complication rates. Furthermore, when complications arise, teens may delay seeking help. Teens may also use less skilled providers and more dangerous methods.[15]

MEDICAL AND SOCIAL COMPLICATIONS OF TEEN PREGNANCY

There has been much debate about the medical and social complications that confront the teen who elects to continue her pregnancy. Older data suggest that teenage pregnancy is a high-risk pregnancy destined for multiple short- and long-term complications. Recent research has attempted to eliminate the confounding factors of race, nulliparity, and disadvantage that have biased previous studies. Are the adverse outcomes attributed to adolescent pregnancy a result of teen biology or are other factors involved? Several outcomes have been evaluated.

HYPERTENSIVE DISORDERS

Nulliparous teens represent the majority of subjects in most studies of adolescent pregnancy. Nulliparity has been linked to increased rates of hypertensive disorders and preterm delivery in pregnancy. Current data suggest that nulliparity rather than age is the primary etiology of the higher rate of pre-eclampsia and hypertensive disorders seen in adolescent pregnancy.[15]

PRETERM BIRTH AND LOW BIRTH WEIGHT

Preterm birth (delivery before 37 weeks) and low birth weight (weight less than 2500 grams) are both increased in children of teenagers.[13,30] It remains unclear if the elevated rates of preterm birth (PTB) in teens is related to teenage biology (i.e. immaturity of organ systems), to African-American race (the rates of PTB are more than twice the rate of whites) or if other factors are involved.[31] Lack of prenatal care has been suggested as a contributing factor to preterm birth. Adolescents tend to register late, if at all, for prenatal care and therefore may miss opportunities for interventions that may lead to improved outcomes.[1,5,30]

The increased rate of low birth weigh (LBW) infants seen in teenage pregnancy may simply reflect higher rates of preterm deliveries. Infants of teens were not found to be at an increased risk for being small for their gestational age.[15] A 2005 study of teenage pregnancy outcomes found no significant difference in rates of preterm births or low birth weight in its adolescent population.[32] The authors

of the study attributed their good adolescent pregnancy outcomes to the provision of high quality prenatal care in their relatively homogeneous Finnish population. According to this 2005 study, teens in Finland are encouraged and expected to participate in the free, comprehensive, and unbiased high quality care. Teens in the study registered early for care and were compliant with prenatal care. The study had a very small proportion of participants less than 16 years old, as do most studies of teenage pregnancy. There were no significant differences in rates of preterm birth, low birth weight or small for gestational age babies between adolescents and the adult population in the study. Other studies have confirmed that there is little variation in outcomes between adult and teen pregnancies when teens receive early adolescent center prenatal care.[33]

PERINATAL AND NEONATAL MORTALITY

Low birth weight and preterm delivery are often good predictors of neonatal morbidity and mortality. Thus, it is not surprising that many studies of adolescent pregnancy record higher rates of neonatal death in children of adolescents. Infants of adolescents have been reported to have three times the chance of dying in the first year of life compared with those born to older women.[5] Other studies have shown that the increased risks of late fetal death and infant mortality were reduced once socioeconomic status was removed as a confounding factor.[33] Unmarried status has also been linked to low birth weight and neonatal mortality. The percentage of babies born to unmarried women increased from 30% in 1970 to 78% in 2000. Pregnancy in unmarried adolescents has followed this same trend. A 1990 study found that unmarried mothers accounted for 15% of all births, but 24% of neonatal and fetal deaths.[34]

MATERNAL MORBIDITY AND MORTALITY

Maternal mortality is the death of a woman while pregnant or within 42 days after pregnancy, related to or aggravated by the pregnancy or its management. Rates of morbidity and mortality are relatively low in the developed world.[15] Most data from developed countries suggest that no differences exist between adolescents and adults once racial disparities, prenatal care, and disadvantage are excluded.[33] In developing countries, however, high rates of maternal morbidity and mortality exist. According to the World Health Organization (WHO) more than 600 000 deaths each year are attributed to complications related to pregnancy and childbirth. Adolescents in such areas are often subjected to many of the same harsh circumstances as their adult counterparts; yet for women aged 15–19 who live in developing countries the maternal death rate has been reported to be as high as twice the rate for older women.[22] Teens with a low gynecologic age and therefore a smaller pelvis may be at higher risk for complications. Female genital mutilation may also affect labor outcomes in teens.[15] A prolonged or protracted labor may cause increased risk of infection, pelvic injury, fistula formation or death.

LABOR AND DELIVERY

Teens without an obstructed labor tend to do well and may have better outcomes than women aged 20 years and older.[22] Adolescents tend to have fewer cesarean sections, and a shorter active phase of labor, with less use of oxytocin for augmentation or induction of labor.[15,29,32,35] There are many reasons for these differences. Attitudes to surgical intervention in young participants may affect management plans. Inexperienced teens may not make the same demands on the labor and delivery staff for shorter labors. Limited prenatal care may affect the course of labor. Teens who have received limited care or no prenatal care are less likely to be induced for problems identified during the antenatal period. They may present with advanced labor. The WHO showed (in 1996) that good support in labor leads to shorter labors with decreased medical and surgical interventions and increased rates of Apgar scores greater than 7.

PSYCHOSOCIAL OUTCOMES

Great debate continues about the psychological and social outcomes of teenage pregnancy. Increased rates of developmental delay, academic difficulty, substance abuse, depression, and early sexual activity have all been reported in the children of adolescents.[9] Furthermore, children of adolescent pregnancies have been shown to have decreased scores in language and communication skills, decreased emotional and physical well-being, and diminished approaches to learning. Once socioeconomic status and background characteristics have been eliminated many of these adverse outcomes are decreased.[30,36] Children of adolescent pregnancies are themselves more likely to become teenage mothers and fathers.[3] Siblings of adolescent mothers are also at increased risk of teenage pregnancy.

Are such problems related to teenage pregnancy? Or are such adverse psychological outcomes related to disadvantage and problems that antedate and are exacerbated by the adolescent pregnancy? Many teen mothers are single (80% of fathers do not marry teen mothers) and depend on public assistance during or shortly after pregnancy.[3] In the United States, children of single-parent families may face increased life challenges.[20] Studies that demonstrate increased psychosocial and development problems in children of adolescents must therefore be evaluated with caution.

BARRIERS TO PREVENTION OF ADOLESCENT PREGNANCY

Teens around the world often face barriers to reproductive health services. Many European countries have a different and more open attitude to teenage sexuality and contraception. Sexual education and contraception are encouraged and integrated into health services and education programs.[18] Countries with more open policies tend to have lower adolescent pregnancy rates and have managed to overcome the challenges that impede teens' ability to prevent pregnancy. Financial, social, and psychological concerns of teens must be addressed if adolescent pregnancy rates are to continue to decline.

Table 16.4 Myths about sex and pregnancy prevention

You can't get pregnant during unprotected sex if the man pulls out
You can't get pregnant 3 days before or 3 days after your menses
You can't get pregnant while having sex standing up or in the shower
It is safe to have sex as soon as you start the pill
Missing one pill doesn't matter
You can't get pregnant having sex for the first time
If you don't want to get pregnant, you won't
If the condom breaks, there is nothing you can do
Urinating after sex washes out sperm and prevents pregnancy
All guys hate using condoms
Injectable contraceptives cause infertility
A girl that takes the pill must be promiscuous
Wearing two condoms will provide extra protection
Douching with cola, baking soda, etc. will prevent pregnancy
You can't get pregnant if you don't have an orgasm
Condoms won't protect against STIs or pregnancy

Information obtained from individual patients and the following websites: www.thesite.org, www.advocatesforyouth.org, and www.pixi.com/v521teen.

Some of the barriers that teens face are their beliefs in the many myths about contraception and pregnancy prevention (Table 16.4). Lack of information or misinformation prevent teens from making good decisions about sex and pregnancy.[27]

Concern about parental notification, denial of pregnancy, anxiety, and problems with communication, finance, and transportation are additional barriers to the prevention of adolescent pregnancy.[26] A 2002 study found that 47.1% of teens less than 18 years old would no longer attend a family planning clinic if parental notification was mandated,[37] and 2 of 10 teens would practice unsafe sex if notification of parents was required.[38] Teens not only need accurate information and contraception, but also assistance with negotiating contraceptive use. Adolescent pregnancy prevention must therefore provide confidential, easily accessible care that

increases the teen's knowledge about contraception and dispels myths. Successful programs promote abstinence while providing contraception.[27,29,30] Pregnancy prevention programs must also be timely. Education must occur well before sexual activity is initiated. Counseling and contraception must be readily available. The documentation of an STI or a negative pregnancy test is an excellent opportunity to discuss options with adolescents. Furthermore, programs must assist teens in developing long-term goals and increasing self-esteem.[27,30] Advocates for pregnancy prevention must insure that teens are in a safe environment and that they know how to get help.

SUMMARY

There is a continued and urgent need to make adolescent pregnancy a health-care priority. The negative outcomes that have been ascribed to teenage pregnancy seem to be less about adolescent biology and more about the health-care disparities that teens in the United States and around the world face. Poverty, violence, lack of knowledge, and access to reproductive health options are challenges that many teens encounter. Declines in the adolescent pregnancy rate over the last two decades provides little solace for the poor inner city teen in the United States or the African teen who gives birth afraid and at risk without a skilled birth attendant. These teens face higher rates of preterm birth, low birth weight infants, and neonatal morbidity and mortality. They are also at increased risk of having psychosocial and financial problems. Furthermore, there is evidence that the recent declines in adolescent pregnancy and birth may be slowing. Preliminary data from 2006 suggest a slight increase in the adolescent pregnancy rate in the US.[39] Additionally, the teenage population is projected to increase and anti-abortion laws are expected to become more restrictive. Societies that provide early education and open access to contraception have lower overall rates of adolescent pregnancy, birth, and abortion.[8,14,18] There is also evidence that many of the disparities in adolescent pregnancy outcomes can be reduced or eliminated with early, adolescent-centered care.[32,33] A comprehensive health-care response must address the issues of education and access to pre-conceptual and general obstetric care.

Educational programs must occur before sexual activity, as evidence suggests that 50% of teen pregnancies occur within the first 6 months of sexual activity. Many US teens do not seek care until they have been sexually active for at least 1 year. Teens must be supported both emotionally and financially. Adolescent health-care advocates must support policies and laws that improve teens' reproductive health-care rights and their safety. Abstinence-only programs and policies do not help the teen who becomes pregnant as a result of being in an abusive or unsafe environment. If the 2015 Millennium Development Goals of decreased child mortality (Goal 4) and improved maternal health (decreased rates of maternal morbidity and mortality) (Goal 5) are to be realized, then adolescent pregnancy and disparities in adolescent reproductive health must be a priority.

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17. Adolescents and sexually transmitted infections

Jill S Huppert and Frank M Biro

DEMOGRAPHICS

Sexually active adolescents continue to be the highest risk group for nearly every sexually transmitted disease (STD). Figure 17.1 utilizes data from the Centers for Disease Control and Prevention, STD Surveillance 2005, after adjusting for prevalence of sexual activity. It demonstrates that sexually active adolescent women 15–19 years of age have the highest rates of chlamydia and gonorrhea.[1] Figure 17.2 examines data from 2001 to 2005, reporting rates in all 15–19-year-old teens, regardless of sexual activity.[1] In Figure 17.2, rates have risen slightly for both teen females and males, but some of this apparent increase may be from the use of noninvasive testing or greater use of diagnostic tests with highest levels of sensitivity.

Overall, the prevalence of reported ever-sexual activity has fallen when examining data from the Youth Risk Behavior Survey between the years 1991 and 2005, although the prevalence in the most recent survey has increased slightly (Figure 17.3). Rates of condom use at the time of last sexual intercourse have increased and those teens who reported four or more lifetime partners have fallen, but use of alcohol or drugs at the time of last intercourse has risen.[2]

OBTAINING A SEXUAL HISTORY

When conducting a sexual history with an adolescent, it is important to discuss issues of confidentiality with the adolescent and their parent/guardian. Adolescents can legally consent to confidential diagnosis and treatment of STDs in all 50 states in the USA as well as in Washington, DC. However, the clinician must also discuss with the adolescent that certain information, such as a threat to the life of the adolescent or another person or history of incest, must be disclosed by the clinician. Additionally, the clinician should incorporate messages for STD risk reduction pertinent to the adolescent. This information should include abstinence, condom use, limiting number of partners, avoiding higher risk sexual behaviors, and the availability and efficacy of several vaccines for specific STDs, such as hepatitis B (if they had not received the series as an infant) and human papillomavirus. Table 17.1, modified from the CDC STD Treatment Guidelines 2006,[3] includes the salient information that should be covered with the adolescent. The responses to these questions will help guide the clinician to specific messages for risk reduction. Of note, the final question has been added to those recommended by the CDC; adolescents who are sexually active are more likely to have a history of sexual abuse, especially those adolescents with younger ages of sexual debut.

This chapter discusses specific organisms followed by clinical presentations. Partner treatment issues are addressed in the discussion of chlamydia treatment. Discussion of HPV infections is in Chapter 8, and the discussion of HIV/AIDS is beyond the scope of this chapter. The interested reader is referred to several other recent reviews regarding identification, management, and prevention of HIV/AIDS.[4,5]

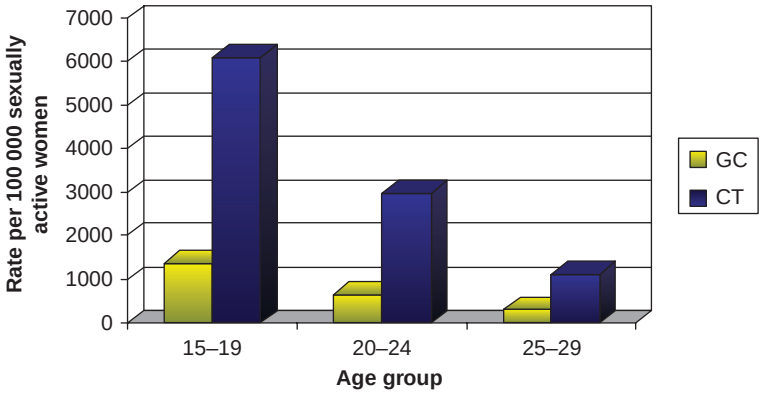

Figure 17.1 Gonococcus (GC) and chlamydia (CT) rates among sexually experienced women, CDC 2005 STD Surveillance demonstrating that sexually active adolescent women 15–19 years of age have the highest rates of chlamydial infection and gonorrhea (after adjusting for prevalence of sexual activity). (Centers for Disease Control and Prevention. Chlamydia. Atlanta, GA: US Department of Health and Human Services, 2006.)

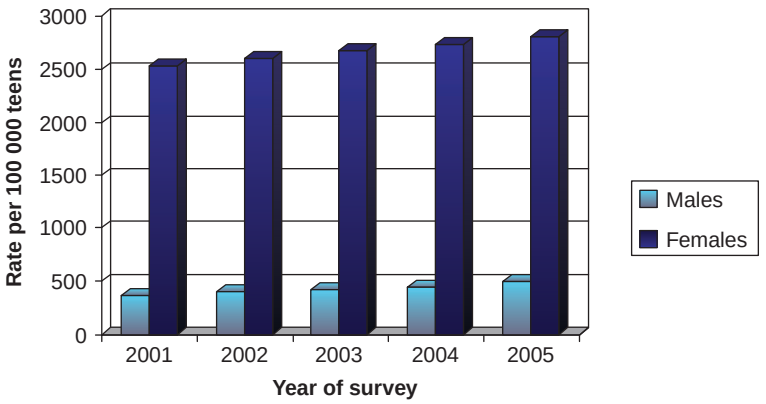

Figure 17.2 Data from 2001–2005, reporting chlamydia rates in all 15–19-year-old males and females, regardless of sexual activity. (Centers for Disease Control and Prevention. Chlamydia. Atlanta, GA: US Department of Health and Human Services, 2006.)

SPECIFIC ORGANISMS

CHLAMYDIA

Chlamydial urogenital infections are the most common bacterial STD. Although chlamydia may cause symptomatic infection, the majority of infections are asymptomatic. Asymptomatic infections are important to consider for several reasons. Complications may occur despite asymptomatic disease, and asymptomatic disease causes a disproportionate total of transmissions. A recent study noted that 75% of females (and 84% of males) with chlamydia were asymptomatic; in this study, 95% of untreated cases were never symptomatic.[6] The major reason for untreated chlamydia (or gonococcus, GC) is that a large proportion of those infected do not have symptoms. In a model describing transmission of

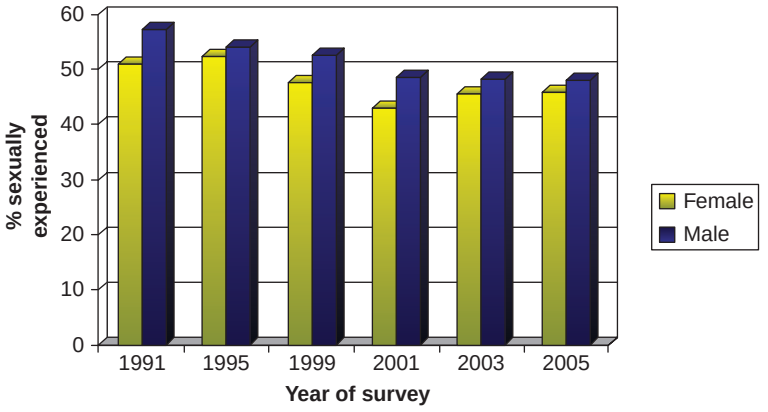

Figure 17.3 Rates of ever-sexual activity among high school students have fallen, when examining data from the Youth Risk Behavior Survey between the years 1991 and 2005, although the prevalence of ever-sexual activity in the most recent surveys has increased slightly. (Centers for Disease Control and Prevention. Youth Risk Behavior Surveillance – United States, 2005. MMWR 2006; 55(No SS-5.)

Table 17.1 Important points in the sexual history

Partners	Are you attracted to men, women, or both? Do you have sex with men, women, or both? In the past 2 months, how many partners? In the past 12 months, how many partners?
Practices: To understand your risks for STDs, I need to understand the kind of sex you have had recently	Have you been kissing? Have you been fondling? Have you had vaginal sex? Do you use condoms never, sometimes, or always? If never, why don't you use condoms? If sometimes, in what situations or with whom do you use condoms? Have you had anal sex? Do you use condoms never, sometimes, or always? If never, why don't you use condoms? If sometimes, in what situations or with whom do you use condoms? Have you had oral sex? Do you use condoms never, sometimes, or always? If never, why don't you use condoms? If sometimes, in what situations or with whom do you use condoms?
Prevention of pregnancy	Are you or your partner trying to get pregnant? If no, what are you doing to prevent pregnancy?
Protection from STDs	What do you do to protect yourself from STD/HIV?
Past history of STDs	Have you ever had an STD? Have you or any of your partners ever injected drugs? Have any of your partners exchanged money or drugs for sex? Is there anything else about your sexual practices that I need to know about?
Violence/coercion	Have you ever been forced to do something sexual that you didn't want to do? Have you ever been touched sexually when you didn't want to be? Have you ever experienced date rape?

Adapted from CDC Sexually Transmitted Diseases Treatment Guidelines, 2006, Clinical Prevention and Guidance. MMWR 2006.

chlamydia, it was noted that 43% of infections in males were asymptomatic and these asymptomatic infections were responsible for 58% of the infections to women.[7]

PREVALENCE

The prevalence of chlamydia among sexually active 15–19-year-old females in the United States, based on data from the 2005 CDC STD Surveillance, is 6.1 per 1000.[8] The overall prevalence based on data from the National Longitudinal Study of Adolescent Health (Add Health) is 4.2%; the rate is 1.29 times higher in females than males; highest among black men and women; and highest in the southeast.[9] Although the CDC Surveillance data note the highest rate in 15–19-year-old females, the Add Health data note that the rates are higher in 18–21-year-olds than 22–25-year-olds. From epidemiologic perspectives, chlamydial urogenital infections are more likely in those with new and/or multiple partners and inconsistent utilization of condoms. Some of the increased risk among adolescents may be a consequence of cervical ectropion and less mature urogenital immunologic responses.

CLINICAL PRESENTATION

As noted above, the majority of chlamydial urogenital infections are asymptomatic. The most common clinical presentation in women is cervicitis, which may present with vaginal discharge or lower abdominal pain. Patients with chlamydial cervicitis may have cervical friability and mucopurulent discharge. Lower abdominal pain with urinary tract symptoms is another presentation, although a recent article noted that urinary tract infections were associated with trichomonal, not chlamydial, infections.[10]

Untreated chlamydial infections can result in pelvic inflammatory disease (PID); it is estimated that 20–40% of untreated women will develop PID. A less common presentation of urogenital chlamydia infections is perihepatitis, also called Fitzhugh-Curtis syndrome. Many clinicians believe that the presence of perihepatitis means that the patient also has PID, since the proposed pathogenesis of perihepatitis would incorporate peritoneal passage of infected material.

Other consequences of infection include chronic pelvic pain and involuntary infertility. Several studies have documented serologic evidence of previous chlamydial infections among those seeking evaluation for infertility, despite lacking a history of clinical PID. Additionally, several international studies have noted increased risk of HIV acquisition among women with chlamydial infections.

DIAGNOSTIC APPROACHES

There are several methods for diagnosis of chlamydial infections. However, the advent of nucleic acid amplification techniques (NAATs) has resulted in the opportunity to utilize new clinical specimens and approaches to assessment. A systematic review from 2005 evaluated several NAATs, comparing urine and cervical specimens. The pooled sensitivity and specificity for PCR (polymerase chain reaction) were 83.3% and 99.5% in urine, and 85.5% and 99.6% in cervical samples; for TMA (transcription-mediated amplification), 92.5% and 98.6% in urine and 96.7% and 99.1% in cervical samples; for SDA (strand-displacement amplification), 79.9% and 99.1% in urine and 93.6% and 97.9% in cervical samples.[11] The approaches that do not utilize nucleic acid amplification have lower sensitivities and are not approved for evaluation of urine specimens. An important caveat to consider in medicolegal cases is that one positive NAAT test is not considered 'definitive' because specificities of the NAAT are less than 100%; however, a positive result from a different NAAT is considered confimatory.

TREATMENT

Treatment regimens for chlamydia are listed in Table 17.2. Several studies have shown the

Table 17.2 Treatment regimens for chlamydia

Type of regimen	Option		Option		Option		Option
Recommended regimens	Azithromycin 1 g orally in a single dose	OR	Doxycycline 100 mg orally twice a day for 7 days				
Alternative regimens	Erythromycin base 500 mg orally four times a day for 7 days	OR	Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days	OR	Ofloxacin 300 mg orally twice a day for 7 days	OR	Levofloxacin 500 mg orally once daily for 7 days

From CDC STD Guidelines 2006.

cost-effectiveness of single-dose, point-of-care administration of azithromycin.[12] Partners of women infected with chlamydia require treatment, and the CDC has discussed the potential of partner-delivered therapy, also known as expedited partner therapy (EPT).[13]

There is a high incidence of repeat infection after the incident infection. One study noted that 16.3% of women diagnosed with chlamydia, gonorrhea, or *Trichomonas* were re-infected at 3 months, and two-thirds of repeat infections were asymptomatic.[14] The median time to re-infection with chlamydia in adolescent females was 5.2 months, and of all cases of chlamydia diagnosed, 52.9% were recurrent infections.[15] Other studies in adolescents also reported 4.8–7.6 months for re-infection with chlamydia.[16,17] Another study in adolescents noted that the median time was 4.5 months until another infection with gonorrhea, chlamydia, or *Trichomonas vaginalis*,[18] with a mean of 4.8 months for recurrent chlamydia. These results suggest that an adolescent diagnosed with chlamydia should be retested at 3–5 months.

TRICHOMONIASIS

Trichomoniasis is caused by the organism *Trichomonas vaginalis* (TV), a pear-shaped, flagellated protozoon that parasitizes the vagina. It has four anterior flagella and an undulating membrane that provides motility and gives it a characteristic jerky motion on wet mount. TV causes local inflammation and epithelial breaks, and alters the vaginal flora. These unique characteristics explain the ability of TV infection to cause symptoms and to increase one's susceptibility to other STIs.

Table 17.3 Estimated yearly incidence of STIs in 15–24-year-olds in the US, 2000[21]

Total	**9.1 million**
HPV	4.6 million
Trichomoniasis	1.9 million
Chlamydia	1.5 million
Genital herpes	640 000
Gonorrhea	431 000
HIV	15 000
Syphilis	8200
Hepatitis B	7500

PREVALENCE

Trichomoniasis appears to be as common as chlamydia infection and more common than gonorrhea in adolescents. Prevalence estimates depend upon the population studied. In an urban teen health center, prevalence ranged from 9% by wet mount to 18% by NAAT.[19] In a national population-based survey, the overall prevalence of TV was 2.4% and was highest in females, African-Americans, and those residing in the southern and midwestern parts of the US.[20] Weinstock et al (Table 17.3) estimated that the incidence of trichomoniasis is second only to HPV in US adolescents.[21]

CLINICAL PRESENTATION

TV has been shown to be a cause of vaginitis in women and non-gonnococcal urethritis in men. Because TV is a vaginal pathogen, TV cervicitis

(strawberry cervix) is rarely seen. Similar to other STDs, the majority of men and women infected by TV are asymptomatic.[20]

In addition to local symptoms, TV has been reported in some series to be associated with atypical PID and poor obstetric outcomes. However, the most important consequence of infection is increased risk of acquiring herpes, HPV, and HIV.[22] TV infection appears to prolong the duration of HPV infection in adolescent women.[23] In men and women affected by HIV, TV infection increases HIV shedding.[24,25]

DIAGNOSTIC APPROACHES

Currently available detection methods for TV include wet mount, culture, and a rapid antigen test; there are nucleic acid amplification tests available in research settings. The relative sensitivities for wet mount, culture, rapid antigen, and NAAT are 50%, 83%, 90%, and 98%, respectively, with specificities of 100%, 100%, 100%, and 98%, respectively.[19] Despite its poor sensitivity, the least expensive and most widely used method is wet mount. The CDC comments that additional TV testing (such as culture or rapid antigen) may be indicated for women who have a negative wet mount. Based on our local data, we have adopted this practice in our clinic.

TREATMENT

CDC guidelines recommend either metronidazole or tinidazole, 2 g orally as a single dose. Both are imidazoles, with 95% efficacy to clear infection. Tinidazole is better tolerated due to fewer gastrointestinal (GI) side effects; however, cost and availability may limit its use. An alternative is to use metronidazole 500 mg bid for 7 days; however, compliance is difficult to achieve. True metronidazole resistance is rare (< 5% of isolates). Persistent cases are most likely to be due to inadequate treatment (non-compliance, vomiting) or re-infection by an untreated or new partner.

GONORRHEA

Infections with *Neisseria gonorrhoeae* (NG), the causative agent of gonorrhea, are less common than trichomoniasis and chlamydial infection. However, because gonorrhea is a reportable disease, it is listed as the second most commonly reported bacterial STD, after chlamydia.

PREVALENCE

In the Add Health data for 18–26-year-old subjects, the prevalence of NG overall was 0.4%; higher rates were seen in blacks (2.1%).[9] CDC data report that 15–19-year-old females are the group with the highest annual prevalence (624 cases/100 000 population).

CLINICAL PRESENTATION

Many men with gonorrhea have symptomatic urethritis. However, the majority of infections in both men and women are asymptomatic.[9] Women with gonorrhea may present with lower abdominal pain or have signs of mucopurulent cervicitis, as described above for chlamydia.

Consequences for women infected with gonorrhea are similar to those associated with chlamydia: PID, infertility, and Fitz-Hugh Curtis syndrome. Men can develop epididymitis and prostatitis. Men and women can develop disseminated infections that present with skin lesions, arthritis and rarely, meningitis and endocarditis. Gonorrhea can infect the oropharynx, rectum, and conjunctiva in exposed adults.

DIAGNOSTIC APPROACHES

Gonorrhea may be detected by Gram stain, culture, or nucleic acid amplification tests. Gram stain is highly sensitive and specific (95% and 99%) when performed on a urethral swab for males with symptoms of urethritis,[26] but it is far less sensitive (~50%) for asymptomatic males and when performed on cervical swabs. Culture has been the mainstay

of diagnosis for years and allows assessment of antibiotic resistance. When performed and transported under ideal conditions, culture has a reported sensitivity and specificity of >90% and 100%, respectively. However, in many settings the sensitivity of culture is closer to 70%.[27,28] NAATs can be performed on specimens from a variety of sources (vaginal, cervical, or urethral swabs, as well as urine samples). All of the commercially available NAATs have similar sensitivities (85–95%) and high specificity (95–98%).[28] However, in populations with low prevalence of gonorrhea, the positive predictive value of a NAAT may be low. The reader is referred to the CDC guidelines for detection and treatment of infections at non-genital sites.

TREATMENT

Ceftriaxone 125 mg IM or cefixime 400 mg orally, both as single-dose therapies, are the recommended first-line treatment for uncomplicated gonorrhea of the cervix, urethra, or rectum. Treatment of non-genital sites, the emergence of drug resistance, and availability of certain drugs from the manufacturer result in frequent modifications in recommendations for treatment. The reader is referred to the CDC website for the most up to date information (http://www.cdc.gov/std/treatment).

GENITAL HERPES

Herpes simplex virus (HSV) is the most common etiology of genital ulcers. Recent studies suggest that there has been a change in the epidemiology of genital herpes. Traditionally, most cases of genital herpes were caused by type 2 HSV, but more recent data suggest that a greater proportion of those newly diagnosed with genital herpes have HSV-1 rather than HSV-2.[29]

PREVALENCE

Data from national surveys provide estimates of the seroprevalence of HSV-2 in the US at 17.0%. There is a rapid increase in prevalence between ages 14–19 and 20–29, with 1.6% seroprevalence at 14–19 years, rising to 10.6% at ages 20–29.[30] Many people are unaware of previous genital HSV infection and asymptomatic disease may reflect earlier infection with HSV-1. Sixteen percent of people with HSV-2 antibody, but lacking HSV-1 antibody, had a history of genital herpes, compared with 5.9% of those who had both HSV-1 and HSV-2 antibody, suggesting those without HSV-1 antibody were more likely to have experienced symptoms of genital herpes.[31]

CLINICAL PRESENTATION

As noted earlier, and similar to nearly all sexually transmitted infections (STIs), the majority of people with genital herpes are unaware of their status; i.e. most infections are unrecognized and asymptomatic. Additionally, those with pre-existing HSV antibodies are less likely to have clinical symptoms. Clinical presentations vary between those with primary, as contrasted to recurrent, genital infection. In primary infections, there are no pre-existing antibodies to HSV-1 or -2. Primary infections may have local as well as systemic symptoms. Systemic symptoms include fever, headache, and malaise; tender inguinal adenopathy is seen typically with first (as well as often in recurrent) episodes. Lesions first appear as clear vesicles on an erythematous base, followed subsequently by pustules, then ulcers, and then crusting of the lesions (Figure 17.4). Of note, there are typically more lesions present, and new lesions may form up to 10 days after the initial lesion in primary infection. Recurrent disease is more likely caused by HSV-2 infection. Typically, there are fewer lesions with recurrent infections. Most patients will tend to have fewer clinical recurrences the longer the time elapsed since diagnosis but will continue to shed virus indefinitely.

DIAGNOSTIC APPROACHES

The historical standard for diagnosis of genital herpes has been culture, which is especially helpful

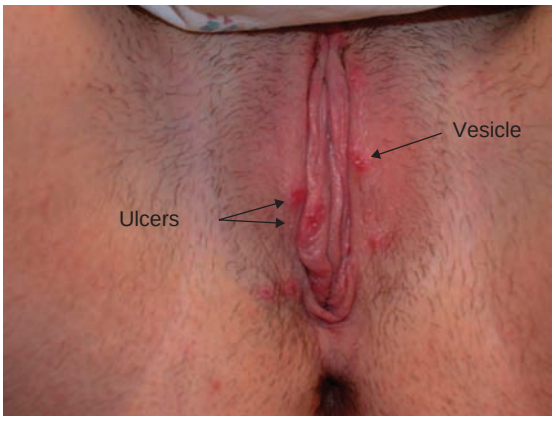

Figure 17.4 Genital herpes: multiple small ulcers and one vesicle on the labia majora and minora of a 15-year-old girl (photo courtesy of Jill S Huppert MD, MPH).

in distinguishing HSV-1 from HSV-2 and evaluating atypical genital ulcers; the sensitivity of culture falls 2–3 days after ulcers develop. PCR has greater sensitivity than culture and is especially helpful for diagnosis of herpes encephalitis, but it is not commercially available. Although the 2006 STD treatment guidelines suggest using type-specific serology when patients request HSV serologic testing, the lower prevalence of HSV-2 in patients 19 or younger (1–5%) results in a poor positive predictive value in those without symptoms (35–70%) because specificity of commercially available serologic tests is 97–98%.[32]

TREATMENT

Treatment of genital herpes differs depending upon the clinical presentation: first episode genital disease, recurrent episodes, or suppressive therapy. Acyclovir was the standard therapy for several years, but requires frequent dosing because of bioavailability. The newer agents, famciclovir and valacyclovir, require less frequent dosing and have similar efficacy with few side effects. Acyclovir is administered as either 200 mg five times a day or 400 mg three times a day, for 7–10 days. Famciclovir is administered at a dose of 250 mg three times a day, and valacyclovir is administered as 1 g twice a day, for 7–10 days.

The other two clinical presentations may be considered separately or together; a recent editorial discussed the use of suppressive therapy after initial treatment of first episode disease, given a high likelihood of recurrent disease, psychological benefit of suppressive therapy,[33] improved quality of life,[34] impact of disease incidence (new cases) on the population,[35] and low rates of resistance.[32] Suppressive therapy can reduce outbreaks by 70–80%.[36,37] Regimens for suppressive therapy include acyclovir 400 mg twice a day, valacyclovir 500 mg or 1 g daily, and famciclovir 250 mg twice a day. Regimens for episodic treatment include acyclovir 400 mg three times a day for 5 days or 800 mg either two or three times a day for 5 or 2 days, respectively; famciclovir 125 mg twice a day for 5 days, or 1 g as a single dose; or valacyclovir 500 mg or 1 g daily for 3 or 5 days, respectively.[3]

SYPHILIS

The causative agent of syphilis is *Treponema pallidum*, a spirochete and one of the first STDs recognized. The US had seen significant declines in cases of primary and secondary syphilis until a plateau was reached in 2000, with an increase in cases in 2004 and 2005.

PREVALENCE

The recent rise in syphilis reveals that rates in women and heterosexuals are increasing faster than in other groups. Among women, the age groups with the greatest incidence rates were 15–19 and 20–24 years (1.9 and 3 cases per 100 000, respectively). Rates for young men aged 15–19 and 20–24 were 2.4 and 8.1 cases per 100 000, respectively. Syphilis rates are highest in the south, among African-Americans, and in those in correctional institutions.[38]

CLINICAL PRESENTATION

Syphilis infections are classified by clinical presentation. Primary syphilis is characterized by a painless genital ulcer (chancre). Secondary syphilis may present with a skin rash, especially one affecting the palms or soles, patchy alopecia, mucocutanous lesions (oral lesions or condylomata lata), and lymphadenopathy. Signs of tertiary syphilis include gummatous lesions of the mucosa, skeleton, or viscera, as well as eye, cardiac, and auditory abnormalities. Infections detected by serology in asymptomatic patients are termed latent and further subdivided as early latent (if less than 1 year duration) or late latent (> 1 year in duration). These classifications direct therapy.

In addition to direct consequences of syphilis infection (neurosyphilis, aortic aneurysm, dementia, or death), those infected with syphilis have increased susceptibility to HIV.

DIAGNOSTIC APPROACHES

If lesions are suspicious for primary or secondary syphilis, a scraping of the affected area can be examined for spirochetes using darkfield microscopy. However, this requires considerable skill and is almost exclusively limited to specialized STD clinics. Serologic testing is most commonly used, starting with a non-treponemal test such as the rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL). These tests detect antibody to a cardiolipin-lecithin-cholesterol antigen and are not specific for *T. pallidum*. They can have both false-positive and false-negative results. Thus, a patient with a positive non-treponemal test should have repeat serology and confirmation with a treponemal test, such as *Tr. pallidum* particle agglutination (TP-PA) or fluorescent treponemal antibody-absorbed (FTA-ABS). These qualitative tests are specific for *T. pallidum* antibody, and generally remain positive for life. Response to treatment is measured by comparing the initial and follow-up titers of the quantitative RPR or VDRL.

TREATMENT

Primary, secondary, and early latent syphilis should be treated with benzathine penicillin (PCN) G, 2.4 million units IM in a single dose. Tertiary syphilis and latent syphilis of greater than 1 year duration should be treated with three weekly doses of benzathine PCN G, 2.4 million units IM. Because of the effectiveness of this treatment over the last 50 years, there have been limited trials of alternative medications. The reader is referred to CDC guidelines for special considerations, such as infections in pregnant women, infants, HIV-infected persons, and persons who are allergic to penicillin.

CLINICAL PRESENTATIONS

CERVICITIS

Cervicitis is not predicted by symptoms, but diagnosed only with a speculum exam. Normal cervical discharge is clear and mucoid. Vaginal secretions can obscure the cervix and should not be confused with cervical discharge. Mucopurulent cervicitis can be distinguished when an endocervical swab looks yellow or purulent. The normal adolescent cervix may have a varying amount of ectropion that is developmentally appropriate. This must be distinguished from cervical friability, identified when the cervix bleeds easily to the touch of a swab. A cervix with punctuate hemorrhages (strawberry cervix) is a rare consequence of a *T. vaginalis* infection.

ETIOLOGIC AGENTS

Several studies have shown that both *Chlamydia trachomatis* (CT) and GC are more common in women with clinical cervicitis than in those without. Bacterial vaginosis (BV) does not cause cervicitis, and TV cervicitis is rare. Infection with HSV can present with cervicitis, cervical ulcers, erosions, and friability. A specific etiologic agent cannot be identified in many cases of cervicitis.[39]

TESTING

NAAT for CT and either culture or NAAT for GC are recommended. In addition, a bimanual exam should be performed on women with cervicitis because of an increased risk of upper genital tract disease, including endometritis and PID.

VAGINAL DISCHARGE

Adolescents are often vague when discussing vaginal symptoms. Some adolescents and providers have difficulty identifying normal, physiologic discharge, which begins with the onset of estrogen production (Tanner stage 2 breast development). Normal discharge is characterized as clear, white, or yellow in color, varying in amount and viscosity with the menstrual cycle, and is not associated with symptoms of odor, itching, burning, or signs of vulvar redness. In addition to describing the discharge, women should be asked to specify how bothered they are by it (on a scale of 1–3) and whether they took action about it (from no action, to self-medicated, to sought medical care).[40]

Abnormal vaginal discharge is traditionally assigned to three etiologies: candidiasis, BV, or trichomoniasis. Itching is most strongly associated with yeast, vulvar erythema predicts trichomoniasis, and no symptoms or signs predict BV.[39,41] The provider must perform an exam and office testing to discern a possible etiology for a patient's complaints.

TESTING

Optimal evaluation of vaginal symptoms should include inspection of the vulva to evaluate for erythema, fissures, or lesions associated with HSV; a speculum exam to evaluate the cervix and vaginal discharge; and vaginal swabs for office testing. If cervicitis is present, a bimanual exam is indicated, as noted earlier.

Vaginal swabs should be tested by wet mount microscopy, pH testing, and amine tests. The interpretation of these tests is shown in Table 17.4. A diagnosis of BV can be entertained if Amsel's criteria are met (three of four present: homogeneous discharge, pH > 4.5, positive amine test, and > 20% clue cells seen on wet mount microscopy) and no other pathogen is present. If the prevalence of trichomoniasis is high, ancillary testing for TV (rapid antigen or culture) is recommended.

For many women who present with a vaginal discharge, no pathogen can be identified. For these women, it is important to enquire about hygiene products and to offer reassurance. One should not medicalize normal discharge, as many women with a physiologic discharge will continue to seek 'management' and potentially foster psychological distress.

Table 17.4 Office diagnostics for vaginitis

	Test results according to type of infection				
Test type	**Normal discharge**	**Candida (yeast)**	**Bacterial vaginosis (BV)**	**Trichomoniasis (TV)**	**Possible CT or GC**
Microscopic exam					
Clue cells	< 20%	+/−	> 20%	> 20%	+/−
White blood cells	+/−	++	Rare	++	+++
Pathogen	—	Yeast buds or branches	None	Motile trichomonads	—
pH	≤ 4.5	≤ 4.5	> 4.5	> 4.5	≤ 4.5
Amine or 'whiff'	—	—	+	+	—
Sialidase	—	—	+	—	—
Rapid antigen TV	—	—	—	+	—

LOWER ABDOMINAL/PELVIC PAIN AND PELVIC INFLAMMATORY DISEASE

The complete evaluation of the female with lower abdominal pain is beyond the scope of this chapter. However, a brief description of PID is necessary. PID is a clinical presentation that represents an inflammation of the upper genital tract, including the uterus, tubes, and ovaries. Symptoms can range from minimal and non-specific (vaginal spotting, mild pain) to severe abdominal pain and sepsis. Untreated PID can result in permanent tubal damage, infertility, and chronic pelvic pain.

DIAGNOSTIC CRITERIA

The gold standard for diagnosis is evidence of tubal inflammation by laparoscopy. However, this procedure is too invasive to be performed routinely. Endometritis diagnosed by endometrial biopsy is used as a surrogate marker for PID in research settings, but has not been proven to be associated with long-term outcomes.[42] Other diagnostic methods are imprecise.

The clinical diagnosis of PID is based on findings from a pelvic exam. The minimal criteria require the presence of one or more of cervical motion tenderness, adnexal tenderness, or uterine tenderness. The reported sensitivity of the minimal criteria is 83%, with a specificity of 22%.[43] Adding additional criteria reduces sensitivity while it raises specificity.[43,44] The general consensus is that patients who present with severe pain or appear very ill should have a greater number of clinical criteria to improve specificity; whereas those with milder presentations should have a smaller number of clinical criteria to improve sensitivity and, with treatment, avoid sequelae.[45]

ETIOLOGIC AGENTS

PID is considered a polymicrobial infection that occurs when an inciting agent breaks the cervical barrier and allows the agent and other vaginal microbes to ascend into the upper genital tract. There is strong evidence implicating both chlamydia and gonorrhea infections with PID. There are several studies that support the link between PID and *T. vaginalis*, as well as weaker evidence that supports BV-associated organisms.

TESTING

Women who complain of pelvic pain should have a speculum exam to evaluate for cervicitis and a wet mount to look for white blood cells in the vaginal secretions. If these findings are normal, PID is unlikely. A gentle bimanual examination should be performed to document the presence of any pelvic tenderness or masses. STD tests should include NAAT for CT and culture or NAAT for NG. Wet mount and culture or rapid test for TV is suggested, and the diagnostic criteria for BV should be used as well. Supportive laboratory tests would include erythrocyte sedimentation rate and C-reactive protein level. A transvaginal pelvic ultrasound may demonstrate thickened tubes or tubo-ovarian complex. The CDC recommends that women with PID be offered HIV testing.

TREATMENT

The CDC recommends that empiric treatment for PID should be offered if the patient is complaining of pelvic pain, is at risk for STDs, meets the minimal criteria for PID, and no other diagnosis can be made for the symptoms. The reader is encouraged to review the most current treatment regimens that are listed on the CDC website (http://www.cdc.gov/std/treatment/2006/pid.htm#pid2), as well as a recent review by Haggerty and Ness.[46] Of note, age at diagnosis (that is, the teen years) is not an indication for hospital admission or parenteral treatment for PID. The sexual partners of women treated for PID should be notified and treated for the most common etiologic agents (CT and NG).

URETHRITIS

Although this is a textbook for pediatric and adolescent gynecology, urethritis is important as a clinical presentation of males, as well as a potential presentation for the sexually active female. Sexually active adolescent females who presented with urinary symptoms, when compared with those without urinary symptoms, were more likely to have a urinary tract infection (UTI) (26% vs 7%) and as likely to have any STI (36% vs 29%). Urinary pathogens were *Escherichia coli* and *Staphylococcus saprophyticus*. Among those with urinary symptoms, utilizing the urine dipstick revealed that nitrites and proteinuria were associated with UTI (odds ratio 71 and 9.2), whereas leukocyte esterase was associated with STI (odds ratio 5.3). History of a previous STI was associated with both UTI and STI (odds ratio 3.2 and 3.0, respectively).[10]

In the male, urethritis suggests infectious causes, typically chlamydia or gonorrhea. Other potential etiologies include *Ureaplasma urealyticum*, *Mycoplasma genitalium*, *T. vaginalis*, HSV, and adenovirus.[47] Of note, one-third of cases of urethritis with identified pathogens did not have associated increase in urethral leukocytes, and oral sex was associated with urethritis in which no pathogen was identified.[47] Recommended regimens for urethritis in males include azithromycin 1 g in a single dose or doxycycline 100 mg twice a day for 7 days; alternative regimens include erythromycin 500 mg four times daily for 7 days or erythromycin ethylsuccinate 800 mg four times daily for 7 days. Although ofloxacin and levofloxacin are listed as alternate therapies, recommendations may change given new evidence of rising levels of resistance to these agents by GC. In recurrent or persistent urethritis, metronidazole 2 g in a single dose, or tinidazole 2 g in a single dose with azithromycin 1 g in a single dose, is recommended.[3]

GENITAL ULCERS

The most likely etiology of genital ulcers is HSV. Other infectious etiologies are much less common and include syphilis, chancroid, and LGV (lymphogranuloma venereum). Aphthosis (similar to oral canker sores) may present as a vulvar ulcer in adolescents (Figure 17.5).[48] Other non-infectious etiologies include allergic dermatitis and Behçet's syndrome. Evaluation for genital ulcers should include a scraping of a fresh lesion for HSV culture or PCR and serologic test for syphilis. Of note, the female adolescent with genital ulcers should be tested for chlamydial infection, gonorrhea, and trichomoniasis, because genital herpes is associated with these pathogens.

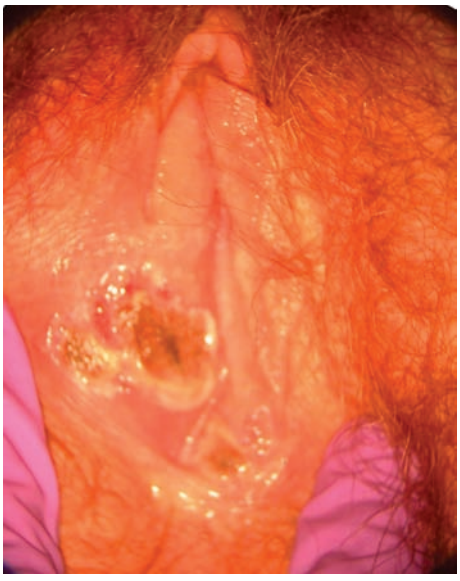

Figure 17.5 Aphthosis: large ulcer with overlying eschar on the inner aspect of the right labia minora; smaller ulcer seen at the forchette (photo courtesy of Jill S Huppert MD, MPH).

SCREENING THE ASYMPTOMATIC ADOLESCENT

As noted earlier, the majority of STIs are asymptomatic. Recommendations for adolescent women include screening for chlamydia every 6 months or with partner changes. Women who had tested positive for chlamydia in the previous examination should be re-tested in 3 months, due to the high

re-infection rates, as discussed earlier. Because the prevalence of gonorrhea is lower, at this time it is recommended that adolescent women be screened annually. The recommendations for HIV testing may vary, in part reflecting the different prevalence rates in different parts of the country. Many feel that the adolescent should be offered HIV screening at least once, and re-offered if other STIs are diagnosed subsequently. Although no screening guidelines exist for *T. vaginalis*, given a high prevalence and frequent asymptomatic nature (up to 90%), routine surveillance may be warranted.

No guidelines exist at this time for adolescent males; as noted previously, the majority of STIs in males are asymptomatic. Screening with urinary leukocyte esterase is not specific, but the negative predictive value among adolescent males is 96%.[49] Screening for chlamydia is cost-effective in preventing PID in female partners when the prevalence in males is greater than 2.8%.[50]

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18. Child sexual abuse

Astrid Heppenstall Heger

Increasingly the adolescent gynecology specialist is asked to provide an expert evaluation of young girls or adolescents who have been victims of sexual abuse or assault or who have presented to the primary care provider with complaints or symptoms that suggest possible sexual abuse. It is therefore important that the gynecologist understands both the normal genital anatomy of the preadolescent and what to expect when a child who reports sexual abuse or assault is referred for a gynecologic examination.

Over the past 25 years there has been a growing recognition of and interest in the identification, diagnosis, and treatment of children who have been sexually abused. Children are evaluated in a wide range of settings by medical professionals with various levels of expertise and training. Because this is the one diagnosis that inevitably results in a criminal investigation, with significant outcomes for both the victim and the alleged perpetrator, it is important that the assessment and diagnosis are done with the utmost care and attention to research and reason.[1]

Child sexual abuse is increasingly identified as a significant social and medical problem. A recent study found prevalence rates of 96/1000 for girls and 67/1000 for boys.[2] Children are ideal victims of sexual abuse. They have limited understanding of what is appropriate behavior between adults and children. They are naturally curious and most often sexual abuse occurs between a child and an adult known to them, who they frequently trust and rely on.

Sexual abuse is defined as any sexual activity with a child that takes advantage of their lack of understanding and/or consent. Sexual abuse may include voyeurism, exhibitionism, fondling, simulated intercourse, oral–genital contact or vaginal/anal penetration. The emotional impact on the child is directly related to the nature of the abuse, the relationship of the abuser to the child, and the duration of the abuse.

The primary medical professional continues to play an important role in the identification and assessment of children impacted by sexual abuse. Most children are initially evaluated by primary care medical professionals when they present with behavior changes, genital complaints or the history of an incomplete disclosure to a trusted adult. The medical diagnosis is difficult and can cause potential harm to children and families by missing the diagnosis or by making diagnosis where abuse has not occurred. It is important that all medical professionals include sexual abuse in their differential diagnosis and have access to expert referral networks. Therefore, because of the potential harm to child, family, and community by a diagnosis made in error, a system of multidisciplinary centers has evolved throughout the world where assessments are completed by professionals trained in interviewing children and in the appropriate examination and diagnosis of child victims. History from the child continues to be the most important part of any evaluation. Historically the system charged with the protection of children has been unwilling to protect the child without medical findings. It can be difficult for physicians to remain above the pressures of this type of system, but it is important that they be well trained in making an appropriate, scientific conservative diagnosis. Understanding the process of child sexual abuse and the nature of the abusive acts will clarify for the medical professional and other team members that most medical examinations are normal.

A careful history of the abuse is the most important part of the evaluation. This history must be appropriate to the age of the victim and done by a

professional trained to take histories that can withstand legal scrutiny. The history is optimally taken before the victim is examined. This information, from the victim, can be valuable to the medical examiner in focusing attention for areas of possible trauma or forensic evidence. Additionally, history taken by the medical professional can be used in court as a basis for diagnosis and can help the case go forward successfully.

Because children are powerless and vulnerable they are the ideal victim. This vulnerability is compounded by the fact that the perpetrator is known to them and that the abuse occurs in private, and is part of a dark secret. This leads to a sense of guilt and responsibility that makes the taking of any history extremely difficult. Clearly the medical professional does not want to precipitate a history that is given in error any more than they want to encourage a child to continue to live with secrets and lies.

The history should be taken by a medical or mental health professional trained to take a non-leading, non-suggestive history. The history must be age and developmentally appropriate for each child and should precede the medical examination but follow the careful interview of parent or guardian. History from the parent or responsible adult can provide the professional with much needed details of the child's life and circumstances that may have contributed to the behavior changes or medical complaints.

The medical professional may be trained to take all histories in cases of sexual abuse or may assign that task to a mental health professional. Particularly in cases of child sexual abuse when there are clear indicators that the child has been abused yet the child refuses to discuss the abuse, the use of a 'forensic interviewer' is important. This mental health professional relies on established protocols and works directly with legal and/or social services investigators to generate a report that will meet a legal standard. Even if the forensic interview is completed by a mental health professional, a medical history should be completed by the medical professional. This history will include a meticulous past medical history from parents or guardians and then a history from the child. The history from the child should focus on what happened and on any pain, bleeding or discharge. In some jurisdictions it is this history from the medical professional that can come into court as the basis for the diagnosis of sexual abuse and in support of the testimony from the child.

THE INTERVIEW

In most settings it is the role of the medical professional to take a careful medical history from any patient. Taking such a history from a sexually abused child requires a different set of skills, and in many multidisciplinary programs is done in conjunction with a child therapist who is trained in the forensic interview. In many jurisdictions, however, it is only the history taken by the medical professional that has weight in the legal system.

THE SEXUALLY ABUSED CHILD: THE INTERVIEW DYNAMIC

Most children who have been abused over time have a learned behavior that must be recognized by the professional if the interview is to have meaning to the victim and the system.

Sexually abused children usually carry the burden of a secret. Some sense the need for secrecy themselves, often instilled in them by the abuser, while other children feel the need to keep the secret because of threats made or perceived. These threats or coercion take many forms to insure that the secret will be maintained. They may be direct threats of physical harm or death of child or loved ones; demonstrations of harm or violence toward child, pets, or toys; threats of consequences of telling, i.e. the child will be blamed, get in trouble and not be believed, or will go to jail or be removed from home; parents or others will not love the child any more if they find out or even that there will be loss of love or contact with an abuser to whom the child is attached.

The threats and the guilt may result in a child who lives in constant fear. This fear may be associated

with avoidance or withdrawal, regression, and an acute anxiety reaction to questions posed by the interviewer or examiner. Regardless of age most children feel a deep sense of responsibility for the abuse that is made manifest by guilt and shame. The guilt is amplified by acute embarrassment, shame about participation or any pleasurable feelings that may have occurred during genital touching. Changes in behavior can be amplified by the child, accommodating the ongoing abuse and repressing memories and blocking out the abuse.

The severity of the behavioral changes depends on a number of variables including the nature of the abusive act – particularly with regard to the degree of seduction, coercion, or violence used – impacts not only the behavior of the child but the degree to which there may be any medical or forensic evidence. Other factors that impact the degree of behavior changes include the age and vulnerability of the child, the relationship of the offender to the victim, the length of time over which the abuse takes place, and the degree of child cooperation and participation.

In many cases the reaction to the abuse is worsened by the reaction of the adults to whom the child confides the story and the social and legal process that inevitably follows.

History from the system is important to the investigation and the protection of the child. Children may present to the medical professional accompanied by social workers and/or police officers. The history from the social worker can provide valuable background on the nature or degree of involvement by the social system or any past history of reports of child abuse or neglect or previous medical assessments. This information can help in the multidisciplinary determination of appropriate placement of the child. When the social system takes responsibility for the child's safety the medical professional must make follow-up appointments for both medical and mental health services.

Law enforcement officials may also provide important information to the medical professional member of the team assessment. They may provide valuable background information on the nature of the disclosure and/or previous investigations by the police. The medical professional can also provide valuable feed-back to the police or prosecution about the child's ability to participate in the investigation and prosecution.

The **past medical history** from the caregiver is just as important in a case of sexual abuse as it is in any other clinical evaluation. The guardian or parent has valuable information as to the disclosure, and behavior changes, as well as changes in the child's environment such as recent divorce, new school, new babysitter or step-parent. Obvious past medical complaints such as discharge, bleeding or painful urination should be explored, as well as prior medical assessments for genital trauma, infections, or procedures. History of previous reports of abuse should be taken.

MEDICAL DIAGNOSIS AND EVALUATION

Over the past 25 years we have made progress in making the diagnosis of sexual abuse in children. The biggest hurdle years ago was persuading medical professionals that sexual abuse was real and that adults use children for sexual gratification. Over the past two decades it has also been difficult to help these same professionals to accept the fact that most child victims remain free of any significant medical findings. This is because of the nature of the abuse and the delay in disclosure. Sexual abuse of the young child rarely involves penetrating trauma, since most perpetrators of child sexual abuse are known to the child and want to have continued access to the child. Most often, children are involved in fondling, manipulation, and oral and anal intercourse. When vaginal penetration (across the hymen) does occur, there are usually diagnostic findings consistent with penetrating trauma. Acute injuries (within a few days) to the vagina or anus are easier to document, but children often delay in disclosing and these abrasions and lacerations resolve quickly. Mucous membranes heal quickly and without significant scarring. Penetration of the vagina and anus in the postpubescent child usually heals completely without significant changes diagnostic of sexual assault.

Although it is important for medical professionals to continue to emphasize the history we also need a sophisticated understanding of those techniques for documenting evidence of possible abuse. There are primarily two types of medical evidence: laboratory and clinical.

The laboratory evidence will include those cases of acute rape in which there is evidence of ejaculation or trace evidence, which helps identify the perpetrator. In addition, there is an increasing understanding by the general population and the legal system that sexually transmitted diseases (STDs) in children are sexually transmitted.

In recent years there has been an explosion of understanding of the medical (clinical evidence) findings in child sexual abuse. Standards for diagnosis have been established and aided by photodocumentation and standardization of terminology that promoted peer review and research that is consistent and can be replicated. The medical professional's understanding of normal and abnormal prepubescent genital anatomy has been greatly aided by the recent use of various techniques for photographic documentation and based in research. Medical evaluators have come to a consensus on certain clinical findings that are diagnostic of sexual abuse as well as what is normal. Research included the study of genital anatomy in children selected for non-abuse[3–9] and reports on anatomical variations in children referred for possible sexual abuse.[10–21] In addition, there have been a few reports of healing trauma.[22–26] Based on these studies, recommendations for diagnostic criteria or standards as well as classification schemes have been developed.[1,27–30]

The evaluation of a child for possible sexual abuse most closely mimics the actual abuse that each child experienced and should be engaged in a positive non-threatening manner with an atmosphere of protecting the child. Since the medical professional is often seen by the child/victim as the most powerful and possibly significant adult during the initial evaluation process, it is important that this interaction is a positive experience. Often the child feels damaged and different from other children and the reassurance from the examiner is vital in starting the healing process.

