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Frontiers in Gynecological Endocrinology

Volume 1
From Symptoms to Therapies

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Frontiers in Gynecological Endocrinology

Volume 1: From Symptoms to Therapies

Springer

INTERNATIONAL SCHOOL OF GYNECOLOGICAL AND REPRODUCTIVE ENDOCRINOLOGY
THE EDUCATIONAL BRANCH OF ISGE

Editors
Andrea R. Genazzani
International Society of Gynecological Endocrinology
Pisa
Italy

Mark Brincat
Department of Obstetrics and Gynaecology
Mater Dei Hospital
Birkirkara
Malta

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List of Contributors

Ibrahim Alkatout Department of Obstetrics and Gynecology, University Hospitals Schleswig-Holstein, Kiel, Germany

Silvia DiBello Division of Obstetrics and Gynecology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Guja Bernacchi Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Johannes Bitzer Department of Obstetrics and Gynecology, Women's Hospital, University Hospital Basel, Basel, Switzerland

Mark Brincat Department of Obstetrics and Gynaecology, Mater Dei Hospital, Birkirkara, Malta

Anna Brona Department of Endocrinology, Diabetology and Isotope Therapy, Wrocław Medical University, Wroclaw, Poland

Jean Calleja-Agius Department of Obstetrics and Gynaecology, Mater Dei Hospital, Birkirkara, Malta

Adrian Campelo Division of Obstetrics and Gynecology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Elena Cecchi Division of Obstetrics and Gynecology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Elisa Chierchia Department of Obstetrics and Gynecology, Gynecological Endocrinology Center, University of Modena and Reggio Emilia, Modena, Italy

Maria Creatsas 2nd Department of Obstetrics and Gynecology, University of Athens-Aretaieio Hospital, Athens, Greece

George K. Creatsas 2nd Department of Obstetrics and Gynecology, University of Athens-Aretaieio Hospital, Athens, Greece

Andrea R. Genazzani Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Alessandro D. Genazzani Department of Obstetrics and Gynecology, Gynecological Endocrinology Center, University of Modena and Reggio Emilia, Modena, Italy

Marie O. Gerval Department of Gynaecology, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK

Royal Brompton and Harefield NHS Foundation Trust, London, UK

Magdalena Montt Guevara Division of Obstetrics and Gynecology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Haitham Hamoda The Assisted Conception Unit, King's College Hospital, London, UK

Diana Jędrzejuk Department of Endocrinology, Diabetology and Isotope Therapy, Wrocław Medical University, Wroclaw, Poland

Abdusattarova Khulkar Department of Obstetrics and Gynecology, University Hospitals Schleswig-Holstein, Kiel, Germany

Felicja Lwow Department of Health Promotion, Faculty of Physiotherapy, University School of Physical Education, Wroclaw, Poland

Paolo Mannella Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Liselotte Mettler Department of Obstetrics and Gynecology, University Hospitals Schleswig-Holstein, Kiel, Germany

Andrzej Milewicz Department of Health Promotion, Faculty of Physiotherapy, University School of Physical Education, Wroclaw, Poland

Monica Mittal The Assisted Conception Unit, King's College Hospital, London, UK

Rossella E. Nappi Department of Obstetrics and Gynaecology, Research Centre for Reproductive Medicine, University of Pavia, Pavia, Italy

Giulia Palla Division of Obstetrics and Gynecology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Nick Panay Queen Charlotte's & Chelsea and Chelsea & Westminster Hospitals, Imperial College, London, UK

Silvia Pisaneschi Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Alessia Prati Department of Obstetrics and Gynecology, Gynecological Endocrinology Center, University of Modena and Reggio Emilia, Modena, Italy

Erika Rattighieri Department of Obstetrics and Gynecology, Gynecological Endocrinology Center, University of Modena and Reggio Emilia, Modena, Italy

Federica Ricchieri Department of Obstetrics and Gynecology, Gynecological Endocrinology Center, University of Modena and Reggio Emilia, Modena, Italy

Susanna Santagni Department of Obstetrics and Gynecology, Gynecological Endocrinology Center, University of Modena and Reggio Emilia, Modena, Italy

Michael Savvas The Assisted Conception Unit, King's College Hospital, London, UK

Joseph G. Schenker Department Obstetrics Gynecology, Hadassah Medical Centre, Hebrew University, Jerusalem, Israel

Tommaso Simoncini Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Stefania Spina Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Thomas E. J. Stevenson Department of Surgery, Frimley Park Hospital NHS Foundation Trust, Frimley, Surrey, UK

John C. Stevenson National Heart and Lung Institute, Imperial College London, Royal Brompton and Harefield NHS Foundation Trust, London, UK

John Studd London PMS and Menopause Centre, London, UK

Part I

Menstrual Dysfunction in Young Women

Pathophysiology and Clinical Assessment of Primary Amenorrhea

1

George K. Creatsas and Maria Creatsas

A significant number of adolescents present menstrual irregularities during the first 2 gynecological years. The absence of menses is defined as amenorrhea and is classified as primary or secondary. Primary amenorrhea (PA) is the absence of menstruation in 16-year-old girls with developed secondary characteristics or in 14-year-old girls with no presence of secondary characteristics. Secondary amenorrhea is defined as the absence of menstrual period, for 6 months or more, in women who had previously normal or irregular menses [1–4, 11].

The classification of PA, in relation to the etiology of the disease, includes the uterovaginal aplasia or congenital uterovaginal anomalies with obstruction, endocrine disorders, chromosomal anomalies, as well as stress and psychological problems [5–7].

Uterovaginal anomalies with obstruction needs immediate repair following excision or/and reconstruction of the obstructive area (vaginal diaphragm or imperforate hymen).

Endocrine disorders presented with PA include cases of congenital adrenal hyperplasia, hypothalamic or pituitary amenorrhea, the premature ovarian failure, and the polycystic ovarian syndrome (PCOS) [8, 9].

PA due to chromosomal anomalies includes cases of gonadal dysgenesis, hermaphroditism, etc. (Fig.1.1) [1, 2]. Gonadal dysgenesis (streak gonads) may be present either with normal XX and XY karyotypes or abnormal karyotypes. The Turner syndrome (45X0) is usually diagnosed in early childhood because of the well-known phenotypic characteristics (short stature, webbed neck, and low hairline), and therefore many patients do not present for assessment of PA.

Stress and psychological problems are common causes of PA in young girls including cases of athletic amenorrhea.

G.K. Creatsas (✉) • M. Creatsas
2nd Department of Obstetrics and Gynecology, University of Athens-Aretaieio Hospital, 76 Vas Sofias Ave., Athens 11528, Greece
e-mail: geocre@aretaieio.uoa.gr; geocre@aretaieio.uoa.gr

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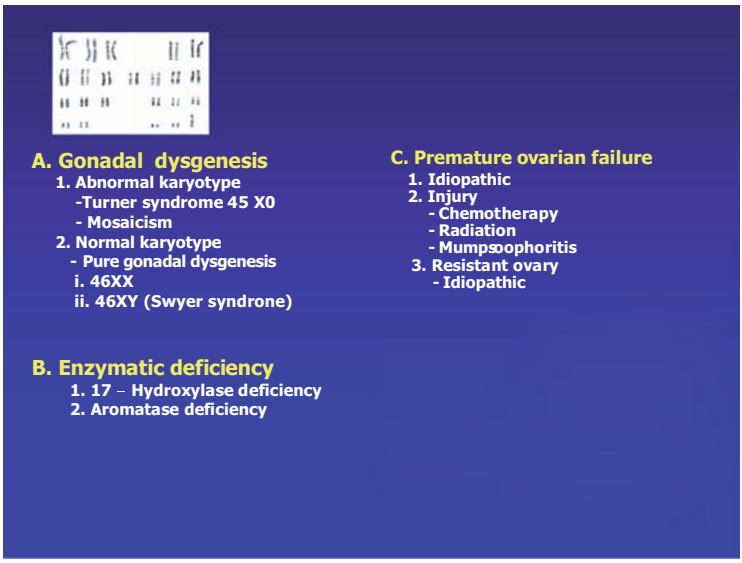

Fig. 1.1 Primary hypogonadism ([2], modified)

Another classification, including the relative incidence of PA causes, is presented in Table 1.1 [1–3, 5, 10–14].

Delayed puberty (DP) is the absence of onset of puberty by >2 SD, later than the average age of menarche. DP is also the absence of menstruation in 13–14-year-old girls who have no secondary sexual characteristic development. The causes of DP are (1) general: constitutional delay of growth and puberty, underweight, and other chronic diseases; (2) gonadal origin (hypergonadotropic hypogonadism): prodromal premature ovarian failure—karyotypically normal, Turner's syndrome, and pure gonadal dysgenesis; (3) autoimmune oophoritis; (4) 17,20-desmolase deficiency; (5) radiation or chemotherapy; (6) FSH receptor mutation; (7) galactosemia; (8) congenital hypogonadotropic hypogonadism; (9) gonadotropin deficiency; and (10) hypothalamic/pituitary lesions [3, 5, 11–14].

Patient's evaluation includes information taken by the clinical history, gynecological and physical examination, X-rays, ultrasonography (US), the hormonal profile of the patient, and rarely endoscopic evaluation (Fig. 1.2).

1.1 Case Presentations

1. Two girls 16 and 18 years old, presented with PA and periodic pelvic pain. The second girl also reported difficulty in sexual intercourse. Both had normal secondary sexual characteristics. The gynecological examination and the ultrasonography revealed *vaginal aplasia and atresia of the hymen*, *respectively*. Both were surgically treated.

Table 1.1 Classification and incidence of PA cases

• No breast development and low follicle-stimulating hormone (FSH) (30 % of PA cases) – Constitutional delay (10 %) – Prolactinomas (5 %) – Kallmann syndrome (2 %) – Other central nervous system lesions (3 %) – Stress, weight loss, and anorexia (3 %) – PCOS (3 %) – Congenital adrenal hyperplasia (3 %) – Other reasons (1 %)
• No breast development: high FSH (40 % of PA cases) – 46 XX (15 %) – 46 XY (5 %) – Abnormal (20 %)
• Breast development (30 % of PA) – Mullerian agenesis (10 %) – Androgen insensitivity (9 %) – Vaginal septum (2 %) – Imperforate hymen (1 %) – Constitutional delay (8 %)

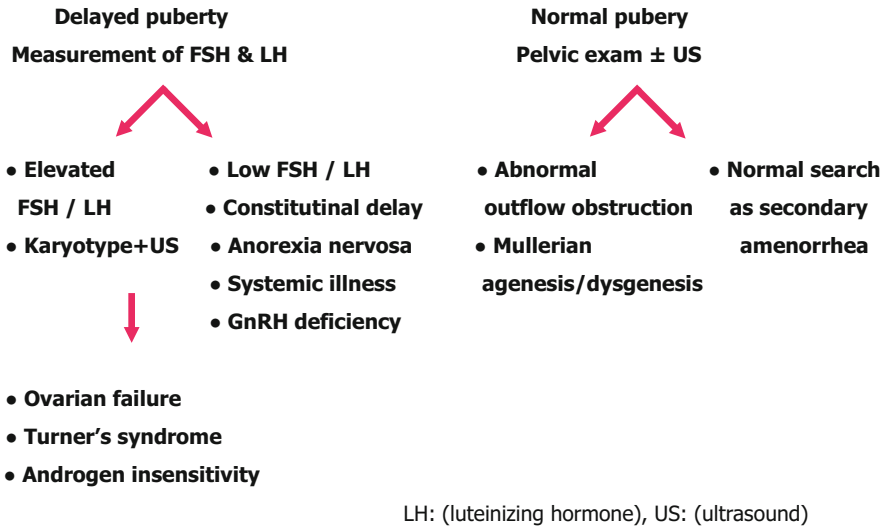

Fig. 1.2 Approach to adolescent PA [3, 4, 11, 13]

2. A young girl 16 years old presented with PA and short stature. The examination showed absence of secondary sexual characteristics. *The karyotype revealed XO—gonadal dysgenesis*. Management: hormone replacement therapy (HRT).
3. Adolescent 18.5 years old. Personal history: hypotonia, congenital cataract. Family history: Hashimoto's thyroiditis and endometrial polyp (mother). Height: 1.54 m (8th percentile), weight: 59 kg (58th percentile). Body mass

index (BMI): 24.8 kg/m^2. Breast: Tanner III, pubic hair: Tanner IV. US: small uterine volume. FSH: 46.6 mIU/mL, LH: 15.3 mIU/mL, 17 estradiol (E2): <9 pg/mL and anti-Mullerian hormone: 0.2 pmol/L. Karyotype: normal (46, XX). DEXA scan: osteoporosis. US evaluation: ovarian volume: 1.6 mL and 1.89 mL, respectively, endometrium not visible, uterus small. Diagnosis: primary ovarian insufficiency (POI) or failure (*The combination of POI*, *congenital cataract and hypotonia poses suspicion of Marinesco–Sjogren syndrome*, *a rare genetic disease*). Management: HRT, calcium plus vitamin D supplement. Recommendation: light weight lifting exercise.

4. Adolescent 16 years old. Free family history. Athlete. Exercise >2 h/day. Height: 1.56 m, weight: 39 kg, BMI: 16.02 kg/m^2. Gynecological and physical examination: Breast: Tanner V, pubic hair: Tanner V. Gynecological examination: normal. Laboratory tests: normal. PRL, testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEA-S), 17-OH progesterone (17-OH-prog), sex hormone binding globulin (SHBG), thyroid-stimulating hormone (TSH): normal. FSH: 0.3 mIU/mL, LH: 0.7 mIU/mL, E2: 12.3 pg/mL. Luteinizing hormone releasing test (LH-RH test): positive. DEXA scan: osteopenia. US evaluation: ovarian volume: 3 mL and 4 mL, respectively, endometrium: 1 mm, uterus: small. *Diagnosis*: *functional hypothalamic amenorrhea*. Management: HRT. Consultation: to improve body weight.
5. Adolescent 14 years old. Height: 1.49 m (5th percentile), weight: 50 kg (50th percentile), BMI: 22.52 kg/m^2, breast: Tanner I, pubic hair: Tanner I. Gynecological examination: normal. PRL, DHEA-S, 17-OH-progesterone, SHBG, TSH: normal. FSH: 1 mIU/mL, LH: <0.5 mIU/mL, E2: 10 pg/mL, LH-RH test: poor response. Magnetic resonance imaging (MRI)—pituitary: normal. US evaluation: small uterine and ovarian volume. *Diagnosis*: *Idiopathic hypogonadotropic hypogonadism*, *GnRH deficiency*, *and GnRH insensitivity*. Anosmia not present. Management: HRT.
6. Adolescent 15 years old. Free family and personal history. Height: 1.76 m, weight: 60 kg, BMI: 19.3 kg/m^2. Breast: Tanner III, pubic hair: Tanner IV, gynecological exam: normal. FSH, LH, E2, Testo, DHEA-S, 17-OH-Prog, SHBG, TSH: normal. PRL (0′, 30′): 50 ng/mL and 45 ng/mL. MRI: pituitary microadenoma. US evaluation: ovarian volume: 5.3 mL and 4.15 m, respectively, endometrium: 7 mm. *Diagnosis*: *hypophyseal microadenoma*. Management: bromocriptine 1.25 mg × 2.
7. Adolescent 16 years old. *Athlete*. Gynecological and physical examination: Normal. US evaluation: atrophic endometrium. FSH, LH: 10.5 mIU and 15.3 mIU/mL, respectively. E_2: 5.3 pg/mL. Treatment COCs.
8. Adolescent 15 years old. Low BMI <18 kg/m^2, gynecological examination: normal, physical examination: No acne or hirsutism, breast: Tanner II, hormonal evaluation: FSH: 16.3 mIU/mL, LH: 18.6 mIU/mL, PRL: normal, E2: 5.6 pg/mL. *Diagnosis: anorexia nervosa.* Management: psychiatric consultation and COCs.

Each patient should be individually treated, avoiding unnecessary tests and overtreatment. In cases presented with obstruction of the genital route immediate

surgery is advised. If hormonal treatment is scheduled, the low-dose, new-generation 17β-estradiol COCs are recommended. Explanation, reassurance, and emotional support are necessary tools for the management of the disease, as in many cases treatment is advisable for a long period of time.

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Dysfunctional Uterine Bleeding During Adolescence

2

Maria Creatsas and George K. Creatsas

Dysfunctional uterine bleeding (DUB) is an abnormal uterine bleeding (AUB) in the absence of organic cause. It is usually a painless, excessive, and irregular endometrial bleeding that may be prolonged, and it is not attributable to any underlying structural or systemic disease. The etiology of DUB arises out of continuing maturation of the hypothalamus, such that the eventual establishment of normal pulsatile gonadotropin release leads to normal menstrual cycle control. The European Society of Human Reproduction and Embryology (ESHRE) defined DUB as excessive bleeding (excessively heavy, prolonged, or frequent) of uterine origin, which is not due to a pelvic disease, complications of pregnancy, or systemic disease. According to ESHRE, DUB can be either ovulatory or anovulatory [1, 2].

Figure 2.1 shows the incidence of DUB in relation to the age of the patients and the seasonal distribution.

DUB is usually seen during adolescence. In about 95 % of cases DUB is due to the late maturation of the hypothalamic–pituitary–ovarian axis. Anovulation is considered the most common cause. However, other causes as pregnancy complications, coagulation disorders, systemic diseases, and anatomical lesions of the uterus should be excluded. The pathophysiology of the disease is related to the lack of maturation of the positive feedback, which results in anovulation, excess estrogen secretion, abnormal endometrial hyperplasia, and profuse bleeding, leading to endometrium apoptosis. Endometrium sampling shows proliferation, hyperplasia, and lack of progestagenic effect [3–5].

As endometrium is a known source of prostaglandin (PG) and especially of PGF_{2a} and PGE_2 production, the alteration of PGF_{2a} (vasoconstrictor) and PGE_2 (vasodilator) ratio have been also considered as a cause of the disease. DUB patients presented with anovulation exhibit a decreased availability of arachidonic acid, the precursor of PG synthesis. The PGF2a/ PGE_2 ratio is found decreased,

M. Creatsas • G.K. Creatsas (✉)
2nd Department of Obstetrics and Gynecology, University of Athens-Aretaieio Hospital, 76 Vas Sofias Ave., Athens 11528, Greece
e-mail: geocre@aretaieio.uoa.gr

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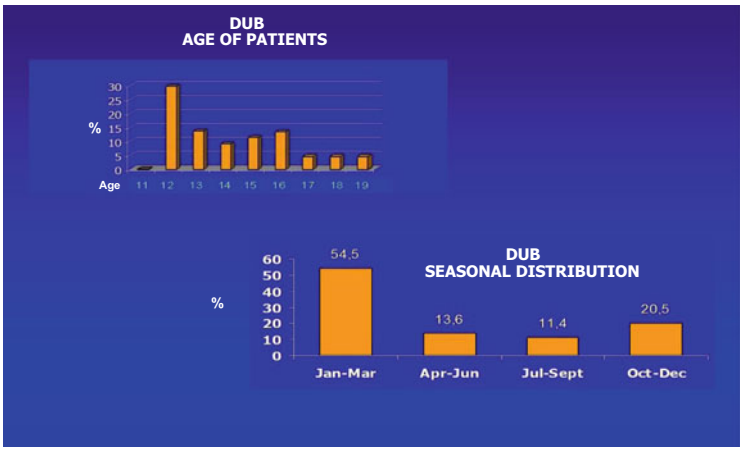

Fig. 2.1 Age of patients and seasonal distribution of DUB cases (personal data)

giving a predominance of vasodilation. Those patients with ovulatory DUB have an increased bioavailability of arachidonic acid that alters the PG ratios [3, 6].

The female reproductive organs are some of the few adult tissues that exhibit regular intervals of rapid growth. They are also highly vascular and have high rates of blood flow. Angiogenesis is therefore an important component of the growth and function of these tissues. Vascular endothelial growth factors (VEGFs) and fibroblast growth factors (FGFs) appear to be major angiogenic factors in the female reproductive organs. DUB, endometrial hyperplasia, carcinoma, and endometriosis are pathologies related to disturbances of the angiogenic process. Angiogenic or antiangiogenic compounds may prove to be effective therapeutic agents for the management of the above pathologies [7].

Cycling endometrium requires repeated, rapid, and short-term proliferation as well as rapid inhibition of neovascularization. Endometrial angiogenesis is regulated by growth factors and cytokines, which in turn are influenced by the levels of estradiol and progesterone during the menstrual cycle. Production of VEGF is stimulated in vitro by both E2 and PGs.

The evaluation of DUB cases includes a detailed family and personal history as well as a careful gynecological examination, including visualization of the cervix, even in virgin young girls (vaginoscopy), laboratory studies: hematocrit (Hct) and hemospherin (Hb) and others (mainly focused on the coagulation profile), pelvic ultrasonography (US), radiological imaging procedures, and rarely hysteroscopy or/and curettage. Endocrinological tests are not always necessary.

Differential diagnosis includes organic causes of AUB as: bleeding related to reproductive tract diseases, trauma and genital injury due to rape or sexual abuse. Young women can also cause injury to themselves when attempting to use tampons.

Infections due to endometritis and pelvic inflammatory disease can cause AUB accounting to less than 10 % of all AUBs. Vaginitis and cervical inflammation or erosion can also cause vaginal bleeding [3, 8–10].

AUB due to systemic–chronic diseases and endocrine disorders maybe related to renal or liver diseases. Patients with liver disease usually have deficiency of the vitamin K-dependent clotting factors (II, VII, IX, and X) or fibrinogen and plasminogen deficiency. Liver disease may also result in abnormal estrogen metabolism, which causes endometrial proliferation and estrogen breakthrough bleeding. Uremic patients with abnormal platelet function and decreased renal clearance of prolactin give rise to hyperprolactinemia and may also present anovulatory DUB. Nineteen percent of adolescents with persistent menorrhagia requiring hospital admission may have a coagulation disorder and more than 50 % of these young women may present a coagulopathy such as thrombocytopenia, von Willebrand's disease, or leukemia [1, 11, 12].

Systemic bleeding disorders are found in 7–20 % of women of all ages presented with menorrhagia [8, 12, 13]. Patients aged 10–19 years old examined for menorrhagia revealed that 13 % had thrombocytopenia, 55 % had immune thrombocytopenic purpura (ITP), and 22 % myelosuppression due to chemotherapy. Eight percent had abnormal platelet function and 11 % had coagulation disorders. Von Willebrand factor's deficiency is a common hereditary bleeding disorder. Among women with von Willebrand's disease, 65 % reported heavy bleeding at menarche. Factor's XI deficiency, Glassman's disease, aplastic anemia, and leukemia may also cause AUB [13–15].

Hypothyroidism may cause menorrhagia accompanied by metabolic symptoms. AUB is also related to abnormal function of corpus luteum, steroid-secreting ovarian tumors, and imminent premature ovarian failure. Differential diagnosis of AUB also includes side effects after treatment with hormonal medications such as implants, intrauterine devices, combined oral contraceptives (COCs), and transdermal patches. Anticoagulant, neuroleptic, and chemotherapeutic drugs can also give rise to AUB.

The disease is classified as mild, moderate, or severe. In mild DUB cases, the use of COCs is occasionally indicated as well as a careful follow-up. In cases of moderate degree, the use of the new-generation 17β-estradiol COCs (E_2-COCs) or the cyclic use of progestagenic compounds are the treatment of choice. Cyclic oral progestogens are administered for the same 10 days every month to prevent the action of unopposed estrogens and stabilize the endometrium [1, 2, 9].

If the young patient has iron deficiency anemia, supplemental iron therapy is recommended. The use of nonsteroid anti-inflammatory medications may reduce the bleeding through the inhibition of prostaglandin synthase [6, 16]. Severe cases need hospitalization. Transfusion is usually indicated to restore hemodynamic balance. The hypovolemic cases need immediate resuscitation with intravenous administration of fluids. It is essential to obtain blood samples to exclude an underlying bleeding disorder before starting therapy.

Surgical procedures as dilation and curettage or hysteroscopy and insertion of mini intrauterine devices are not recommended unless the hemorrhage is heavy and the previous mentioned treatment is unsuccessful. Hemorrhage usually stops within 24 h and changeover of therapy is usually recommended. Alternatively intravenous (IV) administration of estrogen therapy has been used followed by COCs.

Nausea and vomiting are rare complications of IV therapy and can be managed with antiemetics. Tranexamic acid, a synthetic derivative of the amino acid lysine, exerts an antifibrinolytic effect through reversible blockade on plasminogen. Other therapies, such as the use of high doses of progestogens given peros or parenterally, gonadotropin-releasing hormone (Gn-RH) agonists, with add-back therapy, as well as levonorgestrel-impregnated intrauterine devices, are rarely used for the management of DUB during adolescence [6, 17, 18].

The selective progesterone receptor modulators have both agonistic and antagonist activities depending upon the site of action. The above-mentioned compounds have been proposed for the management of the endometrial vascular development [19, 20].

2.1 Personal Data

Between the years 2004 to 2012, 82 adolescent patients visited the Division of Pediatric and Adolescent Gynecology of our Institution due to DUB (Table 2.1). Diagnosis was set after a thorough clinical and laboratory investigation. Conditions as hypothyroidism, disorders of the coagulation cascade, functional ovarian cysts, and other organic pathologies were excluded.

Thirteen patients (15.8 %) required hospital admission due to excessive bleeding and low Hct and Hb. In 52 of them (63.4 %), the (Polycystic Ovarian Syndrome (PCO) was diagnosed according to the Rotterdam criteria at some point during their follow-up.

2.2 Case Presentations

1. Adolescent: 12 years old. Severe menorrhagia during the first menstrual period. Hb: 7.6 gr%. US: endometrial hyperplasia, thyroid function: normal. *Diagnosis*: *DUB*. Treatment: low dose COCs.
2. Age: 10.5 years old. Height: 1.62 m, weight: 47 kg, BMI: 18 kg/m^2. AUB at menarche. free medical history and family history. HCT: 22 %, Hb: 7.3 gr%, coagulation factors: normal. Hormonal profile: normal. US: endometrial thickness 6 mm, ovarian volume normal. *Diagnosis*: *DUB due to immaturity of the hypothalamic–pituitary–ovarian axis*. Management: hospital admission, injection of hydroxyprogesterone caproate 0.5 × 2 Per Os, followed by E_2-COCs and iron supplement.

Table 2.1 Age and BMI of the patients

Patients	Mean	SD
Age	13.46 years	3.07
Menarche	12.04 years	1.63
BMI	20.65 kg/m^2	5.74 kg/m^2

3. Age: 16 years old. The patient presented with abnormal uterine bleeding. Height: 1.62 m, weight: 47 kg, BMI: 18 kg/m^2. Menarche 15.5 years old—oligomenorrhea. Medical and family history: free. Clinical examination: hirsutism. Hormonal evaluation: elevated luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio, elevated testosterone and D4-androstenedione. US: endometrial thickness 5 mm, ovarian volume 12.5 cc and 11.5 cc with a microfollicular ovarian morphology. *Diagnosis*: *AUB due to PCOS*. Treatment: COCs (ethinylestradiol/cyproterone acetate).
4. Age: 14 years old. Height: 1.49 m, weight: 54 kg, BMI: 24.3 kg/m^2. Main symptom: severe uterine bleeding. Menarche: 13 years old, normal menstrual pattern. Medical and family history: free. Blood pressure: 110/60 mmHg. Hb: 6.0 gr %. Elevated thyroid-stimulating hormone and anti-TPO: 5.06 and 2.37, respectively. US: ovarian volume 6 cc and 6.5 cc, respectively, microfollicular morphology. *Diagnosis*: *AUB due to hypothyroidism* (*Hashimoto thyroiditis*). Management: admission to hospital, blood transfusion, COCs (2 tablets daily) until bleeding stops, then decrease dose within 4 days to 1 tablet daily for 60 days plus iron supplement.
5. Age: 9 years old. Height: 1.49 m (96th percentile), weight: 40 kg (95th percentile), BMI: 18 kg/m^2, medical history: free. One episode of severe uterine bleeding. Family history: Mother with Hashimoto thyreoiditis. Hormonal profile: E2: 21 pg/mL, FSH:3.5 mIU/mL, LH: 2 mIU/mL, normal androgen levels. US: endometrial thickness: 4.5 mm, ovarian volume: 8.5 cc and 15 cc, respectively. No presence of ovarian cyst(s). Bone age: 12.5 years. *Diagnosis*: *Idiopathic central precocious puberty*. Treatment: GnRH analogs (leuprolide acetate).
6. Thirteen-year-old adolescent. Height: 1.55 m, weight: 40 kg, BMI: 16.6 kg/m^2. Menarche 12.5 years old, normal MP except two DUB episodes. Severe abnormal uterine bleeding. Medical history: free. Family history: mother beta-thalassemia heterozygote and father with a history of hepatitis. Clinical examination: 6 cm^3 palpable mass in the right adnexa. HCT: 33 %, Hb: 10.3 gr%, E2: 45.91 pg/mL, FSH: 0.1 mIU/mL, LH: 0.43 mIU/mL. Normal tumor markers—except elevated inhibin-β. Endometrial thickness: 6 mm, ovarian volume 4.41 cc and 199.96 cc, respectively. Solid mass with blood flow in the right ovary. *Diagnosis*: *Juvenile granulosa-theca cell tumor of the ovary*. Management: removal of the cyst.
7. Seventeen-year-old adolescent. Menorrhagia twice per month. First diagnosis: PCO, treated with COCs, due to heavy AUB. Further studies revealed Leiden mutation (heterozygosity). The patient also developed venous thromboembolism. Two weeks later, she was admitted to the hospital due to heavy menstrual

bleeding: Hb: 6.9 gr%. *Diagnosis*: *Severe DUB and anemia*. Management: blood transfusion and LHRH analogs.

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Dysmenorrhea, Premenstrual Syndrome, and Premenstrual Dysphoric Disorder

3

Johannes Bitzer

3.1 Dysmenorrhea

Dysmenorrhea is the most common gynecologic complaint among adolescent and young adult females.

Primary dysmenorrhea refers to **recurrent**, **crampy lower abdominal pain** that **occurs during menstruation** in the **absence of pelvic pathology**.

- It is the most common gynecologic complaint among adolescent females.
- Nausea, vomiting, diarrhea, headache, dizziness, or back pain may accompany the crampy abdominal pain.
- The pain and associated symptoms **typically begin several hours prior to the onset of menstruation and continue for 1–3 days.**
- Dysmenorrhea generally is linked to **ovulatory cycles:**
  - Approximately 18–45 % of teens have ovulatory cycles 2 years postmenarche, 45–70 % by 2–4 years, and 80 % by 4–5 years.
  - Dysmenorrhea rarely occurs in anovulatory cycles (mainly with hypermenorrhea with clots).
- Dysmenorrhea in adolescents and young adults is usually primary (functional) and is associated with normal ovulatory cycles and with no pelvic pathology.
- Secondary dysmenorrhea is caused by pelvic pathology. In approximately 10 % of adolescents and young adults with severe dysmenorrhea symptoms, pelvic abnormalities such as endometriosis or uterine anomalies may be found.

There is some controversy whether dysmenorrhea is a natural variation or "real clinical condition". On the one hand, dysmenorrhea is a recurrent benign event, self-limiting condition, there is no threat to health or life, there are no long-term consequences. There is no objective pathology, but a patient reported outcome. On the other hand, it is a chronic recurrent pain condition leading to distress and having

J. Bitzer (✉)
Department of Obstetrics and Gynaecology, Women's Hospital, University Hospital Basel, Spitalstrasse 21, 4031 Basel, Switzerland
e-mail: JBitzer@uhbs.ch

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a negative impact on quality of life and it is contributing to losses and restrictions in personal and professional performance.

3.1.1 Prevalence

- The prevalence of dysmenorrhea among adolescent females ranges **from 60 to 93 %**.
- Most adolescent girls in varied populations report experiencing dysmenorrhea, and **approximately 15 % describe the pain as severe**.
- Many adolescents report limitations on daily activities, such as **missing school**, **sporting events**, **and other social activities**, because of dysmenorrhea.
- Morbidity due to dysmenorrhea represents a substantial public health burden. Based on estimates from the U.S. Census, **approximately two million adolescents**, **or 15 % of the total females aged 13–19 years**, **experience severe dysmenorrhea**.
- It was estimated that dysmenorrhea is the single greatest cause of **lost working hours and school absence in adolescent girls**.
- 15 % of females seek medical advice for menstrual pain, signifying the importance of screening all adolescent females for dysmenorrhea.
- Klein and Litt reported that only 14 % of US adolescents with dysmenorrhea sought help from a physician, including only 29 % of those reporting severe dysmenorrhea.
- Of those who experienced dysmenorrhea, 25.9 % consulted a physician, and 61.7 % practiced self-medication (SM) [1–4].

3.1.2 The Diagnosis

Verbal multidimensional scoring system for assessment of dysmenorrhea

Grade	Working ability	Systematic symptoms	Analgesics
Grade 0: Mensuration is not painful and daily activity is unaffected	Unaffected	None	None required
Grade 1: Mensuration is painful but seldom inhibits normal activity; analgesics are seldom required; mild pain	Rarely affected	None	Rarely required
Grade 2: Daily activity is affected; analgesics required and give sufficient relief so that absence from school is unusual; moderate pain	Moderately affected	Few	Required
Grade 3: Activity clearly inhibited; poor effect of analgesics; vegetative symptoms(headache, fatigue, vomiting, and diarrhea	Clearly inhibited	Apparent	Poor effect

3.1.3 The Differential Diagnosis

A history of painful menses occurring at menarche is unlikely to be primary dysmenorrhea, because most females are anovulatory for several months to several years after menarche. The presence of pelvic pain unrelated to menses also suggests secondary dysmenorrhea.

Menstrual pain that has become progressively worse over time is characteristic of endometriosis, which may present as cyclic or noncyclic pain.

Adolescents who have had pelvic infections (e.g., gonorrhea and chlamydia) may develop adhesions that result in pelvic pain, especially during menstruation.

The most important differential diagnosis is endometriosis which for definitive diagnosis still needs laparoscopy. Rare causes are obstructive disease, irritable bowel syndrome, and pelvic congestion syndrome.

3.1.4 Etiology and Risk Factors

The majority of women with primary dysmenorrhea **do not have any risk factors for the disorder** [5].

In a systematic review that evaluated risk factors for dysmenorrhea, multiple demographic, environmental, gynecological, and psychological factors appeared to be associated with the disorder, **including age <30 years**, **body mass index <20 kg/m^2**, **smoking**, **menarche before age 12**, **longer menstrual cycles/duration of bleeding**, **irregular or heavy menstrual flow**, **and history of sexual assault**.

Younger age at first childbirth and higher parity were associated with a reduced risk.

There appears to be a **familial predisposition** to primary dysmenorrhea.

3.1.5 Pathophysiology

3.1.5.1 Prostaglandin Hypothesis

Some basic observations indicate the pivotal role of prostaglandins in the pathophysiology of dysmenorrhea as:

- Endometrial concentrations of prostaglandin E2 and prostaglandin F2 alpha are elevated in primary dysmenorrhea and correlate with the severity of pain.
- Exogenous administration of prostaglandins reproduces the symptoms of primary dysmenorrhea.

Other observations indicate the importance of the contraction of the myometrium. The cascade of events can be described in the following way:

Phospholipids are part of the cell wall and after the onset of progesterone decline before menstruation, phospholipase A2 leads to the production of arachidonic acid, which can be either metabolized towards PGI prostaglandins (which have a

relaxation effect) or through COX2 enzymes versus PGF2 alpha. PGF2 alpha causes potent vasoconstriction and myometrial contractions, leading to ischemia and pain [6, 7].

3.1.6 Treatment of Primary Dysmenorrhea

3.1.6.1 NSAIDs

- First-line treatment—NSAIDs are considered the first line of therapy. In randomized trials of NSAIDs, approximately 70–90 % of patients have effective pain relief, a value that is greater than that with placebo.
- NSAIDs should be started at the onset of menses and continued for the first 1 to 2 days of the menstrual cycle or for the usual duration of crampy pain. Patients with severe symptoms should begin taking NSAIDs 1–2 days prior to the onset of menses. They should be taken with food to minimize side effects such as gastrointestinal irritation or bleeding.
- *Preferable use of NSAIDs that are COX-1 inhibitors, because of the uterotonic effects reported with COX-2 inhibitors and possible associations with serious adverse events.*

Ibuprofen and naproxen are used commonly for the treatment of dysmenorrhea in clinical practice. Mefenamic acid is unique in that it both inhibits prostaglandin synthase and blocks the action of the prostaglandins that are already formed.

A trial of mefenamic acid should be considered for patients who do not respond to the propionic acid group of medications [8, 9].

3.1.6.2 Hormonal Contraceptives

A review and meta-analysis by the Cochrane Collaboration concluded **that OCs may be more effective than placebo based on 5 controlled trials of OCs compared with placebo** [10].

- In a randomized double-blind, placebo-controlled clinical trial of 76 healthy adolescents aged 19 years or younger reporting moderate or severe dysmenorrhea subjects were randomly allocated to receive either an OC (ethinyl estradiol 20 μg and levonorgestrel 100 μg) or a matching placebo for 3 months.
- At baseline, **42 % of participants described their dysmenorrhea as moderate, and 58 % described it as severe**.
- Of those currently enrolled in school, **39 % reported usually missing 1 school day monthly, and an additional 14 % usually missed 2 or more days because of dysmenorrhea**.
- This trial demonstrated that **a low-dose oral contraceptive was more effective than placebo for moderate or severe primary dysmenorrhea** in adolescents.
- A survey from the Netherlands revealed that almost one-third of young women reported that their primary reason for using birth control pills was for relief of menstrual pain rather than contraception.

Other options are:
- 150 mg MPA (Depo Provera)
- LNG IUD (Mirena)
- Desogestrel 75 μg/day (Cerazette)
- Desogestrel Implant (Implanon)
- Dienogest

3.2 Premenstrual Syndrome: Premenstrual Dysphoric Disorder

Different names like menstrual complaints, late luteal phase disorder, and premenstrual dysphoric disorder (PMDD) are used to define a syndrome which has already been described by Hippokrates as a cyclic disorder which renders women irritable and causes physical and psychological discomfort.

A large number of these symptoms have been described and reported by women:

3.2.1 Physical Symptoms

Breast tension, headache, bloatedness, weight gain, edema, back and lower abdominal pain, fatigue, sleeping disorders, and craving for sweets.

3.2.2 Psychological Symptoms

Irritability, mood swings, depression, concentration difficulties, memory problems, anxiety, aggressive behavior, withdrawal, and crying spells.

For practical purposes, two different clinical conditions should be differentiated.

3.2.3 Premenstrual Syndrome

PMS is defined as a condition with recurrent physical, psychological, and behavioral symptoms which occur during the luteal phase of the cycle (days 14–28) and which are usually relieved by menstruation with a symptom free week (usually days 1–7). The symptoms have a negative impact on the quality of life of the woman.

The most frequent physical symptoms are:

Swelling, breast tenderness, aches, headache, and bloating

The most frequent behavioral symptoms are:

Sleep disturbances, appetite changes, poor concentrations, decreased interest, and social withdrawal.

The most frequent mood symptoms are:

Irritability, mood swings, anxiety, tension, depression, and feeling out of control.

3.2.3.1 Premenstrual Dysphoric Disorder

The following symptoms constitute the syndrome:

1. Depressed mood
2. Fatigue
3. Anxiety/tension
4. Appetite changes/food cravings
5. Mood swings
6. Insomnia/hypersomnia
7. Irritability
8. Feeling out of control
9. Decreased interest
10. Physical symptoms
11. Concentration difficulties

PMDD symptoms are present for most of the time in the week before menses, diminish with the onset of menses, and are absent in the week following menses. At least 5 PMDD symptoms occur in most menstrual cycles for at least 1 year.

At least one of the five symptoms must be one of the first four on this list:

- Feeling sad, hopeless, or self-deprecating
- Feeling tense, anxious, or "on edge"
- Marked lability of mood interspersed with frequent tearfulness
- Persistent irritability, anger, and increased interpersonal conflicts

3.2.4 Etiology and Pathogenesis

PMS and PMDD depend on ovarian function. Before menarche, after menopause, during pregnancy, or after bilateral ovariectomy, there is no PMS but after hysterectomy women may still suffer from cyclic symptoms.

Another proof of the pivotal role of cyclic ovarian function or ovarian hormones is a study in which the application of a GnRH agonist leading to the suppression of ovarian function resulted in the disappearance of symptoms in women suffering from PMS. In the same study, it could be shown that giving ovarian steroids to these women made the symptoms reappear.

On the other hand, there is no difference in ovarian steroid production and concentration in women with and without PMS 18. This is also true for differences in metabolites of progesterone (like allopregnanolone). Furthermore, the use of antiprogestins in the second half of the menstrual cycle did not improve the symptoms.

This means that ovarian steroids are a necessary but not a conclusive condition for PMS and PMDD.

Based on laboratory and animal studies, the hypothesis focus on the observation that fluctuations in estrogen and progesterone lead to various changes in the Opioid, GABA, and Serotonin systems.

In earlier studies, beta endorphin concentrations were lower in patients suffering from PMS indicating the important role of opioids. There was however a lack of confirmation in later studies.

The GABA hypothesis was based on the therapeutic effect of Alprazolam. But again measurements of progesterone metabolites like Allopregnanolone did not show differences between patients and controls.

For the moment, the most promising concept seems to be the central role of serotonin in the pathogenesis of PMS and PMDD.

Women with PMS have lower levels of serotonin in plasma and less uptake of serotonin in platelets.

Another indicator for the important role of serotonin is that SSRIs reduce the symptoms, whereas lack of tryptophan, a serotonin precursor, increases the symptomatology.

The role of psychosocial factors is still under investigation.

On the one hand, it is remarkable that help seeking behavior because of symptoms differs considerably between countries. In the USA, Canada, and Australia more women consult physicians than in Germany, France, or Switzerland. This may be an indirect sign of psychological factors like attributional style, body perception and body image, etc.

Stress seems to increase the symptoms, but it is sometimes difficult to distinguish between stress as a cause or a consequence of PMS.