During the evaluation of the child it is important for the examiner to address guilt and fear and to use language that supports and demonstrates a loving and caring attitude toward the victim. Once the examination is complete the medical professional should take time to personally give parents or guardians interim skills to provide appropriate support to the child/victim and immediately plan for follow-up and support by referring the child and family to therapy.

THE MEDICAL EXAMINATION

Hopefully children who have been identified as sexually abused have access to a private, child-friendly clinic. Do not have children wait with social workers and/or police officers in an open clinic or emergency room! Children should first be interviewed and then introduced to the medical examination, the equipment, and what is going to happen. There should be no surprises that will frighten or traumatize the child.

PROCEDURES AND PROTOCOLS

Traditional guidelines for the examination of acute sexual assault have required emergency evaluations up to 72 hours after the assault and for any patient who is symptomatic. Emergency assessments should also be available for any child who 1) is at risk for out of home placement, 2) is exhibiting potential life-threatening behavioral changes and depression, or 3) presents with medical signs and symptoms.

Urgent examinations are recommended for all cases that have occurred in the past 2 weeks. These examinations may be helpful for forensic evidence but more importantly to document the presence of trauma associated with the assault and to provide appropriate assessments and treatment for possible medical or mental health problems. In cases of child sexual abuse when the disclosure has been delayed, examinations should be scheduled with the regional multidisciplinary child advocacy center where both

a medical and mental health assessment can be provided.

Any medical professional who signs on to provide expert evaluations of the sexually abused child must have an ongoing relationship with the local crime lab and carefully follow their guidelines for preservation of evidence and maintaining the chain of evidence.

Sexually transmitted infections (STIs) are extremely rare in the pediatric population. Screening tools for possible STIs are sensitive for the purpose of identifying children who will need further evaluations and culture. But screening tools do not meet the forensic standard needed to rely on STIs as an indicator of sexual abuse for investigation and prosecution. While it may be standard of care in some practices to presumptively treat adolescents for STI after positive screening this is not true for the child. Culture-proven STI remains the only standard that withstands the forensic scrutiny.

However, in some settings and circumstances where a child has been sexually assaulted by a stranger or by high-risk assailants, HIV prophylaxis is the standard of care. These children are then carefully monitored for possible side effects and retested according to established research protocols.

Clinical documentation of trauma associated with sexual abuse is important evidence of the use of force. With the increase in the use of condoms by assailants, clinical evidence of the assault may be the primary physical evidence. The use of colposcopy and photodocumentation has improved the clinical documentation of injuries associated with sexual abuse and has been the basis for research into normal genital anatomy and post-traumatic changes associated with child sexual abuse.

Photodocumentation is the standard of care.[31,32] The colposcope has become the most widely used tool for photodocumentation and makes each case available for peer review and consultation. This also prevents the need for multiple examinations requested by defense experts. Advances and research in the field of sexual assault have relied heavily on the use of photographs. More recently the use of macrolenses, digital cameras, video colposcopy, and telemedicine has improved the ability of forensic centers to teach and consult with remote sites.

EXAMINATION OF THE SEXUALLY ABUSED CHILD

Since this is the one part of the evaluation process that most closely resembles the sexual abuse it is important to proceed with care and time. In most cases it is possible to effectively examine the child in a supine position with gentle labial traction. If, however, the examiner is unable to document that the posterior rim of the hymen is free of trauma (acute or healed) it is important to verify findings through the use of the knee-chest prone position. The use of water and viscous xylocaine has also been shown to help the examiner delineate anatomy and possible trauma in the young child. Infrequently it is necessary to examine a child under anesthesia, but particularly when the injuries appear to be egregious it is a medical necessity to document that there are no injuries that penetrate into the pelvis and in some cases use this opportunity to repair damage to the vaginal wall and hymen.

CLINICAL DIAGNOSIS OF CHILD SEXUAL ABUSE

The clinical interpretation of anatomic variations relies on an understanding of published research on normal anatomy, non-specific findings, and findings associated with healed trauma (longitudinal studies). In order to interpret the significance of post-abuse findings the examiner needs to understand the normal anatomy of the child and how that impacts anatomic changes. For example, most preadolescent girls have a crescentric or posterior rim hymen. This means that findings such as notches (clefts), peri-hymenal bands of tissue or even absence of hymen in the ventral 180°, i.e. between 9 and 3 o'clock are not diagnostic of previous trauma. This applies even if the examiner has documented acute ventral trauma at the time of the acute injury, since it is the rare patient in which the examiner has a previous exam that documents

the pretraumatic condition of the genital/hymeneal anatomy. However, from both newborn studies and studies of girls selected for non-abuse, we know that girls are not born with nor do they develop clefts to the base of the hymen between 3 and 9 o'clock. The presence of these complete clefts or notches in the posterior 180° must then be acquired secondary to blunt force penetrating trauma. The significance of 'deep clefts' remains a point of debate because of the difficulty in measuring and standardizing degrees of notching.

Recent studies report that only a small percentage of children who are referred for possible sexual abuse have findings diagnostic of genital or anal trauma.[7,10] This is primarily attributed to the nature of the abuse and to the delay in disclosing. The challenge to the examining medical professional is to first understand what research has taught us about normal or non-specific findings and then superimpose on that knowledge what is known about healed trauma documented acutely and then after complete healing. It is only with the latter information that a medical examiner is able to state, without reservation, that findings are diagnostic of blunt force penetrating trauma.

Table 18.1 summarizes[28] a wide range of studies including normal anatomy (newborns and children selected for non-abuse) children who have been referred for evaluation of possible sexual abuse, children who have documented acute injuries and then been followed to healing, and a pair of reports on adolescent girls with and without a history of consensual intercourse. The study group that developed the table of findings also included the report from the AAP Committee on Child Abuse and Neglect on the interpretation of laboratory findings.

The table presents to the examiner three groups of findings. At one end of the spectrum are those findings that are clearly present in research into the group selected for non-abuse. At the other end are those findings present in reports on healing trauma but not confused with the non-abused group. In the middle gray area are the findings that are 'indeterminate.' These are findings that are found in both

Table 18.1 Findings documented in newborns or commonly seen in non-abused children (the presence of these findings generally neither confirms nor discounts a child's clear disclosure of sexual abuse)

Normal variants

1. Periurethral or vestibular bands[3,4,36,37]
2. Intravaginal ridges or columns[3,4,37]
3. Hymenal bumps or mounds[3,4,36,37]
4. Hymenal tags or septal remnants[3,4,37]
5. Linea vestibularis or midline avascular area[3,36,38]
6. Hymenal notch/cleft in the anterior (superior) half of the hymenal rim (prepubertal girls), on or above the 3 o'clock to 9 o'clock line, patient supine[3,5,10,37]
7. Shallow/superficial notch or cleft in inferior rim of hymen below the 3 o'clock to 9 o'clock line[7,10]
8. External hymenal ridge[3,5,36,37]
9. Congenital variants in appearance of hymen, including: crescentic, annular, redundant, septate,[3,5,36,37] cribriform, microperforate, imperforate[39]
10. Diastasis ani (smooth area)[6,40]
11. Perianal skin tag[6,40]
12. Hyperpigmentation of the skin of labia minora or perianal tissues in children of color, such as Mexican-American and African-American children[6,41]
13. Dilation of the urethral opening with application of labial traction[39]
14. 'Thickened' hymen, may be due to estrogen effect, folded edge of hymen, swelling from infection, or swelling from trauma. The latter is difficult to assess unless follow-up examination is done[3–5,7,36,37]

Findings commonly caused by other medical conditions

15. Erythema or redness of the vestibule, penis, scrotum or perianal tissues. May be due to irritants, infection or trauma [17,10,39]
16. Increased vascularity or 'dilatation of existing blood vessels' of vestibule and hymen. May be due to local irritants, or normal pattern in the non-estrogenized state[4,7,10,36,39]
17. Labial adhesions. May be due to irritation or rubbing[10,36,39]
18. Vaginal discharge. Many infectious and non-infectious causes, cultures must be taken to confirm if it is caused by sexually transmitted organisms or other infections[4,10,36]
19. Friability of the posterior fourchette or commissure. May be due to irritation, infection, or may be caused by examiner's traction on the labia majora[10,36]
20. Excoriations/bleeding/vascular lesions. These findings can be due to conditions such as lichen sclerosus, eczema or seborrhea, vaginal/perianal group A streptococcus, urethral prolapse, hemangiomas[39,42]
21. Perineal groove or failure of midline fusion, partial or complete[39]
22. Anal fissures. Usually due to constipation, perianal irritation[6,39,40]
23. Venous congestion, or venous pooling in the perianal area. Usually due to positioning of child, also seen with constipation[6,39,40]
24. Flattened anal folds. May be due to relaxation of the external sphincter or to swelling of the perianal tissues due to infection or trauma[6,39,40]
25. Partial or complete anal dilatation to less than 2 cm anterior–posterior dimension, with or without stool visible. May be a normal reflex, or may have other causes, such as severe constipation or encopresis, sedation, anesthesia, neuromuscular conditions[6,39,40]

(*Continued*)

Table 18.1 (*Continued*)

Indeterminate findings

Insufficient or conflicting data from research studies. (May require additional studies/evaluation to determine significance. These physical/laboratory findings may support a child's clear disclosure of sexual abuse, if one is given, but should be interpreted with caution if the child gives no disclosure. In some cases, a report to child protective services may be indicated to further evaluate possible sexual abuse.)

Physical examination findings

26. Deep notches or clefts in the posterior/inferior rim of hymen in prepubertal girls, located between 4 and 8 o'clock, in contrast to transections (see no. 41)[7,10,11,26,43]
27. Deep notches or complete clefts in the hymen at 3 or 9 o'clock in adolescent girls[43,44]
28. Smooth, non-interrupted rim of hymen between 4 and 8 o'clock, which appears to be less than 1 mm wide, when examined in the prone knee-chest position, or using water to 'float' the edge of the hymen when the child is in the supine position[7,37,45]
29. Wart-like lesions in the genital or anal area.[1,39,40,46–48] Biopsy and viral typing may be indicated in some cases if appearance is not typical of condyloma acuminata
30. Vesicular lesions or ulcers in the genital or anal area; viral and/or bacterial cultures, or nucleic acid amplification tests may be needed for diagnosis[1,39,46–48]
31. Marked, immediate anal dilation to an anterior-posterior diameter of 2 cm or more, in the absence of other predisposing factors[6,39]

Lesions with etiology confirmed: indeterminate specificity for sexual transmission (report to protective services recommended by AAP Guidelines[1] unless perinatal or horizontal transmission is considered likely)

32. Genital or anal condyloma acuminata in a child, in the absence of other indicators of abuse[1,34,46,47]
33. Herpes type 1 or 2 in the genital or anal area in a child with no other indicators of sexual abuse[1,46,47]

Findings diagnostic of trauma and/or sexual contact

The following findings support a disclosure of sexual abuse, if one is given, and are highly suggestive of abuse even in the absence of a disclosure, unless the child and/or caretaker provide a clear, timely, plausible description of accidental injury. (It is recommended that diagnostic quality photodocumentation of the examination findings be obtained and reviewed by an experienced medical provider, before concluding that they represent acute or healed trauma. Follow-up examinations are also recommended.)

Acute trauma to external genital/anal tissues

34. Acute lacerations or extensive bruising of labia, penis, scrotum, perianal tissues, or perineum. May be from unwitnessed accidental trauma, or from physical or sexual abuse[22,26]
35. Fresh laceration of the posterior fourchette, not involving the hymen.[23,26,39,49] Must be differentiated from dehisced labial adhesion or failure of midline fusion.[39] May also be caused by accidental injury[25,50] or consensual sexual intercourse in adolescents[51]

(*Continued*)

Table 18.1 (*Continued*)

36. Residual (healing) injuries. These findings are difficult to assess unless an acute injury was previously documented at the same location
37. Perianal scar. Rare, may be due to other medical conditions such as Crohn's disease, accidental injuries, or previous medical procedures[23,26,39]
38. Scar of posterior fourchette or fossa. Pale areas in the midline may also be due to linea vestibularis or labial adhesions[23,26,39]

Injuries indicative of blunt force penetrating trauma (or from abdominal/pelvic compression injury if such history is given)

39. Laceration or tear, partial or complete of the hymen, acute[23,26]
40. Ecchymosis or bruising on the hymen in the absence of a known infectious process or coagulopathy[23,26]
41. Perianal lacerations extending deep to the external anal sphincter. Not to be confused with partial failure of midline fusion[11,22,24,26,50]
42. Hymenal transection (healed). An area between 4 and 8 o'clock on the rim of the hymen where it appears to have been torn through, to or nearly to the base, so there appears to be virtually no hymenal tissue remaining at that location.[11,23,26] This must be confirmed using additional examination techniques such as a swab, prone knee-chest position or Foley catheter balloon (in adolescents), or prone-knee chest position or water to float the edge of the hymen (in prepubertal girls). This finding has also been referred to as a 'complete cleft' in sexually active adolescents and young adult women[43,52]
43. Missing segment of hymenal tissue. Area in the posterior (inferior) half of the hymen, wider than a transection, with an absence of hymenal tissue extending to the base of the hymen, which is confirmed using additional positions/methods as described above[11,39]

Presence of infection confirms mucosal contact with infected and infective bodily secretions, contact most likely to have been sexual in nature

44. Positive confirmed culture for gonorrhea, from genital area, anus, throat, in a child outside the neonatal period[1,46]
45. Confirmed diagnosis of syphilis, if perinatal transmission is ruled out[1,46]
46. *Trichomonas vaginalis* infection in a child older than 1 year of age, with organisms identified by culture or in vaginal secretions by wet mount examination[1,46] by an experienced technician or clinician
47. Positive culture from genital or anal tissues for chlamydia, if child is older than 3 years at time of diagnosis, and specimen was tested using cell culture or comparable method approved by the Centers for Disease Control and Prevention[1,46]
48. Positive serology for HIV, if perinatal transmission, transmission from blood products, and needle contamination has been ruled out[1,46]

Diagnostic of sexual contact

49. Pregnancy[1]
50. Sperm identified in specimens taken directly from a child's body[1]

Reproduced with permission from J. Adams, The APSAC Advisor 2005; (Summer): 7–13.[28]

groups and those data are not sufficiently conclusive to include them in either the non-abused or abused group.

Notches seem to be one of those troublesome findings that require further delineation and research. This is primarily because of the difficulty in differentiating between 'superficial notches' (less than 50% of the depth of the hymen) and 'deep notches' (more than 50% of the depth of the hymen). Superficial notches have been found in studies of girls selected for non-abuse as well as in studies that have followed trauma to healing. Once the acute trauma of the partial hymeneal tear has healed it is virtually impossible to tell the difference between the superficial tear of the non-abused hymen and the healed partial tear of the abuse victim. In adolescents, although the rates of complete clefts (notches) of the hymen were more prevalent in the group admitting to consensual sexual intercourse, they were also present in a group who denied any sexual contact.

Another difficult diagnostic dilemma is 'narrowing' of the posterior rim. Any finding that is subject to measurements is also subject to error. The error can be magnified by varying techniques, the skill of the examiner, and whether or not water is used to 'float' the hymen. Degree of narrowing, where the measurements are started, and how the measurements are made are all impossible to standardize and therefore are hard to hold up to a forensic, legal standard.

Anal changes have caused great consternation, particularly for child protection professionals in the UK. The concept of reflex anal dilatation (RAD) or the immediate relaxation of the anal sphincter once traction is applied has certainly been documented in numerous studies of the non-abused child. RAD can be caused by any number of non-abuse-related conditions, including the mere presence of stool in the rectal ampulla.

REPORTING ABUSE AND THE LEGAL SYSTEM

In the past 10 years, the most consistent rates of reporting have been documented by studies that relied on photodocumentation and on a classification scale. It is not only technology that has made an impact on child sexual abuse research. The dramatic changes in the process of recognizing and reporting child abuse have also impacted and changed responses. Over the past dozen years a US national campaign of prevention and awareness has improved the vigilance of teachers and caregivers to the signs and symptoms of abuse and thereby increased the rates of children disclosing early in the course of abuse. This early recognition enhances the possibility that children are brought to the attention of the authorities before the abuse progresses.

Regardless, most children will have normal examinations. Both the nature of the abuse and the process of disclosure impact the medical examination. Most children are not abused in a way that leaves permanent physical indicators. They are usually abused by individuals known to them, who want to have continued access to the child. A violent, penetrating assault on a preadolescent child will likely result in significant trauma and discovery. In addition to how children are sexually abused, the vulnerable nature of the child makes disclosure difficult. Children often do not tell immediately. Genital mucosa and epithelium heal rapidly and any delay in reporting or examination can provide sufficient time for healing to occur. The impact from the medical evaluation is felt throughout the community. We play a unique but powerful role in the diagnosis of child sexual abuse. The primary responsibility is to provide appropriate medical and mental health interventions that will promote the physical and psychological well-being of each child. And it is true that appropriate interventions can provide safety and treatment. The legal and social systems rely heavily on the outcomes of the medical evaluation and a positive examination can precipitate the intervention of both the social services and the criminal justice systems. These interventions are not without potentially toxic impact on the child and the family, and research shows that the medical diagnosis is the most significant factor in propelling a case further into the criminal justice system.

One study[33] reported that a positive medical examination was 2.5 times more likely to result in a criminal prosecution and positive physical findings were the single most important factor in the finding of guilt. Another study[34] confirmed that confessions and medical evidence were the strongest predictors of prosecution. Fortunately for both the child and the legal system, most cases of child sexual abuse are resolved before a courtroom trial. However, approximately 15% of cases selected for prosecution do end up before a jury. The impact on the child of testifying in a jury trial is rarely benign and the long-term effect is often toxic.[35]

THE ROLE OF THE MEDICAL PROFESSIONAL IN COURT

The first rule to remember is that when a child is referred for possible sexual abuse or discloses sexual abuse as part of an examination, it is the legal responsibility of the medical professional to report to both the social and legal systems. This will precipitate the examiner into either the legal system set up for the protection of the child or the criminal justice system and the prosecution of the offender.

The trauma of appearing in the legal system and testifying will be less challenging if the medical professional has meticulously documented (photographically and in writing) all aspects of the examination. These medical records should reflect the professionalism of the medical history, the laboratory, and clinical evaluation.

Testifying for the first time can be disconcerting, particularly if you have never been in a courtroom. Ask the District Attorney to introduce you to the layout of the courtroom and to discuss with you in detail the process and the questions that he/she intends to ask. You can then help the attorney to ask the right questions and to establish you as an expert.

Before taking the stand carefully review your case and the literature that you will quote in support of your position. On the stand remember to remain humble, honest, and never overstate your credentials or qualifications. Never volunteer information or speculate about possible answers and always, without exception, tell the truth.

Remember, the medical professional may be the determining factor in the outcomes for the child, the family, and society. Unfortunately, the evolution of medical knowledge and the systematic examination of children for possible sexual abuse have resulted in the fact that medical evidence is too often the most significant factor in the progress of a case through the legal system. The primary goal is always the health and safety of the child and the medical professional should hold a firm line to prevent the focus from shifting from the child to the legal prosecution. The role of the medical professional begins with listening closely to what the child is saying. The medical examination should then progress with careful attention to the needs of the child and in anticipation that most examinations will be normal. This normal medical examination should be understood in the context of how children are abused and that the presence of a normal examination should not preclude our ability, or the ability of the system charged with the protection of the child, to find healing and safety for every child.

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19. Psychiatric disorders and reproductive health

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Medical complications of psychiatric disorders can be extensive and frequently include problems associated with reproductive health. In fact, reproductive dysfunction may be the presenting complaint that leads adolescent females to seek health care. It is vital that providers who treat adolescents recognize the association between reproductive health and mental illness, so that a proper assessment can be made and appropriate interventions can occur. This chapter will cover eating disorders, premenstrual dysphoric disorder (PMDD), depressive disorders, and substance abuse.

EATING DISORDERS

Eating disorders are frequently associated with guilt, shame, secrecy, and denial, and therefore often go unacknowledged until a medical complication precipitates a contact with a health-care provider. Commonly, problems with reproductive health, including primary and secondary amenorrhea, as well as irregular menstrual cycles, are the chief complaint for these girls.

CLINICAL OVERVIEW OF EATING DISORDERS

Eating disorders are complicated and serious illnesses that are increasingly affecting adolescents.[1,2] The etiology of eating disorders is multifaceted, and involves psychologic, biologic, and cultural factors. The three main categories usually diagnosed in adolescents are: anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified (EDNOS), which captures those patients who do not meet full criteria for the first two disorders. Many adolescent girls meet criteria for EDNOS, and current epidemiologic data most likely underestimate the number of girls who do, in fact, suffer from some form of an eating disorder that puts their health at risk. Any of the reproductive issues associated with AN and BN may also be seen in EDNOS.

ANOREXIA NERVOSA

This disorder affects an estimated 0.5% of adolescent females, with two peak ages of onset at 14 and 18 years. Recently, girls have been presenting at even younger ages.[1] Although once considered to be a 'white upper middle class' disease, the incidence appears to be rising in minority populations in the US, as well as in countries that did not formerly identify patients with this disorder. AN is the psychiatric disorder with the highest mortality rate (5–10%), with the majority of deaths from suicide, electrolyte disturbances, and arrhythmias. Outcome studies in AN show that 50% of patients have a good outcome, 25% have an intermediate outcome (relapsing-remitting), and 25% do poorly.[1,2] The diagnostic criteria for AN are listed in Table 19.1, and are highlighted by refusal to maintain a normal body weight, fear of gaining weight, body image distortion, and amenorrhea.[3] Physical signs of AN include but are not limited to: cachexia, lanugo hair, acrocyanosis, hypothermia, bradycardia, and orthostatic hypotension.

BULIMIA NERVOSA

This is a more prevalent disorder, with up to 5% of high school girls affected, and estimates as high as

Table 19.1 Diagnostic criteria for eating disorders

Anorexia nervosa

1. Refusal to maintain body weight at or above a minimally normal weight for age
   - weight loss leading to maintenance of body weight 15% below that expected
   - failure to make predicted weight gain during period of growth, leading to body weight < 85% of that expected
2. Extreme fear of gaining weight or becoming fat, despite being underweight
3. Disturbed body image, undue influence of shape or weight on self-evaluation, or denial of the seriousness of current low body weight
4. In postmenarcheal females, amenorrhea, i.e. absence of at least three consecutive menstrual cycles (presence of menses only after induction with hormonal therapy is considered amenorrhea)
   Subtypes
   - Restricting – no regular bingeing or purging (self-induced vomiting or use of laxatives and diuretics)
   - Binge eating/purging – regular bingeing and purging in a patient who also meets the above criteria for AN

Bulimia nervosa

1. Recurrent episodes of binge eating, characterized by:
   a. Eating a substantially larger amount of food in a discrete period of time (e.g. in 2 hours) than would be eaten by most people in similar circumstances during that same time period
   b. A sense of lack of control over eating during the binge, i.e. a feeling of being unable to stop eating or control what/how much is being consumed
2. Recurrent inappropriate compensatory behavior to prevent weight gain, e.g. self-induced vomiting, abuse of laxatives, diuretics, fasting, or overexercising
3. Binges or inappropriate compensatory behaviors occurring, on average, at least twice weekly for at least 3 months
4. Self-evaluation is unduly influenced by body shape or weight
5. Disturbance not occurring exclusively during episodes of anorexia nervosa
   Subtypes
   - Purging – regularly engages in self-induced vomiting or use of laxatives/diuretics during current episode of bulimia nervosa
   - Nonpurging – uses other inappropriate compensatory behaviors, such as fasting, overexercising, without regular use of vomiting or medications to purge, during the current episode of bulimia nervosa

Eating disorder not otherwise specified

Disordered eating that does not specifically meet criteria for either anorexia nervosa or bulimia nervosa

Adapted from the Diagnostic and Statistical Manual-Text Revision (DSM-IV-TR, American Psychiatric Association, 2000).

19% in surveyed college women.[1] The age of onset of this disorder is slightly older (late high school to college years). To date, no outcome studies on adolescents with BN are available.[4] The diagnostic criteria for BN are also shown in Table 19.1. This disorder is characterized by recurrent binge eating and some form of compensatory behavior to avoid weight gain. While individuals are typically of a more normal weight than patients with AN, there is still a preoccupation with shape and weight.[3] Some physical signs of BN include: dental caries, dental enamel erosion, enlarged painless parotid glands, and calluses or hyperpigmentation on the dorsum of the hand (Russell's sign) from self-induced vomiting. The diagnosis of BN may be more easily missed in young women who suffer from the disorder as the physical signs are not always present or are less obvious than in AN, and the strong sense of shame that is often associated with BN may make it less likely that the patient will divulge their symptoms.

REPRODUCTIVE HEALTH CONCERNS

ANOREXIA NERVOSA

Disturbances in the menstrual cycle are quite common in patients with eating disorders. Females with AN, by definition, are amenorrheic. This criterion can be more complicated when diagnosing an adolescent vs an adult, as there are developmental considerations. A patient can present with either primary or secondary amenorrhea; however, the

former may be difficult to diagnose without a good history of prior pubertal signs, e.g. thelarche. Primary amenorrhea is generally defined as no menses by 16 years of age, in the presence of secondary sexual characteristics, but should be considered earlier when there is delay of thelarche and/or pubarche. With the weight loss seen in AN, there is often atrophy of breast tissue and thus an accurate sexual maturity rating may be difficult to assess on physical examination. An evaluation for amenorrhea should include assays for: luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E_2), thyroid-stimulating hormone (TSH), and prolactin, as well as human chorionic gonadotropin (HCG) when appropriate (see Table 19.2). The first three hormones are all usually low in females with AN, due to hypothalamic hypogonadism caused by impaired release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. There is also activation of the hypothalamic-pituitary-adrenal (HPA) axis, with elevated levels of corticotropin-releasing hormone (CRH) and cortisol, but a blunted ACTH response.[5] This is consistent with 'stress amenorrhea,' and is seen in other states, such as depression and chronic excessive exercise. The stimulation of the HPA axis inhibits GnRH secretion, which leads to attenuation of the hypothalamic-pituitary-gonadal (HPG) axis, and both directly and indirectly suppresses ovarian estrogen production as well.[6] In postpubertal girls with AN, pulsatile secretion of LH is lost, with regression to an immature, prepubertal-like state. While the hypoestrogenism may be caused by the hypothalamic dysfunction, there is also the thought that loss of body fat may lead to lower estrogen levels, as androgens are aromatized to estrogen in adipose tissue.[7]

Table 19.2 Hormonal values in anorexia nervosa

Low	Normal	High
FSH	TSH	Serum total cortisol
LH	Prolactin	Serum free cortisol
Estradiol	ACTH	24-hour urinary cortisol
Leptin		
IGF-1		
DHEA-S		

FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; ACTH, adrenocorticotropic hormone; IGF-1, insulin-like growth factor 1; DHEA-S, dehydroepiandrosterone sulfate.

Initial studies by Frisch and colleagues in the 1970s proposed the 'critical weight' theory, whereby 17% body fat was necessary to achieve menarche, and 22% body fat was needed to maintain regular cycles.[8,9] However, this hypothesis has been criticized for several reasons, e.g. body fat was not directly measured but extrapolated from measurements of height and weight, and some athletes can menstruate at very low percentages of body fat. It is clear that weight loss or body fat percentage alone may not explain the amenorrhea seen in AN. In one-half to two-thirds of patients with AN, amenorrhea occurs before significant weight loss and can persist despite restoration of a normal body weight. This may be influenced by continued 'anorectic' behavior, e.g. poor macronutrient intake, stress, excessive exercise, and other psychological symptoms such as depression.[5,7,10] Resumption of menses (ROM) usually occurs within 6 months of the time that a recovering patient achieves a body weight of approximately 90% of that expected for age and height. Additionally, ROM is most closely associated with serum estradiol levels, and not percentage of body fat.[11]

The hormone leptin, which is encoded by the *ob* gene and produced by adipocytes, may be the link between energy stores and reproductive function. By acting on hypothalamic receptors, leptin regulates the synthesis and secretion of GnRH, LH, FSH, and sex steroids. Leptin levels are high in obese patients and abnormally low in patients with AN. Thin women without eating disorders have higher leptin levels than women with AN, which may indicate a better caloric intake. There also seems to be a threshold level of leptin whereby reproductive function is maintained. However, in AN, normalization of leptin levels is not enough for ROM. In patients with AN, low leptin levels are correlated with low levels of insulin-like growth factor-1 (IGF-1), which is reflective of overall nutritional

status, and may provide the key. However, more research is needed.[12]

BULIMIA NERVOSA

Up to half of women with BN experience amenorrhea or oligomenorrhea,[13] and even more report other menstrual dysfunction.[14] Confounding the determination of menstrual abnormalities in adolescent patients is the typical irregularity noted during the perimenarcheal time period. Whereas most of the literature on BN and menstrual function describes adult populations, one study of adolescents with eating disorders found that more than a third of subjects with BN reported irregular menses at a mean of 15.9 years, which represents an age by which a majority of teens have established regular cycles.[15]

Low levels of gonadotropins and estrogen have been found in patients with BN when compared with healthy women, although the degree of gonadotropin dysregulation seems to be less severe than in AN.[16] Below-normal LH secretion appears to be correlated with current weight as a percentage of past weight, as opposed to expected body weight.[16,17] Clinical features that may be associated with menstrual abnormalities in patients with BN include high frequency of vomiting and decreased dietary fat intake.[13]

An association between BN and polycystic ovary syndrome (PCOS) has been proposed, but studies have been limited and the link remains controversial. Utilizing the new diagnostic criteria for PCOS, an increased frequency of the syndrome was found in bulimic women, with possible increased androgen sensitivity as well.[18] It is felt that perhaps the effects of androgens on both appetite and impulse control may promote bulimic behavior. Overall, patients with BN should be evaluated for menstrual disturbances, and receive treatment as necessary.

FUTURE FERTILITY

Although current fertility concerns are not paramount for most adolescents with eating disorders, future ability to conceive may come into question by patients and their parents, especially as menstrual disturbances may persist, despite resolution of symptoms. On long-term follow-up, women with a history of AN in adolescence, who had resumption of regular menses and desired to become pregnant, did not experience infertility.[19] Similarly, based on 10–15-year longitudinal data, it does not appear that past or current BN significantly decreases the ability to become pregnant.[14]

MANAGEMENT

When a girl is diagnosed with an eating disorder, it is important to make the appropriate referrals for psychotherapy and nutrition counseling, or hospitalize her if the physical or psychiatric condition is severe. The role of the health-care provider is to monitor the medical complications and coordinate care. While nutritional rehabilitation and restoration of a healthy body weight are key elements for recovery, establishing a specific goal weight is often a cause for contention. Using ROM as a clinical indicator of health can make this easier, as patients can generally accept this concept. As mentioned above, ROM usually occurs within 6 months of attaining a weight that is 90% of that expected.[11] A sensible rate of weight gain in the outpatient setting is about 0.5 kg/week, in a patient who needs to gain at least 5 kg. Once a goal weight has been reached, it may also be helpful to monitor serum estradiol levels every few months. If ROM does not occur within a year, there may be persistent eating disordered behaviors that have been concealed, including poor macronutrient intake (e.g. dietary fat) and excessive exercise. Alternatively, another etiology for the amenorrhea may need to be sought.

One complication of prolonged amenorrhea is the development of osteopenia and osteoporosis due to hypoestrogenism (see Chapter 20). Despite the fact that oral contraceptives (OCPs) have not proven to be beneficial to eating disordered patients with decreased bone mineral density (BMD), many providers who treat adolescents with secondary

amenorrhea due to AN continue to use them.[20] Using OCPs removes the very important clinical marker of ROM and may make it more difficult to convince a patient to reach her healthy weight. Thus, OCPs may not be the best tool to treat amenorrhea associated with eating disorders.

PREMENSTRUAL DYSPHORIC DISORDER

BACKGROUND, DEFINITIONS, AND EPIDEMIOLOGY

Premenstrual syndrome (PMS) is a common disorder that affects up to 40% of females of reproductive age. A constellation of characteristic physical and emotional symptoms includes: mastalgia, abdominal bloating, depressed mood, irritability, and anxiety. They occur exclusively during the luteal phase of the menstrual cycle (≤ 5 days before the onset of menses) and resolve within 4 days of the onset of menses. Although there is no commonly accepted definition for PMS, in 2000, the American College of Obstetricians and Gynecologists (ACOG) proposed diagnostic criteria. Patients must experience at least one affective and one somatic symptom, which also impinge upon daily activities, e.g. social or work situations.[21] Older, retrospective studies in adolescents demonstrate that PMS is common, with 50% or more of patients reporting at least one symptom, and up to 89% describing their symptoms as moderate to severe.[22–24] Interestingly, in one study, teens ≥ 16 years old experienced significantly more intense symptoms than younger teens,[23] which may be due to the commencement of ovulatory cycles and ensuing hormonal fluctuations. Prospective data with validated instruments would be valuable in truly establishing the prevalence of the disorder in adolescent girls.

The affective symptoms of PMS appear to encompass a broad spectrum of severity. The American Psychiatric Association (APA) established a separate diagnostic category for the more serious symptomatology, with more significant impact on personal functioning. Originally, the term late luteal phase dysphoric disorder was used, but as more clinical research was presented, the entity was reclassified in 1994 as premenstrual dysphoric disorder (PMDD).[3] The DSM-IV-TR research criteria are presented in Table 19.3. Notably, 5 of 11 criteria comprising mood, physical, and cognitive disturbances must be

Table 19.3 Criteria for premenstrual dysphoric disorder

1. In most menstrual cycles during the past year, presence of ≥ 5 of the following symptoms for most of the last week of the luteal phase, with remission beginning within a few days after the onset of the follicular phase, and absence of symptoms during the week after menses; inclusion of ≥ 1 of the first 4 symptoms:
   - Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
   - Marked anxiety, tension, feelings of being 'keyed up' or 'on edge'
   - Marked affective lability (e.g. feeling suddenly sad or tearful or being increasingly sensitive to rejection)
   - Persistent and marked anger or irritability or increased interpersonal conflicts
   - Decreased interest in regular activities (e.g. work, school, friends, and hobbies)
   - Subjective sense of trouble concentrating
   - Lethargy, easy fatigability, or marked lack of energy
   - Noticeable change in appetite, overeating, or specific food cravings
   - Hypersomnia or insomnia
   - Subjective sense of being overwhelmed or out of control
   - Other physical symptoms, such as breast tenderness or swelling, headache, arthralgias/myalgias, a 'bloating' sensation, weight gain
2. Marked interference with work or school or with typical social activities and interpersonal relationships (e.g. avoidance of social activities or decreased productivity and efficiency at work or school)
3. Disturbance is not just an exacerbation of the symptoms of another disorder, e.g. major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder; however, it could be superimposed on another disorder
4. Confirmation of three criteria above by prospective daily ratings during at least two consecutive symptomatic menstrual cycles (diagnosis may be made provisionally before such confirmation)

Adapted from Diagnostic and Statistical Manual-Text Revision (DSM-IV-TR, American Psychiatric Association, 2000).

present during the luteal phase of most menstrual cycles over the course of a year, with prospective confirmation over two consecutive cycles. Additionally, the symptoms cannot simply be an exacerbation of a pre-existing psychiatric condition, e.g. major depressive disorder, or anxiety disorder, but PMDD may be superimposed on one of the aforementioned conditions. Evidence suggests that PMDD is merely severe PMS with significant impairment.[25]

Between 3% and 8% of women of reproductive age suffer significantly enough to be classified as having PMDD.[26] There are no studies specific to PMDD in adolescents, and no valid population-based data. However, as noted, a high number of teens surveyed in retrospective studies do report moderate to severe, and even extreme, symptoms. Adolescent health-care providers should therefore be able to assess for PMS, as well as PMDD, in the patients they care for.

PATHOPHYSIOLOGY

While the precise etiology of PMS/PMDD is unknown, evidence suggests that ovulation causes changes in neurotransmitters and hormonal systems, including a luteal phase reduction in serotonin.[25] Women with these disorders are thought to be predisposed to an increased sensitivity to the normal fluctuations in levels of sex steroids, which may be partially mediated by serotonin. Notably, there are no hormonal aberrations seen in patients with PMDD.[27]

DIAGNOSIS

To make the diagnosis of PMDD, it is necessary to rule out other causes of the emotional and physical symptoms by taking a careful history and performing a thorough physical examination. Differential diagnosis includes: hypothyroidism, anemia, autoimmune disorders, chronic fatigue syndrome, diabetes, depression, anxiety, panic disorder, and bipolar disorder, as well as substance abuse. The key element in the diagnosis is recognizing the specific timing of symptoms in relation to the luteal phase of the menstrual cycle. Thus, prospective recording of symptoms is very valuable and necessary in making the diagnosis. Several valid and reliable instruments are available to assess premenstrual symptoms. The two most suited to aid in the diagnosis of PMDD are the Daily Record of Severity of Problems (DRSP) (see Figure 19.1) and the Penn Daily Symptom Rating (DSR). The DRSP was specifically developed to diagnose PMDD, but the DSR is also appropriate and easy to use in primary care settings.[27] Both employ a Likert-type scale to evaluate the occurrence, timing, and severity of symptoms.

TREATMENT

While there is no one efficacious therapy for PMS/PMDD, much research has been performed in the area. There are both non-pharmacologic and pharmacologic approaches to treatment, which will be discussed. In all studies, subjects have been ≥ 18 years of age.

LIFESTYLE AND NUTRITIONAL INTERVENTIONS

The initial 2-month period during which the patient tracks her symptoms provides an ideal opportunity to try non-pharmacologic treatment strategies. Mild-to-moderate symptoms may respond to such interventions, which include aerobic exercise, stress management, and reduction of intake of caffeine, refined sugars, salt, and alcohol, with increased intake of whole grains.[25] Some vitamins, minerals, and herbs have also proven to be beneficial for patients with less severe symptoms. Studies of vitamin B_6 (pyridoxine) are limited, due mostly to poor methodology. However, a meta-analysis concluded that doses of up to 100 mg/day may diminish the severity of depressive and physical symptoms.[28] Calcium carbonate in a dosage of 1200 mg/day reduced symptoms by almost 50% in a large sample of women.[29] Chaste berry fruit (*Vitex agnus* castus)

DAILY RECORD OF SEVERITY OF PROBLEMS

Please print and use as many sheets as you need for at least two FULL months of ratings.

Name or Initials _____

Month/Year _____

Each evening note the degree to which you experienced each of the problems listed below. Put an "x" in the box which corresponds to the severity: 1 - not at all, 2 - minimal, 3 - mild, 4 - moderate, 5 - severe, 6 - extreme.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Enter day (Monday="M", Thursday="R", etc) >																																
Note spotting by entering "S" >																																
Note menses by entering "M" >																																
Begin rating on correct calendar day >		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1 Felt depressed, sad, "down,", or "blue" or felt hopeless; or felt worthless or guilty	6																															
	5																															
	4																															
	3																															
	2																															
	1																															
2 Felt anxious, tense, "keyed up" or "on edge"	6																															
	5																															
	4																															
	3																															
	2																															
	1																															
3 Had mood swings (i.e., suddenly feeling sad or tearful) or was sensitive to rejection or feelings were easily hurt	6																															
	5																															
	4																															
	3																															
	2																															
	1																															
4 Felt angry, or irritable	6																															
	5																															
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	2																															
	1																															
5 Had less interest in usual activities (work, school, friends, hobbies)	6																															
	5																															
	4																															
	3																															
	2																															
	1																															
6 Had difficulty concentrating	6																															
	5																															
	4																															
	3																															
	2																															
	1																															
7 Felt lethargic, tired, or fatigued; or had lack of energy	6																															
	5																															
	4																															
	3																															
	2																															
	1																															
8 Had increased appetite or overate; or had cravings for specific foods	6																															
	5																															
	4																															
	3																															
	2																															
	1																															
9 Slept more, took naps, found it hard to get up when intended; or had trouble getting to sleep or staying asleep	6																															
	5																															
	4																															
	3																															
	2																															
	1																															
10 Felt overwhelmed or unable to cope; or felt out of control	6																															
	5																															
	4																															
	3																															
	2																															
	1																															
11 Had breast tenderness, breast swelling, bloated sensation, weight gain, headache, joint or muscle pain, or other physical symptoms	6																															
	5																															
	4																															
	3																															
	2																															
	1																															
At work, school, home, or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency	6																															
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	1																															
At least one of the problems noted above caused avoidance of or less participation in hobbies or social activities	6																															
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	1																															
At least one of the problems noted above interfered with relationships with others	6																															
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Figure 19.1 Daily Record of Severity of Problems

was found to be superior to placebo at a dose of 20 mg daily, with few adverse effects.[30] Despite the fact that St John's wort is known to act similarly to selective serotonin reuptake inhibitors (SSRIs), it has not yet been evaluated in controlled trials.[25] If psychiatric symptoms are more considerable, psychotherapy (especially cognitive-behavioral therapy) may be beneficial, although studies have been inconsistent.[26,27] Experience has demonstrated that by recording symptoms daily, patients can actually understand more about the timing of their symptoms and discover aggravating and ameliorating factors. In turn, this may help them to incorporate some of the lifestyle changes suggested by their health-care provider.[26]

PHARMACOLOGIC INTERVENTIONS

If the patient has PMS with physical symptoms predominating, and has not responded to the interventions described above, nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen or naproxen sodium, can be taken during the luteal phase. Spironolactone, given in doses of 50–200 mg/day during the luteal phase, may help with breast tenderness, bloating, weight gain, and possibly mood symptoms.[25] Until recently, suppression of ovulation with OCPs has been recommended primarily for the somatic complaints of PMS, e.g. cramps, breast tenderness, and appetite changes, as opposed to the mood problems. In fact, there has been concern that OCPs might actually exacerbate depressive features. A regimen of continuous OCPs can possibly help with the fluctuations in sex steroids that may be causing some of the physical and affective symptoms.[27]

A newer low-dose (20 μg ethinyl estradiol) formulation containing drospirenone (3 mg), which has both antiandrogenic and antimineralocorticoid properties, in a 24/4 regimen (24 days active/4 days placebo), has proven to be efficacious in reducing symptoms of PMDD.[31] Drospirenone is a weak analog of spironolactone, which may explain the alleviation of physical complaints. The low dose of estrogen, combined with a shortened drug-free interval, may help explain the positive outcomes seen in patients with PMDD. In October 2006, this drug became the first OCP approved by the Food and Drug Administration (FDA) for the treatment of PMDD.

If the diagnosis of PMDD is established, the first-line therapy for women 18 years and older is SSRIs. Fluoxetine and sertraline have been studied the most. An original study using fluoxetine found that a dose of either 20 mg or 60 mg daily was equally efficacious, but that there were fewer side effects with the lower dose.[32] Subsequent studies have replicated these results. Similarly, sertraline has been shown to be effective for the treatment of PMDD at doses of 50–150 mg/day. Paroxetine and citalopram appear to be beneficial as well.[26]

It is notable that, unlike the experience in depression where peak effect is not recognized until about 4–6 weeks into treatment, there appears to be a more immediate response when treating PMDD, often within the first 24–48 hours. This suggests a different mechanism of action for the SSRIs in PMDD,[32] which prompted the investigation of intermittent dosing of SSRIs, i.e. during the luteal phase only, as opposed to continuous dosing. A meta-analysis concluded that either dosing schedule was effective, but that intermittent dosing would cost less and could decrease the frequency of side effects.[33] In general, the most common side effects from SSRIs include: gastrointestinal symptoms (including nausea), insomnia, fatigue, headache, dry mouth, dizziness, tremor, and hyperhidrosis. These usually resolve within a few weeks of treatment and, as mentioned, may be less bothersome with intermittent dosing.[25] Decreased libido and anorgasmia are also complaints noted with SSRI use, although they are not frequently described in the PMDD literature.[33] There were also no reports of withdrawal symptoms, e.g. dizziness, lethargy, nausea, irritability, worsening of mood, and vivid dreams, with intermittent dosing.[25]

While there is one report of three adolescent girls with PMDD in which treatment with fluoxetine over 2 years produced complete improvement in symptoms,[34] randomized trials of SSRIs in adolescents with PMDD are necessary. It must be

mentioned that fluoxetine is the only SSRI currently approved by the FDA for the treatment of depression in adolescents. However, in 2004, the FDA issued a 'black box warning' about the increase in suicidal ideation in children and adolescents treated with antidepressants, which has received a great deal of media attention. If choosing to use one of the SSRIs off-label, it is important to fully inform patients and their families about the warning and to carefully monitor them in the first few months of treatment.

Other treatments that have been used in adults, but are not recommended in adolescents, include: tricyclic antidepressants, anxiolytics, GnRH agonists, medroxyprogesterone acetate (oral or depot), gonadotropin inhibitors, and bilateral oophorectomy.[25]

DEPRESSIVE DISORDERS

Depressive disorders include major depression (unipolar), dysthymia, and bipolar disorder. Dysthymia is a mild, chronic, dysphoric mood state, which frequently begins before or during adolescence, while major depression is more severe, acute, and episodic in nature. Bipolar disorder is characterized by periods of mania fluctuating with episodes of depression. Epidemiologic studies demonstrate that depression occurs twice as frequently in women as in men, but bipolar disorder seems to affect both sexes equally.[3] Adolescent females are particularly vulnerable to the onset of depressive symptoms, possibly due to the physical and hormonal changes that accompany puberty.[35] Depressive disorders can impact both menstrual functioning and sexual risk-taking behaviors, the latter of which may lead to increased risk of sexually transmitted infections (STIs) and unintended pregnancy. Additionally, some medications used to treat these psychiatric disorders can impact menstrual functioning. Therefore, it is important for adolescent health-care providers to be aware of these conditions in their patients, both for diagnostic purposes and for considerations in preventative services.

HYPOTHALAMIC-PITUITARY-GONADAL AXIS DISTURBANCE IN DEPRESSION

Depression can be considered a 'stress' on the body, and thus fits into the stress model described earlier with respect to AN. Activation of the HPA axis, with increased circulating levels of CRH, has an inhibitory influence on GnRH secretion. Glucocorticoids, e.g. cortisol, may also inhibit GnRH secretion or LH sensitivity to GnRH.[6] While major depression is associated with HPA axis dysregulation, e.g. hypercortisolemia and resistance to exogenous CRH, studies in depressed women indicate that GnRH secretion and pulsatility are normal, and have failed to demonstrate abnormalities in LH secretion. However, decreased levels of estradiol in the follicular phase have been shown, which may be indicative of a gonadal defect.[36]

Despite these findings in adults, in a large, non-referred sample of adolescent females, secondary amenorrhea and irregular cycles were associated with depressive symptoms. Furthermore, girls in the first year following menarche (gynecologic year 1) had higher odds ratios for these symptoms than older girls, which again may reflect the significant physical and hormonal transitions occurring at this time.[35] Thus, adolescent females who present with secondary amenorrhea or irregular cycles may warrant an investigation into the possibility of a depressive disorder.

BIPOLAR DISORDER AND MENSTRUAL FUNCTION

In one study of women with bipolar disorder, 50% of subjects reported menstrual abnormalities that preceded the diagnosis of their illness and treatment.[37] In addition, pre-existing menstrual dysfunction predicted higher levels of free testosterone, as well as development of new menstrual abnormalities. New onset menstrual dysfunction was associated with use of the mood stabilizer valproate and weight gain, the latter of which may be a primary problem in bipolar disorder, or a sequela of the various medications used for treatment. In a retrospective analysis, women with bipolar disorder

were more likely than women with unipolar depression or normal controls to report early-onset menstrual dysfunction that preceded the diagnosis of their psychiatric illness.[38]

Valproate is now a commonly used medication in the treatment of bipolar disorder. Over a decade ago, the association of polycystic ovaries and hyperandrogenism in women undergoing treatment with valproate for epilepsy was demonstrated. The mechanism by which this may occur is thought to be through inhibition of the cytochrome P450 enzymes, with subsequent increases in androgen concentration and decreases in sex hormone-binding globulin. Alternatively, valproate may directly affect ovarian production of androgens.[37] While smaller studies have shown high rates of PCOS in women being treated with valproate for bipolar disorder, a larger study did not find an increased incidence of the syndrome when compared to known population incidence data. However, duration of valproate treatment and free testosterone levels were significantly associated, suggesting a possible cumulative effect of the medication.[37] Valproate is known to cause weight gain and may increase the risk for insulin resistance, both of which may contribute to the metabolic and endocrine abnormalities seen with its use. Lithium, another mood stabilizer, does not seem to be linked to the development of PCOS, although its use is frequently associated with weight gain.[39]

Antipsychotics represent another class of medications that have gained popularity in the treatment of bipolar disorder, even in children and adolescents, despite limited data on their safety and efficacy in pediatric populations. One notable adverse effect of these drugs is hyperprolactinemia, caused by blockage of the inhibitory effects of dopamine on prolactin. The typical antipsychotics all raise the serum prolactin acutely, which can dissipate over time. The atypical antipsychotics have variable effects on prolactin levels. Hyperprolactinemia may cause menstrual disturbances, e.g. amenorrhea or oligomenorrhea, and decreased libido, through suppression of GnRH and thereby LH and FSH, leading to hypogonadotropic hypogonadism. Serum prolactin levels of 60 ng/ml or higher often result in missed menstrual cycles. Through direct action on breast tissue, galactorrhea may occur as well. Individuals seem to vary in their sensitivities to the effects of high serum prolactin, and thus, not all patients develop symptoms.[39] See Table 19.4 for a list of antipsychotic agents and their effects on serum prolactin levels. Most of the atypical antipsychotic agents also tend to cause considerable weight gain, but are not associated with an increased risk for PCOS.[39]

Table 19.4 Antipsychotic medications and effect on serum prolactin

Medication	Effect on serum prolactin
Risperidone	Significant elevation
Haloperidol	Significant elevation
Olanzapine	Moderate elevation
Ziprasidone	Moderate elevation
Quetiapine	Relative sparing
Clozapine	Relative sparing
Aripiprazole	Relative sparing

Many of the antiepileptic drugs (AEDs) that are used in the treatment of bipolar disorder are powerful inducers of the cytochrome P450 system in the liver and can decrease efficacy of OCPs. These medications include: carbamazepine, oxcarbazepine, and topiramate. Estrogen increases the metabolism of another AED, lamotrigine, which can cause fluctuations of the drug's levels by upwards of 60%. If OCPs are discontinued, lamotrigine levels may rise significantly.[40]

DEPRESSION AND SEXUAL RISK-TAKING BEHAVIOR

Risk-taking among adolescents is cause for great concern, as it can lead to a significant degree of morbidity and mortality. For an adolescent with depression, cognitive distortions may impair decision-making with respect to risky sexual activity. Feelings of hopelessness, helplessness, and poor self-esteem may cause disrespect for self leading to increased risk behavior, which can ultimately result

in STIs and unintended pregnancy. Additionally, some patients could use sex as 'self-medication,' seeking its pleasurable effects. A large cohort study of 21-year-olds found that risky sexual behavior was most closely associated with psychiatric disorders that were typified by disinhibition or impulsive behavior patterns, e.g. mania and substance abuse, but that depression was also connected to outcomes, such as risky sex (high number of partners, condom nonuse), development of STIs, and early first intercourse. Additionally, depression coupled with substance abuse increased this risk.[41] Thus, patients with depressive disorders should be targeted for preventative and diagnostic services in relation to STIs and contraception.

SUBSTANCE ABUSE

Adolescence is a developmental stage characterized by increasing autonomy, connectedness to peers, and often risk-taking behavior. Specifically, the commencement of sexual behavior and experimentation with alcohol and other substances frequently occur in adolescence. Most adolescents do not engage in heavy substance use nor do they meet DSM-IV-TR criteria for abuse (a maladaptive pattern of substance use that causes significant impairment or distress).[3] However, the majority have experimented with at least one substance by the time they are 17 years old. Alcohol is certainly the most commonly tried substance among teenagers, and probably serves as a 'gateway' drug to the use of other illicit drugs, e.g. marijuana, cocaine, heroin.

MENSTRUAL DYSFUNCTION

Narcotic drugs have long been known to cause menstrual abnormalities in female users. Observational studies on heroin users and addicts have revealed an increased incidence of amenorrhea, as well as oligomenorrhea and hypomenorrhea. This is felt to be similar to other types of hypothalamic amenorrhea, whereby hypothalamic suppression with absence of pulsatile GnRH secretion leads to anovulation. Malnutrition during periods of substance abuse may explain a portion of this phenomenon, but there is thought to be a direct drug effect as well.[42] Most patients regain menstrual function within 3 months of termination of drug use. The adolescent user may be more sensitive to these effects than adults, due to a young gynecologic age and still developing HPG axis.[43] More recently, investigators discovered that patients on methadone maintenance may begin to normalize their cycle length, despite the putative effects of methadone on the HPG axis as well.[44]

Women who binge drink regularly may experience dysmenorrhea, menorrhagia, irregular menses, and PMS more frequently than other women. Considerable evidence in animals, and some human data, indicate that chronic heavy alcohol use disturbs the HPG axis.[45] There are no known studies in adolescents. Anecdotally, chronic heavy marijuana use has been associated with amenorrhea, which resolves with discontinuation of the substance.

SUBSTANCE USE AND SEXUAL RISK-TAKING

It has long been assumed that 'sex under the influence' of either alcohol or other mood-altering drugs is a risk factor for STIs and unintended pregnancy via early initiation of intercourse, multiple partners, and condom non-use. However, many researchers have questioned the legitimacy of this theory. Certainly, adolescent risk behaviors tend to cluster together, and may fulfill similar developmental requirements. Furthermore, the context of the sexual relationship seems to moderate the effect of substance use prior to sex, e.g. adolescent girls who are not planning intercourse but are drinking are the least likely to use contraception.[46] While many studies demonstrate an association between progressive involvement in substance use and unsafe sexual behaviors,[47] it is difficult to conclude causality in the relationship between the two, especially as most studies have been cross-sectional in nature. There may indeed be a third factor, such as individual characteristics (risk-taking, thrill-seeking, or

unconventionality) that triggers both substance use and unprotected sex.[46,48]

Event-level studies, which inquire about discrete sexual experiences, have provided better data, as they are not cross-sectional and do not rely on retrospective reports for the most part. A strong conclusion from a meta-analysis of many such studies is that drinking alcohol is not inevitably linked to unprotected intercourse. However, drinking specifically at the time of coitarche was associated with decreased condom usage.[49] Binge drinking (four or more drinks in a row for females) among adolescents has been longitudinally linked to sexual initiation, multiple partners, and condom non-use[50] and is also associated with increased risk of sexual victimization, possibly by creating the appearance of vulnerability and/or impairing judgment.[51] Longitudinal data have shown that use of marijuana and hard drugs at 18 years of age is indirectly associated with higher rates of unplanned pregnancy and abortion. Unconventionality seems to be the common path whereby this association exists. There is also a direct relationship between marijuana use by young women and decision to abort, possibly due to fear of drug effects on the developing fetus and/or avoidance of parental responsibility.[48]

Adolescents with DSM-III-R diagnosable poly-substance (e.g. alcohol and marijuana) abuse or dependence, undergoing treatment for such, report earlier age of coitarche, more sexual partners, less reliable condom use, and more STIs than socio-demographically comparable, non-substance-abusing youth. Additionally, these high-risk behaviors seem to persist over time into young adulthood.[52] An event-level study of adolescents with substance use disorders demonstrated that substance use itself is not temporally related to condom use, but that perceived risk of a negative outcome (e.g. contracting an STI, unintentionally becoming pregnant) is a significant predictor of safer sex practices.[53]

CLINICAL IMPLICATIONS

While there is not an overwhelming amount of data demonstrating causality in substance use/abuse and risky sex, it is certainly clear that these behaviors cluster together and may share a common basis. Thus, adolescent health-care providers should feel comfortable about confidentially screening patients for problematic substance use, as discovery of these behaviors may have implications for STI screening and counseling. The six-item CRAFFT questionnaire is a clinically useful tool for this screening (Table 19.5). Each positive response constitutes one point; an overall score of two or more merits further attention.[54] However, when counseling patients, it is important to remember that substance use may in fact serve as an excuse for risky sex by those individuals who believe it induces such behavior. Therefore, prevention of substance use is probably not an effective method to prevent unsafe sexual practices, and may serve to reinforce such views when the two risk behaviors are focused on concurrently.[53]

Table 19.5 CRAFFT substance use screening questionnaire

C	Have you ever ridden in a **car** driven by someone (including yourself) who was 'high' or had been using alcohol or drugs?
R	Do you ever use alcohol or drugs to **relax**, feel better about yourself, or fit in?
A	Do you ever use alcohol or drugs while you are by yourself, **alone**?
F	Do you ever **forget** things you did while using alcohol or drugs?
F	Do your family or **friends** ever tell you that you should cut down on your drinking or drug use?
T	Have you ever got into **trouble** while you were using alcohol or drugs?

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20. Sports-related problems in reproductive care

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From a historical perspective, the venue of female athletic activities has its origins in the ancient Greek Olympics, from which women were banned in 1896.[1] In the 1900 Olympic Summer Games, women were allowed to participate but restricted to golf and lawn tennis. In 1912, women were allowed in the diving and swimming events.[2,3] With the advent of Title IX of the Educational Amendment Act of 1972 by the United States Congress, it was mandated that equal athletic participation occur for males and females who are attending any college or university that receives federal financial assistance.[4] As time has progressed, the number of girls at a high-school level who are currently participating in athletic endeavors is on the rise.[5]

Participation in athletic endeavors for adolescent females is a positive and often a rewarding endeavor. The teen spirit, esprit de corps, and camaraderie speak volumes from the psychosocial aspect of female participation.

A number of problems can be encountered with respect to the female adolescent athlete, including reproductive-related dysfunction, i.e. menstrual aberration. There may also be an association with self-image and related problems in the adolescent. Trainers, coaches, and other athletic supervisors should be well versed with respect to potential reproductive system-related problems. Parents and school officials should also be cognizant of potential concerns regarding athletic endeavors. Monitoring of sports programs is of paramount importance, with development of guidelines to prevent potential reproductive health problems and identify them at their early stages. Regional government oversee of these athletic programs should also focus on the coaching techniques, to prevent female adolescents from potential harm as a result of aggressive and unhealthy overtraining.

PHYSIOLOGY

Beginning with prepubertal girls, sports performance is often placed at the very top of endeavors that a female should participate in. From the ages of 6 through 12, the central nervous system continues to develop. Children can often be introduced to sports-related coordination, i.e. hand–eye coordination. For instance, tennis, basketball, ice hockey, and related sports help the prepubertal individual to develop skills that will be most worthwhile in the future.[2–6]

In the adolescent, as puberty progresses, there is an increase in percent of body fat in females in comparison with males.[2] On average, body fat levels are 13–15% in adult males in comparison with 23–27% for adult females.[2] As athletic endeavors proceed, the percent lean body mass often increases, and this subtle change can affect menstrual cycles.[7] As girls proceed through puberty and complement this with athletic endeavors, cardiac output, stroke volume, left ventricular mass, lung volume, aerobic capacity, and hemoglobin levels will increase. However, this comparison is less than that in males of comparable age.[8] Overall strength in girls is less compared with boys, and muscle fiber size is smaller, although the proportion overall of muscle fiber type is similar.[1,2] Adolescent girls are frequently more flexible and better at balance tasks than boys, and often appropriately pursue such related athletic endeavors, i.e. gymnastics, cheerleading.[9,10]

BREASTS

Breast development, on average, begins around 9 years of age, although variation occurs based on genetics, race, family history, etc. In general, breasts are not prone to trauma during athletic endeavors. Exercise does not appear to affect breast size.[2] The nipple area is the more common site of breast injury in the female athlete. Tight-fitting bras and coarse clothing can lead to abrasive injury as, for example, joggers' nipples.[11] Hematomas secondary to trauma and bloody nipple discharge in association with trauma must be distinguished from other rare but reported entities such as intraductal papilloma and carcinoma.[12] It has been advocated that prevention of exercise-induced nipple injury can be facilitated with use of plastic Band-Aids before and during the exercise, use of a properly fitting sports bra, avoiding exposure to cold temperatures, and use of wind-breaking material over the chest (see Table 20.1).[2–11]

Table 20.1 Management of trauma-related breast injuries

Contusion
Application of cold compresses every 15–20 minutes for several hours
Appropriate analgesia
Firm support
Abrasion
Direct pressure to control bleeding
Suturing may be necessary
Laceration
Close with Steri-Strips or sutures
Use good hygiene principles
Apply a firm dressing after closure
Wear a supportive bra (including at night)
Reduce pain and swelling with a cold pack
Provide tetanus toxoid, if warranted
Antibiotics may be needed, depending on the situation
Hematoma
Most resolve without treatment
Surgical aspiration may be necessary

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HORMONAL INTERACTIONS RESPONSIBLE FOR MENSTRUAL DYSFUNCTION

The menstrual cycle is a reflection of the intricate interaction of the hypothalamic-pituitary-gonadal (HPG) axis. Physiologic development of this axis begins *in utero* at 10–12 weeks following conception. The hypothalamic stimulus is gonadotropin-releasing hormone (GnRH), which is a decapeptide identified in the fetal circulation as early as 10 weeks' gestation.[13] GnRH then enters the portal system, which bridges the gap between the hypothalamus and the pituitary gland. In turn, the pituitary responds by releasing follicle-stimulating hormone (FSH) and luteinizing hormone (LH), for which receptors are identified on the ovary. This allows for follicle development and, ultimately, ovulation.

The onset of puberty and menarche is a reflection of the coordination of the hypothalamic-pituitary-ovarian (HPO) axis. The current state of knowledge is that sleep and adequate body fat are essential for the initiation of development of secondary sex characteristics.[14,15] The sleep-related increase in LH release occurs during stage IV sleep during puberty (Figure 20.1).

The mechanism for onset of puberty continues to be a point of debate. Critical body weight, lean:fat ratio, and secondary sexual development with subsequent menarche have been addressed by Frisch.[16] It is not uncommon that a minimum of 18 months following menarche is necessary before regular ovulatory cycles occur while maintaining these variables in-sync. This phenomenon may require up to 5 years in some women. Whether there are specific hormonal changes in the female athlete is an intriguing concept. Exercise is associated with the release of both pituitary and hypothalamic hormones. LH is more significantly affected than FSH. Serum inhibin concentrations, which have a direct negative feedback on FSH, are increased in animal models during exercise. However, when studied in human males, there was no significant alteration in serum inhibin levels. Similar studies have not been as discretely discerned in the female.[17] GnRH appears to be altered from the perspective of

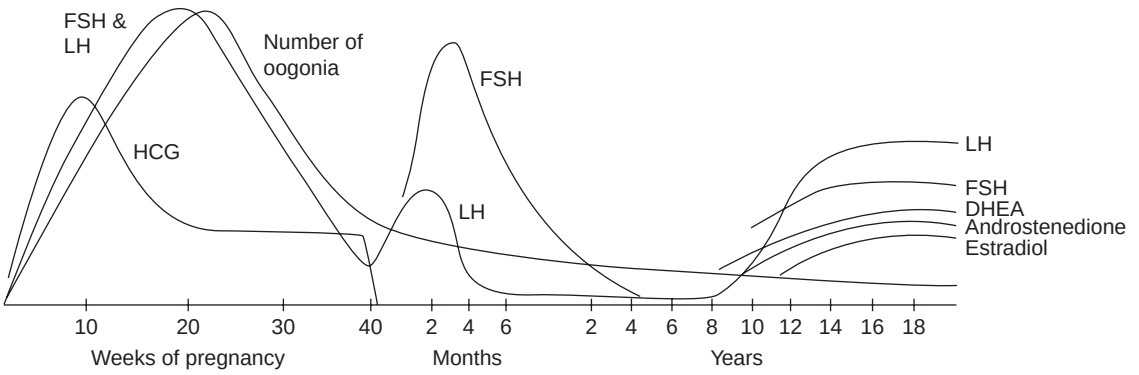

Figure 20.1 Serum levels of FSH, LH, human chorionic gonadotropin (HCG), dehydroepiandrosterone (DHEA), androstenedione, and estradiol in females from prenatal state to 18 years of age. Reproduced from Speroff L, Glass RH, Kase NG. Clinical Gynecologic Endocrinology and Infertility, 5th edn. Baltimore: Williams & Wilkins, 1994: 173, with permission.

both the pulse frequency and pulse amplitude, especially in women who have developed amenorrhea and continue athletic endeavors.

Athletes who did not experience menstrual disturbances were studied by Parke and co-workers: 31 young female athletes, 13 years of age or older, were matched with sedentary controls; all subjects were evaluated during one menstrual cycle over a 6-week period of time.[18] The episodic gonadotropin secretion was measured during the early follicular phase as well as during the late luteal phase. The end result was that, during this assessment, eight athletes developed anovulatory cycles, all of which were associated with decreased progesterone secretion during the luteal phase. Hence, it has been implied that luteal phase deficiency is more common in athletes.[18]

Secretion of corticotropin-releasing hormone (CRH) inhibits GnRH release.[19] As CRH increases, so do beta endorphin levels, which further contributes to GnRH inhibition and increased production of catecholamines and catecholestrogens (see below). The latter are potent inhibitors of GnRH secretion, thus one other contributing factor to onset of amenorrhea.[19]

Prolactin is an 'exercise hormone,' in that athletic endeavors increase release of prolactin.[20] Steroid hormones, free testosterone, and estradiol have been evaluated in marathon runners, as well as untrained athletes, all of whom were eumenorrheic.[21] Estradiol levels of the groups were not significantly different. However, there was an overall increase in the percentage of free testosterone in the untrained group using a standardized bicycle ergometer or treadmill test during the luteal and follicular phases of the menstrual cycle. The free testosterone level increase was noted in the marathon runners as well as in the untrained group of runners.

Leptin is a protein product from the obesity (OB) gene and is a product of adipocytes as well as a protein synthesized by the placenta.[22] Leptin is secreted into the blood, crosses the blood–brain barrier, and acts at the hypothalamic level to regulate food intake, energy expenditure, growth, and sexual maturation.[23] How leptin is involved with respect to GnRH, LH pulsatility suppression, which characterizes menstrual disturbances in female athletes, remains a point of discussion. It is known that leptin receptors are identified in the hypothalamus, including hypothalamic neurons involved in control of the GnRH pulse generator.[24] Leptin may be involved in signaling low energy availability to the reproductive axis.[25] Low leptin levels have been identified in amenorrheic women who exercise regularly at the elite level.[26]

Endogenous opioid peptides include beta endorphins, which play a role in decreasing LH by suppressing hypothalamic GnRH. Beta endorphin exerts a tonic inhibition on the secretion of GnRH and thus inhibits LH release.[27]

Catecholestrogens are the 2- and 4-hydroxy derivatives of estrone and estradiol. Catecholestrogens suppress LH and also induce the LH surge.[27] Catecholestrogens play a role in suppression of prolactin release, probably through interfering with dopamine as well as have an effect on luteolysis via the prostaglandin-$F_2\alpha$ activity.[28] Overall, catecholestrogens may play a role in corpus luteum function and lifespan, all of which play a role with respect to menstrual aberration in athletes.

It has been reported that low T_3 syndrome, a sign of energy deficiency, occurs in amenorrheic and not eumenorrheic athletes.[29] Loucks and co-workers, in a randomized prospective cohort study, noted that low T_3 syndrome was induced by the energy cost of exercise and prevented in exercising women by increasing their dietary energy intake.[30] Glucose homeostasis is impaired during the mid-luteal phase of the menstrual cycle. There may be an effect of altered glucose metabolism in association with exercise-induced menstrual aberration.[31] With a hyperglycemic hyperinsulinemic clamp model, endurance exercise training resulted in a slower decline in muscle glycogen depletion during exercise.[32]

Insulin-like growth factor (IGF) and insulin-like growth factor binding protein (IGF-BP) appear to be a metabolic signal associated with exercise-induced amenorrhea. The hepatic protein (IGF-BP-I) is acutely and inversely regulated by insulin and modulates IGF. These changes contribute to metabolic regulation or dysregulation of reproductive activities and thus may also play a role in menstrual-related problems in athletes.[33]

Exercise of sufficient intensity during daylight hours results in an acute elevation of circulating melatonin levels.[34] The increase in melatonin is independent of menstrual status, whereas nocturnal melatonin secretion demonstrates a twofold amplification in amenorrheic but not eumenorrheic athletes.[34]

MENSTRUAL ABERRATION AND OTHER HEALTH EFFECTS

AMENORRHEA

Ovarian disorders indicative of amenorrhea are initially evaluated by serum FSH levels. If these are above 30 mIU/ml, this is indicative of ovarian failure. The relationship between exercise and amenorrhea has been elucidated to a great extent by observing competitive female athletes, including modern dance and ballet. One study noted anovulatory cycles as well as short luteal phase dysfunction in two-thirds of runners.[35] Critical body fat levels and a stressful environment are involved in absence of menses without the elevation of FSH.

Considering that there are three million girls and young women who compete in American high-school sports, the fact that the incidence of amenorrhea in endurance athletes has been reported as high as 50% is understandable.[36,37]

The female triad is a syndrome of separate but related conditions and includes eating disorders, amenorrhea, and osteoporosis. Calabrese and co-workers noted that student ballet dancers consumed fewer calories (1358) than the recommended dietary allowance of 2030, as established by the National Research Council.[38] Frisch et al reported that collegiate women who began athletic training before menarche consumed less fat (65 g) and protein (71 g) than a group who began training after menarche (95 g of fat and 92 g of protein).[39] It is thus important to remember that the inter-relationship of disordered eating, amenorrhea, and osteoporosis (the female athletic triad) is a very important consideration when clinically evaluating female athletes.

Discussions continue regarding whether there is a single or multiple mechanisms associated with amenorrhea in relation to exercise. Predisposition revolves around training, nutritional status, body composition changes, and stress hormone effects during exercise, as well as immaturity of the reproductive axis. The type of exercise, as well as physiologic background, also appear to play a role.[37]

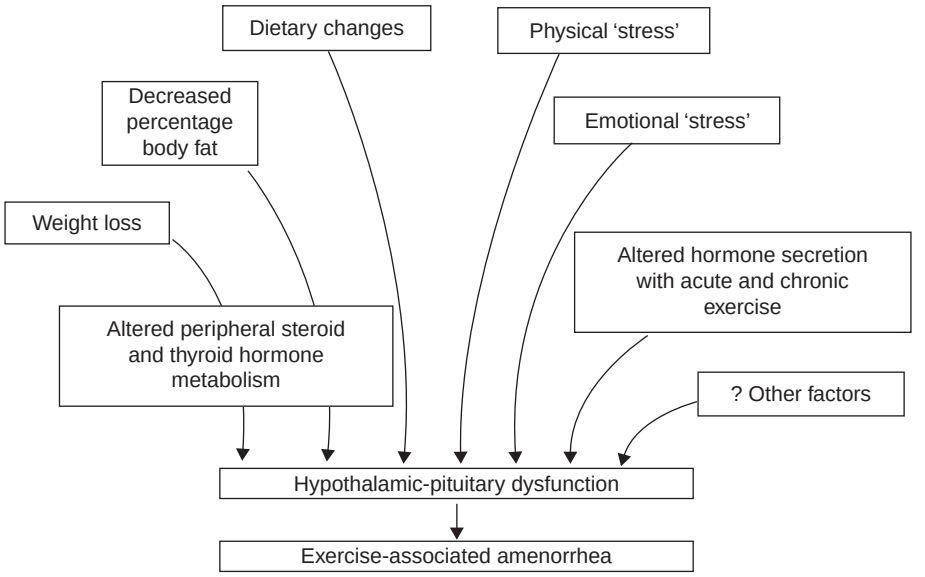

Figure 20.2 Diagrammatic representation of some of the factors involved in the pathophysiology of exercise-associated amenorrhea. Adapted from Rebar RW. Effects of exercise on reproductive function in females. In: Givens JR, ed. The Hypothalamus. Chicago: Year Book Medical, 1984: 245–62, with permission.

The incidence of amenorrhea has been reported in Olympic marathon runners.[40] Intensive exercise was studied in a group of runners who averaged 70 miles per week in association with the 1984 Olympics. Of this group, 19% were amenorrheic. Athletic amenorrhea can occur with or without weight loss. Menses may return without significant alteration in body weight or lean:fat mass ratio.[41] The pathophysiology remains a point of discussion, whether it is related to: 1) energy availability, 2) lean body mass, 3) stress as related to the physical endeavor, 4) changes at the hypothalamic-pituitary axis, 5) type of athletic endeavor, or 6) previous history of interval between menses (Figure 20.2).

OSTEOPOROSIS

Osteoporosis can result from prolonged amenorrhea. This is one of the most disastrous consequences of exercise-induced amenorrhea. The loss of bone mineral density (BMD) leads initially to development of osteopenia and subsequently osteoporosis, all of which predispose the athlete to fractures. Studies have shown that by encouraging the athlete to have a daily intake of at least 1500 mg of calcium with 800 IU of vitamin D can decrease the incidence of bone loss.[42]

Dual-energy X-ray absorptiometry (DEXA) is the technique most often utilized for measuring BMD. It should be offered to athletes who are amenorrheic, and when concern exists regarding osteoporosis.

Warren et al reported that delayed menarche was associated with scoliosis and an increase in stress factors in young ballet dancers.[43] Amenorrheic and oligomenorrheic athletes should be counseled accordingly. The exact mechanism by which physical stress affects bone mass in the amenorrheic athlete is not completely understood, although it has been hypothesized that the primary effect may be on the osteoblast, affecting bone formation.[43]

DELAYED MENARCHE AND PUBERTY

Delayed puberty has been categorized in part based on the level of gonadotropins. The delayed pubertal abnormalities are classified into three types: 1) hypergonadotropic hypogonadism, 2) hypogonadotropic hypogonadism, and 3) eugonadism. Hypergonadotropic hypogonadism is associated with ovarian failure, most commonly gonadal dysgenesis. Other possible etiologies include 17α-hydroxylase deficiency, resistant ovary syndrome, pure gonadal dysgenesis, and ovarian destruction by torsion or inflammatory processes.

Hypogonadotropic hypogonadism is associated with depressed levels of FSH and LH. Many conditions, ranging from physiologic delay to malignant pituitary tumor, have been identified in this category.[44]

Eugonadism is associated with anatomic defects such as müllerian agenesis or imperforate hymen. Normal gonadotropin levels are associated with this entity.

Delayed onset of menarche can be a reflection of degree of athletic endeavor. The physiologic hormone levels can be affected by stress, positive vs negative energy balance, and overall degree of athletic activity. A detailed history should be obtained to identify the level of athletic activity. Modification of such may result in onset of menarche.

ESTROGEN REPLACEMENT THERAPY: PROS AND CONS

In the amenorrheic athlete, especially when a hypoestrogenic state exists in association with amenorrhea, strong consideration should be given to estrogen therapy. Physiologic doses of estrogen (0.625 mg of conjugated estrogens) with medroxyprogesterone acetate can be given, the former on a 25-day per month basis and the latter in dosages of 5–10 mg per day for 10 days of the total 25-day estrogen cycle. Other regimens include daily administration of conjugated estrogens at 0.625 mg plus 2.5 mg of medroxyprogesterone acetate daily. This treatment is an effort to maintain BMD. While low-dose oral contraceptives remain an alternative approach, the efficacy appears to be better for physiologic replacement dosages.[45] Controversy remains with respect to the effect of hormone therapy on bone.[46–48] Prospective randomized studies are necessary to further assess the efficacy of hormone therapy, although the predominance of information leans toward administering hormone therapy in amenorrheic athletes.

CONCLUSION

In light of over three million girls and young women participating in high-school sports-related activities, and being cognizant that participation in sports and fitness programs leads to a healthier lifestyle and higher self-esteem, these activities should continue to be encouraged among adolescents.

Clinicians must be well aware of the female athlete triad, which includes eating disorders, amenorrhea, and osteoporosis. Athletic amenorrhea is associated with significant alterations within the HPO axis, all of which can result in decreased estrogen production, osteopenia, and osteoporosis. BMD assessment merits strong consideration in the amenorrheic athlete. In 1992, the American College of Sports Medicine Task Force on Women's Issues provided a position stand regarding the triad (eating disorders, amenorrhea, and osteoporosis). In one study involving 170 athletes, 18.2% met the criteria for eating disorder, with vomiting noted in 7% as the most common abnormal behavior. The latter was used to control weight and, of these 170 athletes, 24% were either oligomenorrheic or amenorrheic. Rosen and colleagues noted that 25% of female athletes reported routine use of diet pills, 16% reported laxative abuse, and 14% self-induced vomiting.[49] This is in contradistinction to the non-athletic female population, in which 1% have anorexia nervosa and 1–4% have bulimia.[50]

The prevalence of secondary amenorrhea in the general non-athletic population is 2–5%, whereas in the athletic population it varies, depending on the patient population, between 6% and 79%.[51]

Emphasis must be placed on obtaining a detailed history and physical examination of the female

athlete. Preventive medicine is the best medicine with respect to management of sports-related gynecological problems.

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21. Reproductive health care for developmentally disabled adolescents

Elizabeth H Quint and Susan D Ernst

INTRODUCTION

The onset of puberty in the life of any adolescent is a time of transition, associated with challenges for the entire family. This is even more the case for developmentally disabled (DD) adolescents and their families, as their lives and needs are often more complicated, confounded by physical, psychological, and emotional issues.

As care providers we have the opportunity to assist the teens and their families through this transition. This chapter focuses on puberty in teenagers with developmental disabilities and the issues these teens present with, including menstrual irregularities and hygiene issues. We also address the more specific concerns around contraception, mood disorders, seizures, and abuse. Treatments will be discussed, keeping in mind the principle that therapeutic intervention should provide the optimal and least harmful form of care, and should also be evidence-based where possible. The patient's autonomy should always be respected and she should participate in her own care as much as possible.

HISTORY

When teens come for care it is very important to clarify the reason for the visit. The degree of disability will determine how much the patient can be involved. Use basic language to ask the initial questions and to assess how much the patient understands. Address confidentiality issues early in the interview, just as in every adolescent encounter, again dependent on the degree of developmental delay.

If the teen is accompanied by a parent there will be historical and family information available. However, if the patient is adopted or lives in a group home this information may be unknown. Menstrual and behavioral calendars can be very helpful to get written information on menstrual cycles and accompanying symptoms and behaviors. This makes it easier to establish a diagnosis and to assess treatment efficacy.

Obtain a thorough menstrual history specifically asking how the cycles may be influencing the teen's life. Also ask about their home and school situations and inquire about issues with behaviors, moods, concerns about sexual activity, coercion, abuse or depression (common in teens, 2–3%).[1] Finally, determine whether the primary goal of the visit is for education or reassurance, menstrual problems, including 'menstrual control,' behavioral help, or for an evaluation for possible abuse or pregnancy.

EDUCATION

Education is an important part of every health-care visit. Education should include information on basic body anatomy, pubertal events, the menstrual period, reproduction and contraception, appropriate boundaries, and prevention of sexual assault. In general there is a lack of education, as often teens with DD are considered asexual. Although it is challenging to try to teach all of these concepts in the setting of a brief office visit, it is recommended that providers attempt to assess the developmental level and current knowledge base of each patient, then help the family and caregivers with information to continue educational efforts in the home setting, or

alternatively, refer them to community-based resources.

Just as with teaching other subjects to adolescents with learning difficulties, use simple terms and repetition of the topics. All patients may benefit from visual aids, pictures, signs, symbols, and anatomically correct dolls or models to enhance comprehension.

Education focuses on several areas:

1. Normal development, puberty, and menstrual cycles
2. Sex education
3. Abuse prevention education.

NORMAL DEVELOPMENT, PUBERTY, AND MENSTRUAL CYCLES

Many parents and caregivers of adolescents with DD seek information and education regarding gynecologic issues before menarche even occurs. In one study about women with DD, concern over sequence and timing of pubertal events was the second most common presenting complaint.[2] Few studies exist regarding pubertal timing and sequence in girls with DDs, but those that do suggest no change from normal puberty.[3] However, girls with DD are more likely to have other medical conditions or take medications that can affect pubertal events. Once menarche starts, girls with DD may have physical challenges that may make menstrual hygiene difficult. These girls may have cognitive impairment and speech delays that would predictably make it hard for them to understand or communicate about the changes that occur with puberty and the menstrual cycle. Start with a discussion of basic anatomical structures, followed by a simple explanation of where the blood comes out of the vagina. Emphasize this is not 'painful' blood. Discuss the importance of keeping the genital area clean, changing pads on a timed schedule, and changing clothes and underwear when soiled. This is also a good time to reinforce general hygiene practices of hand-washing after toileting, and bathing or showering on a daily basis. Another practical suggestion would be for the mother or sister, if comfortable, to model their behaviors or techniques of menstrual hygiene for the disabled individual.

SEXUAL EDUCATION

Sexual education should ideally be taught in multiple settings including the home, school, and in the physician office.[4] However, it is clear that many girls with DD receive only minimal information. At the most basic level, sex education should include an explanation of the differences between boys and girls and the proper labeling of body parts. Emphasis is placed on the concept of 'public and private' to reinforce acceptable patterns of conduct. We distinguish between public and private body parts, as well as public and private places. It is acceptable to touch private parts, but only in private places. If the teen has a lot of self-stimulation in public places, it can be taught that in private places that same behavior can be acceptable. Persons with DD often may not understand social norms and societal rules of behavior, leading to the common myth that they are hypersexual. Explain about good touch in contrast to bad or inappropriate touch, and in this context introduce the issues of personal space and boundaries. Try to outline very specifically appropriate behaviors and appropriate responses to interactions with other people. Discuss sexual activity and potential consequences of sexual activity including pregnancy and sexually transmitted infections (STIs) and outline contraceptive options as indicated.

It can be difficult to assess the ability of the patient to consent to sexual activity. A definition of the components of consent comes from the Sex Information and Education Counsel for the United States (SIECUS rep 1995): To be judged capable of giving consent one must be the age of majority (age 16), must be able to indicate yes or no verbally or through gesture, must be free of coercion or intimidation, and must understand the potential risks and consequences of their behavior. Discuss with caregivers and patient, alone if possible, if there are any active issues related to sexual activity or consent.

Table 21.1 Sex education/sexual abuse prevention

1. Assess knowledge of body parts and intercourse
2. Teach:
   - Anatomy of men and women
   - Private versus public body parts, activities and places
   - Good touch-bad touch
   - Personal space and boundaries (circles)

In teaching young women with DD about self-protection skills, the content of the education needs to be modified to their level (Table 21.1). One basic strategy used to teach impaired individuals appropriate social boundaries is the 'circles technique' described by Champagne and Walker-Hirsch.[5] This concept places the individual with disabilities in the center circle and teaches them that very few people should enter their inner circle. There are concentric circles out from that individual's center circle of lesser and lesser importance, starting with immediate family members whom it would be appropriate to hug closely. The next group, including teachers, caregivers, and friends, may only be appropriate for a far-away friendly hug or a hand-shake. Then, casual acquaintances, such as bus drivers and janitors, should not enter the inner circle and should be greeted with a wave or high five. Finally it is reinforced that we should not talk to or touch strangers and they should not talk to or touch us. These boundaries may seem somewhat obvious to normally developing children but must be specifically reinforced for children and teens with cognitive impairment.

SEXUAL ABUSE

Unfortunately, many characteristics associated with developmental disability predispose individuals to sexual abuse: physical challenges, reliance on adults or caregivers for assistance with many activities of daily living, learned compliance, affectionate or loving nature, and decreased communication skills. Statistics vary from 25% in published studies[6] to nearly 83% in statistics from the US Department of Justice,[7] but clearly rates of sexual assault are high among persons with disabilities. Perpetrators are often known to their victims (92% in one study).[8] It may be difficult to obtain a history of sexual assault because of lack of verbal skills and the fact that the perpetrator is often someone in a position of authority over the victim. For this reason the rates of abuse and assault may be even higher than reported.

There are multiple studies that demonstrate that women with mild to moderate mental delay can acquire skills for sexual abuse prevention.[9,10] Unfortunately, as stated above, young people with DD often fail to receive the needed sexual education and abuse prevention.[11] One study of sexually abused women with cognitive impairment found that greater than 50% had not received any sexual education until after they were 21years of age.[12] According to a clinical report on sexuality of children and adolescents with DD published by the American Academy of Pediatrics in 2006,[4] the clinician should recognize that children with disabilities are at increased risk of sexual abuse and should advocate for appropriate sex education.

Most agree that a sexual abuse prevention program should include education on how to recognize an inappropriate advance or unwanted touch, how to verbally refuse or physically remove oneself from the unwanted situation, and how to report the incident to a trusted adult. One common theme in abuse prevention education is the NO, GO, TELL model described by Melberg et al.[13] While these words and actions seem simple they may be extremely difficult or complicated for an individual with impairments.

NO: Saying NO requires a strong enough sense of self-esteem to contradict and refuse the inappropriate intentions of an adult who may possibly be an authority figure in their life and threaten them with undesirable consequences. This concept is also challenged by the fact that individuals with disabilities are often taught to comply with commands from adults or caregivers and they may have to disobey a verbal command from the adult to not move or report the event.

GO: The adolescent may not be able to physically remove themselves from a situation or may not know a safe place to go.

TELL: This requires verbal, cognitive, and social skills that may be insufficiently present in cognitively impaired individuals.

As care providers, we need to be vigilant in looking for signs, symptoms or changes in behavior that may be indications of sexual abuse in those patients who may not be able to communicate details of their abuse.

PHYSICAL EXAMINATION

The general physical and especially the gynecological examination of a patient with developmental delay may be complicated due to several issues. Previous examinations, procedures like enemas, or an unknown history of abuse may cause increased anxiety directed toward vulvar and pelvic examinations. Be aware of unexplained bruising noted during the general physical examination.

A pelvic examination is rarely indicated, if the teenager is not sexually active; however, there are some specific indications for a pelvic or vulvar exam (Table 21.2). Likewise, a Pap smear is seldom indicated according to the most recent guidelines from the American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society, and the US Preventive Services Task Force.[14–16] It is suggested that screening for cervical cancer and precursors should start at age 21, or 3 years after onset of vaginal intercourse. Several studies suggest that there is a decreased incidence of abnormal Pap smears among women with developmental disability.[17] However, there are not enough data to suggest different guidelines for this population. Increased rates of sexual assault and difficulty obtaining an accurate sexual history make continued screening necessary in the adult population.

If a vulvar/pelvic examination is necessary there are some specific aspects to address (Table 21.3). Often due to physical handicaps positioning the legs for a gynecological evaluation may be quite different. This may make the exam more unusual, but certainly not unobtainable. Use a Huffman speculum (narrow, but long) as opposed to a pediatric speculum, which is narrow, but often too short for the post-menarchal girl. Bimanual exam if indicated, with one finger in the vagina, can be difficult due to cooperation of the client, body position like scoliosis, and very tight rectus muscles. A rectoabdominal exam can be helpful. Occasionally emptying of the rectum before the exam is needed.

Pelvic ultrasound in adolescents who cannot be examined is rarely needed and should only be used for specific medical indications. Sedation has been used in clinic settings, but the need for teens is very limited. If a thorough evaluation is strongly indicated to rule out pathology, an ultrasound or an exam under anesthesia are much more helpful and less traumatizing.

The HPV vaccine, a quadrivalent vaccine against strains 6, 11, 16, and 18 of the human papillomavirus,

Table 21.2 Indications for vulvar and/or pelvic exam in teens with DD

- History of sexual activity and need to check for sexually transmitted infections (consider urinary screening)
- History of sexual activity/abuse in the past and need for Pap smear (per ACOG guidelines)
- Vaginal discharge
- Complaint of trauma
- Complaint or finding of physical abnormality (masses, etc.)

Table 21.3 Special aspects of a pelvic exam in teens with DD

- Allow a trusted caregiver or family member to be present, if the patient desires
- Usually wear a white coat to clearly establish the professional nature of the caregiver
- Patience, slow down the exam
- It may require several visits to a caregiver before the patient is comfortable
- Practice may help: gowns, instruments, and the examining table
- Allow the patient as much control over the exam as possible by having her touch the instruments and assist if possible
- Patients may have multiple handicaps (neurological or orthopedic)
- Adjust the positions:
  frog-leg position
  V-position
  elevate legs without abduction of the hips
  on their side

was approved by the US Food and Drugs Administration (FDA) in 2006. The Advisory Committee on Immunization Practices for the CDC recommends routine vaccination of females aged 11–12 with three doses of the quadrivalent HPV vaccine.[18] The vaccine series may be started as early as age 9 years. Catch-up vaccination is recommended for females between the ages of 13 and 26. Ideally, the vaccine should be administered before any exposure to HPV, when efficacy is highest. There is no literature on the use of the HPV vaccine in girls with DD. All young women who choose to enter a sexual relationship should be encouraged to receive the vaccine series. For young women who are moderately to severely cognitively impaired, the decision should be made on an individual basis, after education of family and caregivers. Because of the increased risk for sexual assault and the difficulty sometimes encountered in performing cervical cancer screening, the vaccine series may be deemed appropriate for many of these patients.

COMMON ISSUES ENCOUNTERED IN GIRLS WITH DD

BLEEDING ISSUES AND CONTRACEPTION

The most common gynecological reason for the disabled and non-disabled teenager to see a care provider is abnormal uterine bleeding.[3,19]

When the patient comes in with a complaint of abnormal bleeding, the following four issues need to be addressed: Is the bleeding abnormal for the teenage period? Is it possibly medically unhealthy? Does it negatively affect the patient and her daily activities? and are there concerns regarding sexuality, abuse, and pregnancy?

Asking these four questions will lead to a discussion as well as a treatment plan.

IS THE BLEEDING ABNORMAL?

Bleeding irregularities are common in all teens, with 85% of all cycles anovulatory during the first year after menarche.[20] This irregularity is not necessarily an indication of a problem. Often the tolerance for abnormal bleeding (irregular or heavy) is lower in the families of girls with DD, due to the difficulty of managing the cycles.

There are several specific conditions in girls with DD that may make it more likely that bleeding is irregular. These factors include medication use, thyroid disease or weight issues. Women with epilepsy have an increased incidence of reproductive endocrine disorders, including irregular menstrual cycles, anovulatory cycles, amenorrhea, and oligomenorrhea.[21] Polycystic ovarian syndrome occurs in 10–20% of women with epilepsy compared with 5–6% in the general population, and women on valproic acid may have an even higher incidence of up to 60%.[22–24] Neuroleptics and metoclopramide can cause hyperprolactinemia that can lead to abnormal bleeding and ultimately to amenorrhea due to a hypoestrogenic state. Thyroid disease, which can lead to subsequent disturbance of the cycle, is more prevalent in women with Down syndrome.[25] Poor food intake, swallowing problems, and potential need for gastric tubes are other problems seen frequently in the mentally disabled and can lead to low weight and oligomenorrhea or amenorrhea. Care should be taken not to confuse irregular menses during the first year after menarche with chaotic irregular cycles, which may be a sign of disease.

IS THE BLEEDING MEDICALLY UNHEALTHY?

Bleeding is only considered medically unhealthy if it leads to anemia, which is fairly uncommon in teens. In the differential diagnosis consider anovulation, poor food intake (leading to iron deficiency) or bleeding disorders like Von Willebrand disease, and platelet disorders (see Chapter 11).

IS THE BLEEDING NEGATIVELY AFFECTING THE PATIENT AND HER DAILY ACTIVITIES OR HER FAMILY AND CAREGIVERS?

This is often a difficult issue to assess and may lead to a complex discussion with the caregivers.

Many times the families of children with disabilities have a very delicate balance in their lives and menarche may disturb that. The care provider (sometimes, with help of social work or counselors) needs to assess the issues and decide with the patient and their family whether intervention is warranted. Issues may include menstrual hygiene or behavioral changes with the cycles, and menstrual suppression may be the appropriate intervention for these patients and families.

ARE THERE CONCERNS REGARDING SEXUALITY, ABUSE, AND PREGNANCY?

If there is a concern for abuse, either within the surroundings or because the patient cannot be monitored closely enough or is unable to address boundaries well, contraception needs to be considered. The care provider should also assist with evaluation of a potential unsafe situation.

TREATMENT

The decision to medically treat the patient is usually based on an individual assessment of the heaviness and irregularity of the cycle, as well as the tolerance of the patient of the periods and the impact of the cycles on her daily activities. Once the decision is made to treat the patient, a treatment goal should be set. This can be: decrease heaviness of flow, relieve pain or symptoms, provide contraception, or to obtain amenorrhea.

Nonsteroidal anti-inflammatory drugs (NSAIDs). If menorrhagia is the main concern, the patient can be started on NSAIDs, alone or later in combination with other treatments, in appropriate doses, as that may decrease the flow by up to 20%.[26]

Combined contraceptives. If the goal of therapy is more control of the cycle, hormones can be started (Table 21.4). The contraindications for estrogen-containing pills are the same as in the general population. Extended cycling can be used if desired, especially if amenorrhea is a goal. Studies show up to a 90% amenorrhea rate after several months. There may be some troublesome spotting that can be addressed by taking two pills for several days or allowing periodic withdrawal bleeds.[27,28] Some data suggest that the risk for deep venous thrombosis (DVT) may be slightly higher in preparations with third generation progestins and in those patients with limited mobility.[29] DVT is a multifactorial disease with risk factors including immobilization, estrogen-containing hormones, and clotting disorders like factor V Leiden.[30] Immobilization (e.g. wheelchairs) is thought to increase the risk of DVT; however, one study on immobilized persons in wheelchairs did not confirm that.[31] Studies done on immobilization have mostly focused on air travel and have concluded that the hyperbaric hypoxia may be a more important factor than the immobilization.[32] Since factor V Leiden occurs in 5% of the population and is seen in 20% of patients with DVT, it may be prudent to check that level before instituting estrogen-containing medications for a patient in a wheelchair. In a review on who to screen for thrombophilic tendencies, recommendations were made to obtain a detailed family history before starting the oval contraceptive pill (OCP).[33] Recommendations for starting combined oral contraceptives (COC) would then be a low dose (30 μg or less) of ethinyl estradiol in combination with a first or second generation progestin.

In patients for whom swallowing is an issue, the *transdermal patch* can be considered, although there is more estrogen exposure with these and recent studies suggest a twofold increase in DVT compared with norgestimate-containing oral contraceptives (40.8 vs 18.3/100 000 woman-years).[34] If the patient has more risk factors for DVT, such as immobilization, one may consider not using the patch. The patch can also cause a skin reaction as well as some issues with patients pulling it off, especially if the patient has heightened skin sensitivity. Placing it out of range on the lower back may be helpful.

The *vaginal ring* is usually not a good option, due to the difficulty and privacy issues with application. Data on ultra-low dose oral contraceptives (20 μg ethinyl estradiol pills) suggest less bone building with these pills; however, no direct comparison

Table 21.4 Contraceptive methods

Barrier methods (i.e. foam and condoms, cervical caps, sponges, and diaphragms)
- Advantage: protects against sexually transmitted infections
- Concern: rarely able to use secondary to a high degree of personal initiative, intellectual understanding, and physical dexterity required

Intrauterine devices
- Advantage: decrease flow and discomfort
- Concerns:
  1. Inability to report pain or discomfort (complications)
  2. Usually requires anesthesia for insertion

Oral contraceptives
- Advantages:
  1. Decrease in flow and cramping
  2. Extended cycling helpful
- Concerns:
  1. Requires supervisor to administer pills
  2. Women with cardiac and vascular flow abnormalities may increase chance of clotting (consider echocardiogram in women with Down syndrome before oral contraceptive use)
  3. Use of anti-seizure medication may necessitate higher estrogen content
  4. Unclear: wheelchair users and risk of deep vein thrombosis (DVT)

Patch
- Advantages:
  1. Easy to use
  2. Decrease flow and cramping

Concerns:
1. Not studied in this population
2. Patient may pull it off (place on back)
3. Skin irritation
4. Weight limitations
5. More risk for DVT

Ring:
- Advantage: Use every 3 weeks
- Concern: Difficult to place (privacy issues)

Intramuscular medroxyprogesterone (i.e. Depo-Provera)
- Advantage: Often amenorrhea
- Concerns:
  1. Weight gain (may make transfers more difficult)
  2. Long-term use and bone loss

Medroxyprogesterone subcutaneously:
- Advantage: Amenorrhea at 12 months 52–64%; 24 months 71%
- Concerns:
  1. Weight gain (may make transfers more difficult)
  2. Bone density not clear at this point

Progestin only pills
- Advantage: Can be used in women with estrogen contraindications
- Concerns:
  1. More breakthrough bleeding
  2. Less safe for pregnancy prevention

(*Continued*)

Table 21.4 (*Continued*)

Subdermal levonorgestrel implants (i.e. Implanon)
- Advantage: No intervention for 3 years
- Concerns:
  1. Not studied in women with DD
  2. More irregular bleeding (14–20% amenorrhea, 25% abnormal uterine bleeding)

Sterilization
- Consider use of ethics or advisory committee to review sterilization requests
- ACOG (2005) and AAP (2007)
  1. Identify appropriate decision maker
  2. Consider alternatives
  3. Best interest of patient with MR
  4. Legal implications

studies have been done with the 30 and 35 μg ethinyl estradiol pills.[35]

Progestin-only methods. Oral progestins can be used in a variety of settings. The progestin-only pill has a low dose of norethindrone and can cause significant spotting, which may be an undesired side effect. Higher doses of medroxyprogesterone acetate, megestrol, and norethindrone have been used with complete suppression of the cycles. Side effects of these medications include weight gain and mood changes, with megestrol increasing appetite as well.

Although the use of the progestin-releasing intrauterine devices and systems has not been advocated in general for teenagers due to the theoretical potential increase in infection risk, it may be an option for girls with DD. The levonorgestrel intrauterine system has been used for menstrual suppression in perimenopausal women, but this is an off-label indication.[36] In this population, the insertion may have to be done under anesthesia.

Implanon, the implantable etonogerstrel rod, has not been studied in women with DD, and although some women experience amenorrhea, it causes significant irregular bleeding, which makes it less desirable.[37]

Intramuscular (IM) medroxyprogesterone has been used extensively for amenorrhea (around 70%) and birth control. There are two main issues with this for women with DD. The first one is weight

gain. Both subcutaneous and IM depot medroxyprogesterone in patients aged 18–35 years in a large study led to a weight increase of 4.5 and 5.8 kg after 3 years, irrespective of age and body mass index (BMI), but the researchers acknowledged large individual variations.[38] Increasing weight for women who rely on transfers by themselves or others may significantly affect the patient's life.

The second concern is the issue of bone loss. Depot medroxyprogesterone acetate (DMPA) is associated with bone loss, due to its suppression of estrogen. There is early evidence to suggest that some bone returns after stopping the suppression and some studies suggest that most of the loss occurs in the first 2 years.[35] The effect of steroid contraceptives on fractures in the general population has not been adequately researched.[39] A study on women with DD revealed that they appear to have a higher incidence of decreased bone mineral density (BMD) and suggests a twofold increase in fractures in women on either DMPA or antiepileptic medications.[40] Currently the recommendation is still to continue use in adolescents, but consider bone density testing at an earlier age.[41] Data on bone density and the newer subcutaneous preparation of DMPA are not available at this time.

The issue of wheelchair use itself and bone density has not been researched extensively; one study from Europe suggested decreased bone density, however, this was a small sample.[42] There is a suggestion that with low calcium intake (below the recommended 1200–1500 mg/day) and vitamin D, peak bone mass may not be reached, so adequate intake of calcium and vitamin D is very important.

For contraceptive purposes hormonal methods are used most frequently in this population, as the barrier methods may be difficult to use (Table 21.4).

USE OF ANTIEPILEPTIC MEDICATIONS AND HORMONES

Since antiepileptic drugs (AEDs) are so common in teens with DD, we will address this issue separately. AEDs that induce the hepatic cytochrome P450 system can decrease serum concentrations of estrogen and progestin in combined OCPs (Table 21.5).[43] The decline in serum concentrations of estrogen and progestin can lead to decreased contraceptive efficacy and inability to control a normal bleeding pattern. It is estimated that the efficacy of combined oral contraceptives decreases from approximately 0.1% failure rate with perfect use to 2.5% failure when combined with enzyme-inducing AEDs.[43] In addition, women taking combined OCPs and lamotrigine have been shown to have decreased serum concentrations of lamotrigine and may need dose adjustments of lamotrigine when the medications are prescribed together.[44,45] The progestin-only pill has been found to have decreased efficacy and therefore is contraindicated in women on enzyme-inducing AEDs.[46] Implanon is not recommended for use in women with seizure disorders either. However, DMPA appears to be an effective option in women using enzyme-inducing AEDs, but it is recommended that the dosing interval be decreased to every 10 week injections.[47] The levonorgestrel-releasing intrauterine system is also a good option for contraception in women on AEDs because the progesterone primarily acts locally at the uterus and cervix.

Table 21.5 Interaction of antiepileptic medications with oral contraceptive pills (OCPs)

Decrease OCP efficacy	Do not affect OCP efficacy
Carbamazepine (Tegretol)	Gabapentin (Neurontin)
Felbamate (Felbatol)	Levetiracetam (Keppra)
Phenytoin (Dilantin)	Lamotrigine (Lamictal)
Phenobarbital	Tiagabine (Gabitril)
Primidone (Mysoline)	Valproate (Depakote)
Oxcarbazepine (Trileptal)	Zonisamide (Zonegran)
Topiramate (Topamax)	

Do not forget to discuss emergency contraception with patients, as they may have an unplanned sexual encounter and families need to be aware of this option.

Usually hormonal treatment is adequate to address the issues of abnormal bleeding as well as

contraception, although several different options may need to be used. There are several surgical approaches for bleeding issues, which include endometrial ablation or hysterectomy,[48] that can be used in teens with DD. However, these are unusual measures that are seldom necessary. It is important to know the legal and ethical aspects of these methods, as often this also renders the patient sterile.

MOOD DISORDERS

Premenstrual symptoms (PMS) are described in up to 90% of women of childbearing age, with less than 10% having premenstrual dysphoric disorders (PMDD, the severe form of PMS). PMS is described as a menstrual-related mood disorder or cyclical behavior changes that are a combination of behavioral and physical symptoms that occur cyclically only during the luteal phase and disappear at or within the first few days of menstruation. Cyclical behavior changes are a fairly common complaint in women with DDs. In one study 18% of women with DD were found to present with cyclical behavior changes.[49] In women with DD these may include symptoms of temper tantrums, crying spells, autistic behavior, self-abusive behavior or seizures. The diagnosis of cyclical behavior changes is made by documentation. ACOG recommends that one of the described symptoms in the affective and somatic categories has to be present in the 4 days before menses and not reoccur until 12 days before the next cycle in three consecutive cycles.[50] For women with DD it is more practical to track the most difficult behavior on a daily symptom chart for 3 months. Since most teens with DD still live at home, the parents and teachers are requested to do this. The purpose of the documentation is to determine the true cyclic nature to rule out other behavioral, mood or psychiatric disorders. It is also very helpful to document treatment outcomes. In women who may not be able to communicate their feelings, behaviors may be an outlet for pain. Dysmenorrhea is very common in teens and 10–45% of teens miss school due to their periods.[51]

No single therapy has been found to be always successful in treating cyclical behavior disorders.[52] The usual first-line treatments such as dietary and lifestyle changes are often difficult to administer in teens with DD. The first line of treatment for women with DD is an NSAID in adequate doses to start on the day of start of the behavior. This was found to be successful in 65% of 45 patients with cyclical behavior changes.[49] If that approach is unsuccessful, ovulation suppression may be tried. Several studies suggest that an oral contraceptive with drospirenone may be helpful.[53] Complete suppression with DMPA has also been used, although no data are suggestive that progestins are very helpful. Success of these treatments in women with disabilities has not been well studied.

Selective serotonin reuptake inhibitors (SSRIs) have not been used for this indication in women with DD, but are among the first-line therapy in women with severe PMS and PMDD.[54] However, there has been an FDA advisory warning for an increased suicide risk for teens on antidepressants and only fluoxetine is FDA-approved for teenagers with depression. If this treatment is a consideration for a particular patient with troubling behaviors, then the initiation should be done in consultation with a psychiatrist and/or a neurologist because of the potential for suicide and drug interactions.

CATAMENIAL SEIZURES

Epilepsy is a common comorbidity in young women with developmental disabilities. Overall 10–20% of women with DD have epilepsy; however, this rate is up to 50% in women with severe mental retardation.[55] Women with epilepsy may have variability in seizure frequency secondary to hormonal fluctuations throughout the menstrual cycle, a condition known as catamenial epilepsy. Estimates vary but up to 75% of women with epilepsy may be affected by these catamenial seizures.[56]

Varying definitions of catamenial epilepsy exist (Table 21.6). Herzog et al described three different patterns of increased seizure frequency including periovulatory, inadequate luteal phase,

Table 21.6 Catamenial epilepsy

Diagnosis
• Menstrual and seizure calendar
• At least twofold increase in seizure frequency, either ovulatory, luteal phase or perimenstrual
Treatment
• Acetazolamide
• Clobazam (not available in USA)
• Natural progesterone suppositories or lozenges in luteal phase
• Oral or IM medroxyprogesterone
• No data on extended cycle oral contraceptive pills, but anecdotal success

and perimenstrual.[57] The perimenstrual form, with increased seizure frequency 3 days before the onset of menstruation and ending 4 days after the onset, is the most common form of catamenial epilepsy. One basic theory states that seizure frequency is altered in women with catamenial epilepsy secondary to fluctuations in endogenous hormone levels. Estrogen is known to increase neuronal excitability, decrease seizure threshold, and act as a proconvulsant. Progesterone, on the other hand, increases seizure threshold and acts as an anticonvulsant. Other mechanisms may be involved in altering seizure frequency including changes in adrenal hormones, androgens, fluctuations in AED levels, and changes in water and electrolyte balance.[58] Regardless of the mechanism, these women with catamenial epilepsy experience a twofold or greater increase in seizure frequency at one of these times during their menstrual cycle and approximately 30% may have refractory seizures.[58]

Despite the high incidence of catamenial epilepsy, there are few studies investigating treatment for this disorder. Acetazolamide, an inhibitor of carbonic anhydrase, has been used for approximately 50 years to treat catamenial epilepsy.[59] In a retrospective study of 20 women with catamenial epilepsy treated with acetazolamide, 40% had a decrease in seizure frequency. There was no difference in efficacy between those women who used acetazolamide continuously and those who took the medication in a cyclic fashion.[60] There are reports of tolerance to acetazolamide that may support cyclic use. The initial dose of acetazolamide is 4 mg/kg in one to four divided doses.

AEDs have not been studied in a cyclic fashion specifically for treatment of catamenial epilepsy. Clobazam, a benzodiazepine not currently available in the United States, is the only traditional seizure medication that has been studied; 78% of 24 patients had a reduced seizure frequency on clobazam.[61]

Because the suspected pathophysiology of catamenial epilepsy includes hormonal fluctuations, another management strategy is treatment with hormonal medications. The few studies that have been published suggest that progesterone administration may be beneficial. Approximately 70–75% of 48 women had decreased seizure frequency with the use of natural progesterone suppositories and lozenges at a dose of 100–200 mg three times daily for 14 days of the month during the luteal phase of the menstrual cycle.[62–64]

Medroxyprogesterone acetate has been studied orally as well as IM, but with less favorable results. In a study of 14 women with catamenial epilepsy, initial treatment was with oral medroxyprogesterone acetate 20–40 mg/day to induce amenorrhea. If oral treatment did not produce amenorrhea then patients were treated with DMPA 120–150 mg IM every 6–12 weeks. A 39% seizure reduction was noted after 1 year of use.[65]

Despite their frequent use in women of childbearing age, OCPs have not been systematically studied for treatment of catamenial epilepsy. There is no evidence that use of combined OCPs in women with epilepsy increases seizure frequency. The only oral contraceptive product studied for treatment of catamenial epilepsy was a progestin-only pill with noresthisterone, which was found to be ineffective.[66] Theoretically, using a combined oral contraceptive pill in a continuous fashion would create a stable, steady-state hormonal milieu and possibly decrease seizure frequency related to endogenous hormonal fluctuations; however, this has yet to be studied.

Other hormonal medications, such as clomiphene citrate, GnRH agonists, and danazol have been shown to be effective in reducing seizure frequency in women with catamenial epilepsy.[67–70] Side effects, long-term complications with BMD, androgenic effects, and cost limit their usefulness. Newer treatment options including a neurosteroid, ganaxolone,

have shown promising results in preliminary studies, but further investigation is necessary before clinical use.[71]

Overall the teens with developmental disabilities pose a diagnostic and treatment challenge for their gynecological care, with regard to menstrual function. Working with the teen and the family usually results in a satisfying solution of the problem through education, counseling, and medical treatment as indicated.

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22. Contraceptive dilemmas for adolescents with chronic medical conditions

Janice L Bacon

Today's young women have a wider choice of contraceptive methods and formulations than ever before (Table 22.1). The increasing body of contraceptive research has resulted in the identification of non-contraceptive benefits and the enhanced role of contraceptives to assist in managing many medical conditions. Current methods have an excellent efficacy and safety profile as well.

The risks and benefits of a contraceptive must be considered in each patient. In young women with chronic medical conditions, the disease process, its complications, and medications used to treat the medical disorder may alter the efficacy or risks of a particular contraceptive method. However, it must be recognized that the current and long-term risks to a patient who fails to use contraception or appropriately manage her menses may be more severe, even life-threatening. Also, an unplanned pregnancy may place her fetus at risk for teratogenesis or unfavorable outcome. So, if the benefits of contraceptive use are less than the risks associated with contraception, this should be clearly stated to the adolescent and her parent or guardian.

Confidentiality is of great concern to many adolescent women. Those women with medical conditions or disabilities will experience the developmental stages of adolescence and the exhibition of risk-taking behaviors, but because of their reduced autonomy and medical dependence, they may take greater risks. The limits of confidentiality must be discussed with teens and their parents or guardians. Knowledge and understanding of individual state or national regulations will assist in this discussion. Parental desires and teen wishes may conflict, and a failure to resolve these can result in reduced compliance and thus benefits or patients may be lost to future care.

Traditional teaching in gynecology suggested that the initiation of contraception required a complete pelvic exam – genital inspection, speculum visualization of cervix and vagina, and bimanual exam. This should no longer be required for the initiation of birth control or menstrual management. In fact, more than one visit may be needed before a young woman is comfortable enough to tolerate a pelvic examination. The initiation of testing cervical cytology and exclusion of sexually transmitted infections must be individualized and timed according to other gynecologic needs and the onset of sexual activity. The availability of detailed ultrasound imaging allows inspection of the pelvic structures by abdominal, transvaginal or transperineal routes. MRI or CT testing may also be useful imaging modalities if pathologic findings are expected.

The physical exam of the young woman initiating contraception may be individualized, but should include measurement of blood pressure and determination of body mass index (BMI) followed by examination of the thyroid, breast, heart, abdomen, and other specific anatomic systems according to the individual's medical history.

A careful past medical and surgical history, social history, and family history will be imperative in the prescribing of contraception to adolescent women with chronic medical conditions. Some common medical disorders encountered in contraceptive prescribing teenaged patients are listed in Table 22.2.

Medical history may dictate those methods that may be relatively or absolutely contraindicated. The personal needs and desires of young women should be considered (Table 22.3).

Laboratory testing should pertain to the current medical condition or be used to exclude undiagnosed

Table 22.1 Contraceptive methods

Hormonal – combined estrogen/progestin	**Non-hormonal contraceptives**
Oral contraceptives (mono or multiphasic) (OCPs)	Male condoms
Transdermal contraceptive patch	Female condoms
Vaginal contraceptive ring	Diaphragm
Hormonal – progestin-only	Contraceptive sponge
Oral contraceptives	Spermicides
Depot medroxyprogesterone acetate (DMPA)	Copper-containing intrauterine device (IUD)
Levonorgestrel-releasing intrauterine system (LNG-IUS)	
Contraceptive implant	

Table 22.2 Important historical questions for prescribing contraception

- Thrombophilias/bleeding disorders
- Liver/gallbladder disease
- Hyperlipidemia
- Hypertension
- Glucose intolerance – diabetes
- Physical/mental disabilities
- Seizure disorder
- Inherited metabolic disorders
- Eating disorders

Table 22.3 Contraceptive questions for teens

1. What family or past personal medical concerns should we consider when choosing your contraceptive?
2. Are you using your contraceptive method for birth control, for treatment of medical conditions, or for management of menstrual problems?
3. Are you interested in a particular contraceptive? – Why?
4. What experience (good or bad) have you had with contraceptive methods in the past?
5. Are there any contraceptive methods you would not want or feel comfortable using?
6. Do you have any other concerns about contraceptives? (e.g. weight gain, future fertility, costs)

medical conditions indicated by symptoms or family history (i.e. thrombophilias, glucose intolerance, hypertension).

When a contraceptive method is chosen, it is best to include discussion about the following topics:

- Common myths and misconceptions (e.g. the myth that hormonal contraception causes cancer)
- Expectation of effects on medical conditions of a contraceptive method
- Common side effects and management strategies of the contraceptive method.

All except the youngest adolescents are generally capable of understanding the risks, benefits, and use of contraceptive methods. Counseling the teen and an accompanying adult or friend may enhance compliance and allow patients a comfortable environment in which to ask questions. Young women can be informed that alternative methods are available if the initial choice is unsatisfactory. A follow-up appointment is recommended to address side effects and complications, thus enhancing compliance.

The prescribing of contraceptives for birth control or medical management of menses to adolescent women with chronic medical disorders requires special consideration of the disease process, disease complications if present, and medical treatment currently prescribed.

The remainder of this chapter is devoted to a discussion of common medical conditions encountered in adolescent women and information used to assist contraceptive prescribing.

CYSTIC FIBROSIS

Adolescents with cystic fibrosis (CF) may experience a delay in the onset of puberty and menarche, with a mean delay of 2 years. This delay of hypothalamic function affects the release of gonadotropin-releasing hormone (GnRH), and may be experienced even by healthy adolescents with CF. These teens, however, experience the same development of sexual interest and onset of sexual activity as their non-affected peers. When desiring reproduction, these teens display evidence of near normal fertility, although the time of pregnancy represents a period of special needs for these women. The risks of contraception must be weighed against the risks of an unplanned pregnancy.[1]

Continued observation and research in women with CF practicing contraception reveals a wide

range of safe and effective choices. Risk of contraceptive use may vary according to individual medical history, but no methods are particularly preferred or contraindicated in women with CF.

Some medical conditions such as gallbladder disease, due to viscous secretions, may be more likely in patients with CF. In these patients, combined oral contraceptives, progestin-only oral contraceptives, depot medroxyprogesterone acetate (DMPA) and levonorgestrel-releasing intrauterine system (LNG-IUS), reveal that risks generally outweigh benefits (WHO Category II). The benefits outweigh the risks after cholecystectomy.[2]

Combination oral contraceptive pills (OCPs) and progestin-only formulations are recommended choices for adolescents with CF, if no other medical conditions are identified. They neither exacerbate pulmonary dysfunction nor provide less effective contraception in women with CF compared to their healthy peers. Progestin-only methods are suitable for patients with CF, including patients with pulmonary hypertension. With the exception of DMPA, however, progestin-only methods may be affected by liver enzyme function and drugs that induce the P450 liver enzyme system. Concerns that progestins in patients with CF could have increased bronchial mucus thickening, resulting in impaired lung function, have not been substantiated nor has decreased lung function been observed.[3]

Progestin-only methods, except DMPA, maintain estradiol levels above those seen in the early follicular phase – thus allowing the normal adolescent increases in bone density. Women with CF have demonstrated deficits in bone mineral density (BMD) resulting in premature osteopenia and osteoporosis, so caution must be advised when prescribing DMPA, with consideration for bone density testing before administration or at periodic intervals.[3] The new contraceptive implant containing etonogestrel may also be a suitable choice for patients with CF.

Intrauterine devices (IUDs), both LNG-releasing and those containing copper, represent viable choices for patients with CF. Barrier methods are advised for all adolescent females, to prevent sexually transmitted infections (STIs) and assist contraceptive efficacy when combined with another method. Emergency contraceptive regimens are also efficacious.