3.2.5 Diagnosis

The most important feature of both PMS and PMDD is the cyclicity of symptoms and the typical symptom free phase at the beginning of a new cycle. As women may experience many different symptoms and each patient has its own cluster of symptoms, it is important to use prospective symptoms inventories.

Based on the most commonly reported symptoms, the Calendar of Premenstrual Experiences (COPE) was constructed. It includes a four-point Likert scale for each of the ten most commonly reported physical and 12 most commonly reported behavioral symptoms rated daily throughout the menstrual cycle.

A total score on this inventory of less than 40 during days 3–9 of the menstrual cycle combined with a score greater than 42 during the last 7 days of the menstrual cycle has been shown to be an excellent predictor of women who meet inclusion criteria for PMDD.

In addition to the COPE, other commonly used scales for the assessment of PMS are the prospective forms of the Moos Menstrual Distress Questionnaire (MDQ) and the Premenstrual Assessment Form (PAF).

3.2.6 Differential Diagnosis

The differential diagnosis of PMS and PMDD includes:

Cyclic exacerbation of chronic conditions like mastodynia, chronic pelvic pain, dysmenorrhea, hormone withdrawal symptoms, migraine, irritable bowel syndrome, chronic fatigue syndrome, and various affective disorders.

An important differential diagnosis in women over 40 years is perimenopausal depression.

Another medical condition which has to be excluded is hyper- or hypothyroidism.

There is a close link between PMS/PMDD and the risk for psychiatric morbidity.

- The lifetime incidence of significant psychiatric disorder in women with PMS is between 50 and 78 %.
- Women who present with PMS have a much higher incidence of major depression in the past and appear to be at greater risk for major depression in the future.

3.2.7 Treatment

A treatment plan should be established according to the following criteria:

- Predominant symptoms (physical, psychological, and behavioral)
- Impact on quality of life
- Patient preferences

There is a large variety of treatment options, which can be grouped according to the scientific evidence of efficacy on one hand and treatment risks on the other.

3.2.7.1 Basic Therapy

Physical exercise, relaxation techniques, and other body centered interventions lack scientific evidence but have proven in clinical practice to have some therapeutic effect in some women. These interventions have no risk.

In addition, cognitive interventions, which help patients to interpret bodily sensations in a different way (knowing where the symptoms come from, dedramatising the symptoms, reducing catastrophizing thoughts, etc.), have shown some efficacy although well-designed studies are lacking.

It is important in this context to note that in all clinical trials in patients with PMS and PMDD there is a strong positive effect in the placebo group pointing to the importance of care and positive expectations.

3.2.7.2 Low-Risk Interventions with Some Scientific Evidence

Vitex agnus castus has proven in one placebo-controlled trial to reduce symptoms like irritability, anger, headache, and breast tension significantly more than placebo.

Different vitamins, calcium and magnesium have shown some therapeutic effect, but all need further studies. This is also true for cyclic progesterone, *Cimicifuga*, essential fatty acids, and *Gingko biloba*.

Light therapy may be a promising alternative, but there is also a lack of studies.

3.2.7.3 Interventions with Robust Scientific Evidence and Some Risks and Side Effects

Combined Oral Contraceptives

Combined oral contraceptives applied as long cycle (no pill free interval) have proven to be partially effective. The combination of EE with the progestogen drospirenone in a 24/4 regimen has shown in a randomized cross-over trial superiority over placebo. There is an increased risk in of thromboembolic complications compared to one user. But the risk is small in absolute terms.

Serotonin Reuptake Inhibitor

Systematic reviews indicate the efficacy of Serotonin Reuptake Inhibitor (SSRI) (Fluoxetine, Sertraline, Paroxetine, and Citalopram). The response rate is between 60 and 75 %. Typical side effects are headache, nausea, anxiety feelings, and loss of libido in about 15 % of patients.

Other antidepressants like Clomipramine, Nefazodone, and Venlafaxine can also be used.

It is important to note that the treatment regimen can differ from the treatment of depression. Taking the drugs only during the luteal phase was effective although a little less effective than continuous treatment.

Hormonal Therapies (other than COCs)

GnRH Analog and Danazol suppress ovarian activity and thus reduce PMS and PMDD symptoms. The efficacy of GnRH was proven in several studies, especially regarding irritability and physical symptoms, less so for depressive symptoms.

GnRH is rarely used because of the short-term and long-term side effects due to lack of estrogen (hot flushes, osteoporosis, etc.). If used it should be used with an add-back therapy replacing estrogen if necessary with a progestogen. It has been shown that low-dose add-back therapy does not reduce the efficacy of GnRH treatment.

Danazol is rarely used because of androgenic side effects.

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Noncontraceptive Benefits of 17β-Estradiol COCs During Adolescence

4

George K. Creatsas and Maria Creatsas

Adolescent sexuality and reproductive health care is a discussion topic with issues related to adolescent pregnancies, termination of undesired pregnancies, contraception for adolescents, prevention and treatment of sexually transmitted diseases, and other gynecological pathologies [1–4].

In the USA, adolescent pregnancy accounts for more than 750,000 pregnancies per year, of which 82 % are unintended. A large number (64 %) also occur among young women 20–24 years old [5].

The failure rate of combined oral contraceptives (COCs) during adolescence is estimated between 5 % and 15 %. During the last years, an effort was undertaken to reduce the dose of ethinyl estradiol (EE) in COCs. However, the decrease of the dose had negative effect on the physiology of the menstrual cycle. On the other hand, early attempts to develop 17β-estradiol (E_2)-based COCs (E_2–COCs) accompanied with prolonged or heavy uterine bleeding and discontinuation rates [6–8].

In addition, it was found that EE was responsible for several side effects of COCs, related to the liver function, venous thromboembolism and hypertension. Thus, research was directed to the development of new COCs with E_2 and new progestins as the dienogest, drospirenone, nomegestrol acetate, and other components. An emphasis was given to the development of new progestins with both progestagenic and antiandrogenic efficacy [9, 10].

Furthermore, the noncontraceptive benefits of the new-generation E_2–COCs were studied in combination with the favorable effects of the progestins as: the improvement of acne, the regulation of the menstrual cycle, the prevention of endometrial and ovarian cancers, the prevention from benign ovarian cysts, the management of endometriosis, the severity of pelvic inflammatory diseases (PID), the protection of bone mass, the management of the polycystic ovarian disease

G.K. Creatsas (✉) • M. Creatsas
2nd Department of Obstetrics and Gynecology, University of Athens-Aretaieio Hospital, 76 VAS SOFIAS ave, Athens 11528, Greece
e-mail: geocre@aretaieio.uoa.gr

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Table 4.1 No contraceptive benefits of E_2–COCs

Regulation of menstrual cycle
Less menstrual withdrawal, breakthrough bleeding, and spotting
Management of DUB, dysmenorrhea, and premenstrual tension syndrome (PMS)
Management of endometriosis
Improvement of acne and PCO
Prevention from benign ovarian cysts
Decrease of the incidence of endometrial, ovarian, and colorectal cancer
Decrease of the severity of PID
Prevention of bone mass
Beneficial effect on the:
Liver function
Lipid and carbohydrate metabolism
Hemostasis and inflammation markers
Thyroid function
Adrenal indices and SHBG

(PCO), as well as the beneficial effect on the liver function and the lipid profile (Table 4.1) [8, 11].

Regarding the regulation of the menstrual period (MP), a significantly shorter MP was succeeded as well as less menstrual, withdrawal, breakthrough bleeding, and spotting. Furthermore, the new E_2–COCs have been used for the management of dysfunctional uterine bleeding (DUB) and dysmenorrhea, especially in cases with endometriosis [12].

Beneficial effects have been reported on the endocrine—biochemical and haemostatic markers, on the thyroid function, the adrenal indices, the SHBG, the inflammation markers, as well as on the lipid and carbohydrate metabolism [13–16].

Furthermore, the E_2–COCs, as it was previously reported, are used for the management of the menstrual irregularities, dysmenorrhea, and PMS as well as for the improvement of the PCO clinical features.

Adolescents are usually unaware of the beneficial effects of COCs, and especially for the effects of the young generation pills. Thus, consultation on contraception should include franc explanation on the use and action of the pills as well as for their long-term beneficial effects [1, 2].

On the other hand, the COSs "negative effects" should be considered before treatment [17, 18]. The myths and misconceptions on the COCs use and especially the beneficial effects of the new-generation E_2–COCs, as these were very well presented, at the 12 European Congress of Contraception (Athens, 2012), are very much related to the COC's compliance. For this reason, proper consultation should be provided to young people and their families to avoid discontinuation and unwanted pregnancies[7].

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5 The Concept of Endometriosis as Chronic Disease: Surgical and Medical Therapy with Hormonal and Nonhormonal Targets and the Influence of Endometriosis on Obstetrical Outcome

Liselotte Mettler, Wael Sammur, and Ibrahim Alkatout

5.1 Background

As a disease affecting an estimated 176 million females of reproductive age worldwide endometriosis is considered the second most common benign female genital disease after uterine myomas [1]. It has been defined as the presence of endometrial glands and stroma outside the internal epithelial lining of the uterine cavity. Endometrial implants are typically situated in the pelvis (genital endometriosis) but can occur anywhere (extragenital endometriosis) (Fig. 5.1). Figure 5.2 reveals the histopathological picture of an endoscopic lesion.

Clinical manifestations of endometriosis can be separated into pelvic pain, infertility, and pelvic mass. The range of symptoms includes chronic pelvic pain, dysmenorrhea, deep dyspareunia, cyclical bowel or bladder symptoms (e.g., dyschezia, bloating, constipation, rectal bleeding, diarrhea and hematuria), subfertility, abnormal menstrual bleeding, chronic fatigue, or low back pain. In an overview of the literature, 77 % of endometriosis patients suffer from dysmenorrhea, 50 % from abdominal pain, 37 % from dyspareunia, and 40 % from pain during gynecological examinations. Other symptoms, such as dysuria or pain during bowel movements, are less common and dependent on the localization of endometriotic spots. Nevertheless, about 20 % of women without endometriosis report similar symptoms and many women with even severe endometriosis are completely asymptomatic [2–6]. Nevertheless, about 50 % of teenagers and up to 32 % of women of reproductive age operated on for chronic pelvic pain or dysmenorrhea suffer from endometriosis [7]. The percentage of women treated for infertility with a confirmed endometriosis ranges between 9 and 50 % [8, 9]. These figures indicate that the prevalence of endometriosis in the general population is unclear as symptoms are diverse and nonspecific.

L. Mettler (✉) • W. Sammur • I. Alkatout
Department of Obstetrics and Gynecology, University Clinics of Schleswig-Holstein, Arnold-Heller-Str. 3, House 24, 24105 Kiel, Germany
e-mail: lmettler@email.uni-kiel.de

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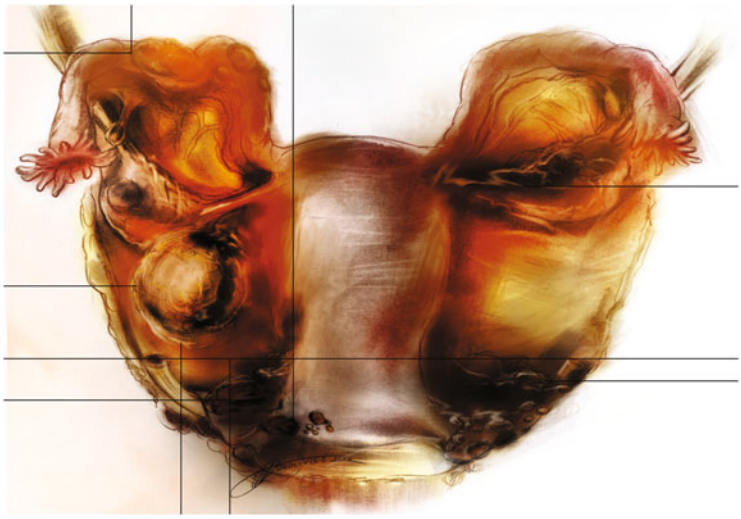

Fig. 5.1 Overview of the typical locations of endometriosis genitalis externa. Implants can be raised flame-like patches, *whitish opacifications, yellow-brown discolorations, translucent blebs, or reddish irregularly shaped spots*

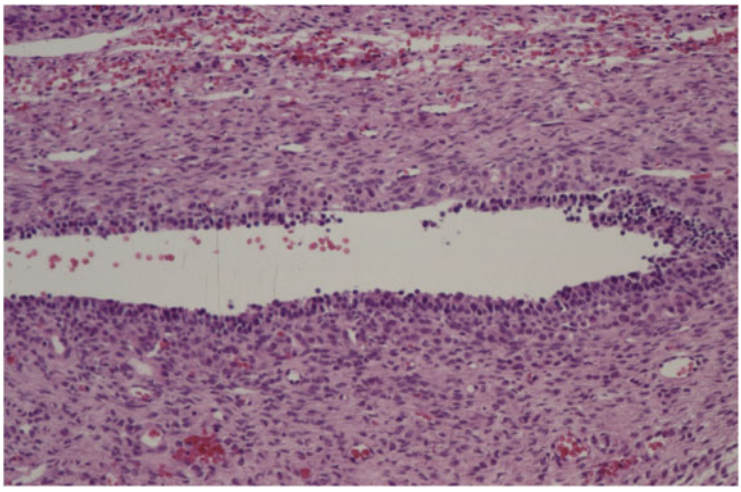

Fig. 5.2 Hematoxylin Eosin (HE staining, EEC stage II) section of an endometriotic lesion in a 32-years-old patient on cycle day 8 showing endometriosis in the fibro-muscular stroma and an unspecific chronic fibrotic infectious reaction with some blood residuals. The subepithelial stroma tissue resembles endometrial glands and stroma. Neutrophil granulocytes or lymphocytes can hardly be found

The time interval between the first unspecific symptoms and the medical diagnosis of endometriosis is about 7 years. The condition is usually diagnosed for the first time between the ages of 20 and 40. In cases of secondary sterility, the frequency increases parallel to the time elapsed since the last pregnancy: <5 years = 7 %, 5–10 years = 19 %, and longer than 10 years = 26 % [10, 11]. Earlier this disease was only assessed morphologically, considering selectively the mechanical spreading. Today we deal with an integrated concept of symptoms that require understanding and treatment.

As the pathogenesis of endometriosis is not clearly understood, a causal treatment is still impossible. Treatment options include expectant management, analgesia, hormonal medical therapy, surgical intervention, and the combination of medical treatment before and/or after surgery. Therapeutic methods can be classified into three groups: medical, surgical, and combined treatment. As it has been demonstrated that endometriosis growth is promoted by estrogen, various medical treatments can be applied [12–14]. A structured therapeutical pathway was introduced by Mettler and Semm in 1983 [15]. It involves diagnostic laparoscopy, removing all visible endometriosis foci as far as possible, a 3- to 6-month endocrine therapy and a subsequent second-look laparoscopy with resection of residual foci, adhesiolysis, and reconstruction of organs. This concept renders also the possibility to evaluate treatment strategies.

The recently established international consensus statement on the current management of endometriosis [1] with the engagement of 56 representatives of 34 national and international medical and nonmedical organizations and persons led to the assumption of endometriosis being a chronic disease with multifaceted appearances and treatment options.

Medical Treatment. In the past the main strategy was the induction of a pseudo-pregnancy and the application of gestagens and later danazol and GnRH analogues [14]. Up to now this theory has been regarded as the "gold standard," but it is now supplemented by a simple progesterone (dienogest—mg per day) treatment or a GnRh analogue treatment with add-back therapy [16]. To prevent side effects of the GnRH agonist, such as bone demineralization, vasomotor symptoms, and mood swings, a serum estradiol concentration of approximately 60 pg/ml is required [14, 17–19]. Every medical treatment today is well tolerable but should only be used as long as necessary. In case it is used as long-time treatment it should reduce the number of surgical interventions and improve the quality of life.

Targeted Treatment. Research work has focused on inhibiting the interaction of various mediators which maintain the illness by way of inflammatory processes, vascularization, and cell proliferation. Specific aromatase inhibitors (such as Letrozole, Anastrozole, or Exemestane) or selective COX-2 inhibitors (e.g., Celecoxib, Rofecoxib) are of great interest and have been studied in clinical trials [20–22]. There is no proven evidence that one medical therapy is superior to another in the treatment of the clinical symptoms of endometriosis or infertility.

Surgical Treatment. As endometriosis is a progredient disease, which can cause the anatomic destruction of the reproductive organs, surgical therapy plays an important role. Laparoscopy provides the only possibility to ascertain the expected diagnosis of endometriosis. Endometriosis has a varying phenotype and can appear as raised flame-like patches, whitish opacifications, yellow-brown discolorations, translucent blebs, or reddish irregularly shaped spots (Fig. 5.1) [2, 6]. In advanced stages, pain and sterility are predominantly caused by organ damage, fibrosis, and adhesions, thus constituting a clear indication for surgical intervention. Early laparoscopy can prevent any delays in diagnosis of the disease or symptom progression. The importance of laparoscopy with biopsy and/or resection is reinforced as visual diagnosis alone can often lead to a misdiagnosis [23, 24]. Risk factors and disadvantages of laparoscopy include damage of organs adjacent to the affected areas and postoperative complications, such as adhesion formation or infection [10, 12, 25–27]. Symptom relief is achieved in most patients after successful ablation/resection of endometriosis and adhesiolysis. Nevertheless, the recurrence rate is as high as 40 % after a 10-year follow-up [26, 28–30].

Combined Treatment. The combined treatment involves diagnostic laparoscopy, removing all visible endometriosis foci as far as possible, a 3- to 6-month endocrine therapy, and a subsequent second-look laparoscopy with resection of residual foci, adhesiolysis, and reconstruction of organs [22, 29–33]. Despite maximal efforts, the therapy of first choice in the management of endometriosis is still unclear [11, 12].

In the following we focus on current treatment possibilities and the obstetrical outcome in endometriosis patients.

5.2 Three-Step Therapy of Endometriosis

In a recent study 450 endometriosis patients underwent one of three different therapeutic strategies (medication, surgical, or combined treatment) at the Kiel University Department of Obstetrics and Gynecology [34]. The evaluation aims at determining the most successful of the available endometriosis therapies.

5.2.1 Patients

Patients were selected among those treated at the Kiel University Department of Obstetrics and Gynecology. Informed consent forms were completed by all patients. This study, which included operation, medical treatment, and a selected second-look operation, was approved by the Ethical Committee of the Christian-Albrechts-University Kiel, Germany (D 426/10). Each patient signed an informed consent form for the use of his specimen and clinical data.

The study comprised 450 symptomatic endometriosis patients for whom two consecutive laparoscopic interventions were to be assessed. Each of the three

groups consisted of 150 patients, 40 of whom did not return for the second-look pelviscopy. The symptoms of the 450 pain and/or infertility patients, aged between 18 and 44 years, were analyzed within the framework of pelviscopic treatment at the Kiel University Department of Obstetrics and Gynecology. Four hundred and ten patients from the original collective returned for a second-look laparoscopy.

Endometriosis was diagnosed or confirmed by laparoscopy and rated according to the Endoscopic Endometriosis Classification (EEC) introduced by Kurt Semm and Liselotte Mettler (Fig. 5.3) [35] which compares well to the rAFS classification.

Figure 5.4 differentiates stage I, II, and III in the laparoscopic appearance.

5.2.2 Tissue Samples

Samples of ectopic endometrium ($n = 450$) were obtained from patients undergoing diagnostic hysteroscopy and laparoscopy for the treatment of endometrioma.

The patients ranged in age from 18 to 44 years and received no hormonal treatment prior to surgery. Cryostat sections were prepared and stained with hematoxylin–eosin. Histopathological assessment confirmed the site of origin, i.e., proliferative endometrium or endometrioma cyst wall, respectively (Fig. 5.2).

5.2.3 Interventions

The 450 patients were randomly distributed to the following three treatment groups, 150 per group. Of the original 450 patients, 410 returned for the second-look pelviscopy and their findings were assessed:

Group 1 ($n = 125$) underwent hormonal treatment after diagnostic laparoscopy with 3.75 mg of leuprorelin acetate depot which was injected subcutaneously in monthly intervals over 3 months. Leuprorelin acetate depot is a GnRH agonist and is commercially available in Germany as Enantone Gyn Depot.

Group 2 ($n = 137$) underwent surgical laparoscopy without any subsequent medical treatment. Endometriosis foci were totally excised, adhesions removed, and the normal anatomy of the reproductive organs was restored. Ureter and superficial bowel lesions were removed. For infertility patients tubal patency was checked and chromoperturbation was performed at the second-look laparoscopy. Patients with deep infiltrating endometriosis with bladder or rectum resection were not included in the study.

Group 3 ($n = 148$) underwent the same hormonal therapy as group 1 over the same time period after surgical laparoscopy. The combined or three-step therapy comprised diagnostic laparoscopy, removal of all visible endometriosis foci, a 3-month endocrine therapy with GnRH agonists (e.g., 3.75 mg of leuprorelin acetate depot), and a subsequent second-look laparoscopy 1–2 months after conclusion of the hormonal therapy with resection of residual foci and reconstructive surgery of organs.

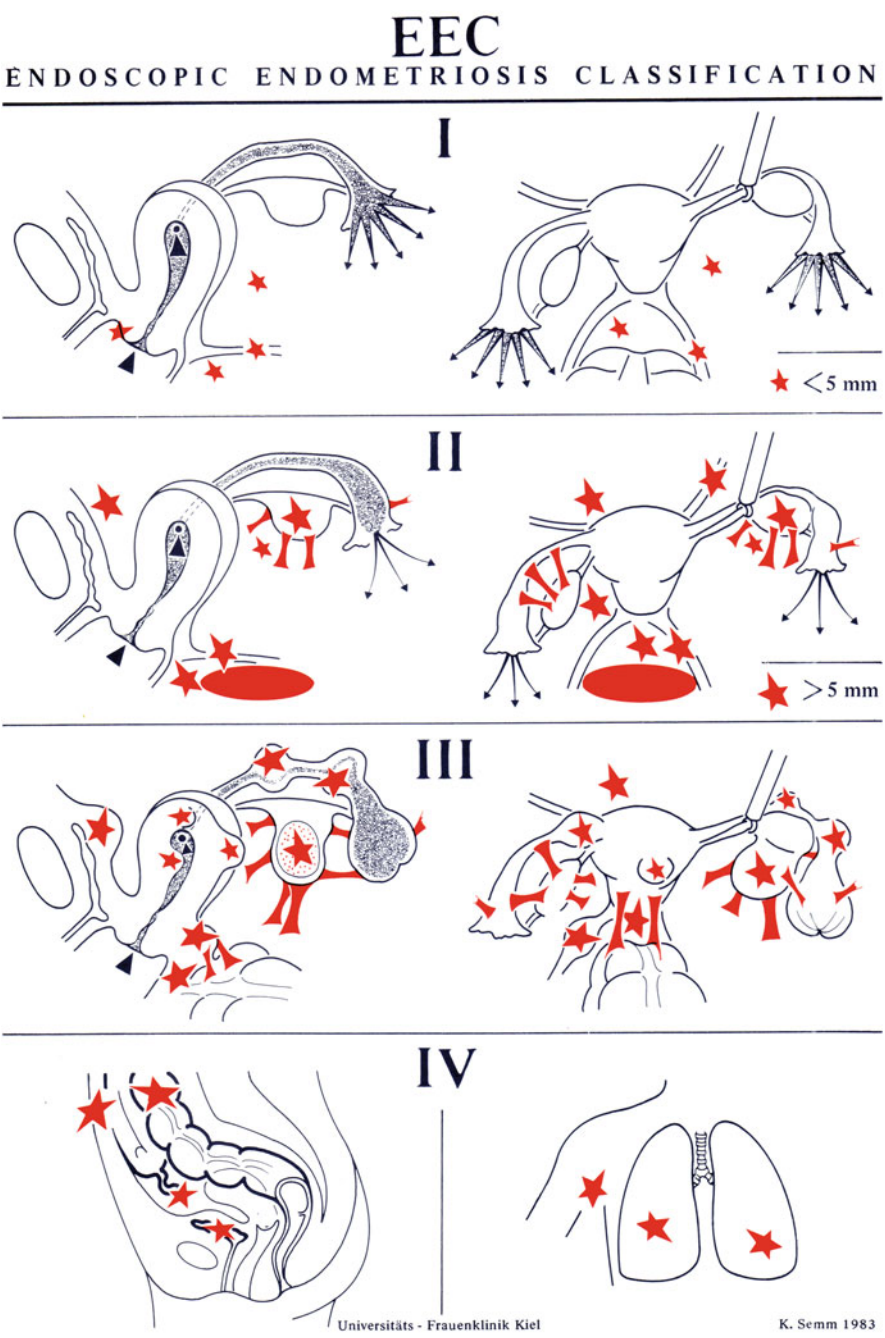

Fig. 5.3 The EEC system is used to classify endometriotic lesions. In contrast to the rASRM classification, the EEC classification includes extragenital endometriosis and is divided into four stages

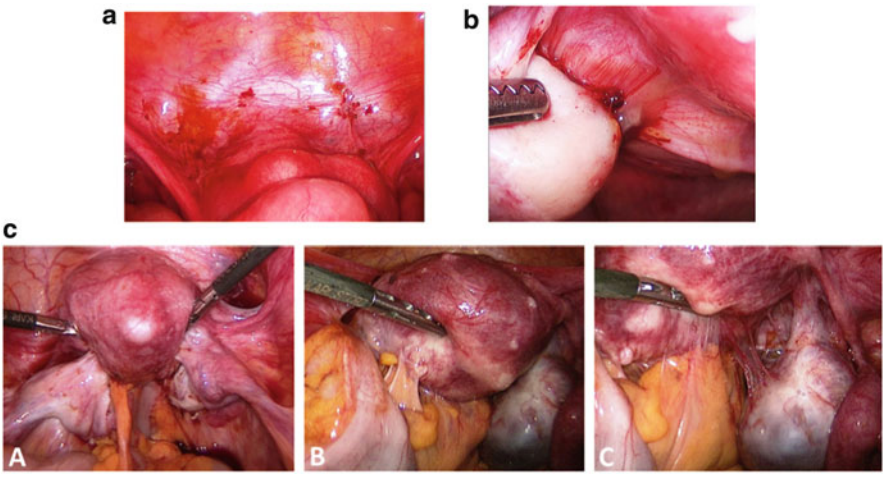

Fig. 5.4 Endoscopic image of endometriosis EEC stage I (**a**), EEC stage II (**b**), EEC stage III (**c**: A–C)

The same team of physicians performed the primary and secondary intervention as well as the primary and secondary endometriosis staging according to the EEC [15, 35]. For groups 1 and 3, a second-look laparoscopy was performed 1–2 months after hormonal therapy, and for group 2, 5 to 6 months after surgical endometriosis treatment. After the second-look laparoscopy patients were monitored over a period of 2 years and completed an extensive questionnaire to determine recurrence of symptoms and pregnancy rates.

5.2.4 Maine Outcome Measures

The central issue for this study was: Which endometriosis therapy is currently the most successful technique? The success of each therapeutic strategy was assessed—independent of the original EEC stage—according to the following criteria after the second-look laparoscopy:

1. A response rate to EEC stages 0 and I of at least 75 %
2. The lowest recurrence rate
3. The highest pregnancy rate

Within the framework of this study, the endometriosis therapy that fulfilled all of the criteria or at least two of them was regarded as the most successful therapy.

5.2.5 Statistical Evaluation and IRB Approval

Our results were statistically evaluated with the chi-squared test and analyzed with a significance level of $p < 0.05$ and a confidence interval of 95 %. Institutional review board approval was obtained at the beginning of the study.

Table 5.1 Distribution of patients to EEC stages after therapy

	EEC stage (in %)			
Therapy methods	EEC 0	EEC I	EEC II	EEC III
Group 1: hormonal treatment ($n = 125$)	50	32	13	5
Group 2: surgical treatment ($n = 137$)	55	13	23	9
Group 3: combined treatment ($n = 148$)	60	18	17	5

5.3 Results

Primarily, the results of the three different treatment groups were analyzed to assess the new endometriosis staging or EEC down-staging, respectively (Table 5.1 and Fig. 5.5).

In group I (hormonal treatment), 40 % of the 125 patients presented at the outset of the study with EEC stage 1, 38 % with ECC II, and 22 % with EEC III. After the hormonal therapy, and independent of the previous EEC stage, 32 % of group 1 had EEC stage I, 13 % EEC II, and 5 % EEC III. In 50 % of the cases, the second-look laparoscopy showed no signs of endometriosis (EEC 0). These patients appeared to be cured (cure rate = 50 %).

In group 2 (surgical treatment) 50 % of the 137 patients originally presented with EEC I, 32 % with EEC II, and 18 % with EEC III. As a result of the second-look laparoscopy the patients could be down-staged. We then found 13 % with EEC I, 23 % with EEC II, and 9 % with EEC III. The total cure rate for the exclusively surgically treated group was 55 % (EEC O).

In group 3 (combined therapy), the 148 patients were classified as 53 % with EEC I, 24 % with EEC II, and 23 % with EEC III. After the combined surgical and hormonal treatment, we found 18 % of the patients with EEC I, 17 % with EEC II, and 5 % with EEC III. With this treatment form we achieved a cure rate of 60 % (EEC 0).

The three treatment options achieved—independent of the initial EEC stage–an overall cure rate of 50 % or higher. The combined treatment reached a cure rate of 60 %, the exclusively hormonal therapy 55 %, and the exclusively surgical treatment 50 %. Within the framework of our study, cure has been defined as a reduction to EEC O. This new endometriosis down-staging was confirmed by the second-look laparoscopy. Regardless of the fact that the combined therapy obtained the best total cure rate, there is no statistically significant difference between the three percentages ($p > 0.05$).

In the second step, we distinguished between light, intermediate, and advanced cases of endometriosis and evaluated therapeutic strategies leading to an improvement of at least 75 % to EEC stages 0–1 as highly efficient. These conditions were met by the combined therapy (three-step therapy) with a response rate of 78 % and the exclusively hormonal treatment with a rate of 82 %.

As endometriosis is generally a disease which causes recurrent pain, we asked our study patients to complete an extensive questionnaire and report on recurrent

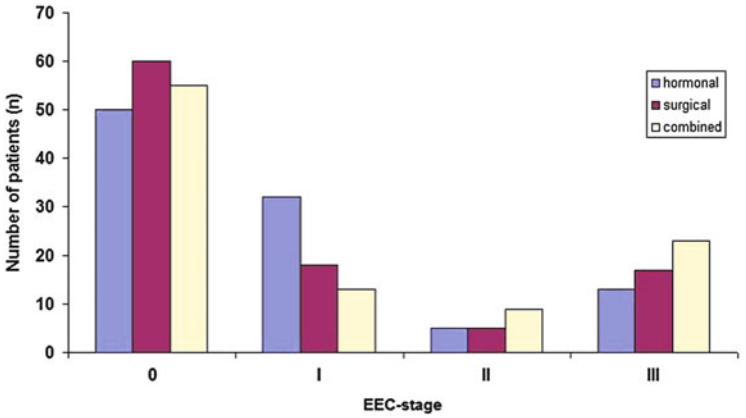

Fig. 5.5 Distribution of patients to EEC stages after therapy

Table 5.2 Comparison of recurrence rates for the three therapy methods after 1 year

	Recurrent symptoms		
Therapy methods	Dysmenorrhea	Dyspareunia	Abdominal pain
Group 1: hormonal treatment ($n = 125$)	28	22	26
Group 2: surgical treatment ($n = 137$)	20	15	24
Group 3: combined treatment ($n = 148$)	16	8	17

symptoms, 1 year after the end of all therapeutic activities. Patients in the combined therapy group achieved the lowest general recurrence rate and the lowest recurrence rates per symptom: 16 % of the patients reported dysmenorrhea, 8 % dyspareunia, and 17 % abdominal pain. In contrast to this, the exclusively hormonal therapy showed the highest recurrence rates: 28 % of the patients complained of dysmenorrhea, 26 % of abdominal pain, and 22 % of dyspareunia (Table 5.2 and Fig. 5.6).

The overall recurrence rate for the combined therapy after 1 year was 41 %, whereas surgical treatment alone resulted in a recurrence rate of 59 % ($p < 0.01$). In comparison with the exclusively hormonal therapy strategy with a recurrence rate of 76 %, the combined therapy had a significantly better success rate ($p < 0.01$).

Since active endometriosis as a functional disorder or endometriosis-related secondary damage can constitute anatomical reasons for infertility, we also assessed the pregnancy rate and the birth and miscarriage rates, with the help of a questionnaire 2 years after the end of each therapeutic strategy.

We determined an overall pregnancy rate of 55–65 % for the three treatment options, independent of the ECC stage (Table 5.3 and Fig. 5.7). The pregnancy rate after the exclusively surgical restoration was 55 %, after the combined therapy 60 %, and after the exclusively hormonal treatment 65 %. There was no statistical significance ($p > 0.05$) between these results.

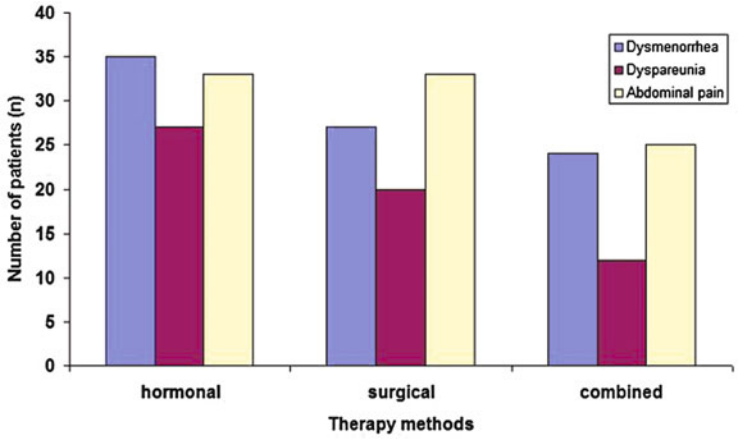

Fig. 5.6 Comparison of recurrence rates for the three therapy groups after 1 year

Table 5.3 Comparison of pregnancy rates for the three therapy methods after 2 years

Therapy methods	Pregnancies	Abortions	Extrauterine pregnancies	Live births
Group 1: hormonal ($n = 125$)	81 (65 %)	10 (8 %)	2 (2 %)	69 (55 %)
Group 2: surgical ($n = 137$)	75 (55 %)	12 (9 %)	1 (1 %)	62 (45 %)
Group 3: combined ($n = 148$)	89 (60 %)	13 (9 %)	3 (2 %)	74 (50 %)

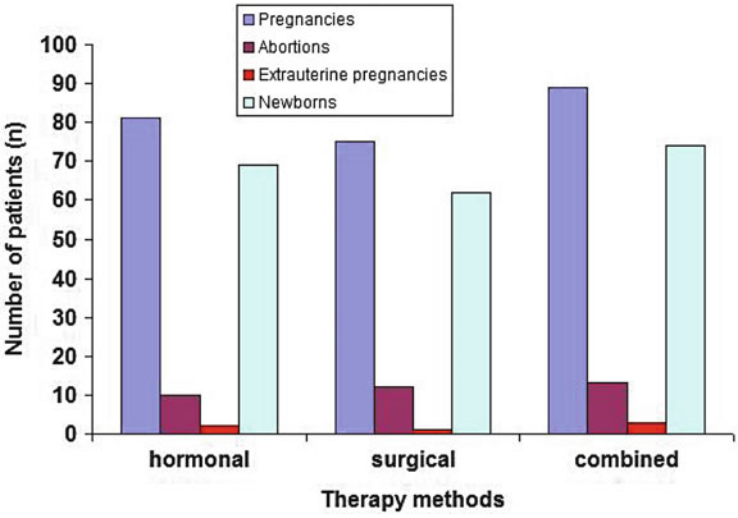

Fig. 5.7 Comparison of pregnancy rates for the three therapy groups after 2 years

Of these 245 pregnancies, 41 (17 %) were not carried to term (6 extrauterine pregnancies, 35 abortions); on the other hand 205 children were born (including one

set of twins). There was no statistically significant difference between the three therapeutic strategies regarding the pregnancies and their course.

Within the framework of our study, the combined therapy turned out to be the most successful treatment for endometriosis. Even though there was no significant difference between the different therapeutic strategies as far as cure and pregnancy rates were concerned, the three-step therapy resulted in the highest response rate or cure for endometriosis. Sixty percent of the cases had down-staged to EEC stage 0 at the second-look laparoscopy. The combined or three-step therapy group also had the lowest recurrence rate of 41 % ($p < 0.01$), 1 year after the end of the therapy.

5.4 Endometriosis and Obstetrical Outcome

The largest study to date of endometriosis in pregnant women has found that the condition is a major risk factor for premature birth [36]. This study was presented at the 25th Annual Conference of the European Society of Human Reproduction and Embryology (ESHRE) in 2009 by Henrik Falconer of the Department of Woman and Child Health, Karolinska Institute, Stockholm, Sweden. His team found that women with endometriosis had a higher risk of pregnancy complications and premature deliveries and were more likely to deliver by Cesarean section.

The researchers investigated the association between adverse pregnancy outcome, assisted reproduction technology (ART), and a previous diagnosis of endometriosis in 1,442,675 single births to Swedish women. They were 13,090 singleton births among 8,922 women diagnosed with endometriosis. Compared with women without endometriosis, they had a 33 % greater risk of preterm birth.

Women with endometriosis were also more likely to have difficulty in conceiving and the use of ART was more prevalent, which in itself may be considered a risk factor for adverse pregnancy outcome, although we strongly disagree with this concept. Once conception takes place the embryo has to prove itself and fight for survival. That certainly promotes a healthy embryo but, of course, we agree that it is tiring to start the fight for life against possible cytokines or antibodies at that early stage.

Among women with endometriosis, 11.9 % conceived after ART compared with the 1.4 % of women without endometriosis who used the technique. This means that patients with endometriosis have a better chance of becoming pregnant with ART than without it.

The risk of preterm birth associated with endometriosis among women with ART was 1.24 and among women without ART 1.37.

Dr. Falconer said that endometriosis appears to be a risk factor for preterm birth, irrespective of ART. The findings of the study indicate that women with endometriosis may be considered a high-risk group and need special care during pregnancy.

Endometriosis is a chronic inflammatory disease, affecting up to 15 % of all women of reproductive age, in which the endometrial cells that line the uterus are deposited in other areas. Such displacement of endometrial cells can lead to

anatomical distortion and also the release of anti-inflammatory cytokines, signaling molecules used in communication between cells. Known symptoms of endometriosis include severe pelvic pain, heavy menstrual periods, and nausea.

One explanation for the interaction of endometriosis with preterm birth has been given by the group of Ivo Brosens with the enigmatic uterine junctional zone [37].

In addition to an increased risk of preterm birth, the researchers also found other differences in the pregnancies of women with endometriosis. Dr. Falconer reported that nearly twice as many women in this group were delivered by Cesarean section. The study group observed that among these women the risk of induced preterm birth was higher than for spontaneous preterm birth. They believe that women with endometriosis are more frequently scheduled for preterm Cesarean section, possibly due to placental complications.

Women with endometriosis were also more likely to suffer from pre-eclampsia, a condition that develops in the second or third trimester of pregnancy and involves the development of high blood pressure and the presence of protein in the urine. However, this is strongly contradicted by others [38].

Antepartal bleeding was also found to be more common among women with endometriosis.

As endometriosis is so strongly associated with infertility, we know that women suffering from endometriosis are of higher maternal age and have fewer children. Even after adjusting for maternal age and other confounding factors, the strong association between endometriosis and risky pregnancies still remains.

Given that endometriosis is relatively common in women of childbearing age, we advise pregnant patients with a history of previous endometriosis to observe extra care, to enable them to have a normal pregnancy and give birth to a healthy baby.

Concerning pain in pregnancy in patients with endometriosis, there are several reports on intensified pain in pregnancy, although others report that pain totally disappears during pregnancy and breast feeding. Pregnancy appears to be a cure for these patients. However, it is a misconception to believe that pregnancy cures endometriosis. The symptoms usually recur after each pregnancy [39].

5.5 Discussion

Our team did basic research in endometriosis as for the distribution pattern of the Macrophage Colony-Stimulating Factor Receptor (M-CSFR) producing cells in endometrial and endometriotic tissue. Membrane-bound M-CSF or soluble M-CSF of peritoneal macrophages may cause the survival of dystopic endometrium by direct interaction, giving rise to endometriosis [40].

We also compared in a c-DNA microarray analysis a set of 940 genes expressed in endometrium and endometriosis and identified 38 genes which were differentially expressed in endometriotic implants compared to uterine endometrium [41]. Based on older extensive studies a lot of further research is necessary

[42–44]. Concerning endometriosis and fertility we advise to use the fertility index of David Adamson [45].

The presented clinical studies comparing medical, surgical, and combined therapy and the assessment of how endometriosis can affect pregnancy and deliveries show the current needs for the treatment of endometriosis and point out some advice for future therapeutic modalities.

5.5.1 Three-Step Therapy of Endometriosis

In the presented study 450 endometriosis patients, aged 18–44 years, were randomly assigned to one of three different therapeutic strategies (medical, surgical, or combined treatment) at the Kiel University Department of Obstetrics and Gynecology, Germany. The success of each therapeutic strategy was assessed—independent of the original EEC stage [35]—according to the following criteria:

1. The therapy after which the patients achieved the highest cure rate (EEC stage 0).
2. A response rate to EEC stages I and 0 of 75 % or higher
3. The lowest recurrence rate
4. The highest pregnancy rate

Within the framework of this study, the endometriosis therapy that fulfilled the majority of the criteria, or at least two of them, was regarded as the most successful therapy. The three treatment options reached an overall cure rate of 50 % or higher. There was no statistically significant difference ($p > 0.05$), but with a cure rate of 60 % the combined therapy ranks first. The combined (three-step) and the exclusively hormonal therapy managed to surpass the 75 % response rate with 78 and 82 %, respectively. Nevertheless, the combined treatment reached the lowest recurrence rate per symptom at a statistically significant level. No statistically significant difference was recorded for the pregnancy rate which ranged between 55 and 65 %, independent of the therapeutic strategy. As an overall result, we have been able to confirm the high efficacy of the combined endometriosis therapy in this study.