HYPERTENSION

Most contraceptive users with hypertension are adults. However, a small but significant number of adolescent women have hypertension, especially associated with other chronic medical conditions such as systemic lupus erythematosis (SLE), diabetes mellitus or renal disease. Current scientific data generally have assessed adult females in greater numbers than adolescents, but physiologic extrapolation may be considered. Adolescents with hypertension enjoy normal fertility. Pregnancy in adolescent women may be associated with an increased incidence of pre-eclampsia. Hypertension with vascular sequelae may also be associated with an increased risk of deep venous thrombosis (DVT).

The American College of Obstetricians and Gynecologists (ACOG) clinical management guidelines for use of hormonal contraception in women with co-existing medical conditions recommend consideration of combined oral contraceptives in women less than 35 years old whose hypertension is well controlled on medication and who have no other contraindications to combined hormonal contraception. Complications and risks of combination oral contraceptives in women with hypertension relate to the number of years of disease and the development of vascular abnormalities. Risks include myocardial infarction and stroke. Risks associated with combination OCPs may be minimized by normalization of blood pressure before initiation of contraception and close follow-up.[4] Rarely, combined OCPs may be associated with mild worsening of hypertension. In contrast, progestin-only hormonal methods are not associated with alterations in blood pressure or an increased risk of complications from hypertensive-associated disorders.

Therefore, progestin-only hormonal contraception may represent an alternative class of contraceptives with improved safety and excellent efficacy for

adolescents with hypertension. Contraindications listed in the package insert are primarily historical, as progestins are not associated with increased vascular or cardiac risks. No change in blood pressure has been documented in women using DMPA, progestin-only OCPs, the LNG-IUS, or the contraceptive implant.

The copper-bearing IUD and barrier methods are also good choices in adolescent women with hypertension. Emergency contraception may be satisfactorily employed.

DIABETES MELLITUS

Adolescent women may have type I (insulin-dependent) or type II (adult onset) diabetes mellitus. Anovulation may be associated with either type of diabetes, especially when the disease process is poorly controlled. Women with obesity and diabetes mellitus may develop insulin resistance and this may be accompanied by elevated androgens. Both anovulation and androgen excess may affect fertility and increase the risk of early pregnancy loss. Improved glucose control with normalization of hemoglobin A1C may increase the rate of conception and improve fetal outcome, while decreasing the risk of fetal teratogenesis. When well controlled, fertility may be achieved by most women with diabetes mellitus. Assistance with ovulatory regulation, preconceptional planning, and pregnancy care in a high-risk setting with re-evaluation of diabetic control postpartum, are essential. Most adolescent women have not yet developed the vascular, retinal, or renal complications of diabetes, but if present, these pose additional contraceptive and pregnancy risks.

Contraception is thus an issue in both managing a young woman's reproductive potential and protecting her from unplanned pregnancy. Few data are available for the adolescent population specifically, but may be extrapolated from study of the physiology in adult and older women. Contraceptive risks relate to the duration of diabetes diagnosis and associated illnesses – thyroid disease, renal disease, hypertension, and vascular complications.

In teens whose diabetes mellitus is complicated by hypertension or vascular sequelae, the risks and contraindications to contraceptive choices are similar to those in older women. In these young women, progestin-only contraception and non-hormonal contraceptive choices are recommended to minimize venous thrombolic events, or worsening hypertension.[2] Young women with type II diabetes mellitus often have insulin resistance and elevated androgens. In these patients, combined estrogen and progestin hormonal contraceptives assist with normalization of testosterone levels and the reduction of long-term sequelae, such as acne or hirsutism. They therefore provide efficacious contraception as well as important non-contraceptive benefits. Women with insulin-dependent diabetes without vascular complications may also use combined hormonal methods.[2] In both of these groups of women, combined oral contraceptives do not alter metabolic control of diabetes, promote the development of complications of diabetes, or increase cardiovascular disease risks. One study of adult women determined a minor elevation of fasting blood sugars of no clinical significance.[4]

Progestin-only methods are a contraceptive choice for all women with diabetes mellitus, as well as for those with diabetic complications. Many of these women are obese as well, and care should be taken to weigh the risks and benefits of each choice for the individual patient. For example, DMPA may be efficacious, but is associated with unacceptable weight gain, which may alter diabetic control. Progestin-only contraceptive pills, the coantraceptive implant or LNG-IUS may be preferred in obese patients with diabetes.[2]

Hormonal contraceptives, which assist with menstrual regulation, may also be of benefit in diabetic patients with anovulation and thus at possible risk for endometrial hyperplasia.

Barrier contraceptives are recommended for all adolescent women, since patients with long-standing type I diabetes may have potential altered immunity. Combining methods may enhance contraceptive efficacy. IUDs, both LNG-IUS and the copper-bearing IUD, are satisfactory choices for

these women. Emergency contraception may be employed if needed.

EPILEPSY

Adolescent women with seizure disorders – congenital or acquired – represent a small but significant portion of the population of teens needing contraceptive protection to prevent unplanned pregnancy. Although most research findings have been obtained from adult women, extrapolation may be made to younger women.

Current antiepileptic drugs (AEDs) can be divided into two groups – older medications which stimulate the P450 liver enzyme activity (thus potentially altering serum estrogen or progestin levels of oral contraceptives), or newer pharmacologic preparations, which would not affect the serum levels of contraceptives. An actual decrease in efficacy from the use of combined hormonal contraceptives and AEDs due to the enhanced liver enzyme activity has not been scientifically proven, but remains a theoretical concern. Compensation may be made by choosing a hormonal combination with 50 μg of ethinyl estradiol combined with a progestin. No higher estradiol doses are available for the transdermal patch or vaginal ring. Lamotrigine levels may be reduced by combination hormonal preparations. Women using a hormonal contraceptive plus this AED may require periodic evaluation of lamotrigine levels. Non-cyclic administration of combined estrogen and progestin hormone contraception may further assist the prevention or reduction of catamenial seizures while increasing contraceptive efficacy and non-contraceptive benefits.

Women with epilepsy have a decreased rate of conception and birth. This is a multifactorial event and potential etiologies include alterations of the hypothalamic-pituitary-ovarian axis or an adverse effect on libido. Side effects of medication may alter ovulatory status and create a clinical picture similar to polycystic ovary syndrome (PCOS). Newer AEDs do not produce this clinical scenario and may be preferred.

Traditional research has indicated that estrogens may stimulate a seizure focus and progesterones reduce the number of seizures. The use of ethinyl estradiol in combined hormonal contraceptives has not been demonstrated to increase seizure activity. However, progestin-only preparations, especially DMPA, may actually improve seizure control, not only by inducing anovulation and maintaining consistent serum levels, but by acting centrally on the seizure foci as well.[5] There are no data available regarding the effect of the progestin-only contraceptive implant on seizure activity, but physiologic understanding of etonogestrel and its decreased serum levels in the face of increased activity by the liver P450 enzymes system should raise concern about this as a choice for women on AEDs. All of the hormonal contraceptives may be used to assist menstrual regulation, if that is the primary goal, rather than contraception.

The copper IUD is a safe and effective contraceptive choice for adolescent women with epilepsy. No data are available for the LNG-releasing IUS. Barrier methods to decrease the risk of STIs and assist contraceptive efficacy are recommended. Emergency contraception may be used.

SICKLE CELL DISEASE

Sickle cell disease represents another medical condition that can benefit from appropriate contraceptive prescribing. Some adolescent women have experienced complications of this hematologic disorder, including gallstones, renal disease, and blood antibodies from multiple transfusions. Repeated pain crises may result in multiple hospitalizations and high levels of narcotic consumption.

Fertility remains generally intact for these young ladies, although they benefit from preconceptional counseling and close observation of mother and fetus during pregnancy. Following delivery, a review of interconceptional events and preconceptional disease manifestations allows the best decision for a birth control method providing excellent safety and efficacy as well as valuable non-contraceptive benefits.

Systemic progestin contraceptives, especially DMPA, provide a recommended birth control method. Studies have reported decreased numbers of crises and decreased intensity of pain crises. Fewer headaches and episodes of body weakness and improved hematologic parameters may also be benefits of DMPA. The venous thromboembolic risk of hormonal contraception combined with sickle cell disease appears primarily theoretical. Progestin oral contraceptive pills may also provide some systemic benefits, although substantial literature is unavailable. All of the progestin-only methods decrease menstrual blood flow, thus assisting with anemia management.

Although research information is available for OCPs alone, the transvaginal patch and contraceptive ring should be physiologically similar. Combined estrogen and progestin oral contraceptives do not adversely affect the patient's platelet activity, thrombin generation, fibrinolysis or red cell deformities.

IUDs, both copper-bearing and LNG-releasing, represent good choices for adolescent women with sickle cell disorders, as do combined estrogen and progestin contraceptive methods. Barrier methods always represent an important addition to a chosen contraceptive regimen as well as providing the reduced risk of STIs in this group of young women whose immune system may perform less than optimally. Emergency contraception may be used.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Contraceptive research regarding risks and benefits of contraceptive options is confined to the adult female population with SLE, but could generally be extrapolated to young women. Adolescent females have fewer complications, particularly hypertension, lupus nephritis, and vascular disease. Most important, before the determination of a contraceptive choice, is the detection of a lupus anticoagulant or anticardiolipin antibodies, since their presence greatly increases the risk of vascular complications during contraceptive use and pregnancy.

Preconceptional evaluation and high-risk pregnancy care may result in a good outcome for mother and baby. Contraception or pregnancy is best begun when the disease is quiescent. Fertility is not impaired.

Clinical presentation or family history may suggest the need to exclude SLE in a patient before initiating contraception. A family history of venous thrombolic disease without a specific personal history of thrombosis or thrombophilia may not increase risks from the use of estrogen and progestin contraceptives. Benefits and risks must be weighed in each individual situation. Older literature suggested estrogen as a causative agent in lupus 'flares,' but current formulations do not confirm this finding. Combined oral contraceptives or transdermal methods are good choices for patients with inactive SLE and no other medical contraindications.[6,7]

When a lupus anticoagulant, anticardiolipin antibodies, hypertension, nephritis or vascular complications are present progestin-only contraceptive methods are commended. These provide both safety and efficacy as well as non-contraceptive benefits. Emergency contraception is also an option if needed for women with any stage of SLE. IUDs, copper-bearing and LNG-releasing, represent good options too.

THROMBOPHILIAS

An adolescent female with a personal history of a thrombophilia requires special consideration when choosing a contraceptive method. A family history of a thrombophilia or repetitive, thrombotic events, such as DVT or pulmonary emboli, may prompt an evaluation for thrombophilia before initiating a hormonal contraceptive containing both estrogen and progestin. Screening for thrombophilias before contraceptive initiation is not currently required, but may be individualized for some families. Most adolescents with a positive family history of thrombophilias will not have clotting events while using contraceptives containing estrogen.[4] Data are primarily confined to combined hormonal

contraception, but physiologically, this may be extrapolated to transdermal combined methods as well. Progestin contraceptives may be most highly recommended for those women at increased risk due to personal diagnosis of a thrombophilia, remembering that unplanned pregnancy causes the highest thromboembolic risk of all. Despite historical package warnings about progestin-only contraceptives and the risks of VTE, the evidence to support this risk is lacking.

Thrombophilias do not alter or impair fertility, but pose a need for high-risk pregnancy care and appropriate initiation of anticoagulants to decrease the risk of clotting and embolic events.

IUDs and hormonal contraceptives are also satisfactory choices, while barrier methods supplement efficacy and reduce STIs. Additional risks for thrombotic events in adolescent women are obesity, hypertension, and diabetes. Emergency contraception may be utilized.

BLEEDING DISORDERS

Hematologic disorders resulting in a failure to produce adequate clotting factors or platelets, or associated with abnormal function of the clotting cascade or abnormal platelet function, may result in life-threatening hemorrhage at the time of menses. Many of these disorders present at menarche. Starting hormonal contraception before or at the time of menarche and administration in cyclic or non-cyclic regimens has provided huge advantages for menstrual management as well as providing non-contraceptive benefits. Non-cyclic administration of combination estrogen- and progestin-containing preparations has further improved menstrual control for many women as well as providing non-contraceptive benefits. Both progestin-only and combined estrogen and progestin contraception methods are satisfactory, and combined preparations may be associated with less breakthrough bleeding. The LNG-releasing IUS may also be a possibility in patients with bleeding disorders not involving platelet number or function. Barrier methods for STI prevention are recommended. Emergency contraception is effective.

CONCLUSION

Contraceptive prescribing for adolescent women considers both contraceptive and non-contraceptive benefits. Careful assessment of possible effects of contraception on medical conditions and their therapies must be considered. Tables 22.4 and 22.5 summarize suggested contraceptive methods for adolescent women with the medical conditions discussed in this chapter. Risks and benefits of specific methods must be considered along with placing risks in the appropriate context of a program to prevent unplanned pregnancy. Today's new contraceptive delivery systems pose additional exciting options for adolescent women.

Table 22.4 Medical conditions for which hormonal contraception may be appropriate

Estrogen and progestin combined contraceptive
Menorrhagia/bleeding disorders
Family history of thromboembolic disease with negative work-up
Hypertension – well controlled without vascular complications
Systemic lupus erythematosus (SLE), without flare and without antibodies
Progestin-only contraception
Migraine headaches with neurologic symptoms
Thromboembolic disease
Hypertension – poorly controlled or with vascular complications
Systemic lupus erythematosus (SLE) with vascular disease or APL antibodies
During lactation
Epilepsy
Lipid disorders
Cardiovascular disease (coronary artery disease, congestive heart failure)

Table 22.5 Contraceptive decision making for adolescent women with chronic medical disorders*

Medical disorder	Combined hormonal preparations	Progestin-only hormonal contraception	Non-hormonal contraception
Cystic fibrosis**	Recommended	Recommended	Recommended
Hypertension			
Controlled	3	2	1
Uncontrolled	4	2	1
With vascular disease	4	2	1
Diabetes			
Insulin-dependent	2	2	1
Non-insulin-dependent	2	2	1
With vascular disease	3/4	2	1
Epilepsy	1	1	1
Sickle cell disease	2	1	1
Systemic lupus erythematosus***			
Without lupus anticoagulant (LA) or vascular disease	Recommended	Recommended	Recommended
With LA or vascular disease	4	2	1
Thrombophilias	4	2	1
Bleeding disorders	Recommended	Recommended	Recommended
Note: IUDs used with caution			

1. A condition for which there is no restriction for the use of the contraceptive method. 2. A condition where the advantages of using the method generally outweigh the theoretical or proven risks. 3. A condition where the theoretical or proven risks usually outweigh the advantages of using the method. 4. A condition which represents an unacceptable health risk if the contraceptive method is used.
*Adapted from WHO Medical Eligibility Criteria for Contraceptive Use, 3rd edn. Note: author's interpretation of the contraceptive categories did not separately designate DMPA and LNG-IUS. Refer to reference 2 for complete details.
**Not classified by WHO.
***Recommend reading: NEJM 2005 Dec 15; 353(24): 2602–4.

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23. Obesity in adolescence

Nichole Zidenberg

INTRODUCTION

Obesity in adolescence has grown to epidemic proportions. The overweight adolescent faces unique challenges to her medical, psychological, and reproductive health. Early intervention is paramount to prevent short- and long-term morbidities associated with obesity. The goal of this chapter is to review the most timely and pertinent information for the overweight adolescent, as well as to provide prevention and treatment strategies for the practitioner caring for such a patient.

DEFINITIONS OF OVERWEIGHT AND OBESE

Body mass index (BMI) is the most widely used tool for assessment of obesity. The American College of Obstetricians and Gynecologists (ACOG) recommends that all adolescents be screened annually for eating disorders and obesity by determining weight and stature, calculation of BMI, and asking about body image and eating patterns.[1] One of the limiting factors in utilizing BMIs for classifying teens as 'overweight' or 'obese' is the inconsistent use of definitions in clinical practice and research. The American Obesity Association (AOA) defines adult obesity as a BMI of 30 (95th percentile) and overweight to correspond to a BMI of 25 (85th percentile).[2,3] The Centers for Disease Control and Prevention (CDC) avoid using the term obesity in adolescents and define every adolescent over the 85th percentile as overweight.[4] ACOG uses this latter definition. The term obesity is now used less frequently to avoid the associated negative connotations, especially for children and adolescents.

PREVALENCE AND TRENDS

In the past 25 years, the percentage of overweight adolescents has more than doubled. Approximately 30.4% of adolescents are overweight and 15.5% are obese. Female and male adolescents have similar rates of being overweight at 30.2% and 30.5%, respectively. Overweight children, aged 10–14, with at least one overweight parent, were reported to have a 79% likelihood of being overweight adults.[2]

According to NHANES 1999–2000 data, 15% of children and adolescents aged 6–19 years were considered overweight; an additional 15% were 'at risk' for becoming overweight. In total, 30% of children and adolescents were either overweight or at risk of becoming overweight. Only approximately 6% of children and adolescents were considered overweight in the NHANES study conducted in 1972–1974 (Figure 23.1).

Adolescents who are overweight have a significantly higher prevalence of moderate to severe asthma when compared with a peer group.[5] Caucasian overweight girls are more likely to develop a negative body image and are at greater risk for the subsequent development of eating disorders. Adolescent females who are overweight have reported experiences with stigmatization such as direct and intentional weight-related teasing, jokes, and derogatory name calling, as well as less intentional, potentially hurtful comments by peers, family members, employers, strangers, and health-care providers. Overweight adolescents report negative assumptions being made about them by others, including that they are inactive or lazy, are stronger and tougher than others, do not have feelings, and are unclean.[2]

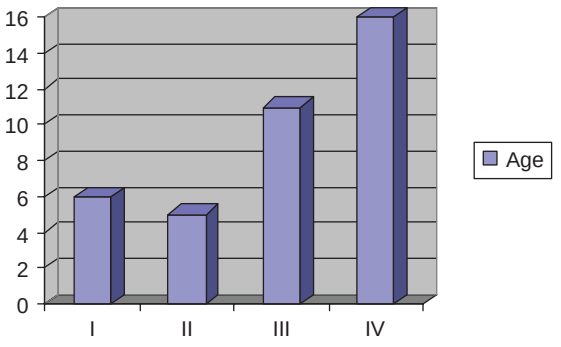

Figure 23.1 NHANES data[41] on overweight children and adolescents. I: NHANES I 1972–1974; II: NHANES II 1976–1980; III: NHANES III 1988–1994; IV: NHANES 1999–2000.

Among adults who were overweight during childhood, there is an increased relative risk of 1.5 for all-cause mortality and 2.0 for cardiovascular disease mortality.[6] Hypertension, sleep apnea, dyslipidemia, increased fasting insulin levels, and sudden death are associated with being overweight.[7–10] More recently, overweight adolescents have been shown to be at increased risk for type 2 diabetes.[11] Bone and cartilage in the process of development are not strong enough to bear the excess weight. As a result, a variety of orthopedic complications occur in overweight adolescents. Overweight status in the adolescent female population has been associated with low educational achievement and income, even after controlling for intelligence and socioeconomic status at baseline. The effects persisted even when the adolescent was no longer considered overweight.[12,13] Overweight adolescents often experience significant low self-esteem and depression.[14–16] Overall, overweight adolescents face increased morbidity and mortality later in life.

OBSTETRIC AND GYNECOLOGIC IMPLICATIONS OF OBESITY

IRREGULAR MENSES

Overweight adolescents often present to their healthcare providers with amenorrhea, oligomenorrhea, or menometrorrhagia. Being an overweight adolescent is associated with elevated levels of free estrogens through increased peripheral aromatization of androgens to estrogens, decreased levels of sex hormone-binding globulin (SHBG), and increased insulin levels that can stimulate ovarian stromal tissue production and androgen. The elevated peripheral estrogen levels are associated with disruption of normal ovulation and subsequent irregular menstrual cycles. Higher degrees of overweight have been associated with higher probabilities of menstrual cycle disturbances.[17]

POLYCYSTIC OVARIAN DISEASE

Obesity has been reported to occur in half of patients with polycystic ovarian syndrome (PCOS). Obesity in adult patients with PCOS is characterized by an increased waist-to-hip ratio or android appearance as opposed to truncal obesity. The presence of obesity compounds clinical risk in PCOS patients for several reasons. Obesity is correlated to decreased SHBG, which increases circulating free testosterone and estradiol.[18] Obese adults have an increased likelihood of dyslipidemias, raising concern for future cardiovascular events.[19] Obesity is associated with insulin resistance, which may progress to diabetes mellitus in PCOS patients.[20]

Lifestyle modification is recommended as first-line management for overweight adolescent females with PCOS. Dietary intervention studies have consistently demonstrated the benefit of weight reduction in overweight females with polycystic ovarian disease to normalize menstrual cycles and hyperandrogenism and improve metabolic variables.[21]

Oral contraceptives are the standard therapy worldwide for PCOS, to provide hormonal suppression of androgen production. Metformin has been approved by the US Food and Drug Adminstration (FDA) for use in patients with type 2 diabetes and is the most common insulin-sensitizing agent used in studies on PCOS, even though the use of metformin in these patients is considered off-label. A recent Cochrane Database review did not reveal

any effect of metformin treatment on body weight, BMI, or waist:hip ratio.[22] For women not planning pregnancy, which includes most obese and PCOS adolescent patients, preliminary data on the efficacy of metformin treatment in regulating menstruation, ameliorating hirsuitism, and reducing acne are promising. Further well-designed trials are needed. Some investigators state that based on current data, metformin can be justified in obese adolescents with PCOS and insulin resistance to improve metabolic and hormonal alterations and possibly prevent long-term sequelae.[23] To date, however, there have been no clinical trials greater than 6 months duration assessing the use of metformin in treatment of adolescents with PCOS.

BIRTH CONTROL

Oral contraceptive pills (OCPs) may have reduced efficacy in overweight women. Recent studies suggest that women in the highest body weight quartile (70.5 kg) have an increased risk of accidental pregnancy compared with women with a healthy body mass (relative risk 1.6).[24] Another study demonstrated that women with BMI greater than 32.2 had higher risk of accidental pregnancy than women with normal body mass.[25] Several mechanisms have been proposed to account for the OCP failure rates in overweight women. Proposed theories include obese women having larger blood volume to transport steroid hormones, fat cells sequestering the steroids, or overweight women metabolizing steroids differently than lean women.[26] In overweight OCP users, the risk of thromboembolism is increased.[27]

Women weighing greater than 90 kg have been shown to have a disproportionate likelihood of contraceptive failure with the transdermal contraceptive patch.[28] Implanon has not been studied in women who weigh over 30% of their ideal body weight.

The effectiveness of the intrauterine device (IUD) in obese adult women is similar to that demonstrated in adults of average weight. Insertion of an IUD can be technically challenging in the obese adult woman and may require the use of a larger speculum for adequate visualization of the cervix. Placing a condom with the tip removed over the speculum blades can aid in exposure, as well as the use of ultrasonography.

Table 23.1 summarizes birth control methods and their effects on weight.

Table 23.1 Birth control methods and their effects on weight[42]

Birth control method	Average weight gain	Does weight affect how well it prevents pregnancy?
Abstinence	None	No
Male condom	None	No
Female condom	None	No
Emergency contraception	None	No
Vaginal spercimide	None	No
Diaphragm	None	If gain or lose 10 pounds or more, may need to be refitted
Cervical cap	None	If gain or lose 10 pounds or more, may need to be refitted
Combination oral contraceptive pills	1–3 pounds per year	If weigh 176 pounds or more, **may** not prevent pregnancy as well
Progestin-only birth control pills (mini-pills)	1–3 pounds per year	If weigh 176 pounds or more, **may** not prevent pregnancy as well
Depo-Provera	8–10 pounds per year	No
Vaginal ring (Nuva ring)	None	No
Patch (Evra)	1–3 pounds per year	If weigh 176 pounds or more, **will not** prevent pregnancy as well
Copper T IUD (Paraguard)	None	No
Mirena intrauterine system	None	No
Sterilization	None	No

ABORTION

In second trimester dilation and evacuation abortions, obesity has been linked with technical difficulty, longer operating times, and more blood loss.[29]

PREVENTION STRATEGIES

ACOG recommends that all adolescents be screened annually for eating disorders and obesity by determining weight and stature, calculating a BMI, and asking about body image and eating patterns.[1] Recent findings of the US Preventative Services Task Force conclude that there is insufficient evidence to recommend for or against routine screening for overweight in adolescents in primary care settings.[30] This statement demonstrates the current inconsistencies in the definitions of overweight and obesity, paucity of evidence that screening improves health outcomes, and that effective therapeutic approaches for adolescents are very limited.

While the research on prevention of obesity in adolescents has resulted in few effective recommendations, some prevention strategies have been generated. Parents play a significant role. Health-care providers should encourage parents to provide healthy foods in the home and encourage daily activity. Sodas and unhealthy snacks should be avoided and not made available in the home. Juice intake should be limited. Leisure activities that are sedentary, such as television viewing, should be restricted to less than 2 hours a day. Parents should also be encouraged to model healthy eating habits and activity and should be informed that food should never be used as a tool for punishment or reward. Eating breakfast and regular meals is important in promoting and maintaining a healthy weight. Health-care providers should promote diet and exercise to adolescent patients and their parents during routine preventative health-care visits.[1,31] The World Health Organization (WHO) reported breastfeeding as a probable protective factor for obesity and a few large retrospective studies have demonstrated this effect.[31]

TREATMENT STRATEGIES

Obstetrician-gynecologists are strongly encouraged to provide sensitive and effective counseling to the overweight adolescent. The patient usually is acutely aware of her weight issue and has likely attempted many of her own weight loss programs. These adolescents need support, guidance, and encouragement. They also need a better understanding of the widespread nature of the disease, so they feel less alone and isolated. Scarce information is available on current standards of evaluating and caring for overweight adolescents. Obtaining a diet history is a suggested tool to assess the adolescent's daily intake. There is no documented valid method to best assess a patient's typical food intake. Some recommend requesting a diary of all food eaten. Physicians often refer patients to dieticians for a dietary assessment. Any proposed diet should be consistent with the dietary guidelines for Americans[32] and allow for a caloric intake that supports gradual, not rapid, weight loss. Discussion of portion sizes that coincide with these recommendations is important.

While we have few data on overweight adolescents, well-designed studies on weight loss interventions in children and adults are available. In adults, there is strong evidence that dietary lifestyle interventions produce weight loss. These interventions are varied, but include diets low in fat and calories (1000–1500 kcal/day). The initial goal involves reducing total body weight by 10% from baseline over a 6-month period. This weight loss should be gradual, consisting of a 1–2 pound loss per week.[33] In adults, low fat diets,[34] low carbohydrate diets,[35] and meal replacement strategies[36] have been compared. There is no statistically significant difference in weight loss between these diets. The overall weight loss was 2–4 kg at 12–18 months.[33,35,36]

There are sufficient adult data to support increasing physical activity for effective weight loss. The amount of time the adolescent spends performing aerobic and sedentary activities should be assessed. The National Heart, Lung, and Blood Institute's

Obesity Education Initiative recommended 30 minutes or more of moderate intensity physical activity on most, and preferably all, days of the week for weight loss and management in the adult.[33] Increased activity and decreased television viewing have been shown to reduce an adolescent's weight.[37] In children, family-based programs that encompass diet, physical activity, reduction of sedentary behavior, and behavioral therapy have been shown to help children lose weight compared with no treatment. The adolescent's psychological well-being also should be evaluated and often collaboration with a mental health professional is indicated.

There are scant data to document the efficacy of prescription medications or over-the-counter drugs for weight loss in adolescents. Because of the recognized long-term deleterious effects of obesity, bariatric surgery is often performed for adults with BMI values greater than 35 with comorbidities and greater than 40 with or without comorbidities. The role of surgical intervention for adolescents with obesity has yet to be established, but some recent studies have suggested that surgical weight loss improves the early mortality experienced by these adolescents.[38]

CONCLUSION

Obesity in adolescents has become a common problem with significant sequelae. There are scarce evidence-based data for the prevention and treatment of adolescent obesity; additional research is needed. Currently, our best tool is the extrapolation of information from data and studies pertaining to children and adults. Sound nutritional recommendations and regular physical activity are essential components for overall good health as they convey a myriad of benefits for growth, brain and cognitive development, self-esteem, immunity, and disease prevention.[39] A new paradigm has been proposed with an emphasis on promoting a healthy lifestyle in overweight and obese patients instead of focusing solely on weight loss. This idea of 'health at any size' may encourage patients to focus on their overall health improvement, rather than only their weight status.[40]

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24. Legal and confidentiality issues in pediatric and adolescent gynecology

Steven R Smith

Physicians treating pediatric and adolescent patients ('minors') face some of the thorniest legal issues of all physicians. Their practices involve difficult emotional, controversial, and unresolved questions of our society, and the law reflects both that passion and ambiguity.

Consider, for example, the first five patients Dr Pag (named for his/her field of pediatric and adolescent gynecology) will see today:

- Patient April, 16, is brought to the office by her mother for a general gynecological examination. In the examining room, April tells the nurse she does not want the exam.
- Patient Betty, 15, is referred by a pediatrician for unexplained vaginal bleeding. She asks Dr Pag not to tell her father about the visit. Later in the day, Betty's father calls.
- Patient Carol, 14, asks for a prescription for birth control pills. In the course of treatment it appears she has a sexually transmitted disease (STD).
- Patient Diane, 13, says she thinks she could be pregnant and wants to know 'how to get unpregnant real fast.' She also seeks permanent sterilization.
- Patient Ellen, 12, is brought in by a school counselor. She has been sexually active and has vaginal injuries that are consistent with sexual abuse.

This chapter discusses the issues Dr Pag will face – questions of consent to treatment, confidentiality, required reporting, and the conflicting obligations gynecologists may have to minor patients and their parents and, in some cases, to society. The legal answers to the questions presented by these patients will depend in part on the state in which Dr Pag practices.[1]

State law has traditionally governed the regulation of medical care, the definition of the legal rights of minors, and the relationships between parents and minors. State law still plays the dominant role in defining and regulating the provision of medical care to minors, although federal law has become increasingly important.[2] State laws vary somewhat among the states. ('Law' is not a simple term; it means a combination of statutes, but also constitutions, case law, and administrative regulations and directives.)

Federal statutes have directly or indirectly (notably through federal funding requirements) increasingly influenced practice,[3] and federal court decisions regarding the constitutional rights of minors are examples of federal rules that have generally changed the law affecting the rights of adolescents.[4]

ALL OF DR PAG'S PATIENTS: THE RIGHTS OF CHILDREN AND PARENTS

Under traditional common law, children were virtually the property of their parents and were completely subject to parental decisions, direction, and discipline.[5] Throughout much of the last hundred years, however, the concept of parental ownership and control of children increasingly has weakened. Although parents still have wide latitude in raising their children, minors are recognized as separate legal entities with their own rights and interests.[6] As a result, the relative authority of parents and their children, especially older adolescent children, in making medical decisions is in flux and often uncertain.[7]

Children traditionally have been protected from their own immature judgment by their limited ability both to enter into contracts (except for necessities) and to consent to medical care (except under very limited circumstances). The law generally considered minors to be incapable of making binding legal decisions until the age of majority. State law defines the age of majority, and most states use 18 for general decision-making capacity.[8]

There have been some common exceptions to minors' inability to make legally binding decisions. The most common is the 'emancipated minors' rule.[9] Emancipated minors may make legally binding decisions because they are viewed as formally free of the control and responsibility of their parents, usually as a result of marriage, military service, or (in some states) economic independence coupled with parental approval.[10] Some states also have recognized that 'mature minors' may make legally binding decisions.[11] The concept of the mature minor is somewhat unclear, but it generally refers to those who are able to understand and make complex decisions even though they have not reached the age of majority.[12]

The legal tendency during the last three decades, consistent with studies of the decision-making ability of older minors,[13] was to give minors the legal authority to make legally binding decisions at an earlier age.[14] This is not an uninterrupted trend, however, and in some cases the trend reverses for a while with somewhat expanding parental control over fundamental decisions, at least for adolescents under 18.[15]

An especially helpful state-by-state review of minor's consent laws is contained as part of the Guttmacher Institute website (www.guttmacher.org) It is frequently updated.

CONSENTING TO TREATMENT: PATIENT APRIL

April, Dr Pag's 16-year-old patient, apparently presents a straightforward treatment issue. Medical care may ordinarily be provided only if the patient has given consent.[16] April's mother, who probably has legal authority to consent, has undoubtedly consented to ordinary examination procedures, probably through a general consent form. How far that consent extends, however, may be in doubt with April.

Consent to treatment is part of the general right of autonomy, the right of all adults to decide for themselves what will be done to their bodies. When the treatment is important or invasive – surgery, for example – the patient must be informed of the risks, benefits, and alternative treatments. That is, the patient must give 'informed consent.'[17] 'Informed' consent requires that the patient be given basic information in order to make a reasonable judgment about whether to accept a proposed medical procedure or drug. This generally includes four kinds of information: (1) the nature of the proposed procedure, (2) the risks and benefits of the procedure, (3) the alternatives that may be available, and (4) the consequences or risks of refusing consent. Emergency care generally can be provided to minors without parental consent, and lifesaving care may be undertaken on the intervention of state social service agencies or courts.[18]

Parents must generally consent to treatment for their unemancipated children. Some modifications of these general rules have been provided, however, for adolescent obstetric and gynecologic care.[19] These have been made by statute in some states and by federal court decisions.[20] Virtually all states allow adolescents to consent to some kinds of gynecologic care, most often for treatment for STD, pregnancy, and contraception.[21] Several states, as part of the increased concern over child abuse, expressly allow the victims of abuse to consent to treatment for the abuse. Other changes have permitted adolescents to seek treatment without parental consent for drug or alcohol dependence. In most states an effort usually has been made to limit the scope of these minor consent laws so that they do not apply to abortion.

The complexity that can occur with consent to the treatment of adolescents is illustrated when April, a 16-year-old, essentially refuses the examination to which her mother has given consent. There are several permutations of consent/involvement

that can occur, illustrated as follows. There are three potential 'involved' parties:

- child
- parent 1
- parent 2.

Each party may:

- consent
- refuse
- decline to be involved (or not be involved).

Each of the participants involved in a minor's medical care may have different interests and legal rights, some of which conflict in fairly complex ways. In the case of April, at least three legal issues face Dr Pag. First, whether April can withdraw the consent that her mother gave. Second, whether the doctor can or must tell the mother about this. Third, whether Dr Pag has additional 'informed consent' obligations. In light of April's age, absent a serious medical issue, it is likely that April can refuse this examination, but her mother should be informed of the refusal. Furthermore, Dr Pag will have the additional obligation of informed consent to tell April of the health risks of refusing the examination. If, for example, STD is a possibility, the risks of leaving the disease untreated must be disclosed to April.

It is also important to note that although consent is a legal requirement, it also presents excellent opportunities for communication with patients and their parents. For example, Dr Pag may want to consider why April does not want the examination and what medical importance that may have. Furthermore, it is an opportunity to discuss the continuing importance of such examinations.

CONFIDENTIALITY: PATIENT BETTY

Betty's referral raises questions of consent and confidentiality. First, there is the question of whether she can consent to treatment without her parents. It is not absolutely certain in some states that Betty can give consent to the examination and treatment. Still, she is 15 and clearly has a medical condition that requires treatment, and her condition could be related to one of the 'juvenile consent' laws. Invasive treatments, notably major surgery, would raise issues that would undoubtedly require some form of parental involvement.

Betty's request that Dr Pag not inform her father of treatment should be of concern to Dr Pag. Physicians have an obligation to respect patient confidentiality. Failure to maintain confidential information revealed during treatment may result in civil lawsuits based on negligence or invasion of privacy and may subject the physician to discipline by licensing agencies. The traditional common law and professional obligation of confidentiality have been strengthened in recent years by a number of state and federal statutes. (The obligation of maintaining confidentiality should not be confused with the existence of a physician–patient privilege.[22] The privilege permits physicians and patients to refuse to reveal, even to courts, the communications that occurred during treatment. Confidentiality is a broader obligation to maintain the secrets of the patient.)

Federal regulations implementing the Health Insurance Portability and Accountability Act (HIPAA) are an especially important example of these private rights.[23] HIPAA does limit in a significant way the ability of physicians and medical entities from releasing some kinds of information about patients, including children. In this area HIPAA generally follows state law. If a minor can legally consent to a medical procedure or may receive it without the consent of parents, parents usually do not have the right under HIPAA to have the minor's health information. In addition, if the parent has agreed to confidentiality between the doctor and child, the parent has given up the right to access the information. In addition, HIPAA emphasizes that health-related communications with parents or anyone else must be conducted in a confidential and careful manner.[24]

Some states have adopted laws that are even more restrictive of the release of medical information than is HIPAA. These laws are enforceable if they are more strict in protecting privacy than is HIPAA. There is considerable variation in state medical

privacy statutes and these laws change with some frequency. For this reason, it is important that physicians remain current with the privacy rules in the states where they practice.

There are, of course, exceptions to confidentiality requirements, such as when the patient has waived the right to secrecy or where the law specifically permits or requires the physician to release information about the patient. There are many reasons for breaching confidentiality. Examples include the effort (with patient consent) to obtain insurance or other third-party payment for services, or the need to report a communicable disease under state law. Any breach of confidentiality should be carefully considered by the physician in light of the legal standards in the state in which the patient is seen.[25]

Under common law, it was assumed that parents were entitled to any important information about their children. This probably reflects current law, although because of individual state statutes and the constitutional privacy rights of minors, some exceptions may exist in the areas of psychiatric, obstetric, and gynecologic care.[26] In many states, however, the right of minors and physicians to withhold general medical information from parents is doubtful. The physician treating an adolescent patient should reach a clear understanding about confidentiality, including any communication with the patient's parents, before treatment begins. Where the treatment involves issues of sexuality or substance abuse, such an understanding is especially important.

The reasons for Dr Pag's concern about Betty's request that her father not be informed of her visit become clear. There appear to be potentially conflicting obligations to Betty and to her parents. Dr Pag should be cautious about promising Betty unqualified confidentiality. The doctor may, for example, want to provide reasonable confidentiality 'within the bounds of legal and professional requirements.'

The question of parents' rights to obtain health data about their children, especially older children, is among the most unsettled questions in this chapter. On one hand, there is the traditional rule of parental control rights over children. On the other hand is the increasing right of minors, especially older minors, to make critical decisions for themselves. Adding to the difficulty is the risk of parental abuse and the fact that it is often unclear which parents have what rights related to their children. Adolescents seeking treatment may come from single-parent homes in which one parent may not have custody rights. In such cases that parent probably does not have a right to the medical information about his or her child, and it may be a violation of the law (including HIPAA) to provide the information. Even where a parent with custody rights requests information, it is not always required that it be disclosed, especially if the disclosure would harm the child.

Dr Pag is not obligated to seek out Betty's father to provide information about her. When Betty's father calls Dr Pag (perhaps because the referring doctor mentioned the treatment by Dr Pag), however, the doctor faces the question of providing the requested information, or in some way declining to do so. Based on legal obligations, the doctor should first consider that it is generally not appropriate to disclose private medical information based solely on the father's claim of parenthood. If Dr Pag is unfamiliar with the father and likely custody rights, the doctor should require from the father convincing evidence of parental custody that includes the right to the medical information. Even with legitimate parental custody, Dr Pag may be legally justified in declining to provide personal information. If, for example, there is reason to believe that providing the information might put Betty's safety at risk, the doctor is likely on solid ground in declining to discuss the matter with the father.[27]

The legal ambiguity of parental rights in many adolescent treatment circumstances inevitably makes it difficult for physicians treating adolescents to be on clearly solid legal ground in dealing with requests for patient medical information.[28] It is safe to transfer such information to other medical facilities for treatment purposes, or where required by law (e.g. reporting statutes discussed below). It is ordinarily safe to do so when there is consent to the release provided by the patient and within the limits

of HIPAA. Beyond that, however, as a general matter it is better to be conservative in the release of medical information.[29] It can usually be released later, but it is seldom possible to retrieve information wrongly released.

CONTRACEPTION AND SEXUALLY TRANSMITTED DISEASES: PATIENT CAROL

Carol's request for a prescription for contraceptives and the discovery that she has chlamydia also raise questions of consent and confidentiality for Dr Pag. The doctor will be at the intersection of common law, modern statutes, and constitutional rights.[30]

Most states by statute would permit Dr Pag to provide treatment for the STD and to give advice regarding contraceptives (except permanent sterilization) and would not require that the doctor notify Carol's parents of these actions.[31] Beyond the state statutes, however, there is a constitutional right of adolescents involved. In *Carey v. Population Services,*[32] the US Supreme Court held that the right of privacy includes the right of minors to have access to some contraceptives. It struck down a New York statute that limited access by minors younger than 16. A state may not, therefore, completely prohibit the use or availability of nonprescription contraceptives to minors.[33] This is an exception to the general requirement of parental consent.

In short, Carol would probably have the right to consent to obtaining contraceptives and certainly will for treatment of an STD.[34] The doctor must remember, however, that *informed* consent is still required, and must include reasonable information about the benefits and risks of the proposed treatment and about alternatives.

Dr Pag will probably not have to tell Carol's parents about the treatment.[35] Most states have laws that exempt physicians from informing parents of contraceptive services for their children or of treatment for STDs. Statutes vary among states and may be affected by case law and constitutional rights. Local legal advice is generally necessary to have a clear understanding of when minors may effectively consent to treatment and when information may be withheld from parents.[36]

Dr Pag will very likely have an obligation to make a report to the state about the diagnosis of an STD. States generally obligate health-care providers who diagnose or treat someone infected with a venereal disease to inform the department of health of basic information about the disease. For example, the required report might include the name, address, sex, name of the disease, and probable source of infection. The reports are not discretionary; they are mandatory. Good faith reporting, however, carries immunity from criminal and civil liability.

PREGNANCY AND ABORTION: PATIENT DIANE

Diane can, in almost all states, consent to medical care related to her pregnancy, and can do so without parental notification. Her desire to seek an abortion, however, puts her and Dr Pag in the middle of a legal and political tempest.[37]

In *Planned Parenthood v. Danforth,*[38] the Supreme Court held that the right of privacy to decide to have an abortion extends to minors, and the state does not have the constitutional authority to delegate to parents the decision of a 'competent and mature minor' to have an abortion. The Court held unconstitutional an ordinance that provided that all minors younger than 15 were too immature to make abortion decisions,[39] but in *Planned Parenthood Association of Kansas City v. Ashcroft,*[40] the Court upheld a state statute requiring all minors to obtain either parental or judicial consent for an abortion. In a judicial bypass process, a minor goes to state court to seek permission (without parental consent) to have an abortion.[41] These courts are *required* to give consent to the abortion if the minor is mature enough to make the decision or if the abortion was in her best interest.

The judicial bypass exception is so complicated that it is unlikely that most minors would be able to negotiate it by themselves.[42] In some areas of the country there are organizations that will assist adolescents with the bypass procedures, and minor patients may know of these from their

friends. Physicians treating minors who may need or want to have an abortion, however, should determine whether a parental consent or notification statute exists,[43] and whether they are permitted to assist the minor in completing the bypass. Several studies suggest that courts overwhelmingly approve abortions when application is made through the bypass process, but the adolescent patient is likely to need assistance in going through the court process.[44]

The Supreme Court has also upheld state laws that require graphic informed consent, including information about the fetus,[45] and a number of states have adopted such laws.[46] Apart from special abortion informed consent statutes, the physician should remember that abortion is a significant medical procedure, and the informed consent of the minor is essential. Except in the most extraordinary circumstances, an abortion should not be done when the minor objects, and then should be done only with court approval.

Most states with specific statutory provisions on the release of abortion information either permit or require the release of information to parents.[47] The trend appears to be toward requiring its release and even requiring the physician to notify parents when a child requests an abortion or contraceptives.[48] In *Ohio v. Center for Reproductive Health* and *Hodgson v. Minnesota,*[49] the Court held that a state may constitutionally require the notification of one or even both parents when a minor seeks an abortion as long as the state also provides for a 'judicial bypass.' In jurisdictions requiring parental notification for certain types of obstetric and gynecologic care, the practitioner should inform minors at the beginning of treatment of this reporting requirement.[50] This is another area where significant changes may be expected in the future, so particularly careful monitoring of changes in federal, state, and local law is important.[51]

It is apparent that Dr Pag will face a difficult time providing abortion services to Diane.[52] As we have seen, Dr Pag's obligations will depend on the state in which the doctor is located.[53] In most states Dr Pag will be required to notify or obtain the consent of at least one parent. If there are good reasons not to have parental notification or consent, before proceeding Dr Pag will need a court determination that Diane is sufficiently mature to make the abortion decision herself, or that it is in her best interest. The vast majority of such judicial bypass efforts are granted by courts, but Diane would probably have to appear before a judge to receive judicial consent.[54] The state may also require a 'shock' informed consent and a 1- or 2-day waiting period between the consent and the abortion.[55] Finally, in some states doctors may be required to report to the state information about the abortion. It should also be noted that if Dr Pag is employed in some institutions, the doctor may not be permitted to participate in the abortion or to directly refer Diane for an abortion.[56]

Diane also has asked to be permanently sterilized. Permanent sterilization of competent minors generally should not be undertaken unless it is necessary to save a life or is incidental to other essential treatment. Some states by statute specifically do not allow minors to consent to sterilization.

Although not an issue with Diane, a more general troublesome question has been whether it is appropriate for minors to be sterilized when parents or guardians consent. Sterilization is usually sought because profoundly incompetent female minors are unable to understand their own sexuality and the consequences of sexual contacts and would be unable to care for any children they might bear.[57] On the other hand, courts are reluctant to remove the fundamental right to procreation and are concerned about the potential for abuse.

Courts currently permit sterilization of profoundly incompetent minors in limited cases after a process to determine that such a step is justified. This usually follows a formal hearing during which a guardian *ad litem* (for this legal process) is appointed for the minor.[58] If she is judged to be permanently incompetent because of profound mental deficiency and it is determined that sterilization is in her best interest, the court may approve the procedure. Even in the absence of express statutory authority, some courts have utilized their 'inherent' judicial authority to order sterilization.[59] These court-ordered sterilizations are appropriately

limited to a narrow group of severely mentally handicapped minors.[60] A physician performing a sterilization pursuant to a court order ordinarily may do so without incurring civil liability. When the court issuing the order does not have authority to do so, it is possible that the physician will be liable. This has led one expert to suggest some caution in implementing these orders.[61]

ABUSE AND NEGLECT: PATIENT ELLEN

Dr Pag will have a clear legal duty as a result of his treatment of Ellen, the 12-year-old who has been sexually abused. All states require that physicians report child abuse or neglect.[62] The statutes vary somewhat from state to state. States usually have adopted broad definitions of reportable events.[63] 'Known' or 'suspected' abuse or neglect must be reported. Abuse includes physical, sexual or emotional abuse.[64] Sexual abuse usually includes sexual assault or molestation, sexual exploitation, or prostitution.[65]

Child abuse reporting statutes are mandatory. Failure to report known or suspected abuse, neglect, or sexual exploitation is a criminal offense in most states and may also give rise to civil liability.[66] Most states provide immunity, however, against liability for those who in good faith report cases of suspected child abuse.[67]

Dr Pag should have in place a routine system for reporting known or suspected abuse. It is clear that he must make that report, or have it made on his behalf, within a short time after examining and treating Ellen.

There is an interesting question of whether Dr Pag might be required to report the abuse of at least one other of his patients, Diane. She was pregnant at 13 and the doctor might well suspect that she became pregnant as a result of rape, notably statutory rape. 'Statutory rape' means sexual contact with someone under the age at which legal consent to sex is recognized.[68] Some suggest that whenever a physician consults with a very young girl about an abortion, there is an obligation to make an abuse report because the physician must suspect statutory rape, which would likely be a form of abuse. Of course, the same argument would generally apply to any diagnosis of or care for pregnancy. To date these suggestions have not received general acceptance.

THE LEGAL PRINCIPLES AND DR PAG'S PATIENTS

The basic legal principles Dr Pag has faced may be summarized as follows:

- The law affecting the practice of physicians varies from state to state and may change quickly, so definitive and permanent answers about treating pediatric and adolescent patients (minors) is not possible. Dr Pag's legal obligations will depend, therefore, on the state in which the doctor practices.
- Diagnosis and treatment can be undertaken only with consent. For minors, parents ordinarily have the legal authority to give consent to treatment.
- The law makes consent exceptions for some minors, or for some kinds of health care. 'Emancipated minors' may generally make decisions for themselves. 'Mature minors' in most states may make certain basic decisions for treatment related to pregnancy, contraception (not including sterilization), STDs, and the like.
- Where there is disagreement between a minor patient and parents regarding care, or between parents of a minor patient, the law in practice often becomes murky. Where the life or health of a minor is at stake, the bias should be toward providing emergency or necessary treatment.
- 'Informed consent' requires that the patient or decision maker be given sufficient information on which to base a sensible decision. This generally includes a description of the treatment or procedure proposed, its costs and benefits, alternatives, and the consequences of refusing treatment. The informed consent process is an excellent opportunity for communication with patients.

- Physicians have a general obligation to protect patient confidentiality. Ordinarily, parents have a right to information about their minor children. It is important, at the outset, to ensure that someone requesting medical information as a parent is a custodial parent with the right to receive the information. State and federal laws, including HIPAA, are further limiting the release of confidential medical information. Where there is doubt about the propriety of releasing information to parents, it is generally better to be conservative under the theory that it is difficult to retract information improperly given out.
- Many states have laws that permit physicians to withhold from parents information about consultation or treatment for STDs, contraception, and pregnancy.
- The laws regarding consent to abortions and parental notification are very complex. It is common for states to require parental consent or a 'judicial bypass' for a minor to obtain an abortion, and parental notification laws are common.
- Permanent sterilization of minors should be undertaken with great care and only for very strong reasons after appropriate external legal review.
- All states require the reporting of child abuse. Known or even suspected neglect, physical or mental abuse, and sexual abuse or exploitation must be reported to a child protective services agency. It is generally a crime to fail to report. Physicians are also generally required to report the diagnosis of STDs.

WILL DR PAG BE PAID?

Under common law, a minor cannot be held to contracts except for necessities, and a parent is obligated to provide the fundamentals of life. Thus, in most cases, a parent is required to pay for the minor's medical services, but if a minor legally contracts for necessary medical services, the minor can be held to that contract. It is not uncommon for states that permit minors to obtain medical treatment without parental consent to also release parents from financial responsibility for treatment to which they did not consent. Ordinarily the minor would be responsible for paying for such services.[69] Successfully securing payment, of course, may be difficult, even if it is legally due.

Obtaining private insurance payment for services may be very difficult if the parent whose policy is covering the service has not been informed of the health service. Insurance company reimbursement notices can become a mechanism by which confidentiality can be breached. Insurers often send notices of payment to the address of the person providing the insurance coverage. Some minors will have coverage by Medicaid, state Children's Health Insurance Program or similar programs.[70]

A WORD ABOUT PROFESSIONAL LIABILITY

A detailed discussion of malpractice liability is beyond the scope of this chapter. The topics discussed as the focus of the chapter – consent by minors, confidentiality of minors, abortion counseling, and abuse reporting – may give rise to liability, but do so relatively infrequently. Of much greater concern is the quality of care: careful practice that is strictly limited to areas of expertise and currency, good supervision of assistants and employees, and maintaining good relationships and communication with patients and their families.

This is not to say that legal issues related to consent by minors, confidentiality, abortion, and abuse reporting can be ignored. In fact, physicians do eventually create problems for themselves and the institutions in which they work if they routinely are ignorant of, or just ignore, legal requirements. When that occurs it can be professionally difficult and unpleasant. As professionals, physicians have a special obligation to take seriously the obligations of society and the failure to do so will, in the long run, decrease the regard in which the profession is held and will likely result in more onerous regulation.

PRACTICAL ADVICE

By way of conclusion there are several practical tips that those treating pediatric and adolescent patients should consider to avoid unnecessary problems and complications.

- Establish an ongoing relationship with an attorney you trust. Ask the attorney to help you understand the legal requirements in your state and seek help establishing procedures and practices that will help you comply with legal requirements. Do not hesitate to contact the attorney as questions or problems arise in practice.
- Have annual check-ups. (You should take the advice you give patients.) Your attorney should help you do an annual review of your practice to make adjustments that respond to changes in the law.
- Understand the elements of informed consent in your state and who may give consent to what procedures involving minors.
- Understand the limits and obligations of confidentiality. Have a plan regarding disclosure to parents that meets the legal requirements and is consistent with HIPAA.
- Discuss confidentiality issues with patients, especially adolescent patients. They should generally understand the limits of confidentiality. Consider making agreements with parents regarding confidentiality, so that they agree in appropriate cases that you will not disclose information to them (parents can agree to give up the right to information).
- Take *informed* consent seriously. Use it as a way of communicating important information with patients and parents.
- If you are involved with abortions or sterilizations, be very clear on the legal requirements of your state.
- Have a system in place to report abuse and neglect.
- Maintain very good records. Keep them honestly and accurately.

It is ultimately important to remember that the law is not a series of random rules. Rather, with all of its faults, it is an effort to implement the most important values and goals of the society. Inevitably there are conflicting values and compromises that produce changing and imperfect rules. Physicians, in cooperation with attorneys when needed, can work sensibly through these rules. The two professions, when they work together, over time can also improve the law to make it a better vehicle for achieving important values.

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Section III: The surgical patient

25. Perioperative care of the pediatric and adolescent gynecology patient

Mary E Fallat

This chapter outlines recommended current practices in the perioperative care of the pediatric or adolescent gynecology patient.

PREOPERATIVE DIET GUIDELINES

Although guidelines may vary depending on local practice, Table 25.1 provides guidelines for elective anesthesia or sedation that represent safe practice.[1] If a patient is on medication for seizures, or cardiac or respiratory conditions, these may be given before operation at the usual time with a small sip of water. Studies have demonstrated that gum chewing before anesthesia increases the amount of gastric residual and results in an increased risk for aspiration on induction.[2] In some institutions, therefore, gum is treated like a clear liquid meal and the case will be delayed accordingly.

PREOPERATIVE LABORATORY EVALUATION

Pubertal and older girls should have a preoperative qualitative human chorionic gonadotropin (HCG) evaluation as a pregnancy test and a complete blood count. Evaluation of electrolytes and renal function is generally unnecessary unless the patient has been on intravenous fluids preoperatively, has other body fluid losses such as through a nasogastric tube, is undergoing a mechanical bowel prep, or is on medications that may affect the values. Coagulation studies are needed in girls who have a personal or family history of easy bruising or bleeding or a history of menorrhagia. Girls with an abdominal mass concerning for malignancy should have tumor markers drawn including lactate dehydrogenase (LDH), alpha-fetoprotein, quantitative HCG, CA-125, and specific hormone evaluation as needed including luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, progesterone, and/or free testosterone. Type and cross-match should be drawn on patients who will have extensive procedures performed, who have large abdominal or pelvic masses, who are already anemic, or who are expected to lose more than 15% of their total blood volume. If there is a luxury of time (at least a month before operation), and the child is age-appropriate and can assent, depending on the procedure planned, autologous blood can be drawn and made available for the surgery date. Although directed donation is possible, blood from relatives, friends, and paid donors is not known to be safer than that from a blood-bank and associated processing costs may be higher.[3]

ANTIMICROBIAL PROPHYLAXIS

It has long been recognized that the risk of surgical wound infections can be reduced by the prophylactic administration of appropriate antibiotics within 60 minutes before making the first incision in clean contaminated and contaminated cases.[4] The goal is to achieve tissue levels of the antibiotic before the incision is made, maintain adequate drug levels during the procedure, and stop the antibiotics appropriately (i.e. soon after the procedure and at least within 24 hours). For most appropriate gynecologic procedures, the drug of choice for prophylaxis is cefazolin at a dose of 25 mg/kg (maximum dose 1 g). The use of a protocol that

Table 25.1 NPO guidelines before sedation or anesthesia

	Age (months)		
Intake	**0–5**	**6–36**	**> 36**
Clear liquids	2 hours	2 hours	2 hours
Breast milk	4 hours	6 hours	…
Formula	4 hours	6 hours	…
Solids/milk	4 hours	6 hours	8 hours

includes an automatic stop order for the prophylaxis achieves not only a reduction in postoperative wound infections, but a reduction in cost.[5]

Recently, the recommendations for prevention of infective endocarditis (IE) were updated by the American Heart Association.[6] The new recommendation most pertinent to the discipline of pediatric and adolescent gynecology is that the administration of antibiotics solely to prevent endocarditis is not recommended for patients who undergo a genitourinary (GU) or gastrointestinal (GI) procedure. The risk of antibiotic-associated adverse events exceeds the benefit, if any, of the prophylactically administered antibiotics. Although a large number of diagnostic and therapeutic procedures that involve the GU or GI tracts may cause transient enterococcal bacteremia, no published data demonstrate a conclusive link between these procedures and the development of IE; and no studies exist to show that prophylactic administration of antibiotics in high-risk patients during these procedures reduces the incidence of IE. In a patient with an established GU or GI infection who must undergo an operative procedure, it may be reasonable to include in the antibiotic regimen an agent active against enterococci such as penicillin, ampicillin, piperacillin, or vancomycin.

MECHANICAL BOWEL PREPARATION

Major procedures that involve reconstruction of the vagina, involve surgery in proximity to the rectum or anus or have a high risk of unintentional entry into the gastrointestinal tract, or include planned operation on the gastrointestinal tract, should include a mechanical bowel prep the day before surgery. A clear liquid diet is preferred for 24 hours before surgery. For infants, toddlers, or patients at higher risk of dehydration, an inpatient preparation is preferred so that intravenous (IV) fluids can be administered simultaneously. Colyte® is given at a dose of 20 ml/kg administered PO or through a nasogastric tube in combination with age-appropriate enemas (Table 25.2). The last few enemas are given with 0.1% kanamycin solution. Oral erythromycin base and neomycin are given the day before at 1300, 1400, and 2300 (based on an 0800 OR time) (Table 25.2). Children and adolescents not at high risk for dehydration may prefer a bowel prep at home that includes drinking a bottle of magnesium citrate PO at 1200, followed by four dulcolax tablets a few hours later. A cleansing enema at the hospital on the morning of surgery will complete the prep.

Table 25.2 Mechanical bowel preparation guidelines

1. Enema volume by age using normal saline until clear

Age	Volume (ml)
Newborn	100
1 year	150
2 years	200
3 years	250
4 years	280
6 years	350
8 years	450
10 years	500
12 years	600
14 years	700
16 years	800

2. Erythromycin and neomycin base PO at 1300, 1400, 2300 (based on 0800 OR time)

Weight (kg)	Dose (mg)
0–7.5	62.5
7.6–15	125
15.1–30	250
> 30	500

PREOPERATIVE COUNSELING AND DOCUMENTATION

Preoperative counseling begins with the provision of information, in understandable and developmentally appropriate language, of the nature of the condition or process, the proposed diagnostic steps and/or treatment and probability of success, what to expect during and after the tests and treatment, risks and potential benefits, and alternative strategies if they exist. This information must be presented by the physician without apparent coercion or manipulation or bias, and there must be an assessment of the parent/patient's understanding of the information and assessment of the capacity of the parent/patient to make the necessary decision. A preoperative note should be written in the chart before surgery documenting that the risks, benefits, alternatives, and side effects of the planned procedure have been discussed in detail with the parents or guardian of the child and with the age-appropriate patient. Laboratory and other test results specific to the procedure should be included in the documentation. An operative permission form should be signed and on the chart. The need for blood or blood products should be discussed as indicated by the procedure, and most hospitals will have a permission for transfusion form that needs to be signed separately. Operative site marking will be dictated by the procedure and should be done before bringing the patient to the operating room.

INFORMED CONSENT, PARENTAL PERMISSION, AND ASSENT

When a patient is a minor, permission for medical treatment must be obtained from a parent or legal guardian.[7] (Discussion in this section covers US law only.) Technically speaking, only patients who have decisional capacity and legal empowerment can give informed consent to medical care. Parents or other surrogates provide informed permission for their children. Most parents seek to safeguard the best interests of their children with regard to health care, and the 'proxy' consent process works fairly well. However, pediatric and adolescent health-care providers have legal and ethical duties to their patients independent of parental desire or proxy consent. Therefore, patients should be included in and participate in decision-making commensurate with their development and provide assent when reasonable.

The age of majority is determined by an individual state, but in most states this is 18 years old. The age of majority for children with disabilities may be different. Exceptions to authorization of medical treatment by the parent or legal guardian include: (1) emergencies (when the risk to the minor's life or health is of a nature that treatment should not be delayed), or (2) emancipated minor (married, has delivered a child, a parent, financially self-supporting and living independently, a member of the armed services, declared to be emancipated by a court). A mature minor type exception is also recognized by some states for treatment of certain diseases including sexually transmitted diseases (STDs), pregnancy, contraception or childbirth, alcohol and drug abuse that allows diagnostic examination and treatment without the permission of or notification of the parent or guardian. This treatment does not extend to abortion or performance of a sterilization procedure. A physician may also provide outpatient mental health services, or examination for alleged child or sexual maltreatment without parental permission. State law may provide that the treating physician or health-care official may inform the parent or legal guardian of any treatment given or needed, where, in the judgment of the physician or health-care professional, informing the parent or legal guardian would benefit the health and treatment of the minor patient.

Court-appointed guardians may usually give permission for medical care and treatment for a minor, upon provision of the orders of appointment issued by a court. A child permanently committed to a state cabinet of health services requiring medical or surgical care may usually receive such treatment with permission by the family services case worker assigned to the child. If parental rights have not been terminated, permission must be obtained from the parent. Foster parents may be

under state supervision, with permission required from the family services worker assigned to the child. When parents are divorced, only a custodial parent may give permission. Step-parents do not have authority to give permission for medical treatment upon their stepchildren. Law enforcement officers may not give permission for or authorize medical treatment or testing of a minor while in police custody or under arrest. Permission must be obtained from the minor's parent or guardian. Adoptive parents possess full and unrestricted authority to make health-care decisions in the best interests of their minor children. Prospective parents in the process of adoption may give permission on behalf of a child provided that they have the appropriate documentation from the court or state that gives this authority.

Special circumstances in the permission for surgery process may apply if the parents have religious objections to blood or blood product transfusion. In this case, the best practice is to have a special consent form that has been prepared with input from the religious denomination of record that details the process to be followed in these patients.

If a minor patient refuses to assent (i.e. dissents) to a procedure, this should carry considerable weight if the procedure or intervention is not essential to his/her welfare, can be deferred without substantial risk, or the patient needs more time to better understand the condition being treated or the intervention proposed, or to seek another opinion.

MEDICAL RESEARCH

Parents, guardians, and minor patients may be asked to participate in clinical trials or medical research. If the child is age-appropriate, there are dual requirements that he or she must assent and the parent(s) or guardian must give permission as a condition of participation. The age of assent is at the discretion of an individual institutional review board (IRB). According to the National Commission's regulations 21 CFR 50.55 (c)(2),[8] assent is not an absolute requirement if 'the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.' However, local IRB regulations may be more strict and will take precedence over the National Commission's Guidelines.

RELEASE OF MEDICAL RECORDS

A parent or legal guardian must authorize the release of medical information regarding a minor patient, unless the minor patient consented to treatment under the mature minor exception or is an emancipated minor. In the latter cases, the minor patient must authorize the release of medical information to any person, including the minor's parent or legal guardian.

PERIOPERATIVE POSITIONING

The patient's position during surgery should provide optimal exposure for the procedure as well as access to IV lines, tubes, and monitoring devices.[9] Attention should be given to the patient's overall safety and comfort, as well as to the circulatory, respiratory, neurological, and musculoskeletal systems. Patient injury can occur due to the alteration of normal defense mechanisms as well as forced prolonged immobility during the procedure. The surgeon, anesthesiologist, and nursing staff should work as a team. This includes a preoperative assessment to determine the patient's tolerance of the planned position, including age, skin condition, height and weight, nutritional status, pre-existing conditions, and physical/mobility limits. Intraoperative factors include type of anesthesia, length of surgery, and position(s) required.

Positioning devices including padding and pressure relief devices should be available, clean, and in working order. Properly functioning equipment and devices contribute to patient safety and provide adequate surgical site exposure. Studies suggest that positioning devices should maintain a normal

Table 25.3 Injury risks and safety considerations for perioperative positioning

Position	Risks	Safety considerations
Supine	Pressure to occiput, scapulae, thoracic vertebrae, olecranon process, sacrum/coccyx, calcanei, knees	Pad elbows, knees, spinal column, heels; align occiput with hips; legs parallel and uncrossed
	Brachial plexus, ulnar and pudendal nerve injuries	Arm boards at < 90° angle, head in neutral position, arm and table pads level with each other
Lithotomy	Hip and knee joint injury	Place stirrups at even height
	Lumbar and sacral pressure	Elevate and lower legs slowly and simultaneously
	Vascular congestion	Minimize external rotation of hips
	Obturator, saphenous, femoral, common peroneal, ulnar neuropathy	Pad lateral/posterior knees and ankles
	Restricted diaphragm movement	Keep arms away from chest to facilitate respirations
		Arms on arm boards at < 90° angles or over abdomen

capillary interface pressure of 32 mmHg or less. Use of gel pads decreases pressure at any given point by redistributing overall pressure across a larger surface area, while pillows, blankets, and molded foam devices may produce only a minimum of pressure reduction. Table 25.3 lists injury risks and safety considerations for the most common positions used in gynecologic surgery.

Special precautions must be taken when the patient is positioned in lithotomy, where the patient is supine with the legs raised and abducted to expose the perineum. Extreme thigh flexion may increase intra-abdominal pressure and impair respiratory function by decreasing tidal volume. With the legs in stirrups, venous return from the lower extremities is enhanced and blood pools in the splanchnic bed. Blood loss during the procedure may not immediately manifest until the legs are repositioned at the end of the procedure. The legs should ultimately be repositioned together (by two persons) and slowly to allow for physiologic adjustment to the extra volume circulating through the lower extremities again. Arms are best extended on arm boards or folded across the torso rather than positioned at the sides, where the hands will be at risk of getting caught in the lower table as it is raised at the end of the procedure.

There are three lithotomy positions described: high, medium, and low. The high lithotomy position is often used in the adult for vaginal hysterectomy, or for patients with frozen joints. The low lithotomy position is used for surgical procedures that require excellent exposure of both the abdomen and perineum.

Stirrups are secured in holders on each side of the operating table at the level of the patient's upper thighs. They are adjusted at equal height so that symmetry will be achieved when the legs are raised. Each of two persons raises one leg by grasping the sole of a foot in one hand and supporting the calf at the knee with the other. The knees are flexed and the legs placed inside the posts of the stirrups. If loop stirrups are used, the feet are placed in the canvas slings at a 90° angle to the abdomen. One loop encircles the sole and the other goes around the ankle. If the legs are properly positioned, both undue abduction and external rotation are avoided, and the lower leg or ankle does not contact the metal part of the stirrup. After the patient is positioned in the stirrups, the lower section of mattress is removed and the bed is lowered. The buttocks must not extend beyond the end of the operating bed. For lengthy procedures, antiembolic stockings or sequential compression devices may be used to minimize the risk of venous stasis and deep vein thrombosis. Other potential risks include pressure sores, and nerve damage or compartment syndrome from prolonged immobilization. When using universal stirrups with a boot, keep the toe, knee, and opposite shoulder in a relatively straight line and avoid knee abduction to gain exposure.

POSTOPERATIVE NOTE

Immediately following the procedure, a postoperative note should be written in the chart to include the preoperative and postoperative diagnoses, operation performed, surgeon, any assistants, findings at surgery, estimated blood loss, drains, specimens, and complications.

POSTOPERATIVE MANAGEMENT

Depending on the procedure, postoperative diet, and expected duration of recovery, postoperative pain control can be managed with oral nonsteroidal anti-inflammatory agents or narcotics, intravenous narcotics, or patient-controlled analgesia (PCA). PCA results in less overall narcotic administered, and less morbidity associated with the narcotic use, because the smaller, more frequent dosing regimen provides more of a steady state of drug delivery and concentration without the peaks and nadirs seen with longer interval dosing regimens. This results in more adequate pain control. Morphine sulfate, fentanyl, and hydromorphone are the drugs most amenable to PCA administration in children. The child must be age-appropriate in terms of ability to understand how to self-administer the medication as needed, as parents are not allowed to participate in PCA administration.

IV fluid administration should be continued postoperatively at a maintenance rate in patients who will be admitted. An order can be written to saline lock the IV system once the patient is tolerating PO liquids well. A patient with external losses such as through a nasogastric tube may be managed with D_5½NS plus 20 meq KCl/L and a patient without external losses with D_5¼NS plus 20 meq KCl/L. If the child will need IV fluids for several days and will be on strict intake and output, IV fluid rate may be titrated to keep urine output greater than or equal to 1 ml/kg/hour average up to 30 ml per hour, which is the minimum urine output expected in an adult. Consideration should be given for supplemental peripheral or central total parenteral nutrition if the patient will be NPO for several days or has a history of significant weight loss or poor nutritional status before surgery. Postoperatively, the safest way to resume oral intake after anesthesia is to initiate clear fluids and advance as tolerated. Patients who have had major intra-abdominal procedures and have been NPO for several days should have diet advanced over a period of days and only as it is tolerated. If a patient required nasogastric suction, non-carbonated liquids are recommended.

Activity following a procedure will be dictated by the procedure and its extent as well as the extent of the incision required. In general, most closed surgical wounds will be sealed within 48 hours, allowing bathing and showering to resume. Laparoscopic procedures require a limited period of reduced activities to allow fascial healing of umbilical and larger access incisions, approximately 2–3 weeks. Major laparotomies require restriction from organized sports and physical education for approximately 4–6 weeks. School age children who need to refrain from carrying heavy backpacks but are otherwise ready to resume attending school may request a second set of books for temporary use at home.

POSTOPERATIVE COMPLICATIONS

The most frequent postoperative complications in children and adolescents are similar to those seen in adults and include complications related to the respiratory tract, urinary tract, and wound. Patients should be encouraged to participate in their own care as soon as possible, including after major operations. Coughing, deep breathing, incentive spirometry, and early mobilization are all maneuvers to aid with minimizing postoperative atelectasis. Foley catheters should be removed as soon as possible to minimize the risk of an acquired urinary tract infection. Wound infections occur with increasing incidence after clean contaminated, contaminated, and dirty procedures. The use of antimicrobial prophylaxis can minimize the risk but not completely prevent it. Postoperative deep vein thrombosis is unusual but can occur in adolescents who require

prolonged bedrest. This risk can be minimized by using sequential compression devices, or with the use of temporary anticoagulation, if needed.

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26. Genital injuries and other gynecological emergencies in children and adolescents

Diane F Merritt

INTRODUCTION

Gynecologic emergencies often produce fear in the hearts of the patient, families who care for the patient, and medical providers who have not developed an organized protocol for assessing and managing these clinical problems. It may be easier for the practitioner to care for these patients if consideration is given to categories of common gynecologic emergencies and the developmental stage of the patient. Common categories of gynecologic emergencies include profuse vaginal bleeding, acute abdominal or vulvar pain, and female genital trauma. Profuse vaginal bleeding in an infant is always inappropriate and if it occurs it is most likely due to a tumor or trauma. Menstruating teens can present with profuse bleeding due to a coagulation disorder, anovulatory bleeding, or as a complication of pregnancy or trauma. Abdominal pain of gynecologic etiology in an infant or child may be related to torsion of the adnexa, tumor, or urinary tract infections. Once an adolescent begins to menstruate, she may present with pain due to dysmenorrhea, ovarian cysts, and hemorrhagic corpus lutea, or a complication of pregnancy. Obstructing anomalies of the reproductive tract may be asymptomatic until menarche, when menstrual bleeding results in hematometra and hematocolpos and pain. Pelvic endometriosis can cause symptoms in adolescents, as can adnexal torsion. Vulvar pain can arise as a result of infections or trauma. Female genital trauma includes injuries to the labia, vulva or vagina, as well as the anogenital and urogenital structures. Genital injuries alone rarely result in death, but may result in chronic discomfort, dyspareunia, infertility, or fistula formation if unattended. Obstetrically related injuries, while outside the scope of this chapter, may arise as a result of difficult or unattended deliveries and from prolonged obstructed labors. Women and children may also be victims of violence including non-consensual sexual intercourse, and sustain injuries as a result. In certain populations, female genital cutting or mutilation (FGM), also called 'female circumcision,' results in partial or total removal of the external female genitalia or other injury for cultural, religious or other non-therapeutic reasons. This intentionally mutilative practice is strongly discouraged by the World Health Organization (WHO) and women' rights groups.

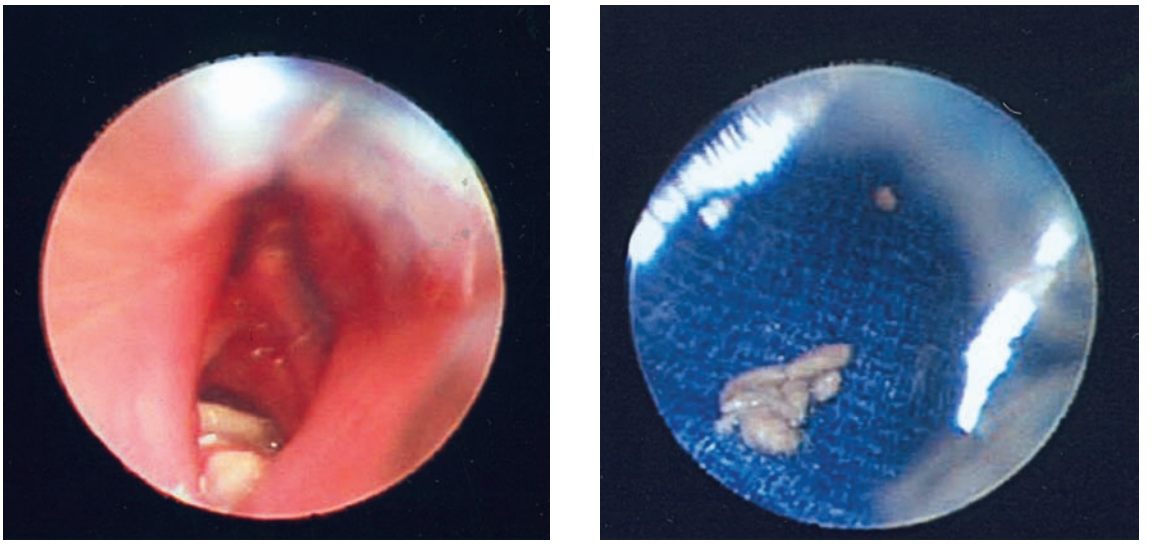
VAGINAL BLEEDING

INFANTS AND CHILDREN

Serosanguineous vaginal drainage in a child can be associated with vulvovaginitis (see below) or presence of a foreign body (Figure 26.1).

Vaginal placement of a pediatric cystoscope will allow visualization of the vaginal vault and allow assessment of foreign objects, lesions, or trauma (see Chapter 9).

Profuse vaginal bleeding in an infant is always inappropriate and if it occurs it is most likely due to a tumor or trauma. A rhabdomyosarcoma is a rare tumor which presents with vaginal bleeding in children (Figure 26.2). For this reason, if the source of bleeding cannot be readily identified, an examination under anesthesia and vaginoscopy is indicated. If a vaginal tumor is identified, the child should be referred to a tertiary care center where there is



(a) (b)

Figure 26.1 (a) Foreign material in the vagina of a prepubertal child as viewed through a vaginoscope. (b) The most common objects found in young girls' vaginas are wads of toilet tissue. These fibers become infected with bacteria and can cause an odor and serosanguineous bleeding. Courtesy of Dr DF Merritt.

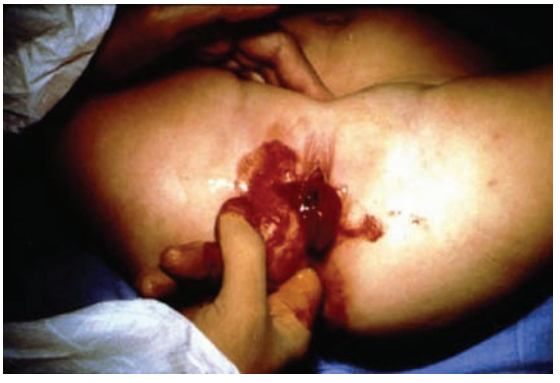


Figure 26.2 The rhabdomyosarcoma of the cervix is a very vascular tumor and usually presents as vaginal bleeding in a prepubertal child. Courtesy of Dr DF Merritt.

expertise in pediatric and gynecologic oncology. Urethral prolapse can result in bleeding in the prepubertal child and may require an emergency evaluation (see Chapter 29). If conservative management fails or if the tissue is extremely edematous and necrotic, the prolapsed tissue may be resected under general anesthesia.

ADOLESCENTS

Menstruating teens can present with profuse bleeding due to a coagulation disorder, anovulatory bleeding, or as a complication of pregnancy, or trauma. A general rule is to contact a health-care provider if the menstrual bleeding persists in excess of a pad an hour, extends beyond 10 days, or if the cycles are shorter than 20 days from the first day of flow to the next first day of flow. Initial evaluation includes a history, physical examination with vital signs, and laboratory testing. A complete blood count and pregnancy test is necessary even if the young woman denies any sexual contact. Coagulation studies are indicated if the bleeding is prolonged, and especially if there is a family history of bleeding problems, or if the teen presents with a history of epistaxis, gum bleeding, bruising or petechia. Thyroid function should be assessed. Pelvic ultrasound is helpful to

rule out any uterine anomalies, and can be utilized to determine if the endometrial lining is thick or thin. If the endometrium is thick, the teen should be treated with progestins (either combination oral contraceptive or medroxyprogesterone acetate). If the endometrium is thin, administer estrogens either intravenously or by mouth in conjunction with progestins. Occasionally the bleeding is due to low platelets, and in this case platelet transfusion is needed. Antifibrinolytic agents, like tranexamic acid or epsilon-aminocaproic acid, may be used to control excessive bleeding; however, this form of management is more common in countries outside the United States. Unlike adults, adolescents should not be subjected to a D&C (dilation and curettage). Adolescents will usually respond to medical management. The first menstrual cycles are often anovulatory, and as a result can be light or heavy and irregular. The medical evaluation and management have already been described above. Oral contraceptives are also effective for managing anovulatory bleeding and may be simpler to use than sequential hormones. In adolescents in whom the bleeding is not severe, oral contraceptives can be administered once or twice a day. Much is written recommending a higher dose of birth control pills (three or four a day) but this higher dose may cause nausea and is not usually necessary. If the pregnancy test is positive, abnormal vaginal bleeding may be associated with a threatened miscarriage, an ectopic pregnancy, or an intrauterine pregnancy. Serial quantitative measurements of B-hCG (human chorionic gonadotropin), and transvaginal ultrasound are useful in the diagnosis of a normal versus a complication of pregnancy (please see Chapter 9 for further management of abnormal bleeding in adolescents).

ABDOMINAL AND VULVAR PAIN

ADNEXAL TORSION IN CHILDREN AND ADOLESCENTS

The adnexal structures may twist in children or adolescents and cause recurrent or sudden episodes of abdominal pain, often associated with nausea and vomiting. In children, normal structures as well as pathologic neoplasms of the ovary may twist. In adolescents, the ovulatory changes that occur in the ovary can lead to enlargement and may precipitate torsion, as can the presence of a neoplasm such as an ovarian teratoma. The diagnosis is made clinically and an ultrasound can be of benefit when there are a unilaterally enlarged adnexa, pain, and nausea. A diagnostic laparoscopy is the most direct means to diagnose and treat this condition, and untwisting of the adnexal structure is currently recommended. Oophoropexy of the affected ovary or the contralateral ovary remains controversial (see the video on the CD Rom).

OVARIAN CYSTS

INFANTS AND CHILDREN

It is common for the ovary in neonates to respond to the uterine environment, which is rich in maternal hormones. Follicular cysts are common in the fetus and neonate. Large follicular cysts may cause respiratory compromise in neonates, and for this reason operative intervention may be indicated. Usually, following delivery, neonatal functional cysts will involute when the maternal hormones decrease, as long as there is no source of endogenous hormone production (see Chapter 30).

ADOLESCENT

Each month several follicles in each ovary are recruited and begin to mature. Usually one follicle becomes dominant; the other follicles will become atretic. Some follicles fail to ovulate and result in large follicular cysts, which may reach 3–8 cm in diameter. These follicular lesions are usually asymptomatic, but may be associated with an aching pelvic pain or severe pain if there is bleeding or torsion. Most follicular cysts resolve spontaneously over a course of 8 weeks. It is unlikely that suppressive therapy with oral contraceptive pills will shorten the course of resolution, but suppressive therapy may

prevent new follicular cysts from forming. Following normal ovulation, the granulosa cells that line the follicle become luteinized. Blood accumulates in the central cavity producing a hemorrhagic corpus luteum. Resorption of the blood results in a corpus luteum, which becomes a 'cyst' if it attains a size greater than 3 cm. Persistence of the corpus luteum may cause pain or tenderness; it may be associated with ovarian torsion, or it may rupture and bleed. The corpus luteal cysts usually resolve spontaneously in 4–8 weeks, and are usually treated conservatively with nonsteroidal anti-inflammatory medication and limited activity.

DYSMENORRHEA

Adolescents can thus experience pain at mid-cycle associated with ovulatory events, and they can also experience dysmenorrhea. Most patients can benefit from nonsteroidal anti-inflammatory agents or suppressive therapy with various forms of hormonal contraception (see Chapter 27).

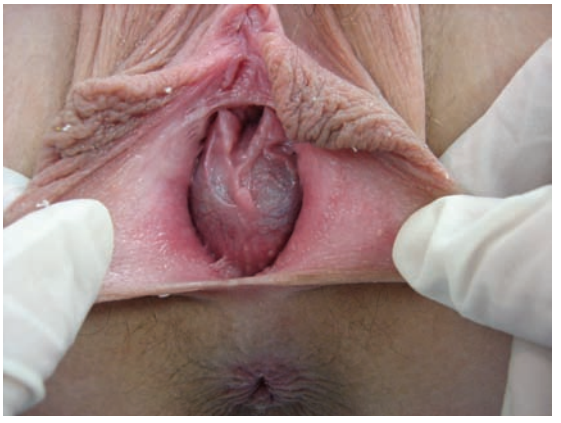


Figure 26.3 The imperforate hymen may be unrecognized until a young woman is menstruating, and the menstrual flow expands the vagina. The distended hymen will bulge out with a valsalva maneuver (straining). A rectal examination should reveal a hematocolpos or mass anterior to the rectum. If the vagina is not bulging and if a mass is not present on rectal exam, consider another diagnosis (vaginal agenesis or vaginal septum). Courtesy of Dr DF Merritt.

OBSTRUCTING ANOMALIES OF THE REPRODUCTIVE TRACT

Failure of development of patency of the uterine outflow tract can result in retained menses, hematometria, hematocolpos, and severe pain with each menses. Such teens will present with a pelvic mass. The obstruction may be at the level of the uterus, cervix, vagina, or hymen (Figure 26.3). A pelvic ultrasound is usually helpful in making this diagnosis, but a pelvic MRI with contrast is indicated to evaluate complex genital tract anomalies. An experienced pediatric gynecologist or reproductive endocrinologist should be consulted in the management of these patients (see Chapter 28).

ETIOLOGY AND MANAGEMENT OF ACCIDENTAL GENITAL INJURIES

STRADDLE INJURY

Straddle injuries occur when the soft tissues of the vulva are compressed between an object and the bones of the pelvis, the pubic symphysis, and pubic rami. This trauma may result in ecchymoses, abrasions, and lacerations. Extravasation of blood into the loose areolar tissue in the labia, along the vagina, the mons, or clitoral area may cause hematoma formation. Examples of commonplace accidental straddle injuries include falling onto the frame of a bicycle, playground equipment, or piece of furniture. Nonpenetrating injuries usually involve the mons, clitoris, and labia, and result in linear lacerations, ecchymoses, and abrasions. Lacerations may require repair under local or general anesthesia (Figure 26.4).

VULVAR HEMATOMAS

Vulvar hematomas (usually sustained as a result of a straddle injury) can be very painful and may prevent a child or adolescent from urinating because of pain and swelling. If the hematoma is not large, the

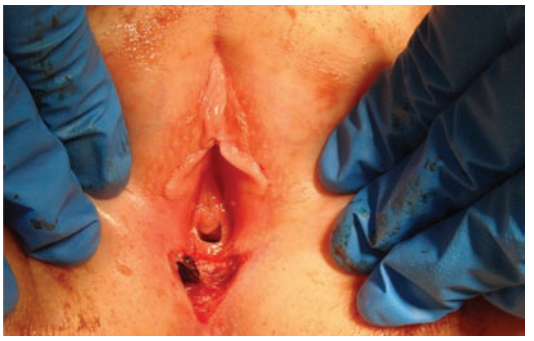


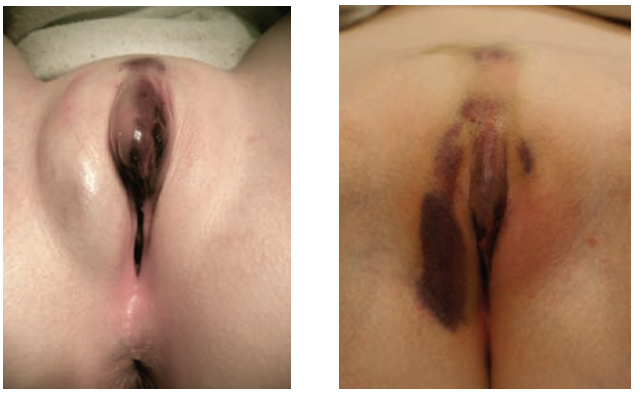
Figure 26.4 Straddle injury. Courtesy of Dr DF Merritt.

perineal anatomy is not distorted, and the patient has no difficulty emptying her bladder, the patient can be managed conservatively with immediate application of ice packs and bedrest (Figure 26.5). As the hematoma resolves, the blood will track along the fascial planes. The ecchymotic discoloration may take weeks to resolve. If the patient has a large vulvar hematoma and is unable to void, place an indwelling urinary catheter, and continue bladder drainage until the swelling resolves. Very large vulvar hematomas may dissect into the loose areolar tissue along the vaginal wall and along the fascial planes overlying the symphysis pubis and lower abdominal wall. Pressure from an expanding hematoma can cause necrosis of the skin overlying the hematoma (Figure 26.6). Evacuating the hematoma will reduce pain, hasten recovery, and prevent necrosis, tissue loss, and secondary infection. When incising large vulvar hematomas care should be taken to start at the medial mucosal surface near the vaginal orifice. The peri-clitoral area has a rich blood supply. Hematomas in this area require careful isolation of the bleeding vessels and hemostasis. If adequate hemostasis is not attained, the patient will be at risk for bleeding and re-accumulation of her hematoma. When the bed of the hematoma has been debrided of clot and devascularized tissue and hemostasis has been attained, place a closed system drain (i.e. Jackson-Pratt) to prevent re-accumulation of blood, to reduce pain, and to reduce the risk of bacterial growth.[1] Allow the drain to exit the skin in a dependent position, and close the skin primarily. The drain can be removed in 24 hours in most cases.

ACCIDENTAL PENETRATING AND INSUFFLATION INJURIES

These injuries occur if the victim falls upon a sharp or pointed object, and impales herself. Many common household objects are at risk for impalement including in-lawn sprinkling systems, pipes, fence posts, and furniture (chair-tops, bedposts, legs of stools). The vulva may display signs of injury, but the vagina, urethra and bladder, anus, rectum, and peritoneal cavity can be pierced by sharp or pointed objects. The physical findings closely mimic penetration by blunt forceful trauma; so sexual assault must be ruled out by history or corroboration by an eye-witness. The family can be asked to bring the object to the hospital for assessment by the trauma team. Generally these patients require an examination under anesthesia to fully assess the extent of the penetrating injury. If the rectum or peritoneal cavities are entered, an exploratory laparotomy or laparoscopy is indicated to determine the full extent of injuries and initiate repairs. Rectal injuries above the sphincter may mandate need for a diverting colostomy.[1]

Insufflation injuries occur when females fall off jet-skis and water-skis, slide down water chutes, and come in direct contact with pool or spa jets.[2–4] As pressurized water enters the vagina, the walls may over-distend and tear. Significant blood loss can occur if branches of the anterior division of the internal iliac artery, which supply the vagina, are avulsed. Such injuries may produce no sign of external genital trauma, and only careful vaginal examination (often under anesthesia) will reveal the source of bleeding and true extent of injury. Patients who participate in water sports can prevent vaginal insufflation injuries by using protective clothing such as wet-suits or cut-off jeans while water-skiing



(a) (b)

Figure 26.5 (a and b) This patient was climbing over a chair when she fell, sustaining a peri-clitoral hematoma. The follow-up photo (b) was taken 6 days later. Once it was determined that her hematoma was not expanding, this patient was managed conservatively. Tracking of blood along the tissue planes can be seen as well as documentation of changes in her clinical examination with the passage of time. Courtesy of Dr DF Merritt.

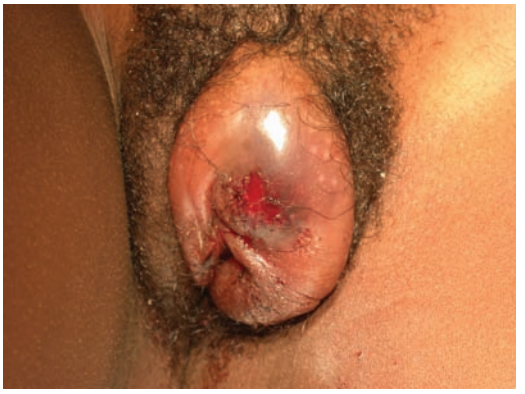


Figure 26.6 Large distorting hematoma. This expanding hematoma needs to be treated with incision and drainage to hasten the patient's recovery. The incision is made in the medial mucosal surface near the vaginal orifice. Courtesy of Dr DF Merritt.

or jet-skiing. When using a water-slide, head-first entries are usually forbidden to prevent head and neck injury, but it is also wise for girls to cross their ankles and/or to keep their feet together when entering water from a water-slide to prevent genital trauma.

CRUSH OR SHEAR INJURIES

Natural disasters or modern warfare may result in collapse of buildings with poor structural integrity, leading to crush injuries for the inhabitants. Motor vehicle accidents can also lead to crush injuries for pedestrians, cyclists, and both driver and passengers. Whenever a pelvic fracture occurs, genital injuries may arise when sharp spicules of the pelvic bone penetrate the vagina and lower urinary tract. This may lead to lacerations of the bladder, urethra, or vagina. Shear forces can lead to lacerations when there is a fall associated with rapid abduction of the lower extremities or from being run over by a slow-moving motor vehicle. As reported by Boos et al,[5] two children had perianal lacerations and two had hymeneal lacerations when the wheel of the vehicle passed longitudinally over the child's torso.

ANIMAL AND HUMAN BITES

Animal bites are a rare but potentially severe cause of genital trauma, and children are the most common

victims.[6] Animal bites are usually caused by the person's pet and, in children, frequently involve the face. Most of the cases of animal bites to the genital area are reported in the urology literature and involve male victims. Human bites tend to occur in children as a result of playing or fighting, while in adults they are usually the result of physical or sexual abuse. According to guidelines published by the American Academy of Pediatrics and the American Academy of Pediatric Dentistry: 'bite marks should be suspected when ecchymoses, abrasions, or lacerations are found in an elliptical or ovoid pattern … bites produced by dogs and other carnivorous animals tend to tear flesh, whereas human bites compress flesh and can cause abrasions, contusions, and lacerations but rarely avulsions of tissue. An intercanine distance (i.e., the linear distance between the central points of the cuspid tips) measuring more than 3.0 cm is suspicious for an adult human bite.'[7] Antibiotics may be given if there is deep puncture or crushing, with much devitalized tissue. Simple scrapes and abrasions are unlikely to benefit from antibiotic treatment. There is consensus that tetanus vaccination should be given routinely as part of wound care of mammalian bites, but no studies have assessed the benefit of this strategy. Vaccination need not be performed if there is a record of a tetanus shot being given in the previous 5 years. Management involves irrigation, debridement, and antibiotic prophylaxis, with tetanus and rabies immunization as appropriate.[8,9]

THERMAL AND CHEMICAL BURNS

The best way to prevent scalding injuries from bathing is by reducing the temperature in domestic hot water tanks, and testing the water temperature before placing an infant or child in the bath. In contrast to inflicted burns, accidental immersion burns, where a child falls into a container of hot liquid, typically have irregular borders and nonuniform depth as the patient is struggling to escape the hot liquid. This thrashing also causes splash marks, which, although they may sometimes be found in forced immersion, are more characteristic of accidental immersion. Accidental burns are also rarely full thickness, as they typically involve shorter contact time. In accidental splash and spill burns, the head, neck, and trunk are commonly involved as the hot liquid is pulled or knocked over from a higher surface and spilt by the child. Accidental contact burns are often patchy and superficial, as the child quickly withdraws from the hot object or the falling object brushes across the skin. They may or may not show a clear imprint. Scalds are the most frequent form of burn abuse. Up to 14% of all pediatric scalds are associated with abuse.[10] 'Tide marks' or clear lines of demarcation, characterize non-accidental bath scalds. They also tend to have uniform burn depth and commonly involve the buttocks, perineum, and lower extremities. Characteristic features of forced immersion include stocking and glove distribution, zebra stripes, and donut-hole sparing. Stocking and glove burns occur when a child's hands and/or feet are forcibly immersed in hot water, resulting in symmetrical, circumferential, and well-demarcated burns. Zebra stripes are due to sparing of the flexural creases secondary to the body's flexed position in the hot liquid. Donut-hole sparing occurs when the child buttocks are pressed against the bathtub, which is relatively cooler than the water in it. Simultaneous scald burns to buttocks, feet, and perineum are highly suspicious for physical abuse and warrant a thorough investigation, as do well-demarcated burns around the buttocks or bilateral symmetric glove and stocking burns. Inflicted contact burns are deeper, may be multiple, and have well-demarcated margins. They are commonly due to hot irons, radiators, hair-dryers, curling irons, and stoves. Contact burns with uniform depth and well-demarcated margins located on typically protected areas of the body suggest abuse. Cigarette burns represent a common form of burn abuse. Inflicted cigarette burns appear as 7–10 mm round, well-demarcated burns that have a deep central crater. They heal with scarring as they extend well into the dermis. Cigarette burns commonly appear grouped on the face, hands, and feet. When accidental, they tend to

be oval or eccentric and more superficial, as the child usually brushes against the cigarette. The location of a burn, although not pathognomonic, can be helpful when ruling out abuse. Face, hands, legs, feet, perineum, and buttocks tend to be predominant sites in abuse. The perineum and buttocks specifically are infrequently involved in accidental burns, and burns in this area are often inflicted as punishment for toilet training accidents.[10] Batteries placed in the vagina may result in chemical burns and have been described in the literature.[1,11] Genital burns can occur from use of medications intended to treat genital warts like imiquimod, podophyllin, or trichloroacetic acid. Such chemical burns should be treated immediately by irrigation to neutralize the chemicals and prevent further damage. The management of genital and perineal burns includes cooling the burn for 20 minutes with cold tap water within 3 hours of the injury to reduce pain and wound edema. It is unknown how effective topical application of antimicrobials and dressings are for the treatment of minor burns. A mixture of a topical antibiotic ointment and estrogen cream has been helpful for minimizing scarring from mucosal burns of the female genital tract. Silver sulfadiazine (SSD) cream has been historically used in burn wound management to minimize the risk of wound infection; however, no randomized trials or controlled clinical trials exist that evaluated the clinical effectiveness of SSD cream. There is no current consensus about the optimal dressing for burns in the genital area.[10]

COITALLY RELATED VAGINAL INJURIES

Consensual intercourse or sexual assault should be considered whenever an adolescent presents with vaginal trauma. The patient may be too embarrassed or distressed to explain her injuries, so the medical history may not give a full account of how the injury occurred. The correct diagnosis may be overlooked or delayed unless a proper pelvic examination is done to evaluate vaginal bleeding. Minor lacerations of the introitus and lower vagina can occur with initial coitus. Adolescents who sustain deep vaginal lacerations from coitus may present with intense vaginal pain, profuse or prolonged vaginal bleeding, and shock. Patients with vaginal agenesis may sustain deep lacerations from failed attempts at penetration. Urethral intercourse may occur in patients who have vaginal agenesis. Predisposing factors for coital injury are listed in Table 26.1.

Table 26.1 Predisposing factors for coital injury

Initial (first) coitus
Resumption of intercourse after a long abstinence
Coital positions that permit deep penetration
Previous vaginal surgery
Pregnancy or postpartum state
Menopausal state
Assault with a foreign object
Inebriation or substance use by either partner
Congenital anomalies of the vagina

SEXUAL ABUSE

Sexual abuse includes coerced or forced vaginal, anal, inter-crural, oral–genital fondling or penetration. This topic is addressed in detail in Chapter 18.

FEMALE GENITAL CUTTING/FEMALE CIRCUMCISION/FEMALE GENITAL MUTILATION

Female genital cutting or mutilation (FGM), often referred to as female circumcision, refers to all procedures involving partial or total removal of the external female genitalia or other injury to the female genital organs whether for cultural, religious or other non-therapeutic reasons. It is estimated that 100–140 million girls and women in the world have undergone some form of FGM, and 2 million girls are at risk from the practice each year. Most of these women live in subSaharan Africa, and some

live in the Middle East and Asia. Due to immigration of women from countries where FGM is practiced to other lands, medical care providers all over the world are now caring for these women. The World Health Organization (WHO), the International Council of Nurses (ICN), the International Confederation of Midwives (ICM), and the International Federation of Gynecologists and Obstetricians (FIGO) have openly condemned this practice of willful damage to healthy organs for non-therapeutic reasons. FGM is considered to be a form of violence against girls and women. The immediate health consequences of FGM include severe pain, shock, hemorrhage, urinary retention, ulceration of the genital region, and injury to adjacent tissue. Long-term complications include cysts and abscesses, keloid scar formation, damage to the urethra resulting in urinary incontinence, dyspareunia, sexual dysfunction, and difficulties with childbirth.

During vaginal deliveries, the infibulated woman has to be opened to allow passage of the baby. If this is not done, she is at risk for formation of vesicovaginal and rectovaginal fistulas, as well as undue suffering, including increased risk of stillbirth and maternal death. After opening an infibulated vulva to allow for childbirth or to treat urinary retention, hematocolpos, or infection, the health-care worker must ethically refuse requests to re-infibulate. This can result in professional and ethical dilemmas for the health-care worker. Increased awareness of the harmful effects of FGM and greater access to health-care services have resulted in requests to 'medicalize' FGM and have the operation performed by health-care professionals in clinical settings. The WHO policy prohibits performing this procedure in a medical setting.[12]

MANAGEMENT

INITIAL FIRST AID FOR GENITAL INJURIES

Initial first aid for a vulvar injury or vaginal laceration is compression of the bleeding. A clean dressing (wash cloth, sanitary pad, towel) can be held in place over the vulva by the patient or caregiver. By compressing the soft tissues against the underlying pelvic bones, an expanding hematoma can be prevented and blood loss can be minimized. The vagina can be packed using tampons or sterile gauze to slow blood loss from a vaginal laceration until a medical examination can take place. Ice packs can be held in position over minor hematomas and lacerations until the lesions can be assessed by a medical expert.

MINOR INJURIES OF THE EXTERNAL GENITALIA AND VAGINA

An apparently bloody injury may be quite superficial or minor. With the patient on an examination table, gently rinse or wipe away blood. Place the patient on a bedpan or fracture pan and pour warm water over the perineum to find the source of the bleeding. Direct inspection of a laceration will then allow the examiner to determine if there is active bleeding or if the bleeding has stopped. If the injury is very superficial and no longer bleeding actively, application of topical antibiotic ointment and good hygiene are all that is needed. A small sanitary pad can be worn in the underwear as the dressing. Avoid trying to tape dressings to the skin of the vulva, as they will quickly become soiled by urine and feces. Minor lacerations can be repaired under local anesthesia or with conscious sedation (Figure 26.7). Superficial abrasions of the hymen do not require suturing. Whenever there is an injury to the mucosal genital surfaces, application of topical estrogen cream can benefit the healing process and decrease scarring. A pea-sized amount can be massaged into the tissues once or twice a day for 3–7 days.[1] Superficial vaginal lacerations that are oozing but not bleeding may be managed with vaginal packing. The packing should be moistened with estrogen cream or saline to allow for easier removal. Vaginal lacerations that are actively bleeding should be sutured by someone with expertise to avoid injury to the urethra, bladder, and rectum.

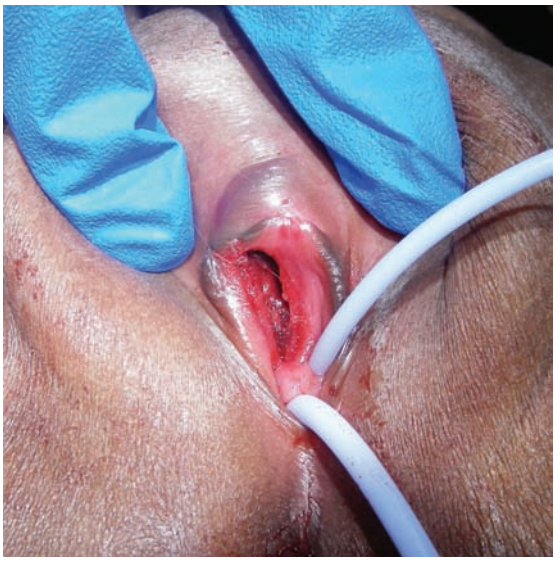


Figure 26.7 This child fell onto a broken metal bed frame and sustained this laceration. Initially we could not find the source of bleeding. A Foley catheter was placed in the vagina as a landmark, then a second catheter was placed in the bladder. The repair proceeded safely with knowledge of the location of the urethra. Courtesy of Dr DF Merritt.

MAJOR INJURIES OF THE EXTERNAL GENITALIA AND VAGINA

Blunt, forceful penetrating trauma to the vagina usually results in lacerations at the posterior aspect of the hymen. These patients may require examination and repair of their injuries under general anesthesia (Table 26.2). Lateral vaginal wall and posterior fornix lacerations can occur. In serious cases, the tear may extend along the vagina and enter the peritoneal cavity, avulsing the cervix from its attachment to the vagina. The bowel, omentum, or fallopian tubes may eviscerate through the laceration (Figure 26.8). These patients present with vaginal bleeding and may be at risk of morbidity or death from exsanguination, unless properly diagnosed and managed. Whenever the vaginal injury extends above the hymen where the true extent of the injury cannot be determined or repaired, an examination under general anesthesia is indicated.

Table 26.2 Indications for general anesthesia

Young or uncooperative patient
Transection of the hymen with inability to see the full extent of an injury
Vaginal hemorrhage
Expanding vulvar or vaginal hematoma
Concomitant injuries which require examination under anesthesia

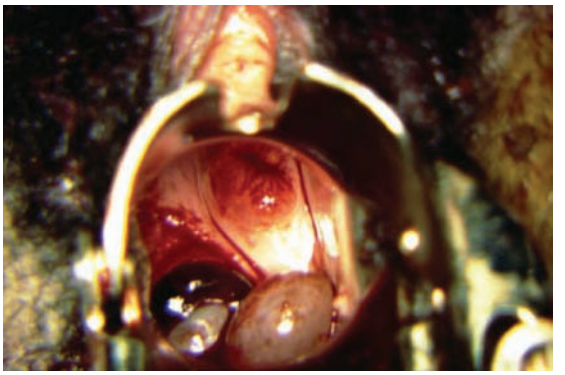


Figure 26.8 This adolescent was forcibly raped and her cervix has been avulsed from the vagina, resulting in evisceration of small bowel and clot into the vagina. This injury should be repaired under general anesthesia. Consideration should be given to performing a diagnostic laparoscopy or exploratory laparotomy to determine the extent of intra-abdominal injuries. Courtesy of Dr DF Merritt.

If it is necessary to inspect the vagina of a trauma victim and if a standard Huffman or Pederson vaginal speculum is too large for a prepubertal child or young adolescent, use a pediatric cystoscope and saline irrigation to visualize the vagina and determine the extent of vaginal injuries. Gently hold the labia together, allowing the fluid to distend the vagina and facilitate careful inspection of the vaginal walls and cervix. This technique is also very useful to determine if there is a foreign body present in the vagina of a child.

The importance of using a suitable light source and proper positioning, and obtaining complete cooperation (which may require sedation or anesthesia) cannot be overemphasized when attempting

to repair vaginal injuries. Perforations into the peritoneal cavity mandate an exploratory laparotomy or laparoscopy to determine if other structures, such as the bowel or blood vessels, have been injured. In the child or young adolescent who has a small-caliber vagina, begin repair of lacerations with the deepest (most distal from the introitus) vaginal injuries first, and end the repair with introital lacerations to allow for maximum working space and visualization. Postoperative application of topical estrogen cream to injuries of the mucosal surfaces of the vagina and introitus may decrease formation of granulation tissue and promote healing without stricture.[1] Every hospital should have a defined protocol for collection of forensic evidence in cases of alleged or possible sexual assault. It is useful and important to provide a clear description of the injuries with accompanying photodocumentation if available.

PSYCHOLOGICAL FACTORS ASSOCIATED WITH GENITAL INJURIES

Young victims of genital injuries and their families should be reassured about the future ability to bear children and have sexual relations. When appropriate, offer reassurance of reproductive capacity, as a patient or her family members will not always verbalize these concerns. Appropriate medical care and family support will allow the patient to recover emotionally as well as physically. Children and teens who are recovering from an isolated genital injury seldom have long-standing psychological trauma from the event. The exception would be an isolated injury, which leaves lasting scarring or vaginal stenosis. Victims of sexual assault may suffer from sleep disturbances, nightmares, flashbacks, anxiety, and anger. Depression is common in these victims, and often is compounded by feelings of guilt and shame. Offer specific referrals for professional counseling to all victims of sexual assault. Counsel the family so that they can be supportive of the young victim. In cases where the abuser is a member of the family or was allowed access to the child, establish that the child will be safe when returned to the home environment and arrange for long-term follow-up with the child and her family.

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27. Chronic pelvic pain and endometriosis

Joseph S Sanfilippo and M Jonathon Solnik

The evaluation of a young patient with chronic pelvic pain (CPP) can be one of the most challenging situations for the pediatrician and gynecologist alike. Often the most difficult aspect of providing care for these patients is the assessment phase, which may, in part, account for the long delays patients experience in both diagnosis and treatment.[1] Pain is a common and completely subjective condition, yet there is a lack of consensus as to how we should define chronic pain. The 2004 published guidelines from the American College of Obstetricians and Gynecologists (ACOG) define chronic pelvic pain as 'non-cyclic pain of 6 or more months' duration that localizes to the anatomic pelvis, anterior abdominal wall at or below the umbilicus, the lumbo-sacral back, or the buttocks *and* is of sufficient severity to cause functional disability or lead to medical care. A lack of physical findings does not negate the significance of a patient's pain, and normal examination results do not preclude the possibility of finding pelvic pathology'.[2] In fact, it is this lack of objective findings that maintains the diagnostic challenge.

The International Association for the Study of Pain (IASP) defines chronic pelvic pain as 'chronic or recurrent pelvic pain that has a gynecological origin but for which no definitive lesion or cause is identified'.[3] IASP has gone one step further and established four criteria focused on the behavioral components associated with chronic pelvic pain.

- Pain that is refractory to medical management.
- Significant impairment of physical function (including sexual function) has occurred.
- Vegetative signs of depression have begun.
- Patient's role within the family has changed secondary to the pain, or the family considers the pain to be the family's highest priority problem.

The incidence of pelvic pain has been reported to be 15% in women older than age 18.[4] This translates to one in seven, or over 9 million women. Of interest, the management cost is equated with an expenditure of close to 3 billion health-care dollars annually, including indirect costs. The analogy has been equated with the incidence of asthma or irritable bowel syndrome (IBS). Dysmenorrhea, or cyclic pain occurring with menses, is altogether more common than chronic pain, affecting up to 90% of adolescent females.[5] The relationship to the menstrual cycle is of significance, with focus on the nature of the pain, i.e. cyclic or non-cyclic. History should include menstrual-related information, i.e. interval, duration of flow, quantification of pain on a 1:10 scale with 10 as the most pain.

As clinicians, we must approach CPP from a multisystem perspective, or we risk failing to appropriately evaluate this large group of patients. Table 27.1 contains a list of nongynecologic causes of chronic pain in women. The more common gastrointestinal etiologies include chronic constipation and IBS. A detailed history focused on this system is important in determining the underlying etiology of the CPP. A comprehensive assessment by a gastroenterologist familiar with pain syndromes is prudent, as ancillary studies may be required to effectively rule out organic causes. However, treatment for conditions such as IBS may be as simple as implementing dietary changes. A visual analogue scale provides useful information from the patient (Figure 27.1).

Disorders of the urinary tract should be a routine component in evaluating young patients with chronic pain. The European Society for the Study of Interstitial Cystitis has worked to create a consensus regarding the diagnosis in light of the lack of agreement among experts. They recommend changing the name to painful bladder syndrome (chronic

Table 27.1 Nongynecologic conditions that may cause or exacerbate chronic pelvic pain, by level of evidence

Level of evidence	Urologic	Gastrointestinal	Musculoskeletal	Other
Level A	Bladder malignancy Interstitial cystitis* Radiation cystitis Urethral syndrome	Carcinoma of the colon Constipation Inflammatory bowel disease Irritable bowel syndrome*	Abdominal wall myofascial pain (trigger points) Chronic coccygeal or back pain* Faulty or poor posture Fibromyalgia Neuralgia of iliohypogastric, ilioinguinal, and/or genitofemoral nerves Pelvic floor myalgia (levator ani or piriformis syndrome) Peripartum pelvic pain syndrome	Abdominal cutaneous nerve entrapment in surgical scar Depression* Somatization disorder
Level B	Uninhibited bladder contractions (detrusor dyssynergia) Urethral diverticulum	–	Herniated nucleus pulposus Low back pain* Neoplasia of spinal cord or sacral nerve	Celiac disease Neurologic dysfunction Porphyria Shingles Sleep disturbances
Level C	Chronic urinary tract infection Recurrent, acute cystitis Recurrent, acute urethritis Stone/urolithiasis Urethral caruncle	Colitis Chronic intermittent bowel obstruction Diverticular disease	Compression of lumbar vertebrae Degenerative joint disease Hernias: ventral, inguinal, femoral, spigelian Muscular strains and sprains Rectus tendon strain Spondylosis	Abdominal epilepsy Abdominal migraine Bipolar personality disorders Familial Mediterranean fever

Level A, good and consistent scientific evidence of causal relationship to chronic pelvic pain; level B, limited or inconsistent scientific evidence of causal relationship to chronic pelvic pain; level C, causal relationship to chronic pelvic pain based on expert opinions.
*Diagnosis frequently reported in published series of women with chronic pelvic pain. Reproduced with permission from Howard FM. Chronic pelvic pain. Obstet Gynecol 2003; 101: 594–611.

pain, pressure or discomfort related to the urinary bladder, accompanied by one urinary symptom).[6] Medical history should include prior surgical procedures, prior treatments and results, medications, and response. Any significant changes in weight should be noted, as well as habits such as tobacco, alcohol and/or substance abuse, fatigue, joint pain, headache, depression, and/or anxiety. It is of paramount importance to inquire about prior sexual or physical abuse in all patients with CPP. The details of the effect of the pain on activities of daily living are especially important; lifestyle changes and effects on the family also need to be correlated with the problem.

Details on the nature of the pain are important, and can facilitate the direction of the assessment. One logical assessment is to proceed with the PQRST assessment (Table 27.2).

As most gynecologists focus on what is most common for their practices, differentiating pain from nongynecologic causes is equally important. Table 27.3 provides a list of differential diagnoses and tools. In adolescents, use of a printed diagram is especially helpful, as they can mark the areas of most intense pain. Sexual history-related information must be obtained in the absence of parent(s). The teen must have the concept of confidentiality explained and understood. In addition, the family history, including evidence of endometriosis, inflammatory bowel disease, fibromyalgia, depression, systemic lupus erythematosus, interstitial cystitis, should be elicited.

A. McGill present pain index.

People agree that the following 5 words represent pain of increasing intensity.

1	2	3	4	5
Mild	Discomforting	Distressing	Horrible	Excruciating

To answer the questions below, write the number of the most appropriate word in the space beside the question.
1. Which word describes your pain right now?____
2. Which word describeds it at its worst?____
3. Which word describes it when it is least?____
4. Which word describes the worst toothache you ever had?____
5. Which word describes the worst headache you ever had?____
6. Which word describes the worst stomachache you ever had?____

B. Visual analog scale

Please place a mark on the line at the location that most appropriately rates your pain severity:

No pain — Worst possible pain

(Line is 10 cm long)

C. Visual analog scale (modified)

Please circle the number that most appropriately rates your pain severity.

0 1 2 3 4 5 6 7 8 9 10

No pain — Worst possible pain

Figure 27.1 Pain index. Reproduced with permission from Howard F, Chronic pelvic pain. Obstet Gynecol 101: 594–611, Copyright ACOG (2008).

Table 27.2 Assessment of chronic pelvic pain

P	Provocative/palliative factors
Q	Quality of pain: sharp or dull
R	Radiation and relief
S	Severity
T	Timing

The salient feature of any adolescent with either acute or chronic pelvic pain is that organic pathology must first be excluded, since the majority of patients will have positive findings at laparoscopy. In an older study, a group of investigators found that 73% of adolescents presenting with chronic symptoms had notable findings at laparoscopy, the most common of which was pelvic inflammatory disease (PID). Also, 19% had documented endometriosis, a diagnosis that was more predictive if severe dysmenorrhea was a presenting complaint.[7] Despite the high prevalence of disease, approximately one-third of patients had a 'negative' laparoscopy, suggesting that disease was not recognized or that patients with chronic pain should be thoroughly assessed before surgical exploration.

Table 27.3 Differential diagnosis and diagnostic tests useful in the evaluation of pelvic pain in women

Symptom, finding, or suspected diagnosis	Potentially useful tests
Endometriosis – endosalpingosis	Pelvic ultrasound; magnetic resonance imaging; surgical diagnosis; tumor markers
Adenomyosis	Pelvic ultrasound; magnetic resonance imaging; histopathologic diagnosis
Pelvic floor tension myalgia	Assess posture; single-digit examination for trigger points
Constipation	Colonic transit time
Depression	Thyroid-stimulating hormone; thyroxine; tri-iodothyronine levels; antithyroid antibody; complete blood count; renal function tests; hepatic function tests; electrolytes; rapid plasma regain; refer for analysis
Diarrhea	Stool specimens for ova and parasites; stool polymorphonuclear leukocytes and erythrocytes; stool cultures; stool for *Clostridium difficile* taxin; stool guiac testing; barium enema radiography; colonoscopy; upper gestraintestinal series with follow-through; computed tomography
Dyspareunia	Urethral and cervical gonorrhea and *Chlamydia* cultures; vaginal cultures; urine cultures; vaginal wet preparations; vaginal pH; pelvic floor assessment
Cystitis	Urinalysis and culture
Interstitial cystitis	Cystourethroscopy; potassium chloride challenge test; urine culture; urine cytologies; urodynamic testing; bladder biopsy
Hernias	Abdominal wall ultrasonography; computed tomography; herniography
Pelvic congestion syndrome	Pelvic venography; ultrasonography ± Doppler
Irritable bowel syndrome	Rome criteria
Müllerian anomaly	Magnetic resonance imaging

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PSYCHOLOGICAL HISTORY

Patients with CPP quite frequently have a history of depression, somatization, and symptomatology related to borderline personality disorder.[8] Inquiry regarding a history of physical and/or sexual abuse must be correlated with the findings of CPP, as noted above. The psychological history includes demographic variables and current mental status. This would include current psychological illness, i.e. depression, anxiety, and mood lability, as well as stress management. Information regarding family dysfunction, chemical dependency, parental divorce, or loss of parent, close relative or friend needs to be determined.[9]

PELVIC PAIN ARISING FROM MUSCULOSKELETAL CAUSES

Quite frequently, adolescents who seek medical advice for chronic pain are left with no conclusive diagnosis. As a result, treatment options often fail since the practitioner does not know what to treat. This presents the question of organic versus functional pain, the latter being defined as pain with no identifiable or physical source. To provide patients with this diagnosis, a thorough evaluation as described in the preceding section must first be performed. These women may represent a group who demonstrate an exaggerated response to a normal stimulus, but otherwise do not suffer from significant physical morbidity. These patients are often diagnosed with associated pain syndromes (e.g. fibromyalgia, IBS). Table 27.4 contains a list of characteristics that help to identify organic from functional pain.