Medical therapy can be applied prior to surgery to decrease the size of endometriotic implants and the extent of the operation [46]. However, so far there is no clear evidence that perioperative hormonal treatment decreases the extent of operation necessary to remove endometriotic implants, delays or prevents recurrence, or increases pregnancy rates. In contrast, several trials were able to report an increased duration of pain relief and delayed recurrence rates using postoperative medical therapy [6, 46, 47]. Schweppe concluded that in all cases of active endometriosis, pelviscopic treatment alone is not sufficient [48]. Schindler demonstrated that the primary surgical intervention reduced the total r-AFS score (revised American Fertility Society) by 34 %, whereas the combined therapy brought about a reduction of 66 % [49].

Our study showed only a weak and statistically nonsignificant difference between the combined treatment (decrease of EEC stage by 60 %) and the solitary

surgical treatment (decrease of EEC stage by 55 %). Regidor found a significant improvement of the r-AFS score after treatment with triptorelin (GnRH analogue). Sixty-three percent of these patients were no longer diagnosed with endometriosis, 30 % presented with stage I residual endometriosis according to the AFS classification, and only 7 % had stage II endometriosis [4]. It could be demonstrated that after administration of buserelin (GnRH analogue) the average AFS score went down from 17.4 ± 12.9 before therapy to 7.2 ± 8.2 after a 6-month therapy [49, 50]. Although up to 90 % of patients experience some symptom relief with medical therapy, medical treatment alone neither enhances fertility, nor diminishes pelvic mass, nor removes adhesions [6, 14].

Similar to Schweppe and Römer [48, 51], we also determined a significantly lower recurrence rate after application of the three-step therapy. Römer reported that retrospective analyses 12–48 months after endometriosis therapy presented a recurrence rate for hormonal and surgical treatment (three-step concept) of only 16.7 %, whereas the recurrence rate for exclusively surgically treated patients was 47 %.

Regidor showed in a long-term follow-up study that 70 of 112 patients (62.5 %) again reported ailments and that the recurrence-free interval amounted to an average of 11 months after finishing the three-step therapy (with the GnRH analogue leuprorelin acetate) [52]. In another long-term follow-up study, Schindler established recurrent endometriosis in 62 of 112 patients (55 %) after a combined surgical–hormonal therapy [14, 41]. Our recurrence rate (41 %) was lower than Regidor's rate (62.5 %) and Schindler's rate (55 %) for the combined therapy. Zupi et al. were able to show that patients treated with GnRH agonists had a significantly higher rate of symptom reduction (pelvic pain, dysmenorrhea, and dyspareunia) than women treated with continuous estrogen–progestin oral contraceptives. Quality of life was increased by extending the GnRH treatment to include add-back therapy [17]. Other investigations comparing oral contraceptives to GnRH agonists found an equal reduction of pain [53]. Sutton 1994 and Abbott 2004 performed a second-look laparoscopy 6–12 months after the primary operation and found that 29–45 % of the patients had disease progression, 22–29 % disease regression, and 33–42 % the disease remained static [28, 54].

Endometriosis can reduce the fecundability rate without completely preventing conception. Impaired fertility might be due to anatomic variations after adhesion formation and endometriomas [55]. An enhancement of fertility rates through ovulation suppression has not yet been proven [14]. In our study after the combined therapy, we had 89 (60 %) pregnancies in 148 patients and 13 abortions and 3 extrauterine pregnancies. Sixteen (18 %) of the 89 pregnancies did not lead to a live birth (13 abortions and 3 extrauterine pregnancies). Regidor reported 55 (60 %) pregnancies for 91 patients for the same therapeutic strategy [52]. Nineteen (34.5 %) of the 55 pregnancies were not carried to term (5 extrauterine pregnancies, 14 abortions). Our pregnancy rate was comparable to Regidor's rate, but our abortion rate was significantly lower than his. After the exclusively surgical treatment we registered a pregnancy rate of 55 %. In comparison, Marcoux et al. presented a pregnancy rate of 29 % [56].

All research focusing on macroscopic or microscopic markers as well as biochemical criteria for assessing the degree of activity of endometriosis are not convincing. Essential factors for deciding the optimal endometriosis therapy are clinical symptoms, the patient's age, localization, severity, duration of the disease, recurrence rate, and activity [57, 58]. Active endometriosis foci are characterized by hyper vascularisation, edema, and infiltration of inflammatory cells [40]. It still needs to be determined how endometriosis activity can best be characterized using macroscopic, microscopic, and biochemical criteria [25]. Laparoscopy currently constitutes one of the most accurate methods of diagnosing endometriosis.

5.5.2 The Influence of Endometriosis on Obstetrical Outcome

Concerning this constellation let us pose two critical questions:

1. Endometriosis is known to interfere with conception and implantation. Is there any effect on the obstetrical outcome?
2. Do women with endometriosis need special care during pregnancy to avoid premature deliveries?

   The effect on the obstetrical outcome seems to be premature delivery.

The question whether endometriosis triggers recurrent spontaneous abortions was investigated following the observation that "Natural Killer (NK) cell activity" is low in endometriosis patients and high in unexplained recurrent abortions. There is good evidence that endometriosis is associated with an opposite regulation of NK cell behavior [59]. From 1991 to 1995 at least nine independent groups reported a functional defect of peripheral NK cells in patients with endometriosis. However, Somigliana et al. in 1999 concluded that the relationship between NK cell activity, endometriosis, and infertility seems to be "more puzzling" than considered so far [59]. These fine implied mechanisms may still reveal interesting biological and clinical possibilities for treatment.

Several case reports deal with obstetrical emergencies arising during delivery through endometriosis. Let us discuss a few of them:

1. A 22-year-old woman with unoperated deep endometriosis of the uterosacral ligament suddenly experienced severe abdominal pain, hematuria, and intrauterine death at 31 gestational weeks. Surgical intervention revealed an active hemorrhage from the right uterine artery and urine leakage from interruption of the right ureter in the area of a laparoscopic documented, but not treated, endometriotic nodule [60].
2. An emergency exploratory laparotomy was performed on a patient 3 days postpartum. This patient had a history of previous laparoscopic treatment for deep infiltrating endometriosis before her pregnancy. Active bleeding was found at the right uterine vein, near the site of previous surgery for deep infiltrating endometriosis [61].
3. A 30-year-old woman, at 24 weeks of gestation, was admitted with acute intraabdominal bleeding. Endometriosis lesions infiltrating the lateral wall of

the uterus, the right ovarian fossa, and the right cardinal ligament were found [62].
4. A case of spontaneous postpartum hemorrhage due to massive preperitoneal implants suggestive of decidualized endometriosis was reported by Mabrouk et al. [63].

5.6 Summary and Conclusions

5.6.1 The Three-Step Therapy

Since the identification of endometriosis as a progredient estrogen-related disease, various substances have been used to suppress ovarian steroid biosynthesis. Currently all modern therapeutic strategies aim at ovarian downregulation with GnRH agonists or gestagens. In most cases therapeutic approaches take into consideration not only medical but also laparoscopic and, if required, laparotomic surgical treatment of endometriosis and the combined therapy. The three-step therapy comprises surgical laparoscopy with removal of all visible endometriosis foci, a 3- to 6-month endocrine therapy and a subsequent second-look laparoscopy with resection of residual foci, adhesiolysis, and reconstructive surgery of the organs [64].

5.6.2 Endometriosis and Obstetrical Outcome

As endometriosis remains an enigmatic disease, there is a growing realization that the origin of major obstetrical complications and problems during pregnancy may lie in very early pregnancy events. Recent studies have focused on the implantation window, particularly in endometriosis patients. The implantation window may not only be responsible for delayed implantation but also for defective deep placentation leading to preterm labor, fetal growth restriction, and pre-eclampsia.

It is a myth that pregnancy can heal endometriosis as severe pain attacks due to endometriosis can also occur during pregnancy. A relation between endometriosis and abortions remains questionable.

Obstetrical emergencies based on endometriosis, such as bleeding endometriotic lesions, uterine arteries, or veins; interruption of ureter; and postpartum hemorrhage due to decidualized endometriosis, have occurred and have to be considered.

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Part II

Metabolism, Hyperandrogenism, Body Weight and Reproduction

Vitamin D, Metabolic Disorders and Reproduction

6

Diana Jędrzejuk, Andrzej Milewicz, Felicja Lwow, and Anna Brona

Vitamin D has been well known for its function in calcium and phosphorus homeostasis and osteomalacia as well osteoporosis, because of promotion bone mineralisation. Vitamin D deficiency is highly prevalent in high-risk patient populations, but the prevalence among otherwise healthy adults is less well defined. This vitamin is produced in skin via UVB radiation, which induces conversion of 7-dehydrocholesterol to provitamin D3, which spontaneously isomerises to vitamin D3 (cholecalciferol). Vitamin D is released into circulation and transported by vitamin D binding protein. Approximately 80–90 % derives from sunlight induced production in the skin, small amount derived from diet and all supplements.

Biological actions of vitamin D3 are presented as: stimulation of reabsorption of calcium and phosphates in bones via increasing RANKL expression in osteoblasts and activation of RANK in precursors of osteoclasts. Vitamin D increases intestinal absorption of calcium and phosphates (stimulation of synthesis of calcium-binding protein) in intestinal system and increases reabsorption of calcium in kidney, if vitamin D3 level is high.

Recently, the pleiotropic actions of vitamin D is presented and discussed, because several papers show that vitamin D receptor (VDR) and hydroxylases activity enzymes are necessary to vitamin D metabolism in most tissues and immune cells. Its active metabolite 1,25 (OH)2 D modulates the immune response: T and B lymphocytes and production of cytokines and immunoglobulins.

D. Jędrzejuk (✉) • A. Brona
Department of Endocrinology, Diabetology and Isotope Therapy, Wrocław Medical University, Pasteura 4, 50-367 Wroclaw, Poland
e-mail: diana.jedrzejuk@gmail.com; abrona@mp.pl

A. Milewicz • F. Lwow
Department of Health Promotion, Faculty of Physiotherapy, University School of Physical Education, Paderewskiego 35, 51-612 Wroclaw, Poland
e-mail: andrzej.milewicz@umed.wroc.pl; felicitas1@wp.pl

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It has been shown that vitamin D also has the influence on production and secretion of several hormones like parathormone, insulin, sex hormones as well has influence on regulation of cellular proliferation and differentiation.

6.1 What About the Metabolic Disorders and Vitamin D?

Several studies show presence of VDRs for 1,25-(OH)2-vitamin D and expression of 1α-hydroxylase in pancreatic beta cells [1, 2]. Vitamin D induces insulin sensitivity through stimulation of insulin receptors expression in peripheral tissues [3]. In other prospective study—The Medical Research Council Ely Prospective Study 1990–2000—inverse associations between baseline serum 25(OH) D and future glycaemia and insulin resistance were reported [4]. On the other hand, non-alcoholic fatty liver disease (NAFLD) is recommended as a sensitive risk marker for diabetes type 2 [5]. Vitamin D level was correlated with ALT (alanine transaminase) level—the marker of NAFLD [6]. Also, the patients with NAFLD had significantly lower vitamin D level and this was associated with severity of liver histology [7].

The other risk factor for diabetes type 2 and cardiovascular diseases is abdominal obesity with waist circumference over 80 cm in women and over 94 cm in men. The National Health and Nutrition Examination Survey (2001–2004) presented EBM data, which included 4,661 males and 5,108 females. The group of abdominal obese women and men separated from these population shows negative correlation between fasting glycaemia and CRP with serum vitamin D. The conclusion from that paper is that the abdominal obese persons should be additionally supplemented with vitamin D [8]. Negative linear correlations between serum vitamin D level and waist circumference, serum triglycerides, glucose levels and insulin resistance were shown [8].

6.2 What About the Diabetes Type 2 and Endogenous Vitamin D Levels?

National Health and Nutrition Examination Survey shows negative correlation between serum vitamin D and prevalence of diabetes type 2 [8]. This observation was supported by Finland observational study (17 years) [9], as well as for Nurse's Health Study (83,779 persons—20 years observation) women received 800 IU vitamin D—shows significant reduction (33 %) of morbidity for diabetes type 2 in comparison to control [10].

6.3 What About Cardiovascular Disease and Vitamin D?

Pilz et al. [11] revealed in 3,299 patients after coronarography dependence between serum vitamin D deficiency and mortality caused by cardiac failure or sudden heart death during 7 years. The persons with vitamin D concentration <25 nmol/l = 10 ng/ml revealed three times higher mortality of heart failure and five times higher mortality of sudden heart death in comparison to patients with vitamin D concentration within normal ranges or above 75 nmol/l = 30 ng/ml. This mortality was higher in the group of patients with no history of circulatory diseases.

6.4 What About Mortality and Endogenous Vitamin D Levels?

EBM presented data in third National Health and Nutrition Examination Survey—NHANES III Study—evaluated mortality in 13,331 persons over 20 years of age during 7 years (1994–2000) shows higher mortality in patients with vitamin D deficiency. Vitamin D deficiency <17.8 ng/ml is an independent risk factor of general mortality. Vitamin D supplementation, physical activity and exposure to sunlight are correlated inversely with mortality. These data were supported by meta-analyses of 18 randomised clinical trials of vitamin D supplementation; significant reduction of all-cause mortality in group with vitamin D supplementation was observed [12].

In conclusions, the vitamin D deficiency is associated with several metabolic disorders: obesity, insulin resistance, metabolic syndrome, NAFLD, diabetes type 2 and is an independent risk factor of general mortality.

6.5 What About the Reproduction and Endogenous Vitamin D Levels?

In women, VDR mRNA has been shown to be expressed in the mixed ovarian cell and in purified granulosa cell culture indicating role in sex hormones production. VDR as well as the active form of 1α hydroxylase gene was expressed in human endometrium (13–15). In women with Premature Ovarian Failure, deficiency of serum vitamin D, zinc, and copper was shown and it was inversely correlated with serum FSH levels [16]. In pregnant women, $1,25(OH)_2D_3$ regulates human chorionic gonadotropin expression and secretion in human syncytiotrophoblasts and increases placental sex steroid production [14]. Lower serum levels of 25(OH)D in pregnant women may result from enhanced maternal metabolism or increase the utilisation of vitamin D in foetus, elevated risk for preeclampsia and bacterial vaginosis [17, 18] and cause in early pregnancy are closely related to low birth weight [19]. The safety and effectiveness of vitamin D supplementation during pregnancy can be recommended 4,000 IU/day until delivery [20].

Vitamin D deficiency plays a role in pathogenesis of insulin resistance and metabolic syndrome in PCOS; however, association with hormonal disorders and

infertility is not clear (insulin gene transcription in human is activated by 1,25 (OH) 2D3). In our study included 202 women with PCOS in comparison to homogenous control (not published data), we found significant correlations between serum vitamin D levels negatively with: BMI, hip circumference, glucose at 0′ of OGTT, insulin at 0′ of OGTT, HOMA and positively with: serum HDL cholesterol levels. Our observations are supported by other study which show that vitamin D deficiency was found to be more common in PCOS women than in controls and there is some evidence that vitamin D deficiency may be involved in pathogenesis of insulin resistance and metabolic syndrome in PCOS [21–25].

VDR regulates more than 3 % human genome including genes that are crucial for glucose metabolism.

It has been shown that VDR-related polymorphisms (Cdx2, Bsm-I, Fok-I, Apa-I and Taq-I) are related to vitamin D metabolism and may contribute to PCOS susceptibility (women from Teheran) [26]. The role of genetic factor VDR was supported by other study which including 545 women with PCOS and 145 controls from Austria. They found association of VDR Cdx2 with insulin metabolism, whereas the VDR Apa-1 variant was associated with hyperandrogenemia [27].

In conclusion, vitamin D plays important role in regulation of sex hormones in women. Vitamin D supplementation (4,000 IU/day) during pregnancy can be recommended. Deficiency of endogenous vitamin D can play important role in ovary function disorders (PCOS and POF).

6.6 What Are the Most Common Reasons for Vitamin D Deficiency? How to Make Diagnosis and How to Treat it?

The most frequent reasons are disturbances of fat absorption in intestines, e.g. Whipple's disease, cystic fibrosis, intestinal inflammations and hepatic diseases. Also, autoimmune diseases (psoriasis and rheumatoid arthritis) as well as drug like: glucocorticosteroids, antiepileptic drugs and antiretroviral. The other frequent reason is the body surface small exposition to sun light (cultural and civilisation regards) and last—but not least—is aging process. The clinical symptoms suggesting vitamin D are presented in Table 6.1.

6.7 When We Can Recognised Vitamin D Deficiency and How Can We Prevent or Treat This Disease?

In Table 6.2, there are shown the serum levels of vitamin D to diagnose deficiency or hypovitaminosis. It is very important to remember the determination of serum PTH and calcium concentrations to excluded hyperparathyroidism as a cause.

Remember!!! Only 15 min exposition to sunlight of 18 % of body surface (forearms and legs) without any filters from 10 a.m. to 3 p.m. is required to produce enough level of vitamin D.

Table. 6.1 Clinical symptoms suggesting vitamin D deficiency

Frequent muscular and osseous pains
Parodontium diseases
Lack of appetite
Diarrhoea
Insomnia
Vision disturbances
Bad taste and burning sensation in oral cavity and throat

Table 6.2 The disturbances in serum levels of vitamin D

Serum vitamin 25 (OH) D levels	
<20 ng/ml	Deficiency
20–30 ng/ml	Hypovitaminosis
>30 ng/ml	Recommended level

According to the prevention—grown-ups—at insufficient exposition to sunlight from October till March and persons over 65 for the whole of the year, recommended daily dose is 800–1,000 IU of vitamin D3.

Administration of 1,000 IU of vitamin D3 daily cause the increase of vitamin D concentration by 1 ng/ml after 2–3 months in preventive measures, exceeding the dose of 2,000 IU is contraindicated in order to avoid side effects. Vitamin D should be administered along with a meal.

In vitamin D deficiency, the treated dose is usually 2,000 IU of vitamin D3 daily till attaining the serum level of vitamin D concentration >30 ng/ml.

Please remember that vitamin D3 activity (cholecalciferol) is higher than vitamin D2 (ergocalciferol) activity by 30 %. Also, very important is that calcitriol and alphacalcitriol are contraindicated in vitamin D deficiency supplementation in healthy population. Indication is only in disturbances of vitamin D hydroxylation in chronic disease of liver or kidneys [28].

6.8 What Side Effects Can We Expect if We Take Overdose of Vitamin D?

It is nausea and vomits, constipation, headaches, weakness, and drowsiness and only in extreme cases—toxic hypercalcaemia and hypercalciuria.

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PCOS from Lifestyle to the Use of Inositol and Insulin Sensitizers

7

Alessandro D. Genazzani, Alessia Prati, Giulia Despini, Giulia Marini, and Federica Ricchieri

7.1 Introduction

Polycystic ovary syndrome occurs in as many as 8–10 % of women of reproductive age [1], with onset manifesting as early as puberty [2]. From the very beginning, diagnostic criteria proposed by the NIH for PCOS were the presence of hyperandrogenism and chronic anovulation with clear exclusion of related ovulatory or other androgen excess disorders (i.e., hyperprolactinemia, thyroid diseases, androgen-secreting tumors, and adrenal dysfunction/hyperplasia) [3]. These criteria did not include the presence of polycystic ovaries at ultrasound examination because it was observed that polycystic ovaries could also be present in healthy eumenorrheic women [4]. A few years later, during the European Society of Human reproduction and Embryology (ESHRE)/American Society for reproductive Medicine (ASRM) conference, the diagnostic criteria were expanded and PCOS was considered as present when at least two of three features were diagnosed: oligo or anovulation, clinical/biochemical hyperandrogenism, and polycystic ovaries as assessed by ultrasound examination [4]. This evolution was relevant because it permitted the inclusion of women with PCOS who were excluded by previous NIH criteria [3]: those with polycystic ovaries affected by hyperandrogenism and ovulatory cycles, or chronic anovulation and normal androgen levels.

More recently, the Androgen Excess and PCOS Society indicated that PCOS should always be considered an androgen excess disorder and concluded that PCOS was, above all, a disorder of androgen biosynthesis, utilization, and/or metabolism in women [5].

Despite the diagnostic criteria, PCOS is still an unclear disease in terms of pathogenesis, both genetic and environmental factors may contribute to the onset of PCOS features [6, 7]. On such genetic predisposition, environmental factors may

A.D. Genazzani (✉) • A. Prati • G. Despini • G. Marini • F. Ricchieri
Department of Obstetrics and Gynecology, Gynecological Endocrinology Center, University of Modena and Reggio Emilia, Modena, Italy
e-mail: algen@unimo.it

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play a key role, such as peculiar lifestyle, types of food, living conditions, and also the impact during the intrauterine growth [7].