To assess the topic of functional pain, the interview can then be directed towards evaluation of the pelvic floor musculature, a component often overlooked by clinical gynecologists simply because of the lack of exposure during their training. A musculoskeletal origin of pelvic pain should receive due consideration in the adolescent. One study noted an incidence of 26% of musculoskeletal as the etiology of CPP.[10] Trigger points on physical exam provided the initial basis for a musculoskeletal origin of the CPP. Trigger points are areas of hyperirritability that are locally tender on compression and cause referred pain and tenderness; the myofascial pain syndrome occurs within taut bands

Table 27.4 Features suggesting organic vs functional pain

Organic pain	Functional pain
Consistently localized	Periumbilical or diffuse
Awakens patient from sleep	Variable location
Precipitated by eating	Exacerbated by stress
Recent onset	Present for months before seeking medical attention
Involuntary weight loss	
Delayed puberty	Functional impairment out of proportion
Systemic symptoms consistent with single disease	No objective findings

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of skeletal muscle that cause pain.[11] Currently, most of the theories related to development of trigger points implicate noxious stimuli to the affected fascia and muscles. Sustained muscle contractions, such as those caused by poor posture or in response to an injury, may be a trigger. Cold or damp weather or a new physical activity in an unconditioned adolescent or adult can also play a role in the etiology of pain.[12] Nevertheless, pelvic floor tension myalgia is common in patients with both organic and functional pelvic pain. In a cross-sectional analysis of 987 women being evaluated for CPP, investigators found that 22% had levator ani tenderness and 14% had piriformis tenderness. Pain at these sites correlated with a greater number of pain sites, previous surgery for pelvic pain, and higher pain scores by validated surveys.[13]

Both acute and chronic pelvic pain can be associated with trigger points in the abdomen, vagina or sacral area. The referred pain is often visceral, similar to dysmenorrhea. This can present as dyspareunia, genitourinary symptoms or gastrointestinal symptoms in adolescents as well as in adults. The trigger points are distinctive areas on physical examination. The referred pain is often poorly localized and does not follow a dermatome pattern. A thorough physical exam is most important in identifying trigger points. The specific technique involves gently pinching the abdominal skin along each dermatome from T10 to L1; contralateral sides should be compared. Sharper sensation is indicative of areas of hypersensitivity and thus a trigger point(s). Palpation of the vaginal and sacral areas will identify trigger points in these areas (Table 27.5).[14]

Table 27.5 Examples of musculoskeletal etiologies of CPP

Iliopsoas spasm
Hernia
Athletic-related injuries
Levator ani spasms

Levator spasms are described as a 'falling out' sensation. The pain radiates to the low back area. There is absence of a cyclic pattern to the pain. In the sexually active teen there may also be an element of dyspareunia or bowel-related complaints, i.e dyschezia. The pain is often in the sacral area. On physical exam, tenderness on palpation is noted and the pain increases with muscle contraction. Piriformis spasms are characterized by pain in the morning when the patient wakes up, and exacerbation with climbing stairs or driving a car. On physical exam, the pain is elicited on external thigh rotation. It may also be palpated over the involved muscle or transvaginally.

Treatment involves injection of local anesthetics such as 0.25% bupivicaine or 1% procaine into the trigger points. Pelvic floor physical therapy, with or without injections, provides exceptional relief for many patients with pain related to pelvic floor dysfunction.[15] Vasocoolants and stretching have also been advocated, as well as chiropractic flexion–distraction in combination with trigger points.[16,17]

PHYSICAL EXAMINATION

Physical examination should include general appearance, gait, posture alterations, and facial expressions. Always begin with a detailed abdominal

exam, or if necessary, delay any exam until a second visit, designed to identify points of maximum tenderness as well as trigger points. This first step is non-invasive and often well accepted by young patients. Evidence for incisional hernia or nerve entrapment from previous surgical exploration, neuropathic pain, and joint disease should also be assessed. As indicated, the pelvic exam should include inspection of the external genitalia, vulva, hymen/vestibule, and urethral meatus for any structural or congenital abnormalities. Assess for vestibular hyperasthesias with a Q-tip or gentle digital exam. Single-digit exam should first be used to assess the pelvic floor musculature. Often, patients with vaginismus or pelvic floor myalgia will accommodate a one- rather than a two-finger exam. Bimanual exam may not be necessary, but always consider rectovaginal examination for patients whom you feel have a high probability of endometriosis. Fibrotic disease, which may include the uterosacral ligaments or retrocervical areas, is not unknown in young patients. These lesions can easily be missed without a rectal examination. Any vaginal discharge, cervical motion tenderness, uterine size, texture, tenderness and mobility as well as evaluation of the adnexa are equally useful (see Tables 27.6–27.10 and Figure 27.2).

TREATMENT OPTIONS FOR CHRONIC PELVIC PAIN

Suppression of ovulation with oral contraceptives (OCPs) may be efficacious with respect to management of CPP. In addition, inhibition of ovulation is associated with reduction in uterine contraction and a positive effect with regard to the effects of prostaglandins.[18]

The controversy continues with respect to continuous vs cyclic administration. Progestins in the form of depot medroxyprogesterone acetate (DMPA) have been utilized for ovulation suppression and pain management and found to be effective.[19] Physical therapy is associated with 65% improvement, especially when pelvic floor myofascial trigger points are noted.[20]

Table 27.6 Pelvic pain-related health-care utilization in the last 3 months for 773 women with chronic pelvic pain

Resource	*n* (%) who used resource*
Health-care provider	
None	583 (75)
Gynecologist	145 (19)
Physician other than gynecologist	75 (10)
Psychiatrist or other mental health professional	10 (1)
Alternative health-care professional (e.g. acupuncturist, chiropractor)	22 (3)
Hospitalization for pelvic pain	24 (3)
Surgery for pelvic pain	19 (2)
Other procedure for pelvic pain (e.g. ultrasound)	58 (8)
Infertility testing or treatment	11 (1)
Treatment at pain management clinic	10 (1)
Medication, any type	516 (67)
Nonprescription pain medication	435 (56)
Prescription pain medication	174 (23)
Oral contraceptives or oral hormones	96 (12)

*Because some respondents reported using more than one resource per category percentages do not add up to 100% for any given category of resource. Reproduced with permission from Mathias S, Kuppermann M, Lieberman R et al. Chronic pelvic pain: prevalence, health-related quality of life and economic correlates. Obstet Gynecol 1996; 87: 321–7.

Table 27.7 Laboratory evaluation of chronic pelvic pain

Complete blood cell count (CBC)
Urinalysis (U/A) and culture
Erythrocyte sedimentation rate (ESR)
Pregnancy test
Cultures for sexually transmitted infections (STIs)

Table 27.8 Imaging studies for chronic pelvic pain

Pelvic ultrasound
Magnetic resonance imaging (MRI)
Voiding cystourethrogram-cystoscopy

Table 27.9 Factors that exacerbate chronic pelvic pain

Physical and sexual abuse
Prior sexually transmitted infection
Endometriosis
Interstitial cystitis
Irritable bowel syndrome
Prior abdominal surgery
Pelvic floor trauma in association with childbirth
Musculoskeletal disorders: kyphosis, bad posture

Reproduced with permission from ACOG Practice Bull No. 51, Chronic Pelvic Pain, March 2004.

Table 27.10 Management of chronic pelvic pain

Analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors
Oral contraceptive pills (OCPs)
Non-medical therapy (neuroleptics)
Physical therapy
Acupuncture
Surgical intervention

Other modalities include magnetic field therapy, which involves placement of magnets at abdominal trigger points. Nerve stimulation with TENS units has also been described.[21,22] Acupuncture and acupressure have entered clinical trials and preliminary data are promising regarding improvement in comparison with placebo.[23]

Surgical intervention in the form of laparoscopy remains an option, especially when medical therapy fails. Song and Advincula reported an abnormal rate of findings ranging from 60 to 75% (Table 27.11).[24]

The role of presacral neurectomy (PSN) remains controversial and appears to be best suited for patients with midline pelvic pain.[2] Findings from Italy suggest that PSN may be a helpful surgical adjunct in patients with endometriosis, but the surgeon should be cautious when offering this procedure to young women given the high rate of postoperative bowel and bladder complaints.[25] Furthermore, the surgeon should be skilled and familiar with the anatomy of the presacral space, given the risk of significant intraoperative hemorrhage.

Incidental appendectomy has been evaluated with CPP. Lyons and co-workers reported on 190 patients with CPP in a retrospective study.[26] The study design evaluated the efficacy of prophylactic appendectomy. Of note, 154 appendices were abnormal. Pathologic findings in this group of patients ranging in age from 16 to 54 years included: endometriosis, carcinoid, chronic appendicitis, periappendicitis, fibrous obliteration, and lymphoid hyperplasia. The authors concluded that prophylactic appendectomy in patients being evaluated for CPP is appropriate in light of the high incidence of abnormal findings.[26]

DYSMENORRHEA AND ENDOMETRIOSIS

INTRODUCTION AND EPIDEMIOLOGY

Endometriosis is a chronic inflammatory condition defined by endometrial stroma and glands found outside of the uterine cavity; this has long been known to affect adolescent girls.[27] Despite the initial series reported over six decades ago, many young patients presenting with chronic pain experience significant delays in diagnosis or treatment due, in part, to the lack of awareness by clinicians. In recent years, this cohort has received more attention, and as a result, we should see improvement in therapeutic outcomes.

Our ability to provide exceptional care for adolescents hinges on prompt diagnosis. Given the high prevalence of disease, particularly among patients who complain of progressive dysmenorrhea that does not respond to first-line therapies,[28] we should not underestimate the impact of such complaints. Rates as high as 73% have been reported in the literature ascribed to adolescents,[29] although most epidemiological assessments quote lower

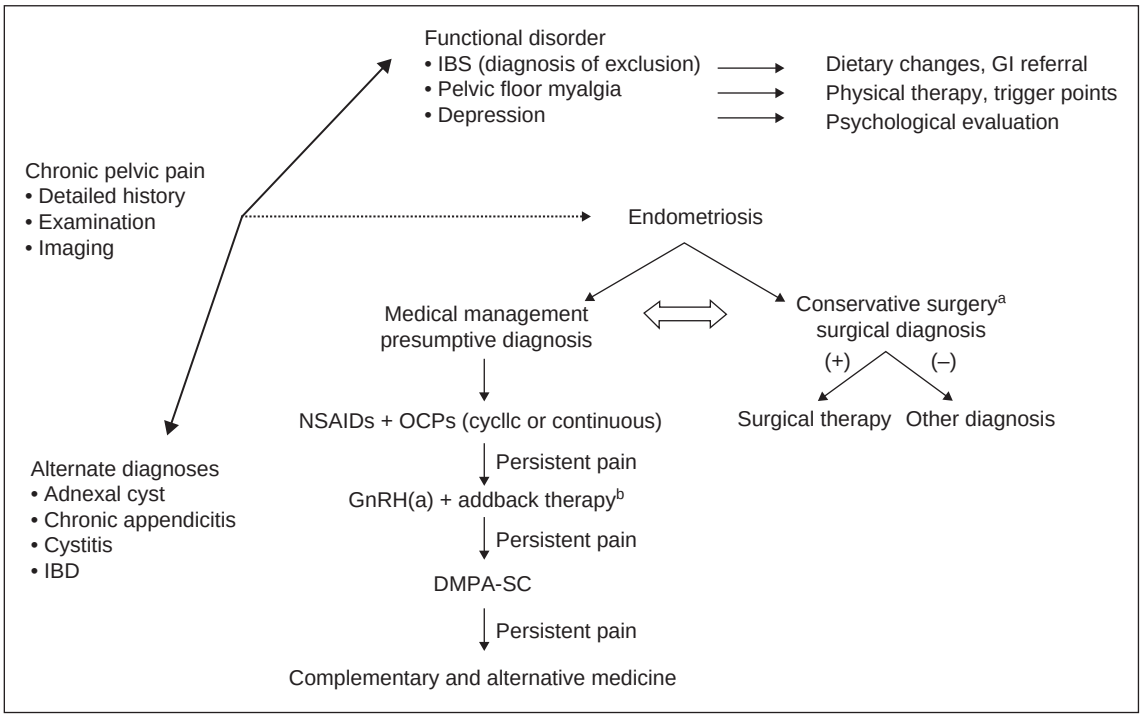

Figure 27.2 Algorithm for treatment of chronic pelvic pain in adolescents
[a]Surgical diagnosis and conservative laparoscopic treatment may be considered at any point but ideally after initial trial of medical management fails. Postoperative suppression with oral contraceptive pills (OCPs) or gonadotropin-releasing hormone (GnRH) agonists may be considered. [b]Add-back regimens include daily norethindrone acetate (5 mg) with or without conjugated equine estrogens (0.625–1.25 mg). GnRH agonists include depot leuprolide acetate (3.75 mg) monthly approved for up to 12 months with add-back therapy; DMPA-SC is subcutaneous depot medroxyprogesterone acetate (104 mg/0.65 ml) every 3 months.[46] IBS, irritable bowel syndrome; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; IBD, inflammatory bowel disease (ulcerative colitis, Crohn's disease). Reproduced with permission from J Solnik. Curr Opin Obstet Gynecol 2006; 18: 511–15.

Table 27.11 Laparoscopic findings in adolescents with chronic pelvic pain

Finding	Incidence
Normal pelvis	25–40%
Endometriosis	38–45%
Ovarian cyst	2–5%
Uterine malformations	5–8%
Postoperative adhesions	4–13%
Pelvic inflammation	5–15%

Reproduced with permission from Proctor M, Smith C, Farquhar C, Stones R. Transcutaneous electrical nerve stimulation and acupuncture for primary dysmenorrhoea (Cochrane Review). In: The Cochrane Library, Issue 4. Chichester, UK: John Wiley & Son, 2003.

estimates of 8–10% in the general population, including adults.[30] Most referral centers will likely encounter higher rates due to self-selection. Such a discrepancy supports our relative inability to correctly identify patients with endometriosis, and further lends support to the concept of 'more heads are better than one'. These same series noted a higher prevalence in older subsets of adolescents, further suggesting that endometriosis may be progressive in certain groups of patients. This raises the question as to whether early intervention in this susceptible group can prevent or minimize adverse outcomes later in life, i.e. chronic pain and infertility.

PRESENTATION

Although progressive dysmenorrhea remains one of the most common complaints among girls with endometriosis, symptomatology can vary significantly. Primary dysmenorrhea, or cyclic pain that occurs in the absence of pelvic pathology, is particularly common in adolescent females, and may be difficult to separate from symptoms suggestive of endometriosis. However, many patients with endometriosis will eventually present with chronic, acyclic pain that may differ in quality from the cyclic component. Often, the ability to distinguish one from the other becomes blurred.

These patients often miss school, their family lives are affected, and they may refrain from activities such as organized sports or social events because of pain. Possibly the most worrisome area of concern is the long delay many patients experience from initial onset of symptoms to diagnosis and eventual treatment. Data from the Endometriosis Association confirmed this delay. Approximately 50% of patients who answered surveys reported seeking medical advice from at least five physicians before receiving acceptable care.[1] The average interval from onset of symptoms to diagnosis in adult patients was approximately 10 years. Failing to seek advice until symptoms are severe and physicians reluctant to treat the younger group of patients probably contribute to such a delay. Needless to say, educating those who care for adolescent patients may reduce this lengthy wait. Our ability to impact disease progression through early treatment is not established, but initiating treatment that could improve the quality of life in patients with pain is indispensable.

PATHOPHYSIOLOGY AND GENETICS

From a mechanistic perspective, retrograde menstruation remains one of the most widely accepted pathophysiologic models to explain the development of endometriosis.[31] As a stand-alone process, this theory fails to explain why only a minority of patients who demonstrate retrograde flow develop endometriosis. Certain patients must not be able to clear the menstrual debris, whereas others may have a structural lesion that increases the cellular burden on the peritoneal surface. The latter can be corroborated by the small group of patients with müllerian anomalies that result in outflow obstruction of the reproductive tract.[32] Most, if not all menstrual effluent is unable to follow the path outward, resulting in a significant amount of consistent exposure to peritoneal surfaces. Once normal anatomy is restored and the obstruction relieved, these patients experience a remarkable transformation and represent a group that can be 'cured' of their disease. Patients with asymmetric lateral fusion defects such as unicornuate uterus should undergo upper abdominal imaging, given the high rate of associated renal anomalies. To help explain the former, various investigators are attempting to establish a link between endometriosis and selectively deficient cell-mediated immune clearance pathways. Patients with more advanced stages of disease may have infiltrating lesions, resulting in peritoneal fibrosis and distortion of the anatomy. Some of these patients may present before menarche, which supports the proposal of müllerian rests, cells present in the female pelvis during embryogenesis. These reactive cells are then stimulated by estrogen produced early in puberty with the activation of the hypothalamic-pituitary-ovarian (HPO) axis. Rather than appearing as surface lesions from retrograde flow, these cells may invade into deeper tissues. Since depth of invasion has been clearly associated with pain symptoms,[33] these patients may be more at risk for pain symptoms at a younger age. The earliest age of onset following menarche was reported to be 10 years.

The role of oxidative stress and generation of free radicals in promoting endometriosis is another area of research, even at the gene level. Perhaps environmental exposures and toxins may facilitate progression in at-risk patients.[34]

DIAGNOSIS AND SURGICAL CHARACTERISTICS

The initial history taking often provides enough information to reach a diagnosis, although physical

exam will clearly be useful in ruling out other or associated causes of pain. It is not unreasonable to have the patient return for a second consultation to perform an exam. This degree of patience may relieve stress associated with the much anticipated visit, and may go a long way to help in establishing a positive and interactive relationship.

Imaging modalities such as transvaginal ultrasound are useful for evaluating pelvic anatomy, and in the setting of endometriosis, may diagnose ovarian involvement. Ovarian endometriomas are not commonly seen in the younger patient. Nevertheless, the absence of pelvic disease on ultrasound does not negate the potential for peritoneal disease. MRI may be useful for detecting infiltrating lesions and so help guide the clinician for surgical intervention, but if the level of suspicion is high, then surgery may be offered at any point in the evaluation.[35] Although surgery often follows, the clinician should take great care not to lead such a patient towards a future of multiple surgeries, since this paradigm not only results in increasing intraoperative risk, but often does not yield therapeutic results.

Direct visualization of implants at the time of surgery and histopathology do not always correlate, since there is no standardized method used by all pathologists and atypical lesions may be difficult to assess without biopsy.[36] Positive predictive values of peritoneal biopsies are between 40 and 50%, but surgical experience may increase the sensitivity to 97%.[37] Approximately 25% of peritoneal biopsies are unrevealing. Surgical characteristics of endometriosis in adolescents favor earlier stage disease, based on the American Society for Reproductive Medicine revised classification system. These are often clear to colored, vesicular lesions superficially imbedded on the peritoneal surface.[38–40] Historically, these were not recognized as endometriotic implants, thus affecting the true prevalence documented in years past. These lesions are active prostaglandin producers, an attribute that substantiates the high rate of dysmenorrhea.[5] More typical lesions seen in adults are often documented at surgery as well. In fact, older adolescents are more likely to have fewer early-stage (formerly considered atypical) implants and their implants are more like those of adults.[33] This suggests a progressive disorder, and unfortunately, deep and painful implants are not unique to adults[39] (Figure 27.3).

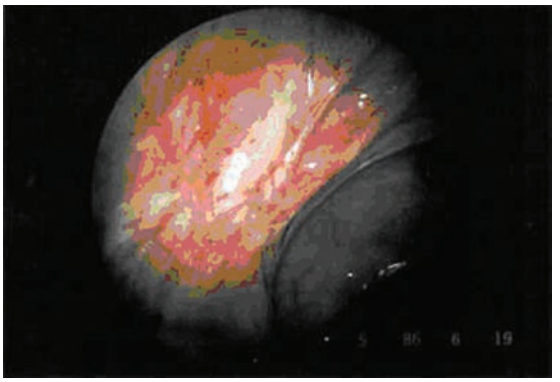

Figure 27.3 Endometriosis implants in adolescents. Used with permission from Suketu Mansuria, MD, University of Pittsburgh Physicians, Pittsburgh, PA, USA.

TREATMENT OPTIONS

Only after a comprehensive assessment that facilitates exclusion of other organic or functional causes of pain should the clinician provide endometriosis-targeted therapies. If empiric therapy is offered too readily, therapy is more apt to fail, resulting in frustration and the possibility of distrust on the part of the patient.

No one therapy has been proven substantially superior to any other and some experts would admit that if pain is the complaint, then reducing pain to an acceptable level should be the goal. Even if treatment is deemed successful, many patients are not cured of their pain, and many will experience recurrent symptoms. Being honest and realistic while providing individualized care will ultimately facilitate a positive interaction and improvement in the patients' quality of life. Needless to say, the best management involves early evaluation and prompt intervention.

Most treatment paradigms used to treat adolescents have been based on research focusing on

adults, with only a small percentage of the literature centering on this group. Although medical management is frequently used as first-line therapy, surgical intervention can be offered at any point in the evaluation or if advanced disease is clinically suspected. Various experts in the field differ in opinion with regards to the timing of surgical intervention, with opponents offering that one surgery at a young age may predispose to several by the time the patient has reached adulthood. Proponents feel that long-term medical therapy, which is often necessary to suppress symptoms, should not be considered until a surgical diagnosis is confirmed.

While no studies have demonstrated that early intervention curbs disease progression, it may allow for a more functional lifestyle if it is focused on managing pain symptoms. Most non-surgical remedies comprise hormonal agents that suppress endometriotic growth, either directly or indirectly. Nonsteroidal anti-inflammatory drugs (NSAIDs) represent a pharmaceutical class that may reduce the inflammatory response produced by this disease process and may limit symptoms.[41] There appears to be positive feedback between prostaglandin (PG) synthesis, aromatase activity, and estrogen production, mediated by abnormally high cyclooxygenase-2 (COX-2) activity in the setting of endometriosis.[42] Superficial, often atypical implants are active PG producers. NSAIDs may improve symptoms by interrupting receptor-mediated signaling pathways. *In vitro* studies suggest that COX-2 inhibitors reduce endometriosis implants through anti-angiogenic properties.[43] Variable response may be seen with different medications in each patient. The only trials designed to assess the impact of NSAIDs studied groups of patients with primary dysmenorrhea, in the absence of endometriosis.[44] Nevertheless, they remain a first-line adjunct to OCPs, since they are relatively safe and have positive anecdotal therapeutic effect.

Along the same lines, OCPs have traditionally been used as first-line agents for patients with presumed endometriosis, yet no study has consistently demonstrated a therapeutic response.[45] One randomized, placebo-controlled trial comparing a low-dose cyclic OCP in adolescents with primary dysmenorrhea found a non-significant improvement in pain scores with fewer days of pain.[5] ACOG supports the use of continuous use of combination OCPs in adolescents to induce amenorrhea, but states that 'this modality can result in significant breakthrough bleeding'. If a patient has no contraindication for use of OCPs, and needs contraceptive measures, these may be the ideal choice. OCPs suppress the HPO axis and subsequent estrogen/progesterone secretion, thereby inducing atrophy of ectopic implants. If given continuously, patients may become amenorrheic and will experience less cyclic pain. Side effects are generally mild and time-limited. These include irregular bleeding, nausea, bloating, headache, and breast tenderness. To reiterate, patients who have symptoms refractory to the above therapies have a relatively high probability of true disease.

Progestins and progestin-containing intrauterine systems (IUS) significantly reduce pain symptoms if used continuously.[46,47] Progesterone induces decidualization and eventual atrophy of implants. Certain formulations also suppress the HPO axis, resulting in decreased steroid hormone stimulation of implants. Many such patients will become amenorrheic. DMPA is a monthly injection that, like OCPs, also serves as an effective form of contraception. Newer, subcutaneous formulations have been introduced and have shown comparable efficacy, but possess less worrisome characteristics such as the impact on bone mineralization.[48] DMPA suppresses the HPO axis, resulting in a hypo-estrogenic state. Since progestins inhibit estrogen and progesterone receptor synthesis, patients experience long periods of low estrogen production at a time when bone mineralization is high. Although we lack long-term follow-up of adolescents being treated with prolonged DMPA, caution should be used when prescribing. Current recommendations support the use of the intramuscular DMPA for up to 2 years.[48]

Gonadotropin-releasing hormone agonists (GnRH[a]) rapidly induce a hypo-estrogenic state by down-regulating the HPO axis. An initial rise in gonadotropins and estrogen (flare) occurs after administration, but chronic exposure provides the desired response. Approximately 85% of patients

with confirmed endometriosis will experience significant reduction in pain complaints.[49] Empiric use in patients with CPP may also be considered, regardless of the diagnosis.[50] However, a recent systematic review found no difference in the positive therapeutic effect of GnRH agonists when compared to other hormonal regimens.[51] Side effects are related to hypo-estrogenism (vasomotor symptoms, vaginal dryness, mood swings). Prolonged exposure (> 6 months) can lead to an irreversible decrease in bone mineral density (BMD), but this loss does not correlate with the age at which therapy was initiated.[52] Since adolescents are at particularly high risk for less bone attainment, the use of GnRH agonists should be used with caution in this age group, and some experts do not recommend their use in younger adolescents.[53,54] To limit vasomotor symptoms and the effect on BMD, GnRH agonists should be administered with add-back therapy with the initial injection, as immediate use has no impact on efficacy and limits the side effect profile.[55] Options include norethindrone acetate or a combination of estrogen and progestin in formulations used for treating postmenopausal symptoms. These regimens are approved by the Food and Drugs Administration (FDA) for up to 6 months' continuous use, but may be extended for another 6 months if given with add-back therapy (Table 27.12 and Figure 27.4).

Although androgens such as danazol have been shown to be equally effective in treating endometriosis-associated pain (and the only pharmacologic agent to show improvement in surgical scoring), the side effect profile may be limiting in adolescent patients.[56] Other investigational agents such as aromatase and progesterone inhibitors, as well as steroid-hormone receptor modulators are emerging as options for adult protocols. These may prove beneficial as long-term options in that side effects are minimized while efficacy is spared. At this point, any patient offered such a drug should be done so under a formal study protocol.

Surgical management is indicated for pain that is refractory to medical management, advanced disease, and associated subfertility (generally not a concern for this cohort). Surgery may also be offered

Table 27.12 Chart demonstrating bone loss with GnRH agonist

Visit	Group A	(*n*)	Group B	(*n*)	Group C	(*n*)	Group D	(*n*)
Final treatment	−5.4±0.71*	(22)	−1.2±0.7†	(22)	−0.2±0.63†	(27)	0.5±0.69†	(22)
Follow-up month 8	−3.4±0.66*	(19)	−0.9±0.6†	(22)	0.2±0.58†	(24)	0.6±0.62†	(21)
Follow-up month 12	−2.3±0.62	(15)	−0.7±0.67	(12)	0.8±0.64	(14)	0.5±0.62	(14)
Follow-up month 16	−1.9±0.98	(9)	−0.03±1.05	(7)	1.2±0.78	(14)	2.3±0.87	(10)
Follow-up month 20	−2.1±0.91	(7)	0.14±0.89	(7)	0.3±0.91	(7)	1.6±1.06‡	(5)
Follow-up month 24	−0.9±1.29	(4)	1.5±0.95	(6)	1.2±1.1	(5)	0.9±1.18	(4)
Final follow-up visit	−1.8±0.53*	(22)	−0.4±0.53	(22)	0.9±0.48†	(27)	1.05±0.52‡	(22)
Number of days in follow-up at final follow-up visit (mean±SEM)	459±39.3		421±47.4		426±39.9		456±40.5	

Means ± SEM percent changes in bone mineral density from baseline for successful completers during the follow-up period.
*$p < 0.001$.
†Statistically significantly different from group A after Bonferroni adjustment for multiple comparisons ($p < 0.017$).
‡$p < 0.05$.
All patients had endometriosis-associated pain and were surgically diagnosed within 12 months of initiating this multi-center trial. All patients received depot leuprolide as well as supplemental calcium (1000 mg). Patients randomized to Group A received daily oral placebo for 'addback', Group B received daily oral norethindrone acetate (5 mg), Group C received daily oral norethindrone acetate (5 mg) plus conjugated equine estrogen (CEE, 0.625 mg), and Group D received daily oral norethindrone acetate (5 mg) plus conjugated equine estrogen (CEE, 1.25 mg).
Reproduced with permission from: Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow up. Obstet Gynecol 99: 709–19, Copyright ACOG (2002).

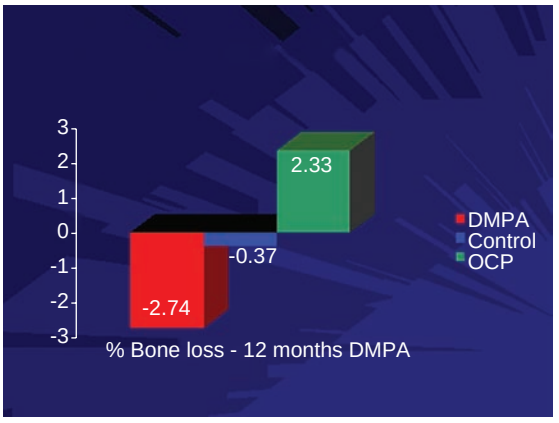

Figure 27.4 Graph demonstrating bone loss with DMPA. Reproduced with permission from Berenson AB, Radecki CM, Grady JJ et al. A prospective, controlled study of the effects of hormonal contraception on bone mineral density. Am J Obstet Gynecol 2001; 98: 576–82.

to confirm endometriosis before initiating medical therapy. Laparoscopically targeted destruction or exclusion of implants and restoration of pelvic anatomy significantly reduce pain in the majority of patients, although recurrence of disease and pain is not uncommon and there is no consensus as to when surgery should be offered.[57–59] Conservative surgical management with laparoscopic excision or ablation of visible implants provides effective treatment of pain-related complaints. Several randomized controlled trials have established a clear relationship between surgical intervention and reduction of pain in patients with endometriosis. One trial demonstrated a significant reduction in pain, lasting up to 6 months, when compared with controls who underwent diagnostic laparoscopy (sham surgery).[57] Another trial confirmed these results and included quality of life measures, which were also improved at 6 months' follow-up. There was a 20% non-responder rate with a 30% placebo effect.[60] In a most recent review, approximately 50% of adolescents were noted to have severe disease at the time of laparoscopy.[39] These authors demonstrated an excellent response to resection, which promotes the use of more aggressive surgical measures to limit recurrence.

Although laparoscopic findings do not always correlate with the degree of symptoms, pain seems to correlate well with the depth of peritoneal invasion.[33] Ablative therapy with electrosurgery or laser effectively provides relief (for at least 6 months) in patients with minimal to moderate disease.[57] Radical excision of affected areas with restoration of normal anatomy is the preferred method of treating symptomatic patients with deep peritoneal disease, and may limit the risk of recurrent symptoms.[33,61,62] Improvement in pain may last up to 5 years after surgery, but the risk of re-intervention approaches 50% in patients with moderate to severe disease. Less aggressive surgical measures and younger age are predictive of recurrence.[63] The ability to identify these patients preoperatively and with minimal delay would improve quality of life for these patients. Notwithstanding the noted improvement, surgery has its risks. Although a small percentage of patients will undergo reoperation due to recurrent symptoms and disease, adhesion formation and altered surgical planes may increase morbidity upon each return to the operating suite.

Appendectomy should be considered in patients undergoing laparoscopic surgery for suspected endometriosis, especially if complaining of right-sided pain. Up to 50% of appendiceal specimens will yield abnormal pathology, but the effect on pain and future adverse outcomes is difficult to assess.[64] Nerve ablative techniques such as laparoscopic uterine nerve ablation (LUNA) and presacral neurectomy (PSN) are also not without risk and have not been effectively studied in the adolescent population.[25,65]

Pre- and post-operative hormonal suppression may improve revised American Society for Reproductive Medicine (ASRM) scores at time of surgery, but clinical benefit, whether it is pain relief or pregnancy, has not been established.[66]

CONCLUSION

- Although prevalence rates have been difficult to estimate because of the various definitions used, CPP in adolescents is a common disorder and may affect up to 15% of girls.

- All disciplines that provide care to young girls and teenagers should be aware of the multitude of inciting causes of pelvic pain so that they can provide appropriate referrals and limit the repercussions of a long-standing disability.
- Functional pelvic pain, or that which has no easily identified source, should be assessed in any young patient presenting with chronic complaints.
- Musculoskeletal disorders of the pelvic floor are often overlooked, do not respond to most medical or surgical options, but may be elicited in up to 20% of such patients.
- A multi-specialty evaluation should be undertaken in any adolescent presenting with chronic pain, especially before initiating therapy. Avoiding delays in effective treatment and limiting undue risks are crucial in caring for this young cohort.
- Endometriosis should be suspected in any female complaining of progressively worsening dysmenorrhea that does not respond to NSAIDs and OCPs.
- Most diagnostic and treatment paradigms used to treat adolescents have been derived from those used in adults.
- The diagnosis of endometriosis can typically be made by history and examination. Ancillary imaging studies may be useful for targeting therapy, but are not absolutely indicated other than to rule out other pathology.
- Medical management of endometriosis focuses on suppressing the HPO axis and inducing atrophy of peritoneal implants. Side effect profiles of any agents should be thoroughly addressed with the patient and her parents, especially those that may impact bone mineralization.
- Conservative surgery may be used to diagnose and treat endometriosis, but is limited by recurrent disease that commonly affects young patients.
- Aggressive resection of endometriosis may provide more long-standing relief from pain and reduce the temptation to perform repeat surgeries, which only incur added perioperative risk.
- Although there is no evidence to support the use of postoperative ovarian suppression (from adult literature), given the long-term potential of recurrence in adolescents and the need for contraception, OCPs may be considered.

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28. Treatment of anomalies of the reproductive tract

D Keith Edmonds

INTRODUCTION

A number of congenital malformations may not manifest themselves until adolescence, while other congenital malformations, especially of the external genitalia, may be present at birth or during childhood and remain a problem throughout the adolescent years, particularly following the onset of puberty and the development of secondary sexual characteristics. The management of congenital malformations of the genital tract requires a multidisciplinary approach. Not only does the team caring for them need to address the anatomical difficulties but there are functional reproductive and psychological issues that also need attention, often by health professionals with particular expertise in this area, especially that related to the psychological well-being of these young women.

CLINICAL ASSESSMENT

In considering the malformations, some universal principles of clinical management need to be employed. It is imperative that the correct diagnosis of the underlying conditions is made and also that patients are fully investigated, not only detailing their genital anatomy and its variance from normal, but any appropriate endocrine and genetic investigations must also be carried out. A large number of these congenital malformations have associated disorders of other organ systems, which also need to be delineated and defined. This may involve a number of forms of imaging depending on the most appropriate to determine the abnormality. Finally, an extremely careful assessment of the psychological status of the patient is imperative. The risks of not involving the psychologists in the management of these patients may cause long-term irreparable damage. Adolescents are very difficult to assess psychologically and intellectually, as intellectual development varies from patient to patient. There is a complete discrepancy between physical maturity and intellectual maturity and whilst physical maturity may be achieved by age 15 or 16, intellectual maturity is not reached until 18–20. This discordance presents a major problem for management, as a number of the malformations that are discussed in this chapter have physical symptoms that demand surgical attention at a younger age than would be ideally desirable in terms of being able to cope with the difficulties that these young women encounter. The risks of ignoring the psychological aspects of these disorders are long-term sexual dysfunction and the inability to integrate into normal society. So profound are these issues that feelings of heterosexuality may mean that these patients have difficulty sustaining relationships due to the psychological harm that has been ignored in early adolescent years. However, the psychological difficulties of adolescence make assessment much more complex than in childhood or adult life and therefore specially trained psychological counsellors are needed for all units carrying out this type of reproductive surgery.

DISORDERS OF THE VULVA

There are three situations that arise with the vulva that may require the attention of the reconstructive gynecologist. These are (1) patients with congenital

adrenal hyperplasia (CAH) who have had surgery performed in childhood and who have progressed through puberty and have ongoing physical problems; (2) patients with late onset CAH in whom clitoromegaly may result; and (3) patients with androgen-secreting virulizing tumors of the ovary who may develop some degree of clitoromegaly.

The management of these children is primarily by a pediatric urologist and the reader is referred to Chapter 29 for more details.

CONGENITAL ADRENAL HYPERPLASIA

The management of CAH currently involves the majority of surgery being performed in infancy. However, although most of the vulvovaginal surgery is carried out as a one-step procedure in an attempt to create an anatomically acceptable and functional vulva and vagina, which will change appropriately during adolescence and adulthood, there are some patients for whom revision of the external genitalia may subsequently be required. In the important study by Azziz et al,[1] 79% of patients required further reconstructive surgery as an adolescent or adult to allow intercourse to occur and 25% had undergone more than one procedure before puberty. Of all patients having repeated vaginal reconstructive surgery, 72% were successful with their second operation and these authors recommended that exteriorization of the vagina be postponed until puberty or thereafter when the young woman has reached a sufficient level of maturity to comply with the use of postoperative dilators. Krege et al[2] report similar findings in 27 patients; 36% of patients developed post one-stage intravaginal stenosis and 14 of 16 patients who were followed up in the long term had overall problems with their body image, vaginal stenosis, anxiety about sexual intercourse, and problems with orgasm. This group also concluded that this type of surgery should be delayed until the beginning of puberty or subsequently, as did the Azziz group. In a retrospective study by Creighton et al,[3] cosmetic results were judged to be poor in 41% of 44 patients who were studied and 98% needed further treatment to the genitalia for either cosmesis, tampon use or intercourse. Some 89% of one-stage procedures required further surgery. Al-Bassam and Gado[4] reported their experience of 52 patients, of whom 78% had satisfactory appearance but 30% required further surgery in adolescence. The timing of genital surgery in CAH is obviously difficult and controversial and an ongoing debate needs to occur as to the best surgical approach. Whilst it is appropriate to individualize management protocols, further research is needed to find the optimum management strategy.

In adolescence, secondary surgery may well be required, particularly for the vaginal outlet. The stenosis that prompts the surgery is complex as there is often significant scar tissue from the original surgery. Enlargement of the vaginal orifice will require individual planning and may require anything from a Fenton's procedure or the use of skin flaps, which may be swung from the labia or the perineum.

LATE ONSET CONGENITAL ADRENAL HYPERPLASIA

This is an uncommon endocrine condition that may occur at puberty following adrenarche when excessive androgen is produced from the adrenal. This impacts on clitoral growth and may lead to clitoromegaly. These patients are extremely embarrassed by the size of the clitoris and its prominence when either swimming or undertaking sporting events that require clothing through which the clitoral enlargement is visible. The role of the clitoris in sexual function is extremely poorly understood by early adolescence and therefore great care and counselling have to occur before any decision is made to correct the clitoromegaly. Therefore clitoral reduction in an adult is an extremely rare procedure and, if a clitoroplasty is required, this should be carried out by a surgeon who is familiar with the technique of conserving the neurovascular compartment whilst only reducing the corpora cavernosa. The success of this approach in terms of subsequent sensation in the sexual function remains unclear, as there are no reported series in

the literature. Case reports suggest that clitoral head sensation can be preserved following this procedure. The approach of clitoral recession, which professes to conserve the clitoris in its entirety by replacing the corporal body beneath the symphysis, has unfortunately not been a successful approach. Too often sensory losses and painful erection of the clitoris have meant that the procedure has now been abandoned. However, we seek further surgical innovations if we are to try to conserve as much of the clitoris as possible for functional long-term gain.

DISORDERS OF THE VAGINA

There are three congenital abnormalities of the vagina that need to be addressed: remnant cysts, obstructive outflow tract disorders, and congenital absence of the vagina.

CYSTS OF THE VAGINA

The majority of vaginal cysts are located on the lateral or posterior walls and most patients complain of swelling in the vagina, which is usually present during adolescence. They often complain that they cannot insert a tampon at period time or may have dyspareunia. The majority of these cysts histologically arise from müllerian remnants or epidermal inclusion cysts, while cysts of Gartner's duct are much less common than generally believed. Management should be by excision but occasionally high, large müllerian duct cysts that contain clear mucus are best treated by marsupialization. Attempts to excise these deep cysts in their entirety may lead to unexpected bleeding or damage to the ureters, which may result from the placement of deep sutures to arrest the bleeding. This approach should be avoided (Table 28.1).

OBSTRUCTIVE OUTFLOW TRACT DISORDERS OF THE VAGINA

The embryological development of the vagina may lead to a number of conditions that result in obstruction to the flow of menstrual blood once menarche occurs. All of these conditions present with primary amenorrhea in association with increasing dysmenorrhea as subsequent cycles unfold. Menstrual loss does not occur but the cyclicity of the pain is diagnostic. Management of these cases is dependent on the level of obstruction and the anatomical and functional success becomes increasingly poor as the obstruction becomes increasingly high.

IMPERFORATE HYMEN

The hymen is a thin, mucous membrane that occurs at the junction of the sinovaginal bulbs with the urogenital sinus and is usually perforated during fetal life, although the mechanism involved in achieving this remains unknown. Failure to develop a perforation leads to the membrane remaining intact and therefore the imperforate hymen results. As puberty unfolds, menstrual blood collects behind the membrane and the vagina begins to distend. This is often painless for some months and eventually the vagina becomes greatly distended and a hematocolpos results. When the mass becomes sufficiently large, it may affect micturition and defecation and even overflow incontinence may occur. Clinically, a mass arising from the pelvis is

Table 28.1 Vaginal cysts

Author(s)	Epidermal inclusion cyst	Müllerian remnant cyst	Cyst of Gartner's duct	Unknown origin
Deppisch[66]	45%	33%	12%	10%
Pradhan and Tobon[67]	20%	56%	15%	9%

palpable abdominally and inspection of the vulva by separation of the labia will reveal a membrane through which menstrual blood may be seen and which appears as a dark blue mass. This appearance is quite unlike the appearance of a transverse vaginal septum (see later) in which the bulging membrane remains entirely pink.

The surgical management of this condition involves a cruciate incision in the membrane from 2 o'clock to 8 o'clock and 10 o'clock to 4 o'clock. The remaining quadrants of hymen may be excised or they may be left *in situ.* No attempt to evacuate the vagina at the time of surgery should be made as there is a risk of perforation of the vagina with the introduction of instruments and the risk of ascending infection through the introduction of swabs into the hematocolpos. In general, drainage is complete within 3–5 days and thereafter there should be no further problems.

There are generally no sequelae following imperforate hymen and its treatment and reproductive performance subsequently compares equally with the normal population.[5]

TRANSVERSE VAGINAL SEPTAE

The incidence of this phenomenon is unclear but it is much less common than congenital absence of the vagina and uterus. The developmental defect in this situation is one that results from incomplete fusion between the müllerian duct component of the vagina and the urogenital sinus component. This incomplete vertical fusion leaves a transverse vaginal septum that varies in both the level and thickness. It would seem that these septae can be classified into those that occur in the upper vagina, the mid vagina, and the lower vagina, with incidences of 46% occurring in the upper, 35–40% in the mid, and 15–20% in the lower vagina.[6] Observations on the degree of absence of the vagina show that greater absence occurs the higher the septal defect. It may be associated with other congenital malformations of the urological tract or rectum and anus and uterine abnormalities, e.g. bicornuate and septate uteri are also described in association with this defect.

Presenting symptoms are similar to imperforate hymen, with increasing cyclical abdominal pain in the absence of menstruation at the time of puberty. It is often the case that the adolescent's diagnosis may be missed for several months. Only when the adolescent is admitted as an emergency with acute abdominal pain and/or urinary retention is the diagnosis made and clinically at this time there is a pelvic mass arising from the pelvis that may extend into the abdomen. The mass is tender to palpation and ultrasound imaging will confirm the presence of a hematocolpos and a hematometra. Occasionally, the presence of a hematosalpinx may be seen or more rarely the presence of an endometrioma.

SURGICAL MANAGEMENT

The principle of the management of transverse vaginal septae is to excise the septal defect and perform a vaginal end-to-end anastomosis between the upper portion of the vagina and the lower. A transverse incision is made in the centre of the vault of the lower short vagina and a passage is made that will eventually allow incision into the upper vagina where the hematocolpos will be apparent. The dissection laterally then allows excision of the septal tissue and this has to be completed in its entirety. The upper vaginal wall may need to be mobilized to bring it in apposition to the lower vaginal portion and an end-to-end anastomosis is usually possible in these circumstances, leaving a vagina that is normal in caliber. It is the author's preference to place a firm vaginal mold at the site of the anastomosis for 10 days postoperatively to try to prevent stenosis occurring subsequently. The use of vaginal dilators for 2–3 months subsequent to the removal of the mold will result in excellent functional results, particularly for the lower and middle septal defects.

The approach for the higher septal defects, which have a greater absence of the vagina, may require an abdominal approach as well as a vaginal one. The upper vaginal portion may be quite short and there is the risk of damage to the bladder or the rectum in trying to enter this through the vagina, rather than

exploring abdominally and placing a probe into the upper vagina to act as a guide for the vaginal surgeon to find the appropriate point of entry. Again, if possible, an end-to-end anastomosis should be attempted but there are a significant number of cases where the length of absent vagina precludes this approach. Here, a mold needs to be placed with a central drainage passage to allow menstrual blood to escape and the mold should be left *in situ* for 3–6 months to allow epithelialization to occur between the two portions of vagina. This process may be promoted by the use of amnion, which may be placed around the mold and which encourages epithelialization. Subsequent to the removal of the mold, again the use of vaginal dilators is imperative to ensure that the vagina remains functionally patent. In some cases of high vaginal septum, when drainage of the upper hematocolpos has been performed before referral for reconstructive surgery, the use of vaginal dilators to extend the lower vagina as much as possible can be a useful approach. Here, suppression of menstruation will allow time for the use of the dilators and the expansion of the lower vagina. This may then allow primary anastomosis to occur at the time of surgery, thereby offering a greater chance of success and reducing the incidence of stenosis. It is the author's belief that this approach is the best one to try to achieve the results that we seek. The difficulty with which we are often faced with these cases is the high vaginal septum in the girl who is only 12 or 13 years of age. Here, the use of dilators in these circumstances is often unsuccessful and therefore suppression of menstruation may be carried out for some 2–3 years so that puberty can progress, and the patient becomes more mature and is able to cope with the idea of the use of vaginal dilators prior to the surgery being performed. Suppression in these circumstances is usually with the oral contraceptive pill continuously and only if this is unsuccessful does surgery need to be attempted earlier.

In the author's own experience of 27 cases of lower third obstruction, sexual function in the follow-up of those patients has been 100% successful. In 12 cases of a middle third obstruction, eight patients were found to have a normal sexual function and four patients had some degree of partial stenosis that has required revision, and one patient remains with some degree of dyspareunia in spite of attempts at revision. In 11 cases of high vaginal obstruction, seven patients have satisfactory sexual function. Of interest, however, is that the incidence of high stenosis remains high, with eight patients having an anatomical stenosis although only three of the eight found this to be a cause of dyspareunia. Similar results are reported in numerous case reports in the literature.

Pregnancy after vaginal reconstruction has been reported by Rock et al,[5] who reported a 100% pregnancy rate in patients with lower third obstruction, 40% in middle third, and only 20% in upper third. The likely explanation for this is the incidence of endometriosis, which is much higher with the higher obstructive disorders. Here, prolonged retrograde menstruation may lead to architectural damage of the pelvis, which may result in anatomical infertility. IVF (*in vitro* fertilization) in these circumstances may be very successful but no data specifically related to these patients are available.

In a further long-term study by Joki-Erkkila and Heinonen[7] they too found no impact on pregnancy outcome in low malformations.

LONGITUDINAL VAGINAL SEPTUM

If the two lateral müllerian ducts fail to fuse at their lower border, uterine and vaginal anomalies may result. The failure of fusion results in a uterus didelphys with two hemi-uteri and two hemi-cervices. Each cervix creates a hemi-vagina and in most cases these two vaginas fuse with the urogenital sinus to give the clinical result of a double vagina. The septum that divides these vaginas may be partial or complete and patients usually present either with difficulty with inserting tampons or the insertion of a tampon fails to stem the menstrual flow as only one hemi-vagina is protected. However, it is not uncommon for patients to not notice the hemi-vagina effect and only present with either dyspareunia or, when they are already pregnant, as an incidental finding during the pregnancy.

Some patients will find that one of the hemi-vaginas is larger than the other, usually the right versus the left, and they are able to have intercourse in the right hemi-vagina without difficulty. However, this may be associated with infertility as sperm are only able then to get to one hemi-uterus. Excision of the vaginal septum is advisable to improve the chances of pregnancy in those women who are trying to conceive and also to avoid difficulties that may arise during vaginal childbirth. Excision is straightforward but caution and care should be taken to ensure that the septum is removed in its entirety, not leaving a band of vaginal tissue between the two cervices, which may in itself cause dyspareunia. The traditional method for removing longitudinal vaginal septum is by excision and ligation, although in time the use of laser may bring better anatomic and functional results.

In some cases, one of the hemi-vaginas may fail to cannulate and reach the urogenital sinus. Here, a blind vaginal cavity exists and at the time of puberty when menstruation begins, menses from the unobstructed vagina are found to flow normally whereas the obstructed hemi-vagina results in accumulation of menstrual fluid. This very confusing clinical situation is often late in diagnosis, as the presence of menses does not alert the clinician to the possibility of an obstructed hemi-vagina. Only when the dysmenorrhea resulting from this becomes quite severe and the patient is admitted as an emergency is the diagnosis made on imaging and this is clearly possible to delineate with real-time ultrasound. It is imperative that screening for renal agenesis is undertaken in these patients as they often have ipsilateral renal agenesis.

Surgical management of these conditions involves careful excision of the vaginal septum in its entirety and this is carried out per vagina but care has to be taken in excising this type of septum as it may be very thick. Postoperative hemorrhage is a complication if care is not taken. Also, if excision is not carried out and simply an attempt to create an ostium through which the menses can flow is performed, bacteria from the hemi-vagina that is functioning normally will enter the previously blind hemi-vagina and accumulation of an abscess may result. This is an extremely serious situation that may result in ascending infection, septicemia, and a life-threatening episode for the girl. It is imperative, therefore, that these procedures are carried out by surgeons with skills that allow them to do this surgery effectively and the operation performed should be the first operation, which should be curative rather than a sequence of operations, which is ill-advised. The results of the surgery are excellent and retraction of the septal pedicles is almost complete. Dyspareunia is rarely a problem and reproductive performance in this group of patients is comparative to patients with solely a uterus didelphus.

CONGENITAL ABSENCE OF THE UTERUS (MAYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME)

Complete vaginal agenesis in association with uterine agenesis or hypoplasia is uncommon and known as the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. The incidence of this syndrome is 1 in 5000.[8] These patients present as adolescents with primary amenorrhea in the presence of normal secondary sexual characteristics other than menarche. Their ovarian function is normal and their karyotype is 46,XX.

GENETICS OF MRKH SYNDROME

MRKH syndrome is not usually found in a familial pattern but it is found quite commonly in conjunction with other malformation syndromes.[9] Although affected siblings have been documented with vaginal agenesis, discordant monozygotic twins have also been reported.[10] This indicates that a single autosomal recessive gene cannot be the explanation for this condition. Although Shokeir[11] proposed an autosomal dominant inheritance from a study of 16 families in Saskatchewan, subsequent studies have failed to confirm this.[12,13] It would therefore seem that the most logical explanation is a polygenic multifactorial inheritance and these inherited

abnormalities normally have a recurrence risk of between 1 and 2%. In the offspring reported by Petrozza et al,[13] none of the female offspring have exhibited müllerian aplasia.

Molecular genetic studies have so far failed to attract any candidate genes to explain this phenomenon. Whilst a number of studies have looked at the possibility of defects in the homeobox series, as yet no abnormality has been found.

DIAGNOSIS

As alluded to above, these patients present with primary amenorrhea and investigation by imaging reveals that there are two forms of the MRKH syndrome. In the first group, the only abnormality is congenital absence of the vagina and uterus and in the second group congenital absence of the vagina and uterus is also associated with renal, ear, and skeletal abnormalities.[14] With regard to skeletal abnormalities, these are well known to occur in some 10–12% of patients.[15,16] The incidence of hearing difficulties in MRKH patients has been reported by Strubbe et al[17] and a hearing loss of some degree was attributed to a congenital origin in 10% of MRKH patients. These findings illustrate the need to evaluate MRKH patients a little more thoroughly for associated abnormalities than perhaps has been previously practiced.

MANAGEMENT

The management of these patients falls into two distinct areas: the management of their congenital anatomical abnormality with the need to be sexually active and the psychological impact of the knowledge that these individuals have no vagina and no uterus.

PSYCHOLOGICAL ASPECTS OF MÜLLERIAN APLASIA

It is difficult to quantify the emotional trauma that is associated with the knowledge that the patient has müllerian aplasia. There are three parties at least involved in this process. The patient herself, who may be a young adolescent aged 14 or 15, and her parents. The shock is considerable to all and the first reference to the need for psychotherapy is cited in 1968 by Kaplan based on nine patients with MRKH syndrome.[18] He described the importance of the impact of a physician's lack of appreciation of the difficulties that may ensue and how this inability to communicate may make the psychological effects much worse. He further developed his hypothesis of the need for psychological input in 1970 when he described a series of cases outlining the great difficulties that these patients have.[19] Poland and Evans[20] studied 54 patients and described the emotional reactions to the diagnosis and treatment, which varied with the age of the patient and her relationship both with her parents and with a heterosexual partner. Many patients were initially depressed and questioned themselves over their gender and their ability to fulfill the female role in the future as an adult. However, rather than the expected difficulty of sexual intercourse, it was infertility that was the most difficult part for these young women to accept. In having instituted a policy of prolonged counseling, they showed that emotional reaction and reinforcement was a vital part of the medical management of these patients but the input of psychological services was fundamental in improving outcome of therapy. In the last 10 years, there has been an evolution in the multidisciplinary approach to the management of MRKH syndrome and the importance of psychological support has been emphasized to an even greater extent.[21] The evaluation of group therapy, which has been ongoing in a number of centers for some years, was first reported by Weijenborg and Ter Kuile[22] and demonstrated the invaluable use of group programs in helping MRKH syndrome patients deal with their psychological stress. Heller-Boersma et al[23] carried out a randomized control trial of cognitive behavioral group therapy (CBT) against controls and showed that group CBT interventions add a significantly greater psychological impact than conventional therapy, further adding to the concept of group therapy for these patients. It is impossible

to emphasize too greatly the importance of psychological input into the preparation of patients, not only for the adaptation to their congenital abnormality and the ability to deal with this currently and in later life, but also in the preparation of the patient for whichever therapy is chosen to help her to achieve a functional vagina. Without adequate psychological assessment and the involvement of the psychological or the clinical nurse specialist in the timing of treatment, then the chances of success are vastly reduced.

Table 28.2 Results of dilator therapy

Authors	No. of patients	Success
Rock et al [6]	21	18 (66%)
Broadbent et al[68]	20	19 (95%)
Roberts et al[69]	51	46 (91%)
Edmonds[70]	242	205 (85%)
Mizia et al[71]	23	23 (100%)
Total	357	311 (87%)

NON-SURGICAL MANAGEMENT OF MÜLLERIAN AGENESIS

While as yet it is not possible to create a new uterus for these individuals, a number of techniques have been described for the creation of a vagina. A recent policy statement by the American College of Obstetricians and Gynecologists (ACOG) emphasizes the primary role of the non-surgical approach with vaginal dilators as being the treatment of first choice.[24] The use of vaginal dilators was first reported by Amussat in 1835.[25] Amussat's technique was to use strong digital pressure on the vaginal dimple over a series of sessions, but in 1938 Frank modified this method to use pyrex tubes.[26] Frank described six cases in his paper, only one of which was not successful but, interestingly, for almost 40 years this technique was only infrequently used. Rock et al reported success with the use of dilators in only 40% of patients[6] and this report further reinforced the lack of enthusiasm for the use of this technique. However, organization of the therapy at that time was poor, had little psychological input, and the patients were given almost no ongoing support from clinical nurse specialists with expertise in these areas. Once this had been introduced into normal practice, a number of reports supported the idea of a non-surgical approach.

The technique involved requires passive dilatation of the vaginal dimple using graduated dilators. The dilators that are used come in a number of formats and also are made of a number of different materials. None of the particular designs is any better than the others and the results are significant in that a well-motivated, well-supported patient can achieve a vaginal length that is totally satisfactory for intercourse in 85% of cases[21] (Table 28.2). It is, however, important that whichever technique is used to try to create a vagina, a proper assessment is made of the results of therapy. This has, in fact, been extremely poorly addressed over many years, and apart from sporadic reports of small numbers, there has been no comparative study until recently. In a study carried out by Nadarajah et al (personal communication) we have shown that in 60 patients followed up for up to 5 years, over 90% of the girls had a totally satisfactory sexual experience. In all, 25% of patients complained that they had either poor lubrication or dyspareunia but this did not interfere with their enjoyment of sexual intercourse and this was extremely gratifying. As stated by the ACOG, non-surgical vaginal dilatation is the procedure of first choice.[27]

In an attempt to improve patient cooperation with this type of passive dilatation, Ingram developed a method whereby a dilator was placed through a bicycle seat stool so that the patient could lower themselves onto the dilator and use her body weight to create the pressure.[28] Ingram reported the use of his technique on 24 women, 50% of whom had primary vaginal agenesis. Twenty of the 24 patients had successful treatment and the 4 who failed to have a successful result had undergone previous neovaginal surgery. This technique is identical to Frank's procedure in terms of its principle and the outcomes are equally gratifying.

SURGICAL MANAGEMENT OF MÜLLERIAN AGENESIS

In those patients who fail to achieve a functional vagina with passive dilatation, a surgical approach may be required. It is extremely important to realize that whatever techniques are used, these patients will need to use vaginal dilatation postoperatively in almost all cases. As a result of this, in just the same way as it is important to prepare the girls for passive dilatation primary treatment, the fact that they have failed primary treatment at least means that they are familiar with the vaginal dilatation technique and it is more likely that they will persevere postoperatively and have a good result. However, failure of the use of dilators sometimes brings a negative approach from the patient, who hopes the surgery will be a one-off event that will then mean they do not need to use vaginal dilatation at all. It is important, therefore, that an appropriate psychological assessment is carried out to ensure that the patients are ready for this type of procedure and that they also get appropriate support postoperatively.

A numerous number of procedures have been described to try to create a vagina that is functional. They fall into a number of categories, as described below (Table 28.3).

Table 28.3 Surgical management of müllerian agenesis

Surgical creation of a neovaginal space	Split-thickness skin graft Full-thickness skin graft Perineal skin graft Amnion Cheek epithelial graft Peritoneum Absorbable adhesion barriers Tissue expansion
Vulvo-vaginoplasty	Flap vaginoplasty
Bowel vaginoplasty	Williams' operation Small bowel Sigmoid colon
Vecchietti's operation	Cecum Laparotomy Laparoscopy

SURGICAL CREATION OF THE NEOVAGINAL SPACE

For all techniques in this group, the initial approach is identical in that a transverse incision is made at the apex of the dimple and a digital dissection of the space between the urethra and bladder anteriorly and the rectum posteriorly is carried out. It is essential that the depth of the neovaginal space reaches the peritoneum that lines the pelvic cavity, as failure to do this results in excessive contracture postoperatively. A mold is then placed in the space and this mold may be lined by a number of materials. In the UK the most widely used material is amnion but in the USA it is more common to use the McIndoe Reed technique with the use of split-thickness skin grafts taken from buttock. The complications of this type of surgical approach involve intraoperative damage to the rectum, urethra or bladder with subsequent fistula formation, with rates ranging from 0 to 7.6%.[6,29] A number of authors have used different mold types, soft, semi-rigid or rigid, and there seems to be good evidence that the use of soft molds reduces the risk of fistula formation, presumably from lack of avascular necrosis from pressure. An alternative to the use of these molds is the use of the inflatable soft stent, which is claimed to reduce the risk of hematoma formation without compromising healing and the risk of fistula formation.[29] In the largest reported series by Alessandrescu et al[30] on the treatment of 201 patients, the surgeons used a rigid mold throughout their experience and had a fistula rate of < 1%. Therefore it may well be that it is not the type of mold that is important but the skill and experience of the surgeon. The functional outcome of the McIndoe type of procedure is summarized in Table 28.4. Although the functional outcome is reported anecdotally with success rates ranging between 80 and 100%, there has not been a specific study surveying sexual satisfaction to ensure that these results are indeed true.

The use of amnion has been described by Ashworth et al[31] and subsequent experience of this technique has shown it to have extremely similar success rates to the McIndoe procedure. It has the advantage that no graft site is required, thereby leaving no external scars for the patient to have to

Table 28.4 Results of McIndoe skin grafting

Authors	No. of patients	Serious complication	Sexual satisfaction (%)
LeDuc et al[72]	15	0	8 (47%)
Garcia and Jones[73]	54	N/A	53 (99%)
Farber and Mitchell[74]	12	2	10 (80%)
Alessandrescu et al[30]	201	N/A	188 (94%)
Wiser and Bates[75]	92	2	89 (96%)
Buss and Lee[76]	47	5	40 (85%)
Rock et al[6]	79	5	79 (100%)
Hojsgaard et al[29]	23	3	18 (78%)
Counseller[77]	150	N/A	142 (95%)
Varner et al[78]	29	3	29 (100%)
Khanna and Khanna[79]	17	1	15 (88%)
Harkins et al[80]	21	3	18 (88%)
Bryans[81]	15	0	12 (80%)
Karjalainen et al[82]	33	1	32 (97%)
Salvatore et al[83]	90	9	81 (90%)
Kunz et al[84]	24	0	22 (92%)
Feroze et al[85]	28	7	21 (75%)
Page and Owsley[86]	21	N/A	17 (81%)
Cali and Pratt[87]	93	N/A	84 (90%)
Jackson[88]	128	4	109 (85%)
McIndoe[89]	96	N/A	91 (95%)
Roberts et al[69]	14	0	14 (100%)
Ozek et al[90]	29	N/A	29 (100%)
Total	1311		1201 (92%)

tolerate. However, it is important that the use of this material is properly governed and that the donors are suitably screened for HIV and CJD.

Lin et al[32] reported in 2003 the use of buccal mucosa for vaginoplasty and in a study of eight cases they reported 100% success. No further reports of this technique are currently available.

The use of adhesion barriers has been reported, although only in small numbers of patients, but in the report by Jackson and Rosenblatt[33] the four patients treated had 100% success in creating a neovagina after 6 months.

The use of peritoneum to line the neovaginal space has been popularized in Russia by Davydov.[34]

BOWEL VAGINOPLASTY

The use of a segment of the intestine to act as a vagina has been carried out since it was introduced in 1892 by Sneguireff.[35] He used the rectum as a substitute for a vagina and created a colostomy and as such the approach did not become popular. The first time that ileum was used was in 1907 when Baldwin reported the use in a patient[36] and this became known as Baldwin's procedure. The advantage of using ileum is that the caliber of the bowel remains constant and there is good lubrication. However, there are disadvantages, as the small intestinal mucosa is very easily traumatized by intercourse and bleeding often occurs. Also, there is chronic secretion of mucus from the loop and in the end this technique has not remained popular.[37] The use of an isolated segment of sigmoid colon was first reported in 1914 by Ruge.[38] He used lower sigmoid colon and, although initially a number of these procedures ended with bowel necrosis and fistulae, over the ensuing 80 years the technique has gradually been modified and improved and is now known as a colocolpopoiesis.[39] The most recent results of the use of bowel are summarized in Table 28.5, where although the success rate overall is between 77 and 90%, the complication rates are not inconsiderable. This technique of using the bowel therefore is generally reserved for more difficult cases where simple vaginoplasties have failed and the post-surgical situation is one that results in excessive scarring. In these circumstances, in order to create a neovagina of some function, the whole neovaginal area needs to be excised and replaced by a loop of bowel and it is recommended that sigmoid colon is the best segment to use.

Syed et al[40] reported the outcome of 18 children who had undergone colovaginoplasty when aged between 1.5 and 8 years. They used sigmoid colon in the hope that this might abolish the problems of the emotional difficulty of reconstructive surgery in adolescence by creating a functional vagina in

Table 28.5 Results of bowel vaginoplasty

Authors	Patients	Success	Complications	Comment
Novak et al[91]	63	59	2 necrosed; 2 prolapse	Sigmoid
Burger et al[92]	9	8	1 stenosis	Sigmoid/ileum
Ghosh and Kwawukume[93]	15	15	?	?
Franz[94]	13	12/13	1 stenosis	Sigmoid only
Hensle and Reiley[95]	31	20/26 (77%)	4 vaginal d/c; 3 stenosis; 1 dyspareunia; 3 patients required repeat procedure	Sigmoid better than ileum
Parsons et al[96]	28 (age 6–21)	14/16 adults (80% satisfied)	4 stenosis; 4 prolapse; 2 partial bowel obstruction; 3 d/c; 3 cases of diversion colitis	
Syed et al[40]	18 (all children)		3 cases of prolapse of sigmoid	? *not* use bowel as primary procedure
Freundt et al[39]			Adenocarcinoma in sigmoid 30 years later	
Hiroi et al[41]			One patient with ileus	
Kapoor et al[97]	14	100%	One patient had necrotizing fasciitis; one case had bowel occlusion; one case neovaginal prolapse	
Imparato et al[98]	58	80.6%		Sigmoid

childhood. Although there were no major complications in the early follow-up period, three patients developed severe vaginal discharge problems within 2–7 years and the histology confirmed diversion colitis. This is a reasonably serious complication and one that has made these authors suggest that childhood bowel vaginoplasty should not be continued.

Finally, the long-term sequelae of this procedure are unknown but a recent report from Hiroi et al[41] describes a mucinous adenocarcinoma arising in a neovagina using the sigmoid colon.

NEOVAGINOPLASTY USING PERITONEUM

Although it had been described earlier, the use of peritoneum to line the neovagina was first reported in a series by Davydov et al in 1974[34] and has since been known as the Davydov operation. In his procedure, Davydov performs a laparotomy having created a neovagina in the normal way and then, by mobilizing the peritoneum from the peritoneal cavity including the rectum, he uses this to line the neovaginal cavity. The advantage of this technique as claimed by Davydov and co-workers is the lack of granulation and scar formation. However, as can be seen in Table 28.6 the success rate is not universally 100%, although the results are remarkably good in terms of vaginal intercourse success rates.

Recently, a laparoscopic approach for the use of peritoneum has been reported by Soong et al.[42] In this series they claim a 100% success rate and suggest that it is unnecessary for this procedure now to be performed through a laparotomy. Similar experience has been reported by other authors.[43–45] An assessment of sexual function following this approach has been recently reported by Giannesi et al[46] and here they report similar success results to other series, with 19 of 28 women getting a good or very good result. The interesting part of this study is that anatomically 26 of 28 patients were judged to have had a successful operation and it is function more than anatomy that is most important and the figures previously alluded to need to bear this paper in mind.

VECCHIETTI'S OPERATION

This procedure involves the creation of a neovagina using dilatation of the vaginal dimple with a traction

Table 28.6 Results of Davydov operation

Authors	No. of patients	Success	Complications
Davydov[99]	200	100%	0
Mobus et al[100]	44	82%	0
Tamaya and Imai[101]	24	24	0

device attached to the abdomen. In the conventional operation, a laparotomy is performed and a suture is passed through the perineal membrane from above. This suture is threaded through a plastic olive and the suture is then passed back through the vault and up through the abdomen. The abdomen is closed and the ligature is then attached to a traction device that is strapped to the patient's abdomen. Traction on the suture is then increased on a daily basis to pull the olive into the neovagina and stretch the vaginal skin to create a vagina. This mimics the technique of Frank but does not rely on the woman herself to use the dilators. After 7–9 days Vecchietti claims to have a vagina of some 10–12 cm in length and at that stage he introduces the use of vaginal dilators to ensure that the skin remains stretched. In Vecchietti's personal series of 522 procedures he claims a 100% success rate and only 9 complications, which included one rectal and one bladder fistula. Table 28.7 outlines the results of the conventional Vecchietti technique.

Recently, a number of series have reported a laparoscopic approach to this procedure, thereby avoiding the laparotomy to insert the suture. The rest of the procedure is as in the conventional technique and the results are shown in Table 28.8.

VAGINOPLASTY USING SKIN FLAPS

The first reported use of skin flaps from the labia minora was in 1921 by Graves,[47] and in 1927 Frank and Geist suggested that a tube graft from the inner aspect of the thigh could be used for vaginoplasty.[48] The principle behind using skin flaps is the advantage of full-thickness grafting. The disadvantage of

Table 28.7 Results of Vecchietti's conventional technique

Authors	No. of patients	Anatomical success	Functional success	Complications
Borruto et al[102]	522	522	522	9
Brun et al[103]	17	15	17	1 (re-operation with skin graft)
Janisch et al[104]	9	9	9	0

the McIndoe technique, which uses a split-thickness graft technique, is the problem of contraction of the vagina postoperatively and in the full-thickness grafts this ought to be avoided. Over the ensuing years a number of procedures have been suggested using gracilis myocutaneous flaps[49] and rectus abdominis myocutaneous flaps.[50] Wee and Joseph in 1989 described a technique of a pudendal thigh flap vaginoplasty[51] and in the follow-up study of 12 patients[52] they found this technique to be extremely useful, particularly in patients who had vulva anomalies secondary to CAH. A further report of using pudendal thigh flaps in eight patients with MRKH syndrome showed this to be successful in 100% of cases in achieving a functional vagina.[53] However, the disadvantage of this technique and any technique that uses hair-bearing skin as the donor site inevitably means that there is some hair growth in the created vagina and this can be a problem, both in terms of dyspareunia and discharge.

The use of a free flap graft from the scapula was first reported by Johnson et al in 1991.[54] This technique was carried out on three women and, although they achieved a good functional length vagina at the end of the procedure, the surgical undertaking was enormous and this technique has not subsequently become popular. Giraldo et al in 1994 reported the use of a vulvoperineal fasciocutaneous flap (the Malaga flap) in the treatment of MRKH syndrome.[55] They reported the results of six cases, which are very encouraging.

Finally, the use of tissue expanders to create excessive vulval skin to act as the donor site was first

Table 28.8 Results of laparoscopic Vecchietti technique

Authors	No. of patients	Anatomical success	Functional success	Complications
Keckstein et al[105]	9	9	N/A	0
Fedele et al[106]	52	52	51	0
Khater and Fatthy[107]	6	5	5	0
Giacalone et al[108]	7	7	6	0
Borruto et al[102]	86	86	85	0

reported by Lilford et al in 1988[56] and they reported their experience of 17 cases subsequently.[57] They reported that vaginal length was satisfactory in 16 of the 17 women, although again they had two patients who complained of vaginal discharge and a number of patients who subsequently complained of hair in the vagina causing dyspareunia. In 1993 Serra et al[58] reported their experience of six patients with 100% success, with only one patient complaining of dyspareunia. In 1997 Belloli et al[59] reported their experience of two patients with a successful result. While this only constitutes 25 patients altogether, the results in creating a vagina seem to be very good. However, the complications of hair-bearing skin make this approach more difficult, although the use of labial skin by Belloli et al may have some promise.

MRKH SYNDROME AND SURROGACY

In MRKH syndrome the ovarian function is normal. Therefore, the possibility of IVF surrogacy is one that has come to fruition in terms of success. In studies initially looking at the ovarian response to gonadotropins, the studies showed that there was an absolutely normal response rate in these patients in IVF programs.[60,61] Petrozza et al in 1997[13] reported on 162 IVF cycles for MRKH syndrome patients, with 34 live children born. The fact that no congenital abnormalities were found in these offspring was very encouraging and strongly suggests that congenital absence of the vagina is not inherited in a dominant fashion. Similarly, Beski et al reported their experience with similar outcome figures and no congenital abnormalities[62] and the experience of Goldfarb et al[63] in their surrogacy program gave equally encouraging results. These reports should encourage clinicians to consider IVF surrogacy as an option for patients with MRKH syndrome who wish to attempt pregnancy.

UTERINE ANOMALIES

The only uterine anomaly in the menstruating teenager that may be a problem is the presence of rudimentary horns. These cause increasingly severe dysmenorrhea and an ultrasound scan should be performed in all teenagers who fail to respond to the normal medication for primary dysmenorrhea, to identify the presence of a rudimentary horn. Occasionally, these may be communicating, in which case no hematometra will be seen, but if they are non-communicating a hematometra is apparent and retrograde menstruation may well lead to a hematosalpinx and/or an endometrioma. Treatment of this problem is excision of the rudimentary horn and reconstruction of the uterus. Reproductive performance in these women is normal if the horn is non-communicating. If they have a communicating horn, care must be taken at the time of surgery to reconstruct the uterine cavity to give it sufficient strength to withstand the physiological changes of pregnancy, and a decision should be made as to whether or not delivery should be by elective cesarean section.

Occasionally, in MRKH syndrome the uterine anlage may have functional endometrium and here excision of the anlage resolves the problem.

CONGENITAL ABNORMALITIES OF THE FALLOPIAN TUBES

These abnormalities are extremely rare and include duplication of the tube or absence of the fallopian tubes. In a fascinating case a woman was reported as having bilateral absence of both fallopian tubes and ovaries.[64] These abnormalities are curiosities and have no clinical significance in teenage years. However, they may have implications for reproduction in later life.

CONGENITAL ABSENCE OF THE CERVIX

This is an extremely rare condition and the literature contains no more than 60 recorded cases. The clinical presentation is extremely similar to obstructive outflow tract disorder, with cyclical abdominal pain presenting in the presence of amenorrhea and normal secondary sexual characteristics. Recurrent retrograde menstruation occurs due to failure of outflow and therefore hematosalpinx and endometriosis are extremely common associations. Diagnosis is usually made on ultrasound, when it is quite possible to demonstrate the absence of the cervix and vagina and the presence of a hematometra. Management is controversial. Most experts would advocate hysterectomy in these circumstances due to the risk of sepsis with attempts to perform a uterovaginal anastomosis. However, the author's own series of 15 patients has given a 50% success rate with ongoing menstruation beyond 1 year, although seven patients have failed their surgery and have therefore been subjected to a hysterectomy.[65] It is also possible to retain the functional uterus using either continuous oral contraceptive pill or GnRH analogs with addback therapy if an attempt is to be made to retain the uterus for subsequent assisted reproduction. What is clear here is that this type of congenital abnormality is rare, the problems of reconstruction are complex, and these cases should only be managed in centers with an existing expertise in the management of this condition.

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29. Pediatric urogynecologic abnormalities

Justine M Schober and Christopher RJ Woodhouse

INTRODUCTION

Developmental biology discoveries have advanced our understanding of anatomic details. Although all malformations of the urinary and genital tracts are not yet explained by embryology, some malformations can be related to stages of development. We continue to elucidate genes, proteins, and pathways related to sexual differentiation. In addition, some have been found to be responsible for organotypic features. The understanding of estrogen receptor (ER) status of vulvar tissue is critical to medical and surgical therapy considerations impacting surface integrity of the vulvar epithelium. Continuing elucidation of the embryology and immunohistochemistry of urogenital tissue may be a step toward the development of molecular tools to treat urogenital abnormalities.

EMBRYOLOGY: CHROMOSOMES, HORMONES, AND RECEPTORS

The development of a bladder and urethra separate from the vagina requires the growth of a membrane from cranial to caudad in the urogenital sinus. Anomalies of female embryogenesis during this process lead to a variety of clinically recognized disorders. Although many of them may be seen antenatally by ultrasound examinations, others are noted during physical examination of the vaginal introitus in the newborn. Others, again, are visually and functionally less obvious and are only recognized by the development of clinical problems such as urinary incontinence, pelvic pain, lack of onset of menses, and sexual difficulties.[1]

In the female fetus organogenesis involves regression of the mesonephric ducts with development, as well as stabilization, of the paramesonephric ducts. This proceeds because of the absence of testicular hormones. At the time of apparent female differentiation in a 46,XX fetus, the comparable undifferentiated structures in the female are irreversibly committed to female organogenesis.[2–6]

It was previously held that female external genital development was passive, a default condition due to lack of androgens. The androgen receptor (AR) is known to be present in human female genital tissue. When it was noted that the ER was actually present (exclusively) in female external genitalia in the fetus, the possibility that there may be more than one mechanism responsible for female phenotypic differentiation of the external genitalia was introduced.[7] The source of estrogen responsible for activation of processes causing this differentiation is debatable. A role for maternal estrogens is likely. However, it has been demonstrated in mammals and in the human fetus that the fetal ovary is not necessary for female phenotypic differentiation and a more complex process is likely.[8,9]

Lack of testosterone production leads to regression of wolffian ducts. Once established, the gonads release sex-specific signaling molecules and hormones, which continue to shape the phenotypic sex of the organism throughout its lifetime, a process broadly called sex differentiation. It is important to note that the gonadal hormones act unilaterally. Therefore, if the gonads on each side are different, the internal genital phenotype will be different.

For the establishment of a phenotypically female individual, the principal requirement is absence of androgens. However, estrogen still has an active contribution to the normal development of external and internal genitalia.

Female organogenesis begins at the end of the embryonic period with fusion of the caudal ends of

the two paramesonephric ducts with the urorectal septum, which separates the future rectum from the urogenital sinus. As soon as the paramesonephric ducts come into apposition with the urorectal septum, and begin to fuse, the uterus is forming (about 63 days gestation). The cephalic ends develop fimbriae, the lower segment, and the uterine tube. Transverse lie of the Fallopian tubes is established by descent of the ovary.[10] The cervix (caudal two-thirds of the fetal uterus) may be of either paramesonephric or urogenital sinus origin.[11] Müllerian ducts develop and form the oviduct, uterine horns, uterine body, cervix, and anterior vagina. An outgrowth of the urogenital sinus meets the müllerian duct to form the posterior vagina. The hymen is present at the junction of anterior and posterior vagina. The genital canal is established (at about 80 days) with absorption of the median septum. The genital canal lengthens, and its caudal end continues to grow and contacts the posterior wall of the urogenital sinus. With additional cellular proliferation, the vagina is formed.[10] (See Chapter 1.)

The external genitalia and the clitoris and labia (including the vaginal introitus) form between 14 and 20 weeks. The vagina opens into the pelvic portion of the urogenital sinus and becomes the vaginal vestibule. Urethral and vaginal openings separate, and then are brought to the surface. Before 20 weeks there is a slow phase of growth of the genital swellings that covers the superior and lateral aspects of the clitoris. Anogenital distance does not change but the phallic portion of the urogenital sinus remains open.[12,13]

The genital folds do not fuse. The phallus (clitoris) does not lengthen but instead bends forward or caudally. It becomes incorporated in the fused anterior ends of the genital folds (labia minora).[14]

After fetal ovarian follicular growth begins there is rapid ventral outgrowth of the perineum (20–22 weeks). Labia minora continue their growth posteriorly. Genital swellings lateral to labia minora become the labia majora continuous anteriorly as the mons pubis. Growth of the labia minora is greater than that of the labia majora at first. They are seen protruding out of the labia majora at 23–25 weeks gestation. After 26 weeks the labia majora have grown sufficiently to cover the labia minora.[15]

Studies of the time sequence of female phenotypic differentiation and ovarian hormones suggest a role for ovarian hormones in female phenotypic development. At midtrimester there is no difference in distribution of ARs between male and female fetuses in the external genitalia, but ERs are present only in the genitalia of the female fetus.[15] External phenotype and other genital characteristics in the female are likely to be dependent on chromosomes, hormones, and receptors.

Growth and development of the genitalia are influenced by hormones, as estrogen is responsible for vascularity and thickness of vaginal tissue.[16,17] Labia minora are the female homolog of male genital structures that undergo ventral folding and fusion to form the penile urethra and corpus spongiosum. Failure of the labia to fuse in the normal female fetus may be due in part to the lack of fetal androgen production and low 5-alpha reductase activity (in part due to maternal estrogen stimulation of ER-positive urethral folds) causing the labia minora to diverge laterally.[18] There is extensive circumstantial evidence that 17-beta estradiol and also progesterone influence the postnatal physiology of extra-genital and especially genital (vulva) skin in the human female.[19] ER positivity in the fetus has been demonstrated in the stroma of the labia minora (highest concentration of ER) and in the periphery of the glans and inner prepuce.[20]

BLADDER EXSTROPHY AND FEMALE EPISPADIAS

Much has been written about classical exstrophy, as it has been recognized for about 2000 years. Exstrophy has been the subject of voluminous surgical literature since the middle of the last century. The results of exstrophy reconstruction, both functional and cosmetic, have improved considerably in the last 25 years. Presently, adult women who were born with exstrophy would usually have had an early diversion and, if they wished, a continent reconstruction when such surgery became available.

Few of them would have had a reconstruction that allowed them to void naturally, and fewer still will have maintained that ability into their third decade.[21] Now, in specialist centers, primary reconstruction is undertaken in the first hours of life. Continence and spontaneous voiding are the norm. Reconstruction with intestine and intermittent clean self-catheterization (ICSC) is sometimes needed.

Exstrophy is an isolated anomaly in otherwise normal children. They grow up normally and, anecdotally, are intelligent and well motivated adults. While the sexuality and erectile deformities of males have been well recognized, the female genitalia have been less well studied (in part because there are fewer affected girls). Psychological reviews have indicated that patients are concerned about the appearance of their genitalia and reconstruction now is designed to give a near-normal appearance.

In classic exstrophy and epispadias in the female, pelvic floor, pelvic and pubic bones, and midline abdominal structures are anomalous. The bladder and urethra are an open disc or plate of atypical urothelium. The ovaries and uterus are for the most part normal but with abnormal supports. The vagina is shortened and positionally atypical in direction. The introitus and all perineal structures are positioned very anteriorly. The vulvar structural abnormalities include bifid clitoris, poorly formed labia, lateral division of mons and pubic hair-bearing areas, and a narrowed introitus with bulky posterior vaginal wall.

In both males and females, the obvious anomaly of the open bladder is associated with abnormalities of the pelvic bones and of the genitalia. There is a rare and more minor variation called epispadias in which the bladder defect consists solely of an absence of the bladder neck. The genitalia still have the same anomalies although often to a lesser degree.

On sagittal section the pelvic organs are each displaced anteriorly. The vagina is shorter than normal, seldom measuring more than 5 or 6 cm, but of normal caliber. The uterus, which is in an almost normal anatomic position, enters superiorly so that the cervix is in the anterior vaginal wall. The ovaries and tubes are normal.[22]

GENITAL APPEARANCE

If uncorrected, the labia and introitus appear to be structures of the lower anterior abdominal wall (Figure 29.1). The introitus is narrow (Figure 29.2).

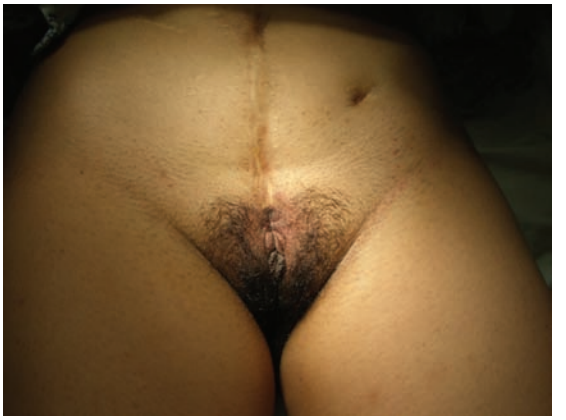

Figure 29.1 Clinical picture of the anterior position of the labia in exstrophy.

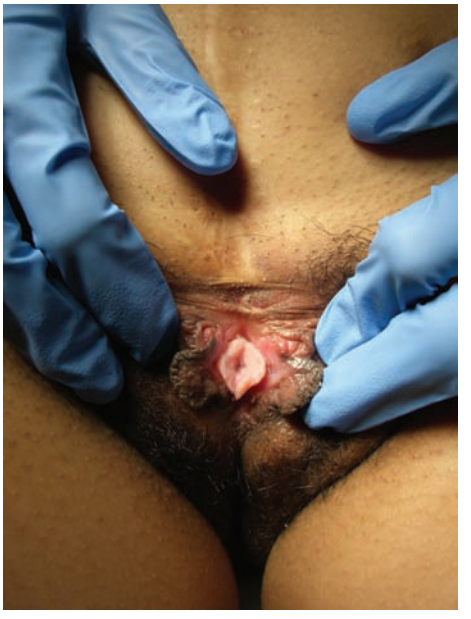

Figure 29.2 Clinical photo of typical introital stenosis of exstrophy.

The narrowing is posterior and is a more substantial layer than the normal hymen, probably being a continuation of the posterior wall of the vagina. The anus is in the position of the normal vagina. The labia, particularly minora, are bifid and rudimentary. In adult exstrophy patients the pubic area is nearly always recessed from the uncorrected divarication of the pubic bones. The pubic hair lies on either side of the midline.

The abnormality is variable and in some females the labia are almost in the correct anatomic position. Those with a working bladder generally have a more normal appearance; otherwise, the original severity of the epispadias seems irrelevant.

RECONSTRUCTION

The object of the genital reconstruction is to unite the two halves of the clitoris and to fuse the anterior ends of the labia to make a fourchette. It is not possible to move the vagina posteriorly to its usual anatomic position, but labial and pubic reconstruction does disguise the abnormality reasonably well.[23] The method of surgical reconstruction has evolved over the last 15 years. In earlier reconstruction efforts, there was less emphasis on the closure of the labia anteriorly, and a number of vaginoplasties were thought to be necessary.

Although the parts of the reconstruction are described separately, they are usually performed together. They are: the fusion of the labia anteriorly, opening of the introitus, and reconstruction of the mons pubis.

Vaginoplasty. In spite of the very narrow introitus, the vagina above is of normal caliber. An episiotomy is made posteriorly from the introitus until a two- to three-finger opening has been created (Figure 29.3). It is usually possible to close the vaginal mucosa to the perineal skin directly but if not a flap of mucosa from the medial aspect of the labia can be rotated on each side to close the defect.

Vulvoplasty. The two halves of the clitoris (assuming that they can be identified) and the anterior ends of the labia are united to make a fourchette.

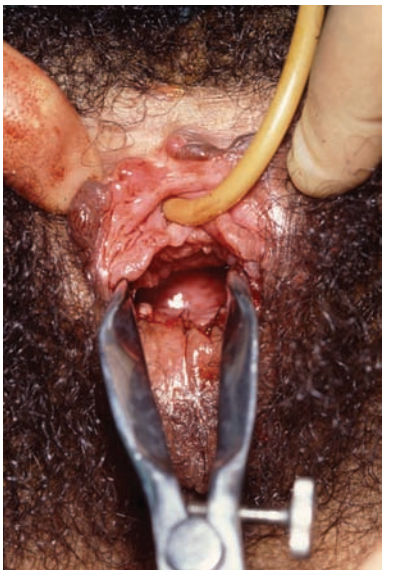

Figure 29.3 Clinical photo of an exstrophy vagina after the introitus has been opened.

No attempt is made to move the vagina posteriorly to its usual anatomic position.

A diamond-shaped area of skin/mucosa is outlined anterior to the labia and extended down onto the anterior ends of each labus and hemi-clitoris. This diamond and the underlying fatty tissue are excised. The defect is then closed longitudinally with fine absorbable sutures.

Monsplasty. It is most important, either in infancy or in adolescence, to rotate hair-bearing flaps of skin and fat to cover the midline defect. The flaps may be based laterally or inferiorly.[23–25] If there is too little skin available, larger flaps can be created by the use of skin expanders.[25] The only problem with the use of tissue expanders (or using flaps under tension) is that the number of hair follicles is not increased. Thus, although good skin cover is achieved, the pubic triangle can look a little 'bald.'

The scarred and non-hairy skin from the midline is excised. This excision may be continuous with that from the anterior end of the labia. The flaps of hair-bearing skin, including all of the subcutaneous fat, are then mobilized and rotated to fill the defect; an example of postoperative appearance is shown in

Figure 29.1. It is important to note that the position of the vagina is only disguised by the mons and the pubic hair. If the hair is parted, the labia can still be seen as structures of the lower abdominal wall.

The emotional problems of all patients born with exstrophy tend to be disguised by a veneer of extroversion. Standard quality of life instruments may fail to show any differences from normality. When questioned specifically, many common anxieties are found. The absence of a normal umbilicus, the presence of scars, and the genital anomalies are particularly important and lead to feelings of sexual inadequacy.

Several females note that the rather broad perineum, which is a consequence of the outward rotation of the pelvis, makes the wearing of modern narrow crotched bathing costumes impractical.

There is now a tendency to reconstruct the genitalia in infancy or childhood. Hohenfellner's group suggest opening of the introitus and uniting the labia at 3 or 4 years of age.[26] This allows easy drainage of secretions and, later, menstrual flow. The more natural appearance in the school years is welcome.

Contemporary techniques of primary reconstruction recognize the distribution of hair-bearing skin and position it appropriately. Unfortunately, the benefit of such surgery may be lost if many revision operations cause unsightly midline scars later on. Excellent results from early reconstruction have been reported in girls reviewed after puberty.[26] However, most of these patients had urinary diversion, and did not have the sequence of revision operations that is so common after primary reconstruction.

INTERCOURSE

It is almost impossible for intercourse to take place unless the introitus has been opened. Thereafter, it should be normal. Considering this author's patients (CRJ Woodhouse), 34 have had sexual intercourse, including all of the 30 patients who have had introital reconstruction. Only 4 of the 12 patients who have not been reconstructed claim to have had intercourse. Thirty-two patients are married or have a regular partner.

The vagina runs directly posteriorly so that when the patient is standing the vagina is almost parallel with the floor. It is also rather shorter than usual. These arrangements normally do not interfere with intercourse. However, in a few patients the upward angle of the erect penis appears to impinge on the cervix and causes dyspareunia. Orgasm has been said to be normal in all patients. In the same series, all of 19 patients over 18 years old were said to have intercourse, but three considered it unpleasant. The source of unpleasantness was not given.[27]

FERTILITY AND PREGNANCY

The cervix enters the superior wall of the vagina and is close to the introitus. This must contribute to the ease with which the girls get pregnant. It is essential to explain to the patients at an early stage that fertility is normal.

In a combined series of 22 patients from Woodhouse and the current literature there were 32 pregnancies. Two ended in spontaneous abortion and two in therapeutic abortion. There was only one obstetric catastrophe, which was the intrauterine death of twins. There were 27 live births. None of the offspring has had exstrophy or epispadias.[28] Pregnancy and delivery can be normal. Elective cesarean should be done in patients with a working bladder or with an artificial urinary sphincter (11 of the 27 deliveries mentioned above). The principal problem is subsequent uterine prolapse.

INHERITANCE

It has been reported from a postal survey of clinics throughout the world that 1 in 70 offspring have exstrophy or epispadias.[29] This figure must represent the worst that can be expected. Screening pregnancies for fetuses with exstrophy is reasonably easy at around 20–22 weeks. Advising the parents on whether or not to terminate an affected fetus at this

late stage is almost impossible. Fetal ultrasound at 18–20 weeks may show that the bladder does not fill. This, combined with a low umbilicus and ambiguous genitalia if the fetus is male, should raise the possibility of exstrophy.

In view of the difficulties with ultrasound diagnosis, fetoscopy seems justified for suspected cases. In two recent pregnancies, classical exstrophy has been confirmed on fetoscopy (Dhillon, personal communication, 1997).

UTERINE PROLAPSE

The defective pelvic floor, open pelvic ring, and poor uterine supports make prolapse common (Figure 29.4). It is a considerable problem to correct.[30–32] It may be found in up to 50% of patients, usually but not always, after pregnancy. The uterus should not be removed as it is the only solid organ in the pelvis that has any hope of holding up the pelvic floor.

For the repair of procedentia, the most successful procedure is the Gortex wrap. The sacral promontory is exposed. A strip of Gortex is sutured or screwed to the periosteum. The end is passed around the cervix through the base of the broad ligament and brought back to the sacrum.[33] This procedure has been successful in all cases with follow-up to a maximum of 6 years, although late relapse, especially after a further pregnancy, is recognized.

Hohenfellner advocates fixation of the uterus to the anterior abdominal wall in childhood. This is said to prevent prolapse but still allow normal pregnancy.[26] Two women were able to have normal pregnancies without prolapse, while one of two women who did not have a fixation had slight prolapse after delivery. This 'prophylactic surgery' may well be helpful; however, once prolapse has occurred, an anterior fixation may not be an effective repair.

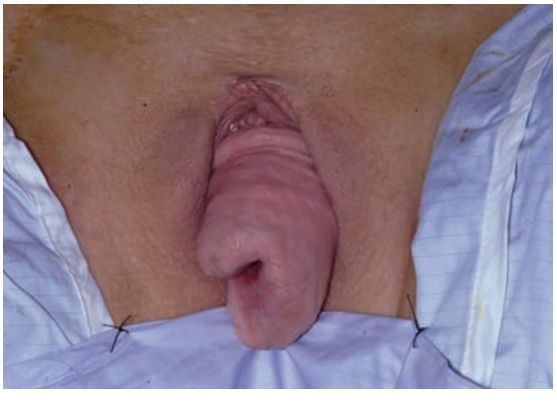

Figure 29.4 Clinical photo of procedentia in a woman with exstrophy.

CLOACA AND UROGENITAL SINUS ANOMALIES

These terms are used to cover a wide spectrum of conditions in which the drainage of the urinary, genital, and gastrointestinal tracts is through a single perineal orifice (true cloaca) (Figure 29.5), or where the urinary and genital tracts are combined (urogenital sinus). This may be one of the most complex developmental malformations of the female

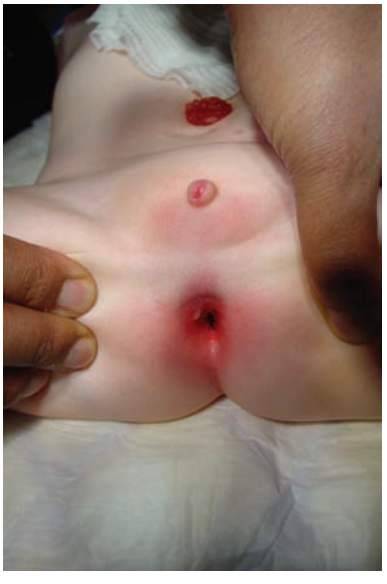

Figure 29.5 Clinical photo of the single perineal orifice of a cloaca (photo courtesy of P. Ransley).

infant. The variability possible makes each case unique. A combination of urogenital sinus with anorectal malformation not amounting to a true cloaca is seen in a wide variety of forms. Decompression of the affected organ systems is paramount, but later functional repair in as few stages as possible is desired.

The combined obstruction of vaginal and urinary drainage may cause dramatic problems in newborns with cloacal and urogenital sinus anomalies. Ongoing failure to recognize and maintain an unobstructed condition of the urogenital system remains the greatest threat in this complicated condition. Persistent or unrecognized hydrocolpos, pyocolpos, persistent bilateral hydronephrosis, megaureters, recurrent urinary tract infections, persistent acidosis, and failure to thrive from persistent undrained hydrocolpos have been identified as the major pitfalls in management of this disorder.

The commonest (and anatomically simplest) of this rare group of anomalies is associated with congenital adrenal hyperplasia (CAH); 90% of cases are due to 21-hydroxylase deficiency and of these half to two-thirds will have salt loss due to reduced aldosterone production. The anus and rectum are normal. The anatomy of the common path of the vagina and urethra, known as the urogenital sinus, ranges from a complete male type of urethra with a high union of the vagina to a confluence close to a perineal introitus. The urethral sphincters are likely to be normal.

Almost all cases are identified at birth or, occasionally, *in utero*. Infants with CAH who have a 46XX genotype will be raised female. Because of the block in adrenal synthesis of steroids, the level of fetal androgens is high. The external genitalia are ambiguous, with an enlarged clitoris that is not corrected with even the most meticulous endocrine control after birth. Surgery in infancy is aimed at the separation of the two tracts. Recent controversy about the sexual outcome in intersex patients has cast doubt about the extent to which the genitalia should be altered in infancy.

The condition must be distinguished from cloacal exstrophy, which is a severe variant of ectopia vesicae and has nothing in common with CAH.

At the other extreme, the most severe form of cloaca is very rare. It is often associated with other major congenital anomalies, especially of the cardiovascular system. With all three channels coalescing, there is almost never an anal sphincter and seldom a urethral one. In intermediate forms the urethral sphincter is normal. Because there is no endocrine association, the internal genitalia are often normal. The urinary anomalies are potentially lethal and the reconstructive surgery in childhood is technically very difficult. There is, therefore, very little information on the long-term outcomes.

Surgery in infancy is aimed primarily at preserving life and only incidentally at separating the three channels. Diversion of both urinary and fecal tracts is usually essential. It will often be possible to create a continent bladder, although emptying may require intermittent catheterization. A continent rectum is more difficult and many children remain clean only by a process of 'controlled constipation' or continue with a colostomy.[34,35]

The reconstructive surgery has improved somewhat in the last 25 years. It is possible to achieve social urinary continence in about 80% of patients with or without the use of intermittent self-catheterization. Fecal continence remains a challenge and is achieved in about 60%. Most women are able to have sexual intercourse. Successful pregnancies have been reported.[36]

Frequent postoperative problems include stricture or acquired atresia of the vagina; stricture or acquired atresia of the urethra; persistent urogenital sinus; recurrent, persistent or acquired fistula from the rectum to a neighboring urogenital structure or the perineal skin.[37,38]

CLOACAL EXSTROPHY

Cloacal exstrophy is a devastating complex of anomalies. It includes exstrophy of the bladder and intestine, exomphalos, partial absence of the intestine, and genital anomalies (Figure 29.6). Until 1960 there were no survivors beyond early childhood. Since then, there has been a gradual improvement in the results of reconstruction. However, the

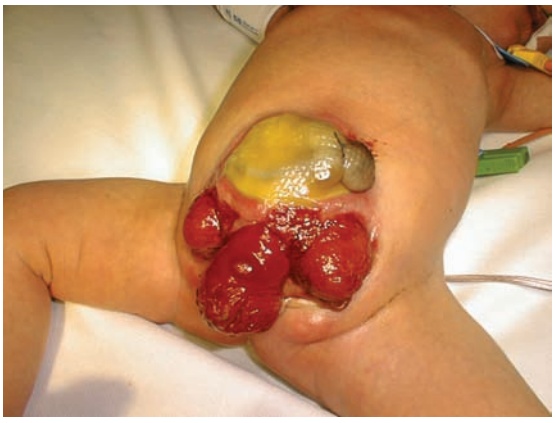

Figure 29.6 Clinical photo of cloacal exstrophy (photo courtesy of P. Ransley).

shortage of intestine has made it unusual for the child to avoid at least one cutaneous stoma. Most will have a cutaneous ileostomy and a continent urinary tract that can be catheterized, usually based on a gastric reservoir.

The most contentious (and so most interesting) aspect of the condition is the decision on the sex of rearing. All genetic females have been raised as females. Historically, about two-thirds of genetic males have been re-assigned as males. It may be the disorder (within the spectrum of ambiguous genitalia) with the most severe effect on genital and perineal development,[39] while at the same time having no alteration of chromosome pattern, endocrine complement or testicular histology/morphology other than no descent.[40] As, in practice, most children have been assigned female at birth, it is a unique and valuable population for study of the influences of prenatal hormone milieu, societal factors, and self-perceived genital appearance on the development of sexual/gender identity.

In male babies with cloacal exstrophy, the phallus is in two widely separated halves, both of which are rudimentary, the scrotum is vestigial and the testes are undescended. Female assignment was chosen in most circumstances because reconstruction of functional male genitalia in childhood was, and remains, difficult.[41,42]

Inevitably, there are few long-term data on the outcome of such management, although they have given important insights into the relative value of the intrauterine hormonal environment and the subsequent medical, surgical, and emotional contributions to gender identity. At least up until puberty, the majority of children have adapted well.[38]

In the genotypic females, the genitalia are abnormal but usually present. The clitoris is bifid. The vagina is present in 75%, but of those, two-thirds have duplication. Nearly all have a uterus but it is duplicated in 95%. The ovaries are present and normal. There has been at least one successful pregnancy.

In the 46XY patients raised as females, the data to puberty are encouraging. There is no difference in behavior, quality of life or social adjustment compared to norms for both genotypes.[38] All of 32 children in three major series who were raised as females continued to live as females.[38,43,44]

In the very small number of genotypic males who have reached adulthood, the results are less good regardless of the sex of rearing. All of those raised as males have continued in this gender. However, in one series of seven such patients, one has committed suicide and four have major psychiatric morbidity.[45]

In those raised as females, 5 of 11 continued in this role and were apparently content although exhibiting some male-type behavior. Two lived as females but probably with some gender dysphoria. Four had re-assigned themselves to the male gender. Dating was only found in those raised as male.[45]

It is even more difficult to discover whether genotypic males with a reconstructed vagina are able to have satisfactory intercourse. The external genitalia do not look normal and lack the areas of known female sexual sensitivity (Figure 29.7). In a review of the recent literature, the authors have been able to identify reports on only six patients who had had vaginoplasties. Two were not sexually active. Only one of the remaining four was unequivocally stated to have satisfactory intercourse. The results of the other three were lost in the generality of vaginoplasties included in the papers.[33,34,46]

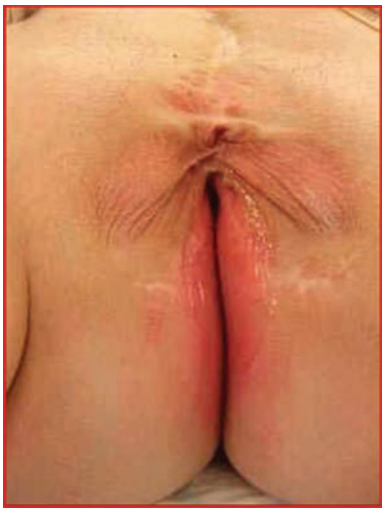

Figure 29.7 Clinical photo of a patient with 46XY cloacal exstrophy who was raised as a female. The ileal vagina is excoriated by inflammation.

It would seem that modern reconstruction can give a good quality of life to genotypic females born with cloacal exstrophy. For males, the data are inconclusive. In a 2006 survey of members of the urology section of the American Academy of Pediatrics, 66% stated that they would raise male infants as males. Although the results of this policy suggest that all of these will live as males and 56% of those raised as females will self-reassign, the price seems to be a high level of psychiatric morbidity. It may be that the burden of living with cloacal exstrophy goes far beyond the specific question of gender.

McKUSICK KAUFMAN SYNDROME (MKKS)

Most often imperforate hymen is an isolated, asymptomatic finding that is undiscovered until puberty. However, in MKKS it may also have life-threatening immediate consequences with vaginal atresia, hydrometrocolpos, persistent urogenital sinus, bladder obstruction, abdominal ascites, and renal compromise.[47] Hydrometrocolpos (Figure 29.8) is the source of obstruction to the urinary tract causing hydonephrosis (Figure 29.9). Additional features of

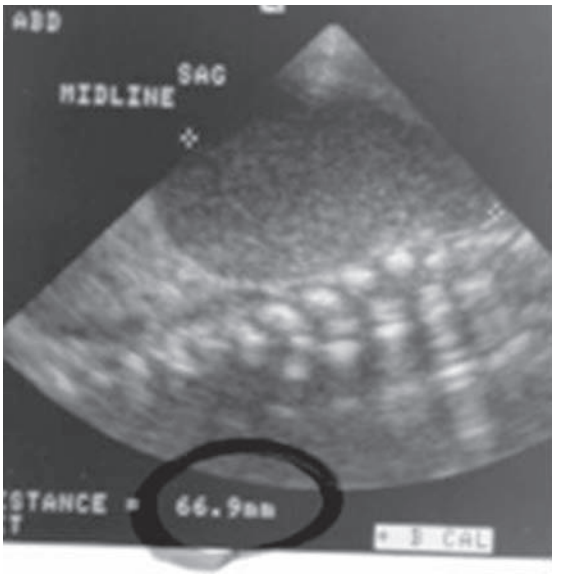

Figure 29.8 Ultrasound showing fluid collection of hydrometrocolpos in the abdomen of a newborn.

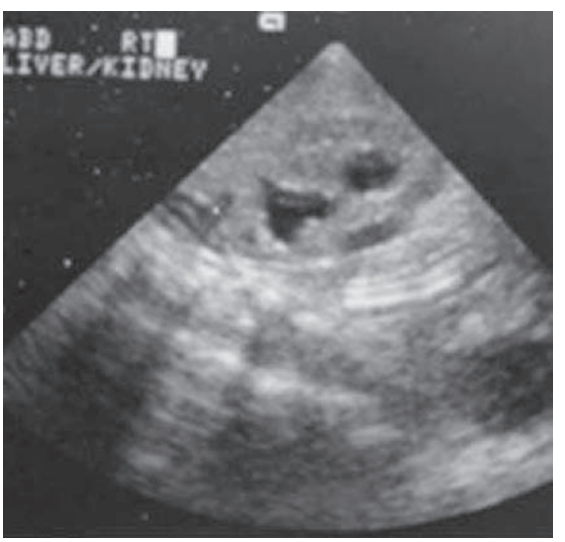

Figure 29.9 Ultrasound showing hydronephrotic kidney in a newborn whose urinary tract is obstructed by hydrometrocolpos.

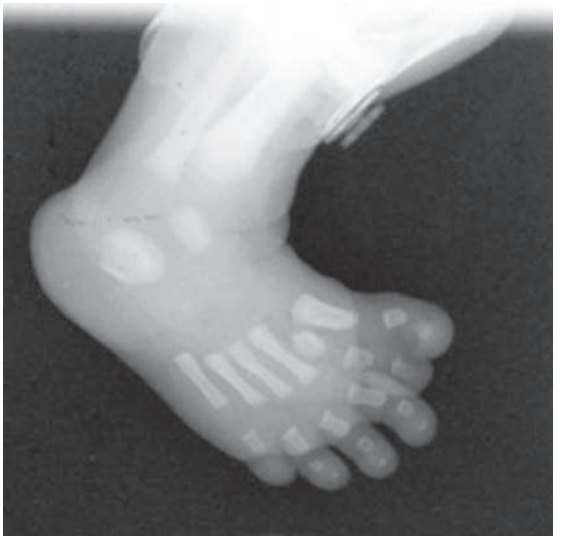

Figure 29.10 Radiologic depiction of mesoaxial polydactyly.

the syndrome include mesoaxial or post-axial polydactyly (Figure 29.10), vertebral anomalies (Figure 29.11), and congenital heart disease.[48,49]

Unusual features such as malformations of the gastrointestinal and ophthalmic structures are also possible.[50,51] Amish, non-Amish caucasian, and Arab Bedouin groups have been noted to have this autosomal recessive disorder with reduced penetrance and variable expressivity.[48,52,53] There is great phenotypic variability within the disorder.

After initial surgical repair, these children require careful medical follow-up, as hydrometrocolpos may recur with bladder obstruction and chronic renal failure.

Alhough most children identified in infancy or childhood with these characteristics would be given this diagnosis, cautious follow-up may lead to a revision of the diagnosis. A genetically heterogeneous group of autosomal recessive disorders called Bardet-Biedl syndrome (BBS) also includes postaxial polydactyly, obesity, nephropathy, mental disturbance, mental retardation, and retinal dystrophy or retinitis pigmentosa. The latter two characteristics do not occur until 10–20 years of age. Upper reproductive tract anomalies (uterine, ovarian, and

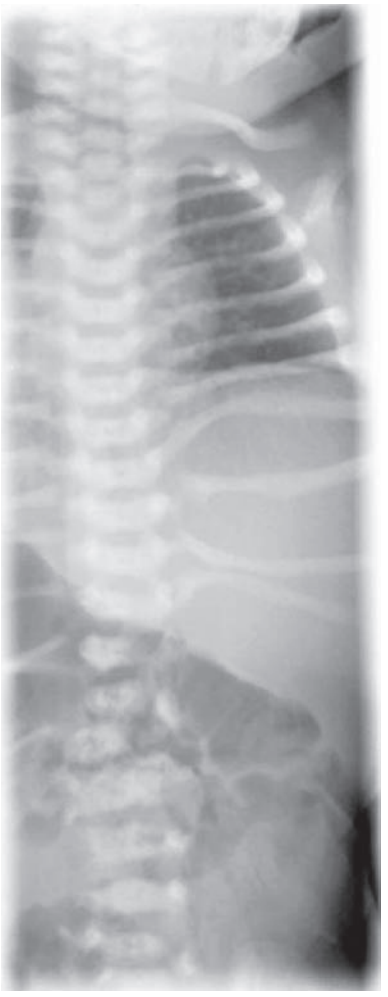

Figure 29.11 Radiologic depiction of vertebral and rib abnormalities in McKusick Kaufman syndrome.

fallopian tube) have not been reported with MKKS but have been with BBS.[54]

Both syndromes have been found to have mutations in the MKKS and BBS6 gene on chromosome 20p12. BBS is genetically heterogeneous with three cloned genes (BBS1, BBS2, BBS4, BBS7, and MKKS) and at least three other known loci (BBS1, BBS3, and BBS5).[53,55,56]

Ultrasonography, CT scan, and vaginoscopy/cystoscopy are of great value in diagnosis. Surgical

address varies from hymenal puncture to careful hymen excision, but could require reconstructive vaginoplasty such as the anterior sagittal transrectal approach (ASTRA) with colostomy in cases of vaginal atresia or persistent urogenital sinus.[57] No long-term information is available regarding sexual function, pregnancy, obstetric or renal function outcomes.

SURGERY ON THE CLITORIS

Surgery on the clitoris (Table 29.1)[58–71] is most commonly required in disorders of sexual development (DSD). However, other conditions, such as incontinence and genital cancer may require surgery of or about the clitoris.

It is now recognized that the clitoris is an erotically important sensory organ worth saving. Instead of burying or submerging the nearly intact glans and corpora, clitoroplasty techniques seek a more feminine appearance without loss of sensory/erectile tissue. In most, some corporal tissue is removed. Schmid was the first to report excision of corpora, leaving the glans on a neurovascular pedicle to preserve some sensation.[72] Most clitoroplasty techniques today are based on this concept. Recently, our understanding of the external and internal anatomy of the clitoris and anatomic relationships of the urethra and clitoris has been elucidated via fetal and cadaveric studies.[73] Anatomic studies of the human clitoris by Baskin et al have expanded our understanding of the nerve distribution and supply.[74]

The tunica of the corporeal body of the clitoris is densely innervated via the pudendal nerve. As the nerve passes under the pubic bone, it becomes the cavernosa or dorsal nerve of the clitoris. The glans clitoris forms a cap at the distal end with its highest nerve density dorsally; nerve branches are absent at the 12 o'clock position. Dorsally perforating branches innervate the glans. Pfaff detailed these neural receptive fields in the rat.[75] However, little knowledge existed regarding these areas in the human female. The first study by Baskin et al[74] detailing nerve density lends support to noted

Table 29.1 History of surgery on the clitoris

1939	Ombrédanne[58]
•	Overlap the undiminished clitoris with skin flaps
1957	Stefan and Pinsker[59]
•	Obliterate the corpora with mattress sutures without disturbing the neurovascular bundle
•	Reduce glans circumference
•	Bury the glans under the skin
1961	Lattimer[60]
•	Submerge the clitoris without removing corporal tissue
•	Reduce the glans circumferentially by trimming the corona
1961	Schmid[61]
•	Amputate the corpora, leaving the glans on a vascular pedicle with dorsal nerve intact
1965	Pellerin[62]
•	Relocate the corpora inferior to pubic arch
1966	Gross et al[63]
•	Remove all tissue of the corpora and glans
•	Transecting suspensory ligament and also removing corpora as they divide beneath the pubis
1970	Randolph and Hung[64]
•	Replace the corpora beneath the pubis posteriorly
•	Reconstruction suturing shaft to periosteum of lower border of pubis of mons veneris to cover clitoris
1973	Spence and Allen[65]
•	Excise the entire clitoral shaft preserving glans
•	Suture the stump of glans to undersurface of the pubis
1974	Kumar et al[66]
•	Preserve neurovascular bundle with partial excision of the corpora
•	Reduce glans by excision along dorsal coronal margin, preserving ventral glans and frenulum
•	Approximate glans to the crura clitoris
1981	Mollard et al[67] and 1982 Rajfer et al[68]
•	Resect the fused portion of corpora preserving the neurovascular bundle
•	Approximate the two (glans shrinks postoperatively, so reduction is unnecessary; ventral frenular blood supply is preserved)
1983	Kogan et al[69]
•	Incise tunica with intact neurovascular supply to glans proximal and distal suture ligation of corpus cavernosum
•	Wedge reduction of glans

(*Continued*)

Table 29.1 (*Continued*)

1989	Passerini-Glazel[70]
•	Partial excision of the clitoral corpora with neurovascular preservation. The glans is reduced by cutting out two lateral triangular wedges along its outer circumference and then submerged beneath created labia minora. The urethra is opened and the urethral flap is sutured to the clitoris to create a mucosa lining below the clitoris. Distal portion of mucocutaneous plate is converted to a cylinder whose intersurface is mucocutaneous
1993	Sagehashi[71]
•	Separate all corporal tissue carefully from a designed 'lump' of glans without damage to the neurovascular bundle
•	Affix preserved glandular tissue to pubic bone

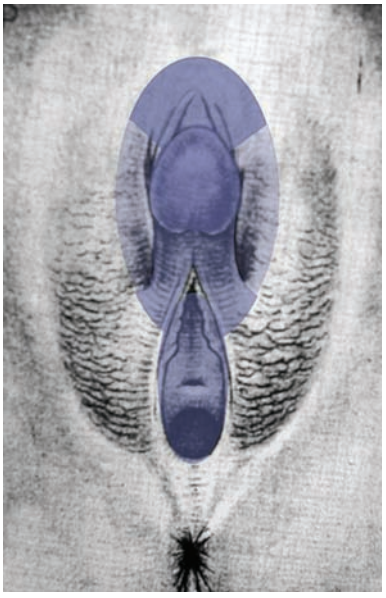

Figure 29.12 Genital sensitivity ratings for sexual orgasm intensity depicted by intensity of blue shaded areas.

genital sensitivity patterns in women. Initial studies by Schober and Meyer-Bahlurg indicated that highly sensitive areas (Figure 29.12) correspond with areas of nerve density shown by Baskin et al[74,76] (Figure 29.13). Zones of highest sensitivity were noted on and above the clitoris. Respecting and preserving these areas during surgery may lower the risk of sensory loss.