7.2 Endocrine Profile of PCOS Patients

Polycystic ovary syndrome is characterized by increased ovarian and adrenal androgens, increased luteinizing hormone (LH) levels, high estrogen levels (especially estrone) due to extraglandular conversion from androgens, lower levels of sex hormone-binding globulin (SHBG), and higher levels of insulin, the latter often in presence of overweight or obesity. Hyperandrogenism is a key feature of the syndrome, although it is not constant [8]. It is mainly of ovarian origin with an adrenal contribution, since a certain percentage of PCOS patients might show a mild steroidogenetic defect in adrenal glands (such as for 21-hydroxylase) or just a higher adrenal hyperactivation due to stress [9]. Androstenedione and testosterone are the best markers of ovarian androgen secretion, whereas dehydroepiandrosterone sulfate (DHEAS) is the best marker of adrenal secretion. Great part of testosterone is derived from peripheral conversion of androstenedione and from direct ovarian production. Dysregulation of cytochrome p450c17, the androgen-forming enzyme in both the adrenal glands and the ovaries, is the central pathogenic mechanism underlying hyperandrogenism in PCOS [10]. Additionally, estrone plasma levels, a weak estrogen with biological activity 100 times less than estradiol, are increased as a result of peripheral conversion of androstenedione by aromatase activity. All this results in a chronic hyperestrogenic state with the reversal of the estrone:estradiol ratio that might predispose to endometrial proliferation and to a possible increased risk for endometrial cancer [11].

Normally, <3 % of testosterone circulates as unbound in the serum. In fact, most circulating androgens are bound to SHBG, thus being biologically inactive. The presence of hyperandrogenism reduces the hepatic synthesis of SHBG and lead to a relative excess of free circulating androgens. In PCOS, hirsutism usually occurs with decreased SHBG levels and obesity [12, 13].

A great percentage of PCOS patients show overweight up to severe obesity, and typically any excess of weight can induce a reduction of peripheral tissues sensitivity to insulin, thus inducing the compensatory hyperinsulinism. It is relevant to say that hyperinsulinemia may be central to the pathogenesis of the syndrome in many cases, because it can induce higher ovarian androgen production and anovulation [14, 15], sustained also by the abnormal LH secretion, with a higher frequency of menstrual abnormalities than in normoinsulinemic women with PCOS [16]. Insulin resistance and compensatory hyperinsulinemia are metabolic disturbances easily observable in at least 45–65 % of PCOS patients, and frequently appear to be related to excessive serine phosphorylation of the insulin receptor [10, 17].

7.3 Metabolism and PCOS

In PCOS patients, there is an increased risk of developing type 2 diabetes and coronary heart disease (CHD) [18, 19]. Such risk has also been demonstrated to be higher in postmenopausal women, previously demonstrated to be PCOS during fertile life [20]. PCOS has been reported to have an increased risk of metabolic syndrome (MS), which refers to a clustering within the same individual of hyperinsulinemia, mild-to-severe glucose intolerance, dislipidemia, and hypertension, and an increased risk for cardiovascular disease (CVD) and diabetes [21, 22].

In 2006, the International Diabetes Federation defined the features of the MS, and defined central obesity as present when the waist circumference is above 80 cm; in European women, this was considered as a necessary prerequisite risk factor for the diagnosis of MS [23]. However, it is of great relevance to point out that although the MS has been identified for more than 80 years, only in these last years has controversy about its definition emerged [21].

The risk factors for MS are: waist circumference is over 80 cm, elevated triglycerides ($\geq$1.7 mmol/l), reduced HDL ($<$1.29 mmol/l in women), specific treatment for lipid abnormalities, elevated blood pressure (systolic $\geq$130 mmHb or diastolic $\geq$85 mmHg), specific treatment or precedent diagnosis of hypertension, fasting plasma glucose at least 5.6 mmol/l, and previous diagnosis of type 2 diabetes mellitus.

The prevalence of MS in polycystic women is approximately 40–45 % [24], and the main predictor factors are the elevated free serum testosterone and reduced serum SHBG level [25]. The association of MS with PCOS appears to be particularly strong in those PCOS women who are young ($<$30 years) and overweight or obese (BMI $>$27 kg/m^2) [26].

Women with PCOS have lower HDL levels, higher LDL:HDL ratios, and higher triglyceride levels than healthy eumenorrheic women [27]. All these are inductors of subclinical atherosclerosis as demonstrated by the increased thickness of the carotid intima media and by the higher endothelial dysfunction observed in PCOS patients [28], probably related to the insulin resistance and/or to the higher free testosterone plasma level [29, 30].

Indeed, several studies reported an increased risk factor profile for CVD in women with PCOS [31]. It is of great relevance the fact that women with PCOS have an increased risk for impaired glucose tolerance and type 2 diabetes mellitus [32, 33], with a tendency to an early development of glucose intolerance state [34]. In fact, the decrease of insulin sensitivity in PCOS women appears to be quite similar to that observed in patients with type 2 diabetes mellitus and to be relatively independent from obesity, fat distribution, and lean body mass [35]. On the other hand, there is strong evidence that obesity, particularly the abdominal phenotype, represents an important independent risk factor for glucose intolerance in PCOS women [31].

7.4 Lifestyle in PCOS Patients

Lifestyle modification is very important in the treatment for PCOS, as weight loss and exercise have been shown to lead to improved fertility and lowering of androgen levels. It also reduces the long-term risk of diabetes, heart disease, and possibly endometrial cancer.

Useful changes include the following: dietary modification (reduction in calories by limiting daily intake to 1,400 kcal, avoid sugary drinks, avoid snacking between meals, and have more low glycaemic index fruits and vegetables), regular moderate exercise (at least 30 min a day at the very least), stopping smoking, and moderate alcohol/caffeine intake.

Some studies [36, 37] have shown that lifestyle changes (in this case, intensive exercise with a goal of $\geq$150 min/week of activity) resulting in weight loss reduced the risk of type 2 diabetes [38]. The same studies found lifestyle changes to be superior to metformin administration. Thus, all women with PCOS should be encouraged to follow a healthy diet and to engage in regular exercise. Their chance to achieve a pregnancy will improve and the risks during pregnancy will be reduced. A healthier lifestyle will also reduce their long-term risks for diabetes, hypertension, dyslipidemia, and CVD. It is important for all primary care providers to identify patients who may have PCOS. These patients need to undergo the appropriate screening tests and should be counseled about diet and exercise. Pharmacologic intervention could be combined with this approach as appropriate, but the above-mentioned studies suggest that lifestyle modification is the first-line treatment.

7.5 Rationale of Metformin Use in PCOS Women

As additional therapeutical factor to counteract insulin resistance is the insulin sensitizers administration. The logic for the use of insulin sensitizer drugs, such as metformin, to treat patients with PCOS is the fact that 45–65 % of PCOS patients have been demonstrated to have insulin resistance and a compensatory hyperinsulinemia that negatively affect ovarian function in terms of steroid biosynthesis and follicular recruitment and maturation [6, 39]. Obviously, when insulin resistance is present independently from obesity, whatever the weight gain that might occur, it certainly exaggerates insulin resistance and more severely alters the glucose metabolism and, later on, the hormonal profile.

Excess insulin increases androgen concentrations blocking follicular maturation and increasing cytochrome P450c17a activity, a key enzyme in the synthesis of both ovarian and adrenal androgens [6, 34]. This situation typically increases 17-hydroxyprogesterone (17OHP), androstenedione, and testosterone plasma levels. The excess of intraovarian androgens negatively modulates follicular function and ovarian activity, thus inducing the typical stromal hypertrophy and maintaining ovarian atresia and anovulation [6, 40].

When abnormal insulin sensitivity is diagnosed, the use of metformin might be suggested [6, 41]. Metformin reduces hepatic glucose production from 9 to 30 % and on peripheral tissues, such as muscle cells and adipocytes, and acts by increasing glucose uptake through the glucose transport system.

Metformin positively acts on hormonal PCOS abnormalities through a direct and/or indirect action on steroidogenesis [6]. In fact, the recovery of normal ovulatory function is probably due to the direct modulation of metformin on the ovarian tissues and to the metformin-induced normalization of the ovarian steroidogenesis (lowering androgen production), thus determining the normal feedback on pituitary, lowering LH secretion, and LH pulse characteristics [42, 43]. Metformin improves steroidogenesis not only at the ovarian but also at the adrenal level, since insulin plays specific modulatory roles on these two distinct endocrine glands that have the same enzymatic pathways [44]. In fact, it has been demonstrated that metformin administration ameliorates adrenal enzyme activities in PCOS patients [45].

A recent meta-analysis of the published studies demonstrated that the use of insulin sensitizers do not reduce hyperandrogenism better than oral contraceptives [46], but as recently reported, the typology of PCOS to be treated is of great relevance, since only when insulin sensitivity is abnormal metformin shows a greater efficacy on all the PCOS features including hyperandrogenism [43]. Obviously, it cannot be excluded that other metabolically active hormones (e.g., leptin, resistin, adiponectin, and ghrelin) are positively activated by metformin administration and thus participate in the improvement of the reproductive function at the hypothalamus–pituitary–ovarian level [47]. However, we have to remember that metformin effectiveness on reproductive and on metabolic parameters is mainly exerted in association with a reduction of circulating insulin levels, thus supporting the hypothesis that a high insulin level is one of the main effectors/modulators of the clinical and endocrine dysfunctions of PCOS [6, 12].

7.6 Inositol Integrative Administration

In the last decade, a higher attention has been given to the role of inositolphosphoglycan (IPG) mediators of insulin action [48–50] and growing evidences suggest that a deficiency of D-chiro-inositol (DCI) containing IPG might be at the basis of insulin resistance, frequent in PCOS patients. Recent papers reported that PCOS patients have abnormally high urinary clearance of DCI [51] and that metformin administration in obese PCOS patients improves the release of DCI–IPG mediator [52].

Recently, more clinical emphasis has been given to the use of inositol, both as Myo-inositol (MYO) [50, 53] or DCI [54], keeping in mind that a precise relationship exists between MYO and DCI. In fact, DCI is synthesized by an epimerase that converts MYO into DCI and, depending on the specific needs of the two molecules, each tissue has a typical conversion rate [55]. Considering that ovaries never become insulin resistant [56] and being MYO administration able to induce regular

menses in both lean and obese hyperinsulinemic PCOS patients [50], a possible modulatory role of MYO on the insulin-mediated endocrine effects has been hypothesized [50]. In fact, recent studies suggest that some abnormal action of insulin might be dependent from IPG mediators of insulin action and suggest that a deficiency in a specific DCI-containing IPG may underlie insulin resistance, similarly to type 2 diabetes. DCI administration has been demonstrated to reduce insulin resistance both in lean and obese PCOS patients improving ovarian function and decreasing hyperandrogenism [49, 57]. Such studies have suggested the putative presence of a defect in the insulin-signaling pathway in which DCI-PG is the mediator of insulin action, thus contributing to the pathophysiology of the insulin resistance of PCOS [51]. Besides DCI, MYO has been reported to be greatly correlated to ovarian function [58] and oocyte quality in patients undergoing IVF procedures, independently from circulating plasma levels [59]. Such data support a specific role also for MYO on gonadotropin-induced ovarian function [53] though not confirmed by others [51].

Indeed, MYO administration has been demonstrated to modulate insulin sensitivity in overweight PCOS patients improving all hormonal parameters and improving insulin sensitivity [50, 53]. The daily dosage was 2 g, taken during the morning. Such treatment has been reported to be effective in hyperinsulinemic obese PCOS with fasting insulin levels above 12 mU/ml [53]. Such insulin level seemed to be a putative cut off that suggests when MYO administration might give higher chances of success not only on hormonal parameters but also on hyperinsulinemia and insulin sensitivity [53].

In conclusion, PCOS is a quite complex syndrome and it cannot be considered as "an easy to treat" disease. PCOS needs a precise clinical screening that might give suggestions on what hormonal and metabolic parameters need to be treated. Recent data clearly indicate that hormonal and metabolic aspects are tightly related and the therapeutical approach for PCOS patients need to consider these two aspects together. Metformin as well as inositol integrative administration might be easily used to solve the metabolic aspects of PCOS impairments. Lifestyle as well as hormonal treatments has to be considered relevant therapeutic tools to be used together with insulin sensitizer drugs.

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Pathophysiology and Clinical Assessment of Hyperandrogenic States

8

Susanna Santagni, Erika Rattighieri, Elisa Chierchia, Giulia Despini, and Alessandro D. Genazzani

8.1 Introduction

A regular reproductive function depends from regular gonadotropins release, in particular of LH (Luteinizing Hormone), all along the menstrual cycle. The most notable feature of the female reproductive system is the total absence of steady state, as demonstrated by the gonadotropins pulsatile release from pituitary cells, with different characteristics of amplitude and frequency during the course of menstrual cycle. Whatever event interferes with the dynamics of the long as well as the short-term fluctuations of female reproductive system may cause a pathophysiological change and might induce a steady state so that chronic anovulation occurs.

The chronic anovulation depends both on peripheric endocrine disorders with an abnormal modulation from peripheral systems and glands and on central (CNS–hypothalamic–pituitary) dysfunction with an abnormal control of hypothalamus, pituitary, and ovary. In both of cases, the symptoms are a mixture of the following: oligomenorrhea or amenorrhea, hyperandrogenic signs, altered BMI, infertility, and stress.

Therefore, the chronic anovulation syndrome has many different origins as summarized in Table 8.1.

Hyperandrogenism falls in the pathogenesis of chronic anovulation as an inappropriate peripheral feedback mechanism, independently from the origins of androgen excess (adrenal or ovarian). In fact, hyperandrogenism might origin from an excess of extraglandular hormones production, as in case of overweight (BMI >25) or obesity with androgens synthesis by fat tissue, or during ovarian functional hyperandrogenic state or adrenal disease able to increase circulating androgens and to induce specific changes in neuroendocrine pathways as well as in ovarian

S. Santagni • E. Rattighieri • E. Chierchia • G. Despini • A.D. Genazzani (✉)
Department of Obstetrics and Gynecology, Gynecological Endocrinology Center, University of Modena and Reggio Emilia, Modena, Italy
e-mail: algen@unimo.it

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Table 8.1 Pathogenesis of chronic anovulation

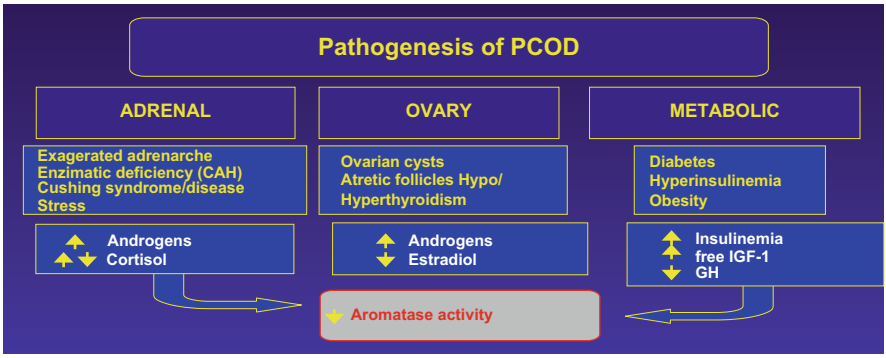
Chronic anovulation syndrome	
Hypothalamic anovulation	Altered or inappropriate GnRH secretion
Pituitary anovulation	Defect/Dysfunctions of gonadotropes (receptor abnormalities, altered subunit synthesis)
Inappropriate feedback	Use of oral contraceptives Excess of extraglandular estrogen production (obesity) Functional hyperandrogenism (adrenal or ovarian) Androgen/estrogen producing tumors Autoimmune disorders
Inappropriate feedback due to central/peripheral dysfunction	Excessive cortisol/androgen production (Cushing's disease/syndrome) Hypo/Hyperthyroidism Hyper PRL/GH Malnutrition

morphology and activity. A hyperandrogenic state can be found in many different endocrine disorders as diabetes, obesity and/or overweight, and thyroid dysfunction. All these clinical conditions can induce the Polycystic Ovarian Syndrome (PCOS).

8.2 Ovarian Hyperandrogenism: PCOS and Chronic Anovulation

PCOS is the most common androgen excess disorder, where the ovary is the main source of androgens [1]. Although no genetic ovarian enzymatic deficiency has been detected [2], ovarian hyperandrogenism represents the main pathogenetic mechanism of the syndrome [3] and the increased androstenedione and testosterone production by the ovary results not only from the increased LH (and insulin) drive but also from the increased primary androgen secretion by theca cells [4, 5]. It is well known that the PCOS patients show the amplification of the spontaneous pulsatile LH release, with high LH levels (30 % or more) than in healthy controls: since FSH remains stable, the result is an overall increased LH/FSH ratio. The causal mechanism of this change of LH secretion is already unclear but various hypotheses have been proposed. One suggests that hyperandrogenism and hyperestrogenemia can augment the pituitary sensitivity to GnRH, increasing mainly LH pulse amplitude, whereas other hypothesis states that hypothalamic dysfunction increases GnRH secretion as the result of the reduction of neuroendocrine modulation, and/or of the absence or inadequate levels of progesterone and estradiol modulation. Last but not least, an inappropriate feedback system might alter the whole neuroendocrine regulation, since androgen excess increases peripheral conversion to estrone (E1) and this hyperestronemia alters gonadotropin secretion, mainly FSH drive.

Table 8.2 Summary pathogenetic mechanisms of Polycystic Ovarian Syndrome



However, in many women with PCOS, there is more than one source of androgens and not rarely adrenal androgen secretion is increased [6]. The adrenal hyperandrogenism could be due to P450c17 hyperfunction in reticular area of the adrenal cortex; this abnormality affects about 20–40 % of PCOS patients who show increased DHEAS and 11β-OH androstenedione levels or increased response of 17-OHP after ACTH stimulation test. On such basis, it has been proposed the "theory" of the exaggerated adrenarche responsible, before pubertal maturation and ovary activation, for the production of excessive amount of androstenedione, in part produced by the extraglandular (fat tissue) conversion to estrone.

The final result, independently from the origin of hyperandrogenism, is that an altered GnRH-gonadotropin secretion occurs with no chance for follicles to develop and/or mature correctly and oligomenorrhea takes place (Table 8.2).

It is of certain relevance to say that quite frequently the hyperandrogenic condition of PCOS is also characterized by metabolic problems, in particular overweight/obesity, insulin resistance, and hyperinsulinemia. It is well known that obesity shows up in 25–50 % of PCOS women and hyperinsulinemia affects more than 50 % of PCOS subjects. The 70–80 % of obese patients is hyperinsulinemic and it is of interest to say that insulin resistance and hyperinsulinemia concern also 30–40 % of lean or normal weight women with PCOS. During the 1980s, it has been proposed the concept of the "steroidogenetic role" of insulin, able to synergize with LH and FSH on the activities of both theca and granulosa cells, respectively. It has been supposed that persistent elevated levels of insulin could be able to induce a hyperstimulation state of the theca cells so that to trigger together with LH synergism the typical hyperandrogenism of PCOS [7] (Fig. 8.1).

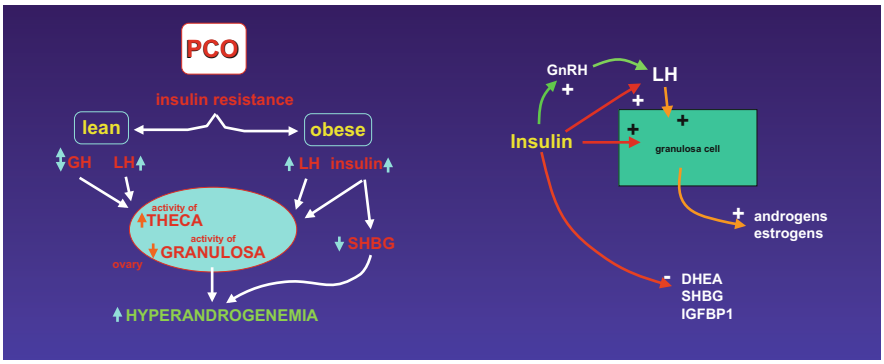


Fig. 8.1 Metabolic pattern and insulin role in PCOS. Insulin plays a tremendous role in the modulating LH stimulation of granulosa cells as well as in affecting GnRH discharge from hypothalamic neurons. Independently from BMI, if insulin resistance is present, the compensatory hyperinsulinism alters the effects induced by LH stimulation on granulosa cells so that to have a higher rate of androgens produced

8.3 Hyperprolactinemia and Thyroid Disfunction as Causes of Chronic Anovulation and Hyperandrogenism

Chronic anovulation and hyperandrogenism might arise from a peripheral endocrine disorder. We always have to investigate the thyroid function as well as prolactin release. In general, abnormal PRL levels are present in the 60–70 % of all cases of oligo/amenorrhea, chronic anovulation, and/or galactorrhea [8]. Hyperprolactinemia affects reproductive function through several pathogenetic mechanisms, such as reducing GnRH discharge through the increased opioidergic tone and/or a short feedback on TIDA neurons, responsible of the dopamine (DA) release: if TIDA neurons are inhibited, lower dopaminergic tone induces a higher release of PRL. High levels of prolactin cause a luteal phase defect because of abnormal modulation on progesterone secretion from luteal cells, because of decreased aromatase activity and a lower FSH action on granulosa cells, resulting in anovulation and infertility. Some patients show a moderate hirsutism: this is caused by both a higher ovarian production of androgens and elevated adrenal DHEAS secretion and also by elevated free-testosterone levels due to androgen-induced SHBG reduction. In general, women with hyperprolactinemia might also show other disorders such as galactorrhea, lower bone density, reduced ovarian steroidogenesis with hypoestrogenism and hyperandrogenism (Androstenedione, DHEA, and DHEA-S), increased insulin resistance and hyperinsulinemia, this last due to direct action of on pancreatic beta cells. When hyperprolactinemia is present, it has to be evaluated whether it is due to a pituitary adenoma or dysfunctional. This latter is usually due to drugs use (estrogens, neuroleptics, metoclopramide, etc.), renal or

liver insufficiency, hypothalamic tumors, endocrine disorders (Cushing's syndrome), PCOS, or hypothyroidism.

In general, the thyroid diseases, both hypo- or hyperfunction, may lead to reproductive impairment since induce menstrual irregularities, menorrhagia or oligo/amenorrhea, hyperandrogenism, hyperestrinism, chronic anovulation, and PCOS. In the case of hypothyroidism, the pathogenetic mechanism is in great part based on a hyperprolactinemic condition, induced by an increased hypothalamic TRH secretion. The more frequent clinical hypothyroidism is due to the Hashimoto's thyroiditis that usually shows lethargy, paresthesias, hypothermia, deep-tones, and slow speech. If the disease occurred years before, it might be the cause of a higher risk of miscarriage if pregnancy occurs. When autoantibodies are high, an elevated risk of oligo/amenorrhea, chronic anovulation, and POF (premature ovarian failure) has to be taken into account.

Conversely, hyperthyroidism, such as Grave's disease (or toxic diffuse goiter), presents general symptoms such as heat intolerance, weight loss, sweating, palpitations, and tremors and these are not to be confused with those of the perimenopause. In these cases, it is quite frequent to observe oligo/amenorrhea, chronic anovulation, hyperandrogenism, increased levels of SHBG, and higher levels of estrogens (specially estrone, E1) and LH throughout the menstrual cycle [9].

8.4 Chronic Anovulation and Adrenal Hyperandrogenism

The adrenal hyperandrogenism syndromes derive from an exaggerated adrenal function, that increases the production of DHEA and androstenedione, converted to testosterone by extraglandular tissues; this last hormone is the responsible of the majority of clinical signs of virilization. This might happen for various reasons: stress-induced adrenal activation and partial or complete enzyme deficiency, which can be congenital or acquired.

The congenital adrenal hyperplasia (CAH) is caused by enzymes deficiency; in physiological conditions, the pathways of adrenal steroid hormone biosynthesis start from cholesterol and cortisol and aldosterone are synthesized through several androgenic intermediate products. The result of enzyme's deficiency is hypoaldosteronism and hypocortisolism: this last hormone is the most important adrenal steroid. ACTH regulates both cortisol and adrenal androgens production and when enzyme deficit is present, a higher amount of ACTH is released in an effort to maintain normal cortisol levels, with the result of an increased amount of adrenal androgens secretion. The late onset or NCAH (nonclassical adrenal hyperplasia) is the most frequent forms of adrenal hyperandrogenism, characterized by peripubertal onset and normal menstrual cycle with adrenal androgens levels slightly above the normal range in basal conditions and a marked increase under ACTH-stimulation test. The clinical features of NCAH are hypotension, hypoglycemia, lethargy, loss of hair, hyperandrogenism, and anovulation, depending by the level of enzymatic defect in the pathways of steroids synthesis, in particular

21-hydroxylase deficiency (the main defect), 11β-hydroxylase deficiency, and 3-β-hydroxysteroid dehydrogenase deficiency.

Last but not least important, hyperandrogenism might be related to a temporary adrenal hyperfunction, typical in a chronic stress condition, as demonstrated by the fact that there is a synchronism between cortisol and androstenedione levels in stressed hyperandrogenic PCOS women [10].

8.5 Clinical Assessment of the Hyperandrogenic States

Usually, patients with hyperandrogenism refer specific symptoms like irregular menstrual cycle (oligomenorrhea/amenorrhea), infertility and hyperandrogenic signs such as acne, seborrhea, and hirsutism up to signs of virilization as alopecia, reduced voice's tone and clitoromegaly. The anamnesis is fundamental for the diagnosis because the features of onset and duration of the hyperandrogenic problems permit to drive towards the main pathogenetic hypothesis (Table 8.3).

After the anamnestic interview and the clinical visit, it has always to be noted the signs of hyperandrogenism and their severity, using a visual scale (e.g., Ferriman–Gallwey scale for hirsutism and the Global Evaluation Scale of FDA 2002 for acne). The hormonal evaluation has to be performed in most cases, especially when the patient is looking for a pregnancy more than for just regular menstrual cycles. The hormonal screening might start with two different samples in two distinct moments of menstrual cycle: if eumenorrheic, blood sampling is performed on day 3–6 and on day 16–20 of the cycle, if oligomenorrheic (with cycle >40 days) on day 3–6, 16–20, and 26–30, if amenorrheic on two random samples, 15 days apart one from the other. The hormonal parameters to evaluate on each blood sample are: LH, FSH, E2, P (only during luteal phase), Androstenedione, T, 17-OHP, PRL, and Insulin. SHBG, TSH, fT3, and fT4 only on one of the blood withdrawals.

Typically, PCOS is now diagnosed using the criteria of Rotterdam 2003 [11] that include also the clinical or biochemical hyperandrogenism. The hormonal diagnosis of PCOS is sustained when, on day 3–5 control, the hormonal parameters are abnormal, such as LH >10 mIU/ml, LH/FSH >2.5, A >2.5 ng/ml, T >1 ng/ml, 17-OHP >2 (suspect CAH), and metabolic parameters like basal Insulin >15–20 μU/ml and Glucose/Insulin ratio <4.5.

When insulin is above 15 μU/ml (in some Gin Endo units the limit is above 12 μU/ml) and/or Glucose/Insulin ratio is altered, independently from BMI (kg/m^2) (normal or high, >25), there is the suspect of hyperinsulinism and it should be helpful to perform a OGTT (Oral Glucose Tolerance Test) with 75 g of glucose to evaluate the presence of insulin resistance [12, 13].

If 17-OHP >2–3 ng/ml or higher, we have to suspect a CAH; the correct diagnosis has to be completed performing a suppression test with Desametazone (DXM), administered at the dose of 2 mg the night before and sampling the following day at 7 a.m. for A, T, 17-OHP, and cortisol: if the 17-OHP, A, and T are significantly reduced, is probably confirmed the suspect of CAH. Also, ACTH

Table 8.3 Possible anamnestic questions

Anamnesis Question: *Since when have you had hyperandrogenic problems?*	
Answer	**Hypothesis**
I have never had them before. They started with body weight increase and menstrual irregularities	Metabolic problem (thyroid, hyperinsulinism, abnormal eating habits, diabetes)
They started with puberty and increased in growing up	Abnormal ovarian regulation/function, hyperinsulinism
They started a few months ago and worsened	Ovarian/adrenal secreting adenoma/tumor
Some signs already appeared as a child and worsened progressively, as it happened to my mother and my sister	Late onset of adrenal enzyme defect, hyperinsulinism

test (0.25 mg) permits to disclose an adrenal dysfunction, especially the late-onset forms, which respond similarly to controls under ACTH test, but show higher baseline levels of A, cortisol, and 17-OHP than healthy groups [14].

If TSH >5 or TSH <0.2 (i.e., hypo or hyperthyroidism), the suspect of a thyroid disease is clear in these cases and PRL levels and the Ab-anti-TPO, anti-TG, and anti-TSH has to be controlled.

In the case of a hyperprolactinemia with PRL >25–30 ng/ml (500–600 mU/L), it might be useful to check PRL, with an heparin well inserted in an antecubital vein 30 min before starting the test and the samples should be drawn at time 0, +15, and +30 min: the most reliable value is the last. If PRL is above 60–80 ng/ml, it should be better to perform also an RMN scan of the pituitary area for the suspect of a secreting pituitary microadenoma.

8.6 Conclusion

It is easy to understand that minimal endocrine or metabolic changes might induce abnormalities of the reproductive function, inducing a chronic anovulation state that is often coupled with oligomenorrhea, sometimes this last occurs before the menstrual disorders, together with the first clinical or biochemical signs of ovarian hyperandrogenism or less frequently adrenal hyperandrogenism. Before to decide for any kind of treatment, a well-based diagnostic screening has to be performed to avoid mistakes and to correctly treat the endocrine cause of the disorders, not only the symptoms.

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Part III

Ovarian Stimulation, Surgery and Insufficiency

Ovarian Surgery from Puberty Through Reproductive Age and After Menopause

9

Liselotte Mettler, Abdusattarova Khulkar, and Ibrahim Alkatout

9.1 Introduction

9.1.1 Oogenesis: From Gonad Development Via Menarche to Menopause

In human embryos, ancient germ cells from the yolk sac migrate into the indifferent gonadal streak. These ancient germ cells can be found in humans in the yolk sac in the Carnegie stages 8 and 9. The differentiation of germ cells to oogonia does not depend on sex chromosomes of the germ cells but is regulated by somatic cells in the gonads. The germ cells of the ovaries, the oogonia, reproduce meiotically. At 5 months of embryonic development, the oogonia inside the ovaries enter the first meiosis and differentiate to primary oocytes. At this stage, there are about seven million oocytes in the ovary. They decrease until delivery to two million. As primordial follicles they remain quiet until puberty, when, due to abortive growth, many primordial follicles deteriorate resulting at the beginning of puberty in only 40,000 primary oocytes. About 400–500 of these mature during the following ovarian cycles into mature oocytes from menarche to menopause [1–5].

In human embryos, primordial germ cells reach the genital ridges from the yolk sac endoderm 5–6-week post-fertilisation. These primordial germ cells or primordial follicles form the basic reproductive unit of the ovary. There is evidence that all dominant preovulatory follicles are already selected from the pool of germ cells at 24 weeks gestation. In each primordial follicle, an immature oocyte is surrounded by a single epithelial cell layer composed of granulosa cells. These are surrounded by a basal lamina creating a microenvironment that does not directly interact with the surrounding cells. As all primordial follicles are formed before birth, only a few

L. Mettler (✉) • A. Khulkar • I. Alkatout
Department of Obstetrics and Gynecology, University Hospitals Schleswig-Holstein, Arnold-Heller-Strasse 3/24, 24015 Kiel, Germany
e-mail: profmettler@gmx.de

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Table 9.1 Summary of the development of primordial germ cells, oogonia, oocytes and primordial follicles

Stage	Oocyte development
6 weeks	Primordial germ cells reach the genital ridges from the yolk sac endoderm
9–10 weeks	Differentiation into oogonia, migration of stroma cells from the medulla, morphologically distinguishable ovary
12 weeks	Oocytes as germ cells in meiosis and interstitial cells appear
20–24 weeks	Formation of primordial follicles
24 weeks	Germ cells reach a peak of approximately 6–7 million
Birth	Two million primordial follicles are present
Birth to menarche	The number of primordial follicles decreases from several million to several hundred thousand
Reproductive years	Only 350–400 of oocytes will develop into full maturity, reach ovulation and corpus luteum formation. After recruitment 99.9 % become atretic
Menopause	Few if any primordial follicles are remaining, menopause is the permanent cessation of menstruation resulting from the loss of ovarian follicle activity

survive until menopause. The development of the oocytes and ovary is summarised in Table 9.1.

Isolated oocytes do not grow in culture without their companion somatic cells, the granulosa cells, attached. Their intimate and complex relationship extends from follicle formation to ovulation and affects the development and function of both cell types. Details of the interaction and nature of this intimate relationship are just beginning to emerge. Knowledge comes primarily from in vitro experiments. Cutting-edge knowledge will come from trials of artificial oocyte production of pluripotent somatic or embryonic stem cells [6, 7]. However, data in this field are still limited. Human oocytes spontaneously complete nuclear maturation when they are released from antral follicles and cultured in vitro for up to 48 h. Germinal vesicle breakdown (GVBD) occurs after 12 h, but this does not happen simultaneously and in some oocytes GVBD does not begin until 24 h after the beginning of in vitro culture. The molecular mechanism involved in human oocyte maturation is very interesting. Monocyte-derived pluripotent stem cells can today be transformed into oestrogen and progesterone-producing cells [7].

9.1.2 Ovulation

After menarche, in every ovulatory cycle, one recruited follicle grows during the follicular phase up to a diameter of approximately 22 mm, ruptures and, depending on the stimulus of follicle-stimulating hormone (FSH) and luteinising hormone (LH) at the time of ovulation, releases the oocyte for fimbrial pick-up and fertilisation or for digestion by macrophages. Healing mechanisms of cytokines immediately close the follicular defect and help to form the corpus rubrum or, in cases of pregnancy, the corpus luteum graviditatis. The pre-ovulatory phase is characterised by an oestrogen rise, low progesterone values and the direct initiation

of ovulation triggered by an LH peak. Subsequently, progesterone rises until the end of the cycle. Ovulation can be detected by a sudden rise of progesterone, an LH and FSH peak, by direct ultrasound measurements of the follicle and of course using direct observation during laparoscopy or laparotomy. A rise in basal body temperature of about 0.5–1 °C accompanies ovulation. A progesterone rise over approximately 6 pg/ml confirms ovulation and is a post-ovulatory marker.

9.1.3 Embryology, Physiology and Endocrinology

When a girl is born her ovaries contain all the oocytes she will ever possess. The primordial germ cells reach the genital ridges from the yolk sac endoderm at 5–6 weeks post-fertilisation and form the basic reproductive unit of the ovary. There is evidence that all dominant pre-ovulatory follicles are selected from the pool of germ cells as early as at 24-week gestation. In each primordial follicle, an immature oocyte is surrounded by a single epithelial cell layer composed of granulosa cells. These are surrounded by a basal lamina, creating a microenvironment. As all primordial follicles are formed before birth, only a few survive until menopause. This is completely different from the male, who starts producing spermatozoa only at puberty and then continues to do so until the end of his life.

Isolated oocytes do not grow in culture without their companion somatic cells, the granulosa cells, attached. Cutting-edge knowledge about oocyte maturation comes from trials of artificial oocyte production of pluripotent somatic or embryonic stem cells. Human oocytes spontaneously complete nuclear maturation as they are released from follicles and cultured in vitro for up to 48 h. Typical GVBD occurs after 12 h, but this does not happen simultaneously, and in some oocytes GVBD does not begin until 24 h after the beginning of culture.

After menarche, in every ovulatory cycle one recruited follicle usually grown during the follicular phase up to a diameter of approximately 22 mm, ruptures, and, depending on the stimulus of FSH and luteinising hormone (LH) at the time of ovulation, releases the oocyte for fimbrial pick-up and fertilisation or for digestion by macrophages. The follicular defect is immediately closed by a healing mechanism of cytokines, which also form the corpus rubrum or, in the case of pregnancy, the corpus luteum graviditatis.

9.2 Therapy

9.2.1 Ovarian Stimulation Using Assisted Reproductive Techniques

To create a healthy child using artificial reproductive technologies, the growth of multiple follicles is stimulated by an endocrine trigger. Multiple follicles facilitate the collection of multiple oocytes. Mature metaphase II oocytes are fertilised. The intrauterine transfer of multiple embryos leads to a higher pregnancy rate than a single embryo transfer. However, as multiple pregnancies occur in a high

percentage of cases, in Germany only up to 3 embryos in the 2–16 cell stage are allowed to be transferred into the uterine cavity (German Embryo Protection Law 1991). Ovarian stimulation may achieve pregnancy rates ranging from 20 to 50 %. The success after assisted reproductive technology depends largely on the applied techniques and the quality of ovulation stimulation. In vitro fertilisation (IVF) and intracytoplasmatic sperm injection (ICSI) followed by embryo transfer can only be applied as a routine method after successful ovarian hyperstimulation. Egg retrieval in spontaneous cycles has a low pregnancy rate.

The introduction of GnRH agonists and antagonists in the mid-1990s allowed additional therapeutic control over ovarian hyperstimulation and helped to avoid premature luteinisation of the ovary. Various protocols have been developed, such as the long protocol using the agonistic GnRH analogs or the short protocol with daily application of drugs. It was thought that GnRH antagonists would take over in this field, but no conclusive guidelines have yet been produced [8]. A systematic meta-analysis of phase 3 studies has shown that clinical pregnancy rates, after controlled ovarian hyperstimulation using GnRH antagonists, are not increased [9]. An analysis of the data of the German IVF registry also showed no significantly better results after application of GnRH antagonists [10]. There were 5,332 IVF cycles after controlled ovarian hyperstimulation with GnRH antagonists and subsequent embryo transfer which resulted in an average pregnancy rate of 22–26 % using FSH and 25 % using recombinant FSH and HMG. The long agonist protocol resulted in pregnancy rates of 29–30 % for HMG cycles and 29 % for recombinant FSH cycles. The application of agonists compared to antagonists was found to be superior in both IVF and ICSI cycles [11]. Ovarian overstimulation, presenting with ascites and hydrothorax, should be avoided by careful monitoring and transvaginal ultrasound control. Ovarian stimulation with purified and gene technologically synthesised FSH/LH agents in combination with GnRH agonists and antagonists is currently under comparison to aspiration and selection of the one ideal oocyte for IVF, ICSI and ET. However, a final conclusion has not yet been reached.

The field of in vitro maturation (IVM) aims at maturing immature oocytes from the germinal vesicle stage in vitro. With this technology immature oocytes are retrieved from small antral follicles (5–12 mm) from patients with polycystic ovary syndrome (PCOS) or from normal menstruating women at the beginning of each cycle. However, maturation in vitro takes approximately 28–36 h. After careful patient selection and adequate preparation, it is possible for a larger proportion of oocytes to resume meiosis in vitro. This is then followed by intracytoplasmatic sperm injection. Over 500 healthy children have been born worldwide after application of this technology. However, IVM does not yet have the potential to replace standard hyperstimulation [12, 13].

Hormone levels in the pre-ovulatory phase are characterised by a rise in oestrogen levels, low progesterone levels and an LH peak that directly triggers ovulation. Subsequently, progesterone rises until the end of the cycle.

A normal cycle comprises various contributions from the central nervous system (CNS), the limbic system, the hypothalamus, the hypophysis and the ovaries, which

have to work together. Disturbances in these interactions lead to ovarian dysfunction with follicular maturation disturbances, inadequate ovulation, inadequate functioning of the corpus luteum and resultant bleeding abnormalities. The 1973 World Health Organization (WHO) classification of ovarian dysfunction still gives the best general idea of diagnostic techniques and therapy. Women exhibit menstrual irregularity followed by menopause when the average number of primordial follicles per ovary decreases to approximately 100. Inhibin B is a major regulator of FSH secretion and a product of small antral follicles. Its levels respond to the early follicular phase increase and decrease in FSH. The age-related decrease in ovarian primordial follicle numbers, which is reflected in a decrease in the number of small antral follicles, leads to a decrease in inhibin B, which in turn leads to an increase in FSH. Concurrently, the concentrations of testosterone do not change significantly.

Anovulatory cycles occur at increased frequency in the last 30 months before final menses or menopause. Anti-Müllerian hormone correlates with follicle numbers and shows a large age-related decrease to reach undetectable levels at menopause.

9.2.2 Conception

Conception defined as the fertilisation of an ovum by a sperm, marks the beginning of human development. Currently, a biomarker of conception is not available; as conception generally occurs shortly after ovulation, the latter can be used as an approximation of the time of conception. In the absence of serial ultrasound examinations, ovulation cannot be readily visualised. The most commonly used proxy measures include charting basal body temperature, monitoring cervical mucus, measuring urinary metabolites of oestradiol and LH or measuring serum or saliva oestradiol and LH levels.

Today, assisted reproductive techniques (ARTs) mean it is possible to create pregnancies not only in cases of fallopian tube obstruction or male subfertility but also in various forms of ovarian dysfunction such as PCOS.

In ART, the growth of multiple follicles is stimulated by an endocrine trigger. Multiple follicles facilitate the collection of multiple oocytes. Mature metaphase II oocytes are fertilised. The intrauterine transfer of multiple embryos leads to a higher pregnancy rate than a single-embryo transfer. However, as multiple pregnancies are in unwanted complication of multiple-embryo transfer, in Germany only up to 3 embryos in the 2- to 16-cell or blastocyst stage are allowed to be transferred into the uterine cavity [14]. Success rates after ART depend largely on the techniques used and the quality of ovulation stimulation, with the pregnancy rate ranging from 20 to 50 %. The introduction of gonadotropin-releasing hormone (GnRH) agonists and antagonists in the mid-1990s allowed additional therapeutic control over ovarian hyperstimulation and helped to avoid premature luteinisation of the ovary. In 2006, we summarised some of our results concerning this topic [15].

9.2.3 Ovarian Hyperstimulation Syndrome

Ovarian Hyperstimulation Syndrome (OHSS) remains a major complication of IVF, ICSI and embryo transfer. Triggering ovulation with human chorionic gonadotropin (hCG) as a surrogate for LH is a major factor in the initiation of OHSS. The pathological process usually intensifies if pregnancy is achieved, as the rising endogenous hCG over-stimulates the corpora lutea. Reducing the hCG trigger dose does not prevent OHSS. GnRH agonists (GnRHa) induce endogenous LH and FSH surges that reliably trigger ovulation, even if a GnRH antagonist is used during ovarian stimulation. Moreover, such a trigger quickly and irreversibly induces luteolysis, thereby preventing OHSS. Contrasting reports regarding clinical outcome probably reflect different approaches to luteal phase support. A GnRH trigger might be the key to OHSS prevention.