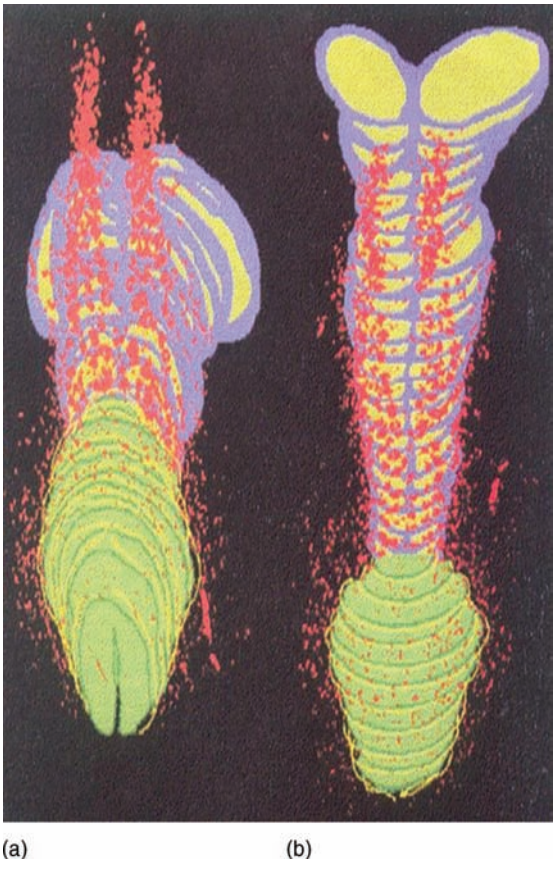

Figure 29.13 Innervation of the clitoris, shown overlying the corpora (A) and glans (B). (Reproduced with permission from J Urol and Lawrence Baskin.[74])

An intimate relationship exists between the perineal urethra and surrounding clitoral erectile tissue.[73] Partial or total urethrectomy, urethral or vaginal suspension procedures, and partial or total vaginectomy may disrupt this relationship. In feminizing genitoplasty for DSD, the mobilization of the genital sinus and separation of the genital sinus from the urethra are examples of maneuvers that may interrupt the innervation demonstrated by some of these newer studies. Support from the bulbs of the clitoris may also impact on vaginal structure and function by maintaining the vagina's rigidity on the anterior wall, facilitating intromission.

Therefore, the impact of surgery on internal or proximal structures from excision of portions of the clitoris must be considered.

Clitoroplasty for DSD has three distinct surgical steps: 1) separation of the glans from preputial and shaft skin; 2) excision of a portion of the glans; and 3) excision of a portion of the shaft or erectile tissue.[70,77,78]

Success of clitoroplasty is judged upon three criteria: appearance, sensitivity, and requirements for modification. Clitoral atrophy, unsightly clitoral appearance, and risks to genital sensitivity are higher than anticipated.[79]

Adults who have had a cliteroplasty in childhood have been found to have reduced sensation for temperature and vibration. Sexual sensitivity and the ability to have an orgasm are reduced both in those who had surgery in childhood or if it was delayed until adulthood.[80] Repeated modification to achieve an 'ideal' clitoral appearance may continue to harm sensitivity.[80]

VAGINAL CONSTRUCTION

No settled opinion is available for the best way to manage vaginal atresia or agenesis. A very long history exists of surgery employing a myriad of native and exogenous materials for construction of the vagina. Several types of repairs have documented surgical success in creation of a vagina but there are few data on sexual outcomes (Table 29.2).[70,72,77,81–106]

In considering the long-term outcome of the vaginoplasty, the literature may be reviewed for two criteria of success: 1) maintaining size (depth and width) of the vagina and 2) ability to perform and enjoy coitus. Each repair is considered separately in Table 29.2; these include vaginal tract without skin graft, split-thickness skin graft, skin flap, bowel segment, amnion, peritoneum, and bladder mucosa. Some of the unique characteristic advantages and disadvantages of each are described and long-term follow-up is included, if available.

No specific surgery has emerged as the perfect answer for augmenting or constructing the vagina. The risks for surgical vaginoplasty are different for

Table 29.2 Surgical revisions and materials used in vaginoplasty

1817	Dupuytren[81]
•	Dissect a pouch to epithelialize – no mold used
1892	Siriecieke[82]
•	Attempts to line vagina with rabbit intestinal graft
1898	Abbe[83]
•	First to use skin over a mold for creation of vagina
1904	Baldwin[84]
•	Uses intestinal segments. The sigmoid was used first; later the double loop of ileum was used. Two weeks post-operatively, a spur between the loops was crushed to establish a single barrel canal. Twenty-four percent mortality rates noted later
1911	Schubert[85]
•	Uses sigmoid for vaginoplasty
1921	Graves[86]
•	Uses labia minora as the donor tissue with pedunculated flaps
1932	Masson[87]
•	Uses intestinal segments – in 14% (2/14) of cases, surgical deaths resulted from sepsis
1938	Frank[88]
•	Applies simple pressure; dilation for 2–4 hours per day for 4+ months using penile-shaped Pyrex tubes
1938	McIndoe and Bannister[89]
•	Uses free grafts
•	Uses thin, split-thickness skin graft in one piece; continuous dilatation over a wound until the contractile phase is over
1938	Wharton[90]
•	Creates perineal pouch with subsequent spontaneous epithelialization
1948	Counsellor[91]
•	Dissects space between bladder and rectum; epithelialization occurs without the use of a skin graft
1952	Schmid[72]
•	Uses sigmoid for vaginoplasty
1954	Jones and Jones[92]
•	Simple incision perineal skin over urogenital sinus
1960	Sheares[93]
•	Posteriorly based flap lines posterior vagina; soft mold worn through epithelialization of the anterior vagina
1961	Pratt[94]
•	Revisited bowel vaginoplasty using a sigmoid loop

(*Continued*)

Table 29.2 (*Continued*)

1964	Forunoff, Lattimer, and Edson[95]
•	Uses skin flap; flap is in shape of inverted U, with the apex near the opening of vagina or sinus
1964	Williams[96]
•	Marsupialization of a U-shaped perineal incision. The labia are each separated into two layers. The inner layers are joined in the midline and pouch created and directed inward
1969	Davydov[97,98]
•	Creates vagina using pelvic peritoneum
1980	Hendren and Donahoe[99]
•	First to use bilateral rotated buttock flaps and labial flaps to repair difficult urethrovaginal fistulas
1986	Ashworth et al[100]
•	Places amnion over the vaginal mold. Approximated labium holds the mold in place. Performs vaginal dilatation after the mold is removed
1988	Claret I et al[101]
•	Uses bladder mucosa over an inflatable mold
1989	Passerini-Glazel[70]
•	All native tissue by flaps. This one-stage procedure uses phallic shaft skin to create inner labia and fold with lateral labia majora. Uses a wide inverted U flap for introitus for less outlet stenosis
1991	Johnson et al[102,103]
•	Uses tissue expanders in the labia to create an elastic and large skin flap
•	Free flap vaginoplasty; skin flap attached to its original blood supply to a place remote from the original skin flap
1992	Pena et al[104]
•	Uses transanorectal approach
1994	Jackson and Rosenblatt[105]
•	Uses Interceed® absorbable adhesion barrier; nonadherent gelatinous layer between cavity and mold allows epithelialization without adherence to stent
1997	Pena[106]
•	Uses total urogenital sinus mobilization
1998	Rink and Adams[77]
•	Uses posterior sagittal pararectal approach to the urogenital sinus without colostomy from a prone approach

high and low confluence of the urethra and vagina in DSD. The two most common surgical techniques for low confluence are cut back vaginoplasty and posterior flap vaginoplasty.[77] These probably carry lesser risks and complications than surgery for high confluence but no specific long-term outcomes have been published for these procedures. Vaginoplasty technique is discussed in depth in Chapter 28.

TUMORS AND DISEASES OF EXOGENOUS TISSUE USED IN GENITOPLASTY

When exogenous tissue is used for any reconstruction, dysplasia may be expected because it is subjected to new contacts or stresses. Skin grafted to form vagina loses hair follicles and sweat glands. A reduction in the number of elastic fibers and hyperplasia of epithelial cells occurs. Grafts accumulate large amounts of glycogen,[107] which is typical of vaginal mucosa, but almost never occurs in normal skin. Tumors associated with the exogenous tissue still have the potential to express the expected tumor or inflammatory change as in the tissue's natural environment. Obviously, such problems must be anticipated and monitored in long-term follow-up of the patient with feminizing genitoplasty.

Carcinoma of a neovagina is very rare. Cancer types appear to be related to the type of transplanted tissue. All recorded cases of squamous cell carcinoma are related to split-thickness skin graft or McIndoe variations, and all adenocarcinomas to intestinal grafts. No malignancies have been reported in vaginas made from amnion or peritoneum.[108]

Development of these tumors varies from 8 to 30 years, reflecting a younger age range than carcinoma of the natural vagina. Peak incidence for carcinoma of the natural vagina is 65 years of age, while carcinoma of the neovagina is documented in patients between the ages of 25 and 53 years.

In almost every case, cancer of the neovagina presents with a bloody or clear vaginal discharge or postcoital bleeding. As is common with natural vaginal carcinomas, all lesions occur in the posterior vaginal vault. Invasive vaginal cancer tends to be undifferentiated and development of squamous pearls is unusual. In contrast, cancer of the neovagina presents with squamous lesions that typically represent mature squamous cell carcinoma, with pearl formation. Carcinoma of the neovagina is

distinct in its occurrence in a young population and in its histopathologic cell type, but the risk of development after reconstruction is no greater than the reported incidence of vaginal cancer even though the age is younger.

Disease survival is significantly related to the stage of disease at diagnosis, just as with carcinoma in a natural vagina.[109] The first four reported patients with cancer of the neovagina were treated with primary radiation therapy. Three developed recurrence, suggesting a high percentage of failure with radiation as a primary treatment modality. The 10 most recent cases were treated with primary surgical therapy; one has recurred.

Ulcerative colitis in the neovagina has also been reported from a colonic vaginoplasty.[110] Clinical examination shows erythema, edema, ulceration, and bleeding. Treatment is with short-chain fatty acids, steroid enemas, and mesalazine. Some require surgical reduction.[111]

INTERLABIAL MASSES

The differential diagnosis of interlabial masses includes prolapsed ectopic ureterocele, prolapsed urethra, urethral polyp, paraurethral cyst, hydro(metro)colpos, and rhabdomyosarcoma of the vagina (botryoid sarcoma). Although these masses may appear similar, the appearance of urethral prolapse is similar to a donut with the urethral meatus centrally. Urethral polyps are usually smaller and linear, while paraurethral cysts are smallish and displace the urethral meatus, causing an eccentric stream. Hydrocolpos is usually a smooth midline mass that fills the vaginal introitus, and rhabdomyosarcoma is often a cluster of small grape-like masses exiting the introitus.[112]

PROLAPSING URETEROCELE

Prolapsing ureterocele usually presents as a vulval or interlabial mass. It may be present continuously or only during micturition. This cystic structure, which is prolapsed out of the external urethral meatus, can be found initially in infancy, childhood or adolescence. This is usually a smooth mass that allows urine to exit circumferentially.

Additional symptoms may include bladder obstruction with acute urinary retention, interruption of voiding, dysuria, hematuria, urinary tract infection, urosepsis, and hydrocolpos.[113–115] This can be due to a single system ureterocele or very rarely bilateral ureteroceles. Obstructive uropathy, contralateral hydronephrosis, and oligohydramnios are possible and progressive outcomes. Sudden cessation of voiding or urethral stream may occur from bladder neck or urethral obstruction. Prolapse is more common with an ectopic ureteocele but can also occur with intravesical ureterocele.

Endoscopic puncture and conservative endoscopic procedures that include reduction into the bladder are appropriate initially and may provide effective short-term correction. It is indicated in urosepsis and functional bladder neck obstruction. This procedure may facilitate and obviate subsequent open surgery. However, permanent renal and bladder damage may be a long-term outcome.[116,117]

URETHRAL PROLAPSE

Urethral prolapse is a rare condition that may be related to life stages during which estrogen levels are low, such as prepuberty and postmenopause. Although the cause is unknown; it has been related to increased abdominal pressure from trauma and medical conditions that cause increased abdominal pressure (severe cough and constipation).[118]

This entity presents visually as a circular protrusion or eversion of distal urethral mucosa. Both partial and full circular protrusions have been noted. Most commonly occurring between ages 3 and 7, it is more common in black girls.[119] It is responsible for emergency room visits and admissions for vaginal bleeding, irritative voiding symptoms, acute urinary retention, and protruding vaginal mass.[120] It is often confused with acute sexual trauma from abuse.

Vascular congestion and edema of the prolapsed mucosa are progressive and the extent can be

variable. The congestion commonly appears dark red to bluish and can bleed and become necrotic. Therapy has most often been supportive with warm soaks, antibiotics, and estrogen cream.[120–122] Such conservative management has been found to be very effective. Several weeks of therapy are necessary. If medical management is ineffective, urinary retention persists or recurrences become problematic, surgical treatment includes urethral catheterization and excision of the prolapsed tissue with re-anastomosis of the urethral margin.[122–124] Other surgical methods are surgical ligation over a catheter, cautery, fulgeration, and cryosurgery. The prolapse may be recurrent even after surgery and stenosis may be a later outcome.

THE SMALL PAINFUL BLADDER

Bladder symptomatology in female children and adolescents may include chronic complaints of urinary urgency, daytime urinary frequency, dysuria, nocturia, terminal hematuria, and pain, unrelated to an acute bacterial infection. This type of painful bladder syndrome is thought to be rare in children. The hallmark features are irritative voiding and chronic pelvic pain. Pain can be localized to the suprapubic, pubic, vaginal, and genital areas. On physical examination, tenderness can be elicited in the suprapubic and anterior vaginal locations.[125] Although seen relatively infrequently in children and adolescents, it may be confused with voiding dysfunction, creating a delay in diagnosis.[126] Etiologies of painful bladder may include interstitial cystitis (IC), eosinophilic cystitis, bilharzia (schistosomiasis), tuberculosis (TB), and ketamine abuse.

INTERSTITIAL CYSTITIS

Interstitial cystitis (IC) may occur in up to 7.5% of the general female population.[127] Evidence-based, clinical practice guidelines for IC are not available because of lack of consensus on definition and etiology of the disease. The International Continence Society definition of painful bladder syndrome may be helpful in diagnosis, including 97 clinical variables.[128] Onset of symptoms for IC has been reported in the literature as early as 2 years of age, with age of diagnosis as early as 3 years.[129]

Diagnosis may be made histologically (biopsy) and with cystoscopic inspection (Hunner's ulcers) with hydrodistention (moderate to diffuse glomerulations apparent).[130] Exclusion of infection and TB is necessary before diagnosis is made. Drug-associated side effects must also be ruled out. Tiaprofenic acid, a nonsteroidal anti-inflammatory drug (NSAID) used in the UK has been shown to cause severe IC.[131] Conservative management is suggested initially but the use of intravesical dimethylsulfoxide has been reported.

EOSINOPHILIC CYSTITIS

In children, eosinophilic cystitis is a very rare disorder with less than 30 reported cases in the literature.[132] Parasitic associations have been found in rare circumstances due to *Toxocara canis* and *Echinococcus granulosus.* Drug sensitivity reactions may also be a cause. These may affect the bladder diffusely or in a localized form. Associations with allergies or asthma are usually related to diffuse disease. Some cases may be associated with eosinophilic gastroenteritis. Differential diagnosis must be made from tumors. If the antigenic stimulus can be identified, it should be removed. Initial treatment for the majority of patients has been combinations of corticosteroids, antihistamines, and antibiotics. Treatment with azathioprine or intravesical dimethylsulfoxide has been reported but relapse is common. Unremitting progression is possible, with some cases necessitating partial cystectomy. Biopsy before diagnosis is necessary.[133]

BILHARZIA (SCHISTOSOMIASIS)

A rare parasitic disease most commonly found in tropical, sub-Saharan countries, Africa, Asia, and the Middle East, bilharzia can cause severe urinary tract compromise.[134] Clinical symptoms feature dysuria, bladder pain, and hematuria. Schistosoma eggs may

be found in the urine. Cystoscopically, inflamed and ulcerated bladder mucosa are noted. Bladder biopsy is necessary to identify the nematode *Schistosoma haematobium* and schistosome eggs, and to rule out malignancy.[135] Squamous metaplasia and infiltration of plasma cells and eosinophilic granulocytes may also be noted. Treatment is with praziquantel. Follow-up cystoscopy and urinalysis after treatment is prudent.

TUBERCULOUS BLADDER INFECTIONS

Hematogenous spread of primary pulmonary TB both with and without renal involvement has been reported.[136] The genitourinary tract is the most common site of extrapulmonary TB. Both pulmonary and extrapulmonary TB have been increasing over the past decade due to the rising number of patients with acquired immunodeficiency syndrome (AIDS) and development of drug-resistant strains of *Mycobacterium tuberculosis*. Inflammatory symptoms of dysuria, bladder pain, urinary frequency, and hematuria are notable. Radiological imaging with abdominal radiographs (KUB), ultrasonography (US), intravenous pyelogram (IVP), retrograde cystography, and computed tomography (CT) scan may show granulomas. Considering the bladder, urography, CT or ultrasound may demonstrate diffuse or irregular wall thickening in both the mucosal and muscularis layers. Rarely, calcification of the whole bladder wall may be seen.[137] Immediate diagnosis may be made by polymerase chain reaction (PCR) examination of the urine to detect the Koch bacillus. Urine culture and histologic investigation of surgical biopsy specimens confirms the diagnosis.[138] Treatment with isoniazid (INH), ethambutol (ETB), rifampicin (RIF) according to sensitivity profiles; and sometimes BCG (if a bladder tumor is found), is carried out only after identification of the mycobacteria and antituberculous susceptibility testing.[139]

KETAMINE ABUSE

Very recently a relationship between the recreational use (or abuse) of the drug ketamine and ulcerative cystitis was reported. Clinical presentations were of severe dysuria, frequency, urgency, and hematuria by those who used the drug on a daily basis. Microscopy may identify inflammatory findings that include microhematuria, but urine culture is sterile. Radiologically, CT or ultrasound may identify bladder wall thickening. Cystoscopy may identify the ulcerative cystitis. Biopsy would aid diagnosis, with features of epithelial denudation, inflammation, and eosinophilic infiltrate. Stoppage of ketamine use may relieve symptoms. Pentosan polysulfate has also been found helpful for symptomatic relief.[140]

CONCLUSION

The proximity of the genital and urinary structures in female children often necessitates multidisciplinary consideration in regards to congenital malformations, developmental disorders, and urologic and gynecologic problems. Physicians involved in the care of young female patients must recognize the inter-relation of these two distinct systems so as to provide comprehensive care. Teams consisting of urology and colorectal surgeons, and gynecologists may be necessary for the proper care of children with these disorders.

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30. Adnexal masses in the neonate, child, and adolescent

Lisa Allen, Nathalie A Fleming, and Julie Strickland

FETAL AND NEONATAL OVARIAN CYSTS

The etiology of a fetal or neonatal ovarian cyst almost universally is a functional cyst.[1–3] Only rarely will pathology such as a mature teratoma,[1,2,4] granulosa cell tumor or cystadenoma[5] be present. Management of the antenatal or neonatal ovarian cyst requires consideration of ovarian preservation and avoidance of complications, in particular ovarian torsion, a challenging diagnosis in infancy.

INCIDENCE, ETIOLOGY, AND DIAGNOSIS

Primordial follicles are present in the fetal ovary as early as the 20th week of gestational age, peaking at 33 weeks.[2] Ovaries are not quiescent during the antenatal or neonatal period, with small physiologic ovarian cysts of diameter less than 1.4 cm visible in 84% of sonographic images.[6] The detection of clinically relevant ovarian cysts greater than 2 cm is less frequent, being diagnosed in 1:2625 pregnancies.[7] The pathogenesis of the fetal ovarian cyst is believed to be related to follicular stimulation from placental chorionic gonadotropin (hCG), maternal estrogens, and fetal gonadotropins. Conditions of excess placental hCG secretion or enhanced placental permeability to hCG such as maternal diabetes mellitus, gestational hypertension, and Rh isoimmunization are associated with fetal ovarian cysts.[8] However, the majority of fetal and neonatal ovarian cysts occur in the absence of one of the aforementioned conditions.[9,10] Fetal conditions of hypothyroidism and congenital adrenal hyperplasia with 21-hydroxylase or 11beta-hydroxylase deficiency in association with ovarian cysts has also been reported.[10,11] The bilateral rate of ovarian cysts in this age group ranges from 1.4 to 27%.[3,5,9,12,13] At birth, levels of follicle-stimulating hormone (FSH) rise rapidly due to the withdrawal from maternal estrogen and progesterone sources. This level peaks at 3–4 months of age then gradually falls thereafter to the low prepubertal levels that will be maintained throughout childhood. The regression of neonatal ovarian cysts over the same time period can be expected. With the increasing use of ultrasound during pregnancy, the majority of recent reports contain series of primarily antenatally diagnosed ovarian cysts.[5,13–18] Antenatal ovarian cysts are reported to be diagnosed at an average of 33 weeks of gestational age[2,9,13] but have been identified as early as 19 weeks.[19] The diagnosis *in utero* must be considered presumptive as confirmation is not feasible until post delivery. The differential diagnosis of an ovarian cystic mass includes mesenteric cysts, intestinal duplication, intestinal obstruction, megacystitis, hydronephrosis, omental cysts, anterior meningomyelocele, lymphangioma, urachal cysts, hydrometrocolpos, and choledochal cysts.[11,13,20]

In the neonatal period, an ovarian cyst may be diagnosed due to a palpable abdominal mass, symptoms such as respiratory distress, vomiting, irritability or failure to thrive, or incidentally during imaging for other medical conditions.[16,21]

NATURAL HISTORY, RISK, AND COMPLICATIONS

Given the functional nature of the majority of cysts in infants, resolution of many would be expected with expectant management. While resolution is documented, cyst complications such as torsion

and hemorrhage do occur in both the antenatal and neonatal period.

There is a significant risk of *in utero* complication when cysts are diagnosed prenatally. Between 25 and 70% of cysts initially found to be simple on imaging will develop complexity either by the final prenatal scan or by the first postnatal confirmatory imaging.[5,13,14,19] *In utero* torsion appears to cause few sequelae for the newborn. Most are asymptomatic, although bowel adhesions,[10] autoamputation,[22–24] and loss of ovarian function are possible sequelae.[14,16] Bilateral ovarian cysts can place the neonate at risk for complete loss of ovarian function.[22] Polyhdramnios[4,11,15,25] has been associated with fetal ovarian cysts. The etiology is speculated to be related to a partial small bowel obstruction or compression of the umbilical cord.[15,25,26] Soft tissue dystocia at delivery from abdominal distention, while possible is rare, hence most authors advocate cesarean section for obstetrical indications only.[11] Presumptive diagnosis of antenatal torsion has been shown to be unreliable and does not justify any obstetric intervention to expedite delivery.[27]

Ovarian torsion in the neonate can be difficult to diagnose but is occasionally associated with serious sequelae including death.[14,28–32] Symptoms from ovarian cysts in neonates include vomiting and failure to thrive due to small bowel obstruction or volvulus from bowel adhesions,[9,12] respiratory distress due to mass effect,[4,25] and anemia or hypovolemic shock due to hemoperitoneum associated with cyst hemorrhage and rupture.[25]

While a 4 cm size has been advocated as a threshold for active management of infantile ovarian cysts,[12] not all series have been able to identify a cyst size threshold that predicts expected complications.[1,13]

MANAGEMENT

ANTENATAL CYSTS

The management of both antenatal and postnatal ovarian cysts is not standardized and remains controversial. In only rare cases will interventional therapy be indicated. Arguments for both expectant and active management have been put forth in the medical literature. The criteria for interventional management are usually based on size and complexity of the cyst during sonographic evaluation.

Given the high rate of *in utero* torsion, consideration has been given to antenatal intervention by aspiration to help avoid this complication when fetal ovarian cysts are diagnosed.[9,33] Comparison of the outcomes of anechoic cysts > 5 cm in diameter managed prospectively by a policy of *in utero* aspiration to a historical control of non-aspirated cysts demonstrated a statistically significant reduction in infants requiring surgery for ovarian torsion with a drop in the rate of subsequent oophorectomy from 85% to 14%.[9] In a recent series of 14 cyst aspirations, 12 were resolved without sequelae.[9] As not all cyst complications can be predicted based on size criteria alone, intrauterine aspiration has anecdotally been extended to the smaller ovarian cyst with successful technical application.[34]

Hemorrhage, preterm labor, premature rupture of membranes, needle injuries to fetal intra-abdominal organs, and infection are potential risks of *in utero* aspiration.[34] These risks may be minimal due to the later gestational age at which cysts are diagnosed and hence managed.[9] The greatest risk of antenatal aspiration is the risk of misdiagnosis. A policy of routine aspiration of presumed ovarian cysts antenatally may result in aspiration of other intra-abdominal cystic masses.[1,9] While careful sonographic imaging will be able to differentiate many of these lesions, antenatal aspiration could result in inadvertent aspiration of a non-ovarian etiology.

NEONATAL CYSTS

Expectant management (Figure 30.1)

The risk of malignancy in fetal and neonatal ovarian cysts is extremely low, allowing a non-surgical approach to be contemplated in their management. The following criteria have been suggested as justifying expectant management in the asymptomatic neonate.

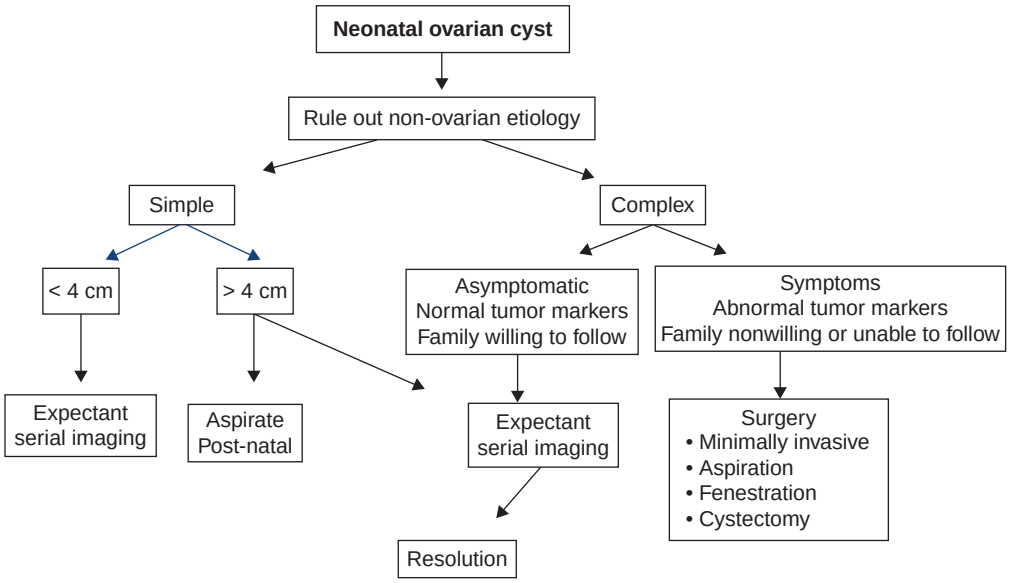


Figure 30.1 Algorithm for management of neonatal ovarian cysts.

1. The cyst is clearly of ovarian origin.
2. There is no solid component on ultrasound beyond septations and debris from hemorrhage.
3. Tumor markers are negative, i.e. alpha-fetoprotein (AFP), chorionic gonadotropin (βHCG), lactate dehydrogenase (LDH).
4. The family is willing and able to comply with follow-up.[8]

Cautious interpretation of tumor markers in the newborn is required, with application of age-referenced norms.

When expectant management with serial ultrasound follow-up is chosen in the newborn period, cyst resolution has been documented for both simple and complex cysts[13,14,16] (Table 30.1). The time to resolution for complicated cysts is longer than for simple cysts.[13] Many simple cysts will resolve by 6 months of age.[13,15] Final resolution of complex lesions may require up to 16 months.[5,13,16] If surgery is only undertaken for symptoms, inability to continue follow-up, for increasing size or persistence, then 81–100% of cysts diagnosed in the antenatal period resolve without intervention.[13,14,16] Resolution of cysts as large as 8 cm in diameter has been recorded[10] (Figures 30.2 and 30.3).

As complexity may represent antenatal torsion, not surprisingly after cyst resolution on imaging the majority of ipsilateral ovaries will not be visualized, reflecting absence of function.[13,14,16] Of the 10 complex cysts followed expectantly by Luzzato et al, only 20% of the children had both ovaries visible after resolution of the complex mass.[13] Enriquez et al reported on 2 groups of infants managed in their institution, a retrospective surgical cohort of 9 infants and a prospective expectant cohort of 11 infants, all with prenatal or postnatal diagnosis of ovarian cysts. Of the non-surgical group, while all cysts involuted between 3 and 15 months of age, 100% of the infants had a single ovary remaining on pelvic ultrasound.[16]

The persistence of a neonatal cyst, especially in the presence of complex elements, should raise the consideration of the rare diagnosis of an ovarian teratoma. In these circumstances surgical management is indicated.[1,2,4]

Table 30.1 Conservative management of neonatal ovarian cysts

Study	*n*	Complexity and postnatal US size	Resolution	Time to resolution	Ovarian status at follow-up
Meizner et al[19] (1991)	9	Simple Volume cm^3 11.1–27.8	9/9 (100%)	2–6 months	…
Brandt et al[2] (1991)	19	Simple/septae alone (16) Complex (3) 0.8–7.0 cm	16/19 (84%) 13/16 simple/septae (3 lost to follow-up) 0/3 complex	0.5–6.0 months	Not recorded for all 8 both ovaries visible
Bagolan et al[12] (1992)	6	Simple (6) 1.5–5.0 cm	4/6 (67%)	1–4 months	…
Spence et al[21] (1992)	5	Simple (3) Not specified (2) 1.0–4.9 cm	5/5 (100%)	3–18 months	…
Luzzato et al[13] (2000)	20	Simple (7) Complex (13) 2.0–6.2 cm	17/20 (85%) 7/7 simple 10/13 complex	1–16 months 1–5 months simple 2–16 months complex	7/7 simple cysts both ovaries visible 2/10 complex both ovaries visible
Chiaramonte et al[10] (2001)	17	Simple (17) 2.8–8.0 cm	12/17 (71%)	5–10 months	…
Bagolan et al[9] (2002)	34 simple cysts 34 complex*	Simple 2.4–4.4 cm (34)	26/34 simple < 5 cm 9/34 complex*	…	…
Heling et al[1] (2002)	46	Simple (32) Complex (14)	16/46	2–10 weeks	…
Comparetto et al[15] (2005)	16	Simple, < 4 cm (16)	16/16 (100%)	2–6 months	…
Enriquez et al[16] (2005)	11	Complex (11) 2.4–6.1 cm	11/11 (100%) (2 residual calcifications)	3–15 months	0/11 both ovaries visible
Foley et al[14] (2005)	11	Simple (3) Complex (8) 0.7–7.0 cm	9/11 (81%) 3/3 simple 6/8 complex	…	3/3 simple and 2/8 complex bilateral ovaries visible
Kwak et al[5] (2006)	9	Simple (7) Complex (2) 1.0–4.8 cm	9/9 (100%)	1–16 months 1–10 months simple 10–16 months complex	…

*Groups not mutually exclusive.

Postnatal aspiration

Postnatal aspiration is less commonly employed in comparison with either expectant serial imaging follow-up or surgical therapy, but may have a role in the management of the larger simple ovarian cyst.[13] Aspiration of complex cysts is controversial because in the rare circumstance of a mature teratoma, aspiration and spillage of cyst contents could theoretically lead to chemical peritonitis and pelvic adhesions. A recent report of postnatal aspiration of both simple and complex cysts > 4 cm undergoing an ultrasound-guided drainage within 24 hours of delivery found that 66% of the infants followed to 1 year had bilateral normal ovaries post aspiration in comparison with only 25% of the eight patients taken to the operating room in the same time period.[17] Non-ovarian pathology must be excluded before aspiration.

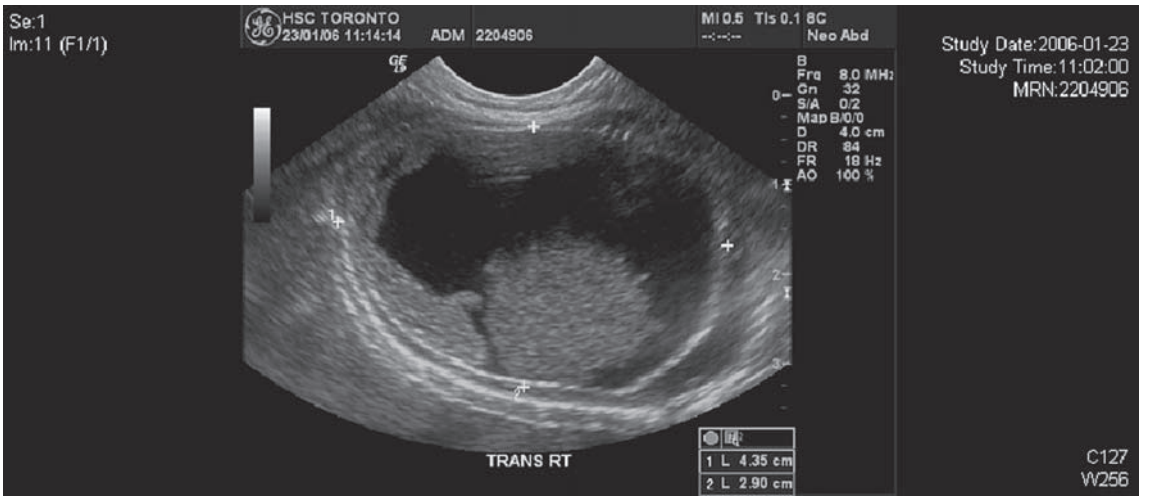


Figure 30.2 Postnatal appearance of antenatal diagnosis of a simple ovarian cyst, but complex by delivery.

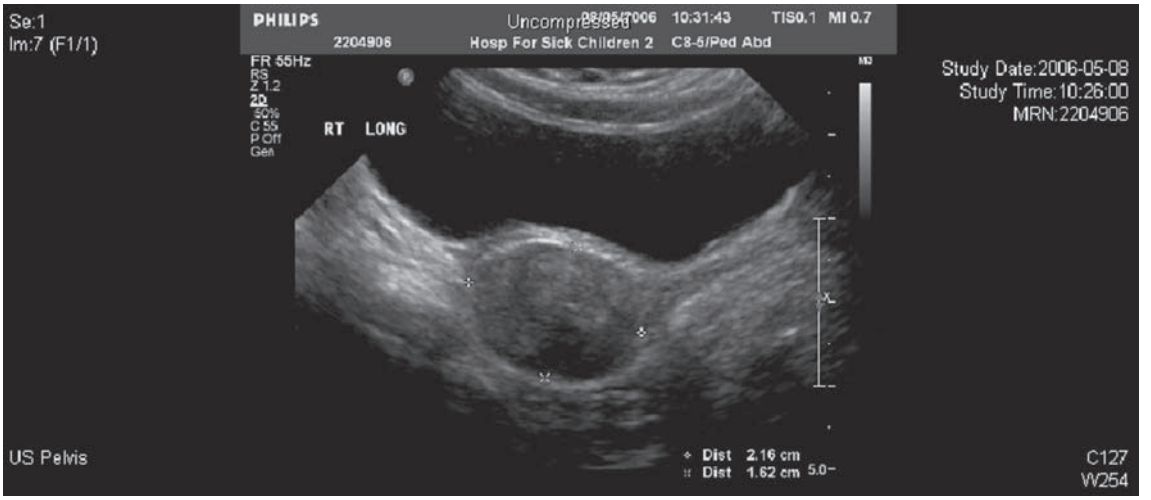
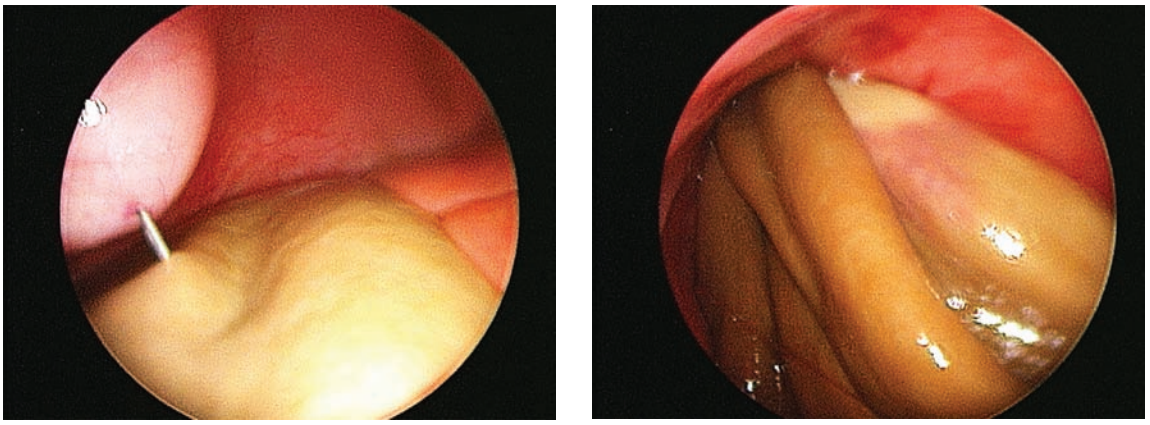


Figure 30.3 Six-month follow-up image of cyst shown in Figure 30.2, gradual resolution of size.

Surgery

Most authors direct surgical management based on a size criterion of > 4–5 cm and complexity of the cyst on ultrasound imaging.[3]

While most surgeons agree with expectant management of simple ovarian cysts less than 4 cm, surgical management of other lesions has been advocated, based on the belief that active management will decrease the risk of complications subsequent to diagnosis. The approach to surgery in infants is evolving towards minimally invasive techniques. Laparoscopy,[3,18,24] laparoscopic-assisted minilaparotomy, and minilaparotomy[23] are all reported. Laparoscopy does allow an enhanced



(a) (b)

Figure 30.4 Laparoscopic aspiration for decompression of twisted large ovarian cyst. Oophorectomy undertaken after decompression through small abdominal incision.

visualization of the pelvis and abdomen compared with the view obtained through a minilaparotomy incision. Regardless of the approach to surgery, the guiding principle in surgical management of neonatal cysts should be the least aggressive surgery to preserve the maximum normal ovarian tissue.[1] Surgically guided cyst aspiration, fenestration or unroofing of the cyst or cystectomy is preferable to oophorectomy in simple ovarian cysts. The autoamputated or necrotic torsed ovary is non-salvageable and should be managed with oophorectomy (Figure 30.4).

CHILDHOOD OVARIAN CYSTS

Adnexal masses are reported less frequently in childhood than in the adolescent owing to the low levels of gonadotropins. As a result, fewer functional cysts will develop in prepubertal ovaries.[35] Consequently, if an ovarian mass is noted in this age group, a reasonable index of suspicion of neoplasia must be maintained when deciding on the approach to both investigations and management.

INCIDENCE

The incidence of all ovarian masses in childhood is quoted as approximately 2.6 cases/100 000 girls per year. With the widespread use of ultrasound, ovarian cysts may currently be diagnosed more frequently. Microcysts (< 9 mm) and macrocysts (> 9 mm) exist within the ovaries of 2–9-year-old girls.[36] These simple, small, and transient cysts are not clinically significant and caution should be applied in attributing symptoms to their presence.

Ovarian neoplasms are said to constitute not more than 1% of all childhood tumors; 8% of all malignant abdominal tumors in children are of ovarian origin.[37] The proportion of childhood masses that are malignant is difficult to determine, as many series report neonates, children, and adolescents together. In some series the percentage of premenarchal patients in the study population is as low as 7%, others have larger proportions of children upwards of 31% aged 1–8 years.[38,39] In general, the incidence of neoplasms overall is higher in adolescence compared with childhood, up to 10-fold, but the proportion of malignancies in neoplasms is

higher in the first decade of life compared with the second, 56% and 29%, respectively.[40]

PRESENTATIONS

Ovarian masses in children may present with abdominal pain, mass effect or rarely with endocrine disturbance.[41] Girls have a proportionally long infundibulopelvic ligament and a small unyielding bony pelvis, which may result in symptoms from ovarian pathology being abdominal rather than pelvic in children.

Acute pain, the most common symptom, results from a cyst complication of hemorrhage, rupture or torsion. An ovarian etiology for abdominal pain syndromes in girls must be contemplated and appropriate imaging undertaken.[42] The most common misdiagnosis of a childhood ovarian mass is appendicitis.[42,43] Identification by palpation is less frequent, ranging from 21.7% to 35.7%.[41,44] Associated symptoms may be nonspecific such as vomiting, fever, anorexia, constipation, weight loss, abdominal distention, urinary frequency, urinary retention, and dysuria. Less commonly, masses present with endocrine manifestations such as isosexual precocious puberty, virilization, and/or vaginal bleeding. Sex cord-stromal tumors traditionally are associated with endocrine manifestations but other non-neoplastic and neoplastic lesions may also lead to endocrine disturbance. Follicular cysts, ovarian edema, and germ cell tumors have all been reported in association with hormonal production and symptoms.[35]

ETIOLOGY

The differential diagnosis of the adnexal mass in childhood includes functional ovarian cysts, benign and malignant ovarian neoplasms, paratubal or para-ovarian cysts, and müllerian anomalies, as well as non-gynecologic pathology (Table 30.2).

In the child age range, the most common origin for neoplasms is the germ cell line, accounting for approximately 70% of tumors, although all histologic lines have been described.[35,44] Both epithelial and stromal tumors are uncommon in the first decade of life, accounting for 14% and 11% of neoplasms, respectively[35] (Figure 30.5). The most common ovarian neoplasm in children is the mature cystic teratoma.[35,38,41,44] The malignant germ cell tumors consist of dysgerminomas, endodermal sinus tumors, immature teratomas, and embryonal carcinomas.[45]

Table 30.2 Differential diagnosis of pelvic mass in children

Ovarian
1. Functional
   - Corpus luteum
   - Theca lutein cyst
2. Benign
   - Germ cell (mature cystic teratoma, functional teratoma, gonadoblastoma)
   - Epithelial cystadenoma (serous, mucinous)
   - Stromal (thecoma, fibroma)
3. Low malignant potential
   - Serous
   - Mucinous
4. Malignant
   - Germ cell (dysgerminoma, endodermal sinus tumor, immature teratoma, embryonal, polyembryoma, choriocarcinoma, mixed)
   - Epithelial cystadenocarcinoma (serous, mucinous)
   - Stromal (juvenile granulosa cell tumor, Sertoli-Leydig tumor)
5. Metastatic
   - Lymphoma

Embryologic remnants
- Paratubal
- Paraovarian cysts

Adnexal torsion

Müllerian anomaly

Gastrointestinal
- Mesenteric cyst
- Appendiceal abscess
- Intussception

Urologic
- Wilms tumor

INVESTIGATIONS

The diagnostic approach to a pelvic mass in childhood combines careful physical examination as the

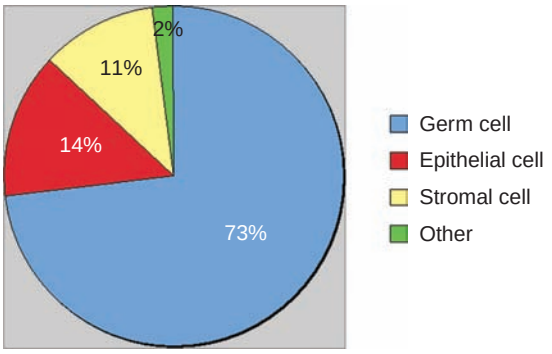


Figure 30.5 Histologic proportion of neoplasms in children. Adapted from DaSilva et al.[35]

initial step with imaging and investigation of tumor markers. Height, weight, and general appearance should be documented. On abdominal examination the size of the mass is ascertained, and the presence or absence of abdominal tenderness or ascites. As ovarian cysts may be secondary to other medical conditions, a physical examination must address potential related pathology. Café au lait spots on the skin may indicate McCune Albright syndrome and a thyroid nodule may be related to hypothyroidism. Evaluation for signs of hormonal production with Tanner staging of the breast and pubic hair is necessary. As tumors may produce either estrogen or androgens, the examiner should look for isosexual precocious puberty and virilization or hirsutism. The external genitalia should be inspected for signs of estrogenization of the hymen and for signs of virilization such as clitoromegaly.

Imaging is essential in characterization of the ovarian cyst. Ultrasound is the initial imaging modality of choice to assess for size, characteristics of the lesion (wall thickness, mural nodules, excrescences, septations, shadowing), bilaterality, pelvic fluid (hemoperitoneum or ascites), and prepubertal or pubertal appearance of the uterus and may identify extra-ovarian disease. Ultrasound Doppler can document the presence or absence of flow to an ovarian lesion. Ultrasound imaging may be complemented by computed tomography (CT) scanning. In particular, CT is useful to rule out appendiceal pathology and to assess for presence of pelvic or para-aortic lymphadenopathy and extra-ovarian disease.

Tumor markers in childhood should include, as a minimum, AFP, LDH, and βHCG, if malignancy is suspected. These tumor markers are positive in multipotential germ cell tumors (embryonal carcinoma) and extra-embryonal tumors (endodermal sinus tumor and choriocarcinoma) (Table 30.3). A mature or immature teratoma that contains malignant elements may secrete AFP. LDH is positive but nonspecific in dysgerminomas. CA 125, while positive in serous epithelial tumors, is a non-specific indicator of peritoneal inflammation and has limited value in premenopausal patients. If examination suggests hormonal production by the tumor, determination of serum estrogen and androgen levels can confirm the clinical suspicion. Granulosa cell tumors are indicated by an elevated inhibin level, although this test is not routinely available.

MANAGEMENT

The management of ovarian cysts in children is dictated by the symptoms, the likelihood of neoplasm, and in particular the concern for malignancy. In many surgical series of ovarian masses in children and adolescents, pathology-confirmed functional cysts occur in a proportion of the surgically treated group. Conservative follow-up of simple ovarian lesions is feasible in children and should be the method of choice in selected cases of simple, small ovarian cysts. While most neoplasms will be 5 cm or larger, the largest cyst diameter that resolved in a conservative follow-up of large ovarian cysts in children was 7.3 cm.[46]

Criteria modified from Warner et al[46] may be useful in deciding on surgical management.

1. Persistent non-resolving symptoms.
2. Suspicion of torsion.
3. Signs and symptoms of a large mass associated with complications (hydronephrosis).
4. Evidence of neoplasm (complex/solid mass, metastasis, ascites) on imaging or with positive tumor markers.

Table 30.3 Tumor markers in childhood ovarian tumors

Tumor	AFP (alpha-fetoprotein)	βHCG (beta human chorionic gonadotropin)	Inhibin	LDH (lactate dehydrogenase)	CA125	Androgens
Dysgerminoma	−	−/+	−	−/+	−/+	−
EST (endodermal sinus tumor)	+	−	−	−/+	−/+	−
Immature teratoma	−	−	−	−	−	−
Embryonal carcinoma	−/+	−/+	−	−	−	−
Choriocarcinoma	−	+	−	−	−	−
Mixed GCT (germ cell tumor)	−/+	−/+	−	−	−/+	−
Granulosa cell	−	−	+	−	−	−/+
Sertoli-Leydig	−	−	−/+	−	−	+
Epithelial tumor	−	−	−	−	−/+	−

5. Unclear origin of mass.
6. Failure of cyst resolution or cyst growth on serial imaging.

As with ovarian masses at other ages, a surgical approach by laparoscopy or laparotomy must be planned. Guiding principles in surgical management of ovarian lesions should be towards ovarian preservation and minimization of adhesion formation to preserve fertility.[39] Surgical management of ovarian lesions by experienced health-care providers is important, and has been shown to enhance the likelihood of the patient receiving an ovarian-conserving surgery.[42]

If there is a low index of suspicion for malignancy, a laparoscopic approach with ovarian cystectomy is the surgical procedure of choice. Occasionally benign masses may be too large to approach laparoscopically. In these situations, diagnostic laparoscopy can confirm the ovarian etiology of the mass. A minilaparotomy incision may then allow decompression of the ovarian cyst. Once exteriorized an ovarian cystectomy may be completed. Cystectomy is appropriate for surgical management of epithelial cystadenomas, para-ovarian or paratubal cysts, and mature cystic teratomas. The surgical approach for mature cystic teratomas remains controversial, particularly due to the theoretical risks associated with intraoperative spill. Ovarian cystectomy of dermoid cysts by laparoscopy is associated with higher rates of spill than by laparotomy, upwards of 52%.[47,48] In a series of 52 children, of whom 14 were managed laparoscopically, there were no incidences of chemical peritonitis.[47] Additional risks of increased recurrence rates have also been reported. When obtaining parental consent for laparoscopic treatment of dermoid cysts, the risk of spill and recurrence rate should be discussed.

Surgical staging is paramount for malignant ovarian neoplasms, as stage of disease guides decisions for postoperative adjuvant chemotherapy. Pediatric germ cell tumors are staged using the system developed by the Pediatric Oncology Group. Epithelial tumors are staged according to the International Federation of Gynecology and Obstetrics (FIGO) system for primary carcinoma of the ovary. Rupture of a malignant neoplasm at surgery can result in upstaging of the patient, hence most suspicious tumors are optimally approached by laparotomy. If a germ cell tumor is suspected the primary tumor is resected with a unilateral salpingoophorectomy. Intraoperative staging includes collection of ascites or peritoneal washings for cytology, biopsying peritoneal surfaces, inspecting the contralateral ovary, sampling the pelvic and/or para-aortic nodes bilaterally if enlarged, and an omentectomy. Extensive germ cell tumors should be biopsied for diagnosis but aggressive surgical procedures are not undertaken at the risk of harm

to vital structures due to the effective response observed to multiagent chemotherapy in these tumors. Postoperative chemotherapy with bleomycin, etoposide, and cisplatin has resulted in marked advances in survival compared with previous regimens.

Epithelial cystadenocarcinomas are extremely rare in childhood. Management of these lesions would be as per adult guidelines. Low malignant potential epithelial tumors are managed in young patients with unilateral salpingoophorectomy, omental biopsy, and resection of all visible disease. If the lesion is of mucinous histology an appendectomy is recommended to rule out a gastrointestinal primary.

Stromal cell tumors are often present in an early tumor stage and can be treated effectively with surgery alone, rarely requiring postoperative chemotherapy.

Several studies confirm ovarian function as evidenced not only by ongoing menstruation but also by pregnancy following fertility-sparing approaches to surgery and platinum-based adjuvant chemotherapy regimens in the treatment of pediatric malignant ovarian tumors.[39,49]

ADOLESCENT OVARIAN MASSES

Ovarian cysts are more frequently encountered in adolescents when compared with children. However, the proportion of cysts or masses within the ovary that represent either tumors or malignancy is even lower, hence management styles in this age group must reflect the propensity towards formation of functional ovarian cysts post-menarche.

ETIOLOGY AND DIAGNOSIS

Functional ovarian cysts often result from the failure of the maturing follicle to ovulate and involute and represent up to 50% of adolescent ovarian cysts.[39,50] Often these cysts are simple on ultrasound, with thin walls. They are benign and self-limiting and over time will involute. Functional cysts may also reflect the persistence of the corpus luteum.[51,52] Often functional cysts will regress within two to three menstrual cycles.

Functional cysts may become complicated by hemorrhage. Following ovulation both the luteinized theca cells and the granulosa cell layer of the follicle become vascularized. These vessels are fragile and may rupture easily, leading to a hemorrhagic cyst.[53] The average diameter of a hemorrhagic ovarian cyst is 3.0–3.5 cm but they may range up to 8.5 cm on ultrasound.[53] A hemorrhagic ovarian cyst often presents with an abrupt onset of lower abdominal or pelvic pain midcycle or in the luteal phase without fever or leukocytosis. If the cyst wall ruptures, a hemoperitoneum may develop and peritoneal signs or postural hypotension may be evident on examination. A hemorrhagic cyst has been termed a great imitator, as its appearance on ultrasonography may be confused with an ectopic pregnancy, an ovarian tumor or inflammatory process such as a tubo-ovarian abscess.[54] The hallmark of a hemorrhagic ovarian cyst is its evolution over time from acute hemorrhage, through clot retraction to resolution.[53] While acute pain is often the presentation, the symptoms gradually resolve without intervention.

The differential diagnosis of the adolescent functional ovarian cyst includes endometriomas (rare in adolescence), benign and malignant ovarian neoplasms, disorders of the fallopian tube (hydrosalpinx, paratubal cyst), ectopic pregnancies or nongynecologic etiologies (peritoneal cysts, periappendiceal abscesses).[52]

Similar to the childhood age group, of the tumors that may present in the adolescent ovary, germ cell tumors predominate, with a benign cystic teratoma the most common neoplasm noted.[44] Even among masses considered to require surgery, the incidence of malignancy in adolescents is low at 2.1–4.4%.[44,50]

MANAGEMENT

In the adolescent with an adnexal mass it is important to illicit a full menstrual and sexual history in

addition to the history of the presenting symptoms. The differential diagnosis in this age group includes complications of pregnancy, hence investigations should include a βHCG in sexually active adolescents. A speculum examination in the sexually active adolescent for cervical cultures for chlamydia and gonorrhea should be performed, as well as a bimanual examination to assess for adnexal and/or cervical motion tenderness associated with pelvic inflammatory disease. In an adolescent an abdominal and pelvic ultrasound is the initial imaging modality of choice; however, in the sexually active adolescent a transvaginal ultrasound may assist in the diagnosis.[50]

The adolescent ovarian cyst should be managed conservatively. Functional ovarian cysts may be either simple or complex on ultrasound imaging. Given their propensity for resolution in the absence of symptomatology requiring immediate surgical diagnosis (i.e. suspicion of torsion or malignancy), follow-up sonography at 6-week intervals will document resolution in the majority of adolescent ovarian cysts. The use of an oral contraceptive pill does not aid in regression of the functional ovarian cyst over time.[55] Instructions should be given to both the adolescent and if possible her family during the observation period concerning symptoms of adnexal torsion that should lead them to seek assistance. A hemorrhagic cyst with a frank hemoperitoneum rarely may require surgical management. Patients on anticoagulants or with a bleeding diathesis are at greatest risk.[49]

Surgical management of an adolescent adnexal mass should be undertaken if there is an absence of regression after two or three menstrual cycles, if there is a suspicion of malignancy or if acute symptomatology is present. Similar to with children, the guiding principle in surgical management should be to maintain future fertility options. The approach to surgery is dependent on the presumptive diagnosis. However, laparoscopy is a reasonable approach to the management of the majority of cysts in this age group. Ovarian cystectomy should be performed unless there is a high index of suspicion of malignancy.

ADNEXAL TORSION

Adnexal torsion is reported in approximately 3% of all emergent gynecologic surgeries.[56] Torsion of normal ovaries occurs more commonly in young girls than in women.[57] Although adnexal torsion can be associated with ovarian pathology, the etiology of torsion of normal ovaries is less understood.[58] Proposed theories suggest an excessively mobile mesovarium or fallopian tube resulting from congenitally long ovarian ligaments,[59] and impeded venous return causing vascular congestion[60] as possible etiological factors. The right adnexa is more likely to tort than the left, suggesting that the sigmoid colon may help prevent torsion.[61] Torsion of the adnexa results in ischemia and rapid onset of acute pelvic pain. It may be associated with nausea and vomiting.[62] Clinically, the young woman will appear ill with mild fever, and will present with an acute abdomen and pelvic mass.[62]

Preoperative diagnosis of adnexal torsion in a girl is often challenging and requires a high level of suspicion. There is often a delay in diagnosis as signs and symptoms are similar to other conditions such as appendicitis, constipation, gastroenteritis, inflammatory bowel disease, volvulus, and bowel obstruction.[63] Furthermore, symptoms may mimic urinary causes including pyelonephritis, renal calculi, cystitis, urethritis, or urinary retention.[63] Psychologic causes of abdominal pain should remain a diagnosis of exclusion. Definitive diagnosis of adnexal torsion is based upon surgical findings. The difficulty in diagnosis was illustrated in a series of 115 cases of adnexal torsion that revealed correct preoperative diagnosis in only 38% of these patients.[64] Ultrasound of the pelvis and abdomen might detect ovarian enlargement and possibly presence of an ovarian cyst and presence of free fluid; however, these features are non-specific. Color Doppler sonography may be helpful, but unfortunately the presence of normal blood flow on Doppler does not exclude the diagnosis of torsion.[65,66] The positive predictive value for torsion if venous flow is absent is 94%.[67] Expedient

diagnosis is important, however, as a delay or a missed diagnosis may compromise fertility. Unfortunately, there is often a delay in diagnosis of adnexal torsion in a child. The clinical presentation, combined with a high level of suspicion, and possibly imaging, will lead to the probable diagnosis.

The paradigm has now shifted from ovarian removal to ovarian evaluation and likely preservation. Conservative management of primary adnexal torsion by untwisting the involved adnexa to preserve ovarian function and prevent adverse sequelae of torsion is now well recognized.[68] Laparoscopic adnexal untwisting will be successful in preserving ovarian function in 93% of cases.[62] The incidence of recurrent adnexal torsion may increase as the trend toward conservative management progresses. Although controversial, oophoropexy – defined as stabilization of ovarian tissue – has also been described for a salvageable ovary that has already twisted.[69] The most commonly encountered complication of oophoropexy is postoperative fever, and this can be managed conservatively.[70] The effect of oophoropexy on fertility is yet to be discovered; however, reasonably, some authors recommend an elective oophoropexy of the contralateral normal ovary following adnexal torsion,[59] as such children are at increased risk of repetitive events for either ovary. Interval cystectomy is safest in cases where adnexal torsion is associated with an ovarian cyst, as edema and hemorrhage may lead to a more difficult excision, compromising the rest of the ovary. Cohen et al described ovarian dysfunction in 72% of patients with immediate cystectomy at the time of adnexal untwisting.[71]

Historically, removal of the affected ovary had been the standard treatment of the twisted ovary as it was believed that restoring normal anatomy via untwisting could dislodge a clot in the ovarian vein or leave a necrotic vestige.[72] However, pulmonary embolism is reported in only 0.2% of cases with adnexal torsion treated by adnexectomy, yet not more frequently when the adnexa was untwisted.[73] In fact, in 1946, Way was the first to demonstrate that routine adnexectomy because of the risk of embolism is not mandatory.[74] The effects of bilateral oophoropexy on long-term tubal function remain to be demonstrated with the collection of prospective data.

CONCLUSION

Ovarian cysts and masses may present across the ages, from the antenatal period, through childhood, and into adolescence. Functional cysts, neoplasms, and malignancies occur within the ovaries of children and adolescents at varying frequencies. Careful and often conservative management in most circumstances can lead to appropriate ovarian-preserving treatments. The symptomatic ovarian cyst is often due to complications such as hemorrhage and ovarian torsion. Ovarian torsion represents a true surgical emergency, a high index of clinical suspicion must be maintained to avoid inadvertent delay in therapy.

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