9.2.4 Polycystic Ovary Syndrome

With a prevalence of more than 5 %, PCOS is one of the most common diseases in young women. PCOS cannot be defined as a unique entity since various heterogeneous morphological forms and clinical symptoms have been described. The 2003 Rotterdam criteria with presence of two of the first three criteria such as oligo—and/or anovulation, signs of clinical hyperandrogenism (HA-C) and/or biochemical signs of hyperandrogenism (HA-b) and polycystic ovaries (PCO) on ultrasonography after exclusion of specific identifiable disorders—is the most widely accepted definition so far. Further characteristics include the frequently seen increased insulin resistance and obesity, although even very slender patients can be affected.

The consideration of insulin resistance has established insulin sensitisers as a new option for the treatment of PCOS. For example, metformin increases insulin sensitivity, reduces glucose uptake and inhibits glucose synthesis. In obese women, metformin supports weight loss and improves the regularity of the menstrual cycle, with increased ovulation rates. With metformin therapy, serum testosterone decreases and symptoms of hirsutism significantly improve. In ovarian stimulation, metformin improves response to clomiphene or FSH with increased pregnancy rates. Some studies suggest a positive effect of metformin even in early pregnancy, leading to reduced miscarriage rates. Various combination treatments, including oral contraceptives and metformin as well as ethinyl oestradiol and metformin, have been suggested. Surgical treatment with ovarian drilling via laparoscopy offers the possibility of releasing the ovarian capsule and the retained fluid; this procedure can be performed with mono- or bipolar electricity, laser or ultrasound (see Fig. 9.1). Ovarian drilling is generally accepted and is certainly indicated in selected cases with the typical “strong pearls” cysts on ultrasound.

Molecular genetic findings on the origin of PCOS have not yet led to any practical therapeutic treatment modalities but have provided some insight into the genetic background of the disease. The related genes can be grouped into four

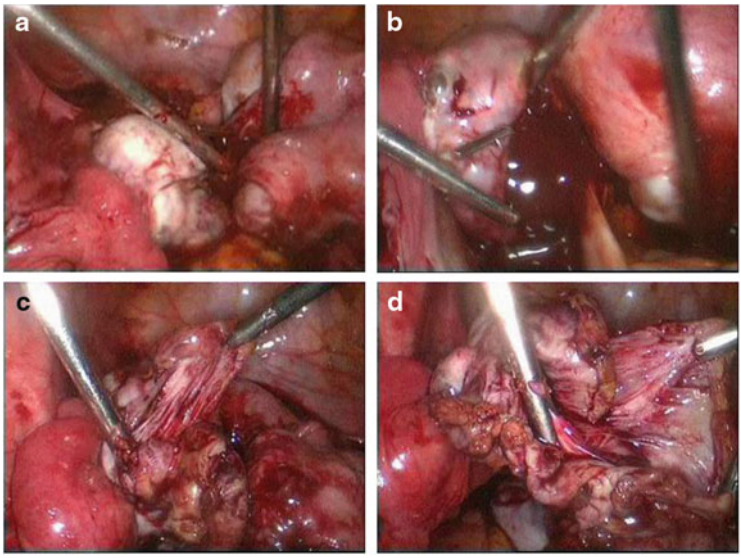

Fig. 9.1 Ovarian endometrioma enucleation, (**a**) kissing ovaries, (**b**) spilling of chocolate fluid, (**c**) and (**d**) stripping of endometrioma

categories: those related to insulin resistance; those that interfere with the biosynthesis and action of androgens; those that encode inflammatory cytokines and other candidate genes. Despite intensive investigation, the aetiology and underlying mechanisms of PCOS remain unclear, warranting further investigation. Better understanding of the molecular and genetic basis for PCOS might lead to the invention of novel therapeutic approaches. Long-term interventional studies are needed to address the question of whether lower androgen levels in women with hyperandrogenism might protect against metabolic and cardiovascular co-morbidities.

9.2.5 Premature Ovarian Failure

Premature ovarian failure (POF) is the occurrence of hypergonadotropic hypooestrogenic amenorrhoea in women under 40 years of age. POF is idiopathic in 74–90 % of cases but can be familiar (4–33 %) or sporadic. The known causes are: genetic aberrations; autoimmune ovarian damage; iatrogenic following surgery, radiotherapy or chemotherapy; environmental factors (viruses, toxins, etc.) and metabolic (galactosaemia, 17 hydroxylase (17-OH) deficiency, etc.). Genetic aberrations can involve the x chromosome (monosomy, trisomy or translocations) or be autosomal. Genetic mechanisms include reduced gene dosage and non-specific chromosome effects impairing meiosis, decreasing the pool of

primordial follicles and increasing atresia due to apoptosis or failure of follicle maturation [16].

Although it was once thought to be a permanent condition, a substantial number of patients experience spontaneous remissions and even pregnancy. Hormone replacement therapy (HRT) remains the cornerstone of treatment, and the only proven method of achieving pregnancy in POF patients is by ovum donation. New alternatives to HRT and fertility preservation are under development [17].

9.2.6 Contraception

Contraception means the separation of sexuality and reproduction, which allows active family planning.

The contraceptive effect of breastfeeding is the single most important determinant of human population growth rates in traditional societies without access to modern forms of contraception; lactational amenorrhoea is nature's contraceptive. Even today, in many developing countries breastfeeding still prevents more pregnancies than all modern forms of contraception. Afferent neural inputs from the nipple pass via the spinal cord to the hypothalamus, where they cause a local release of beta-endorphin. This acts to depress GnRH secretion, thereby inhibiting pituitary gonadotrophin secretion, ovarian follicular development, ovulation and menstruation. The hypothalamic beta-endorphin release also inhibits dopamine production, resulting in increased pituitary prolactin secretion. The higher the suckling frequency, the more beta-endorphin is released, and hence the longer the duration of lactational amenorrhoea [18].

Today, there are various products on the market worldwide that make it easy to adjust contraception to an individual patient. Such products include intrauterine devices (IUDs), slow-hormone release-implants or vaginal rings and, of course, contraceptive pills.

The risk–benefit ratio of hormonal contraception [oral contraceptives (OCs)] is positive in adolescents as well as in women over 40 years of age if some essential rules are respected. In adolescents, the acquirement of a normal peak bone mass has to be guaranteed by the use of the OC. The dosage of the OC has to be adapted individually to the basic hormonal situation. Ovulation–inhibition contraception cannot be recommended for young girls who have not yet had their first period or are not yet ovulating regularly. In women over 40 years of age, those with contraindications, such as hypertension, obesity, smoking or dyslipidemia, have to be actively excluded. In both age groups, the risk of a correctly indicated OC is inferior to the risk of an unwanted pregnancy [19]. A non-contraceptive benefit of reducing the number of ovulations with OC's is a reduced risk of obtaining certain benign as well as malignant tumours, such as benign breast tumours, uterine fibroids and ovarian cysts. Modern low-dose OCs do not increase the risk of liver cell adenomata or carcinomata. OCs do not influence melanoma. Modern data do not suggest a significantly increased risk of breast carcinoma in OC users. Long-term use of OCs leads to a decreased risk of endometrial and colorectal

carcinomata. Cervical carcinoma is not influenced directly by OC, but probably indirectly through a change in sexual behaviour. There is no increase of vulvar or vaginal carcinoma, even after long-term use of OCs [20, 21].

9.2.7 Ovarian Surgery by Laparoscopy or Laparotomy (Operative Therapy and Follow-up Studies)

Ovarian cysts are a problem frequently seen in gynaecological practice. They affect women of all ages. The ultrasound diagnosis may imply an abnormal finding that requires systematic assessment and treatment. In the USA, the number of women who are hospitalised for ovarian tumours ranges from 160,000 to 289,000 per year. It should be highlighted that 80–90 % of these women will undergo a surgical procedure [22, 23]. It has been estimated that 5–10 % of all women during their lifespan will eventually have surgery to treat an ovarian cyst [23]. It is well known that this entity is more prevalent during the reproductive years and dominated mainly by endometriomas, serous cystadenomas, follicular cysts, corpus luteum cysts and benign teratomas. This distribution of histopathological diagnosis has been confirmed in a study of 641 adnexal tumours in Kiel, Germany [24, 25].

Laparoscopy is considered the gold standard for treatment of benign ovarian cysts and adhesions and the safety of the procedure has been widely demonstrated [24–27]. Compared with traditional surgery by laparotomy, operative laparoscopy is associated with shorter hospitalisation, faster patient recovery, decreased costs, and a lower incidence of de novo adhesion formation [28, 29].

The surgical technique of ovarian cyst excision by laparoscopy differs from traditional surgery performed at laparotomy. It must be performed under intermittent irrigation. Using laparoscopy, most surgeons perform the so-called stripping technique: two atraumatic grasping forceps are used to pull the cyst wall and the normal ovarian parenchyma in opposite directions, thus developing the cleavage plane (Fig. 9.1). After excision of the cyst wall, hemostasis is achieved by using bipolar forceps, CO_2 laser or the harmonic scalpel with ultrasound energy. The residual ovarian tissue is mostly not sutured and the ovarian edges are left to heal by secondary intention [20]. Some authors advocate the placement of sutures to bring together the ovarian edges after enucleation of large cysts to form a normal ovary. It is advisable to use as little bipolar energy or laser as necessary because this may subsequently damage the ovarian parenchyma and the ovarian reserve. This is especially important for patients wishing to become pregnant [24, 25, 30] (Table 9.1, Fig. 9.2). In a recent study, the sizes of the enucleated ovarian cysts (Fig. 9.3) and the histopathological patterns (Fig. 9.4) were evaluated [31]. After menopause we advise to preserve the healthy ovaries till the age of 65; however, there are exceptions. Of course, the patient also presents her views and wishes. Ovariectomy is mostly combined with tube-ectomy.

It has been suggested that invaginated ovarian coelomic epithelium in endometriomas undergoes metaplasia into typical glandular epithelium and stroma [32]. Others have suggested the role of ovarian follicles in the pathogenesis of

Table 9.2 Treatment options for benign ovarian cysts

1. Laparoscopy
(a) Conservative treatment: enucleation of large cysts after aspiration
(b) Drainage and destruction of inner lining using any energy
(c) Drainage, GnRH agonists (12 weeks), second look laparoscopy, vaporisation
(d) Ovariectomy
(e) Adnexectomy
2. Laparotomy
(a) Cyst enucleation
(b) Ovariectomy
(c) Adnexectomy
3. Ultrasound-guided aspiration
(a) In ovarian hyperstimulation syndrome following ART

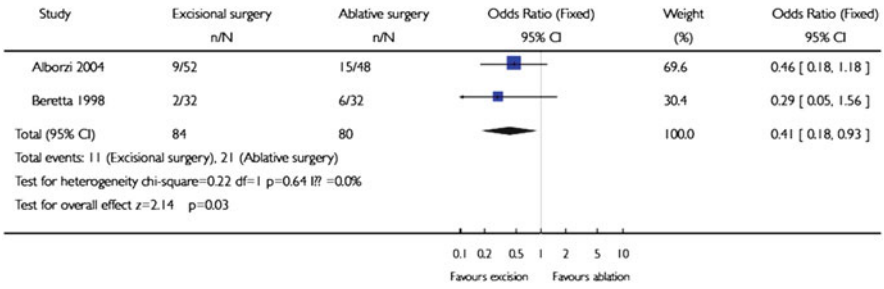

Fig. 9.2 Meta-analysis giving the odds ratio of the recurrence risks of studies comparing ablative versus excisional surgery of ovarian endometrioma. In the excised patients, relapse is substantially decreased ([30], Copyright Cochrane Library, reproduced with permission)

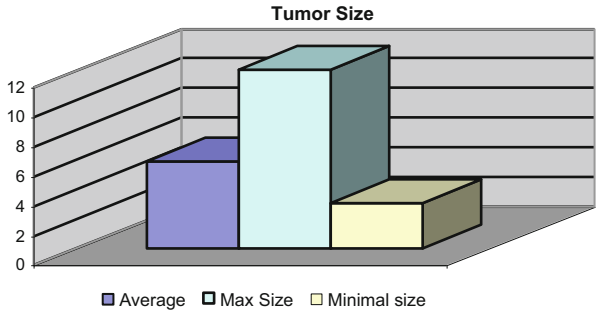

Fig. 9.3 Distribution of sizes of ovarian cyst

chocolate cysts, due to the ability of follicular fluid to induce endometrial cell growth. This theory has been supported by laparoscopic findings of chocolate cysts [33].

The laparoscopic surgical procedure itself has raised concern that cystectomy might not be a tissue-sparing technique and other alternatives should be sought to preserve as much ovarian tissue as possible, especially in women of reproductive age. Women should be offered the best chance of achieving a healthy pregnancy.

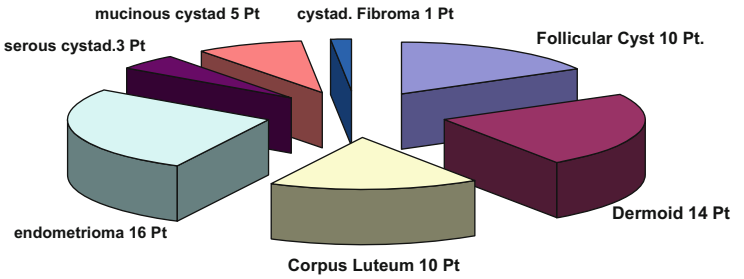

Fig. 9.4 Histopathological pattern of ovarian cyst enucleations

Several authors have addressed this topic using a wide variety of studies designs, with controversial results. One approach was to compare a previously operated ovary to a non-operated one, regarding the response to hormonal stimulation in ovulation induction or the ovarian volume prior to infertility treatment. Damage to the ovarian reserve has been demonstrated after stripping the capsule in the treatment of ovarian endometriomas [34, 35]. In 38 patients who received hormonal stimulation for IVF and ICSI, a reduced number of dominant follicles, oocytes and embryos was found in a previously operated ovary compared to the non-operated side. However, fertilisation rates and good quality embryos were similar from both ovaries suggesting a quantitative damage to the ovarian reserve more than a qualitative one. In a further series of 188 patients with a history of infertility and previous ovarian cystectomy, a reduced follicular response in natural and clomiphene-stimulated cycles in women younger than 35 years was shown [36]. More reassuring findings were found in IVF patients where it was demonstrated that stripping of the ovarian cyst is an appropriate treatment and did not negatively affect the ovarian response to IVF [37]. Cystectomy was found to be ovarian tissue sparing after histological analysis of ovarian cystectomies in 42 women of reproductive age [28].

Electrical energy as part of the routine surgical technique in the management of ovarian cysts has raised some concern regarding damage to surrounding ovarian tissue, thus decreasing ovarian reserve. In a study of 47 patients with previous ovariectomy, ovarian cysts in the remaining ovary were treated using either bipolar coagulation ($n = 21$) or sutures ($n = 26$) to obtain hemostasis. Subsequently, ovarian reserve was studied by measuring basal FSH 3, 6 and 12 months after surgery. The results of the study show that bipolar electrocoagulation of the ovarian parenchyma during laparoscopic removal of endometriotic ovarian cysts adversely affects ovarian function. This can be explained by the destructive effect of bipolar energy on healthy ovarian tissue which is absent when the ovary is sutured [38].

Further consideration was given to the question whether endometriomas should be excised or vaporised/coagulated. A systematic meta-analysis in the Cochrane database shows that excision decreases the risk for relapse by about half (OR 0.41) [39] (Fig. 9.2).

We recently investigated the ovarian reserve biochemically to predict the outcome after assisted reproductive techniques. Ovarian reserve was defined as the quantity and quality of the follicular pool in patients who had previously undergone cystectomy for unilateral or bilateral ovarian cysts. In a systematic literature review, a series of tests was analyzed to assess ovarian reserve. The results of the review show that the basal FSH level is not adequately sensitive to predict poor outcome. The same is true for other parameters, including basal oestradiol, the FSH/luteinising hormone ratio, anti-Müllerian hormone and inhibin-B levels. The clomiphene citrate challenge test (CCCT) has a low sensitivity, but this sensitivity is greater than that of the basal follicle stimulating hormone [40]. Therefore, it was decided to study ovarian reserve as a predictor for outcome in ARTs using the CCCT.

A retrospective analysis was carried out of all patients aged between 18 and 35 years, who underwent previous unilateral or bilateral ovarian cystectomy between January 2004 and October 2005. Enucleation of the ovarian cyst had been performed as previously described [24, 25, 30]. Endocoagulation or bipolar coagulation, incision of the capsule of the cyst using micro scissors and sharp and blunt enucleation without cyst rupture had been carried out. Two atraumatic grasping forceps had been used to pull the cyst wall and the normal ovarian parenchyma in opposite directions. The final pedicle of the cyst, containing most of the vessels, was coagulated with thermal or bipolar energy. The remaining ovarian tissue was coagulated, with borders either sutured or left open. Exclusion criteria were partial or complete oophorectomy and patients currently receiving infertility treatment or ovarian suppression medication.

The CCCT involves the administration of 100 mg clomiphene citrate on days 5–9 and the measurement of FSH concentrations on days 3–5 and 10–11. In patients with normal ovarian reserve, there is a clomiphene citrate dependent rise in FSH. This rise will be suppressed by inhibin-B produced by the follicles. An abnormal test is defined as an abnormally high FSH on day 3 or day 10.

A total of 60 patients were enrolled in the study. All patients were contacted by mail and invited to come to the hospital for an interview. Twenty patients replied and an appointment was scheduled. Two patients refused the test and a further three did not return to have their blood taken. The remaining 15 patients were interviewed at the hospital.

These 15 patients underwent the CCCT. This group was compared to the 60 not taking the CCCT, regarding age, regular/irregular menstrual pattern, parity, infertility, endometriosis, previous ovarian surgery, unilateral/bilateral ovarian cysts and size of the cysts. There were no significant differences in age, menstrual pattern, parity, endometriosis, unilateral/bilateral ovarian cysts and size of cysts between the two groups. Previous infertility was higher in the group taking the CCCT (4/15 26.6 %), compared to the control group (10/60 16.9 %) and previous ovarian surgery was lower in the group taking the CCCT (2/15 13.3 %), compared to the control group (13/60 22.3 %).

In the study group, FSH, LH and oestradiol were measured on day 3–5 and 10–11, as previously described for the CCCT. Basal FSH was 6.36 IU/ml (range

3.7–10.7 IU/ml). After stimulation FSH was 7.32 IU/ml (range 4.9–11.2 IU/ml), indicating a negative CCCT test, because no abnormally high FSH could be observed on day 3 or 10. Therefore, it could be speculated, that these 15 patients had a good prognosis for assisted reproductive technology. In addition, previous ovarian surgery had little or no effect on ovarian reserve in the study group, but previous ovarian surgery was substantially decreased in this group (2/15 13.3 % versus 13/60 22.3 %).

These results may indicate that ovarian cystectomy using microsurgical techniques does not change ovarian reserve or decrease pregnancy rates in subsequent assisted reproductive techniques.

9.2.8 Should the Ovaries Be Conserved at the Time of Surgery After Menopause, Beyond the Age of 45, or Be Taken Out at Hysterectomy?

Ovarian conservation up to the age of 65 benefits long-term survival for women at an average risk of ovarian cancer when undergoing hysterectomy for benign disease. The role of prophylactic oophorectomy at the time of hysterectomy has long been a controversial issue. It is thought that the role of the ovary is for reproduction and hormone production and when each of these functions ceases the ovary serves no purpose other than generating mischief. It is also known that ovaries produce other essential cytokines important for the continuation of life; on the other hand, even unsuspicious-looking ovaries may develop ovarian cancer. Therefore, only an individual decision tailored to the patient's family history, personal history, previous surgery, present status and wish can be taken [41]. A calculated increase in mortality associated with oophorectomy in the absence of oestrogen therapy derives almost entirely from an enhancement of coronary heart disease; however, the validity of the findings can easily be questioned. Nevertheless, the authors have shown that even if no coronary heart disease increase is seen with oophorectomy, there remains no demonstrable advantage to the procedure in terms of longevity. In the already complex discussion regarding oophorectomy in perimenopausal women, the issue of potential effect upon mortality must be brought up, because it has been shown that patients without oophorectomy live longer. It is our responsibility as physicians and patient advocates to continuously challenge new findings with a critical eye, a reasoned perspective and whenever possible a smattering of imagination. Regarding the decision whether to take out the ovaries or not in females beyond the reproductive age, it seems certain that beyond the age of 65 the ovaries should be taken out in cases of hysterectomy as malignant transformations seem to be further increased from that age onwards. Before the age of 65, the decision whether to leave the ovaries in situ or not remains a decision between the doctor and his patient.

9.3 Factors Likely to Affect the Choice of Therapy

9.3.1 Infertility

If ovarian surgery for cysts, fibromas, adhesions or adnexal tumours is indicated in infertility patients, the major goal of any surgical intervention is to preserve as much undamaged ovarian tissue as possible. Many comparisons of laparoscopic ovarian cyst enucleation versus minilaparotomy or laparotomy have been carried out and the outcome clearly shows that no matter what type of ovarian surgery is performed, it should be with ovarian tissue conservation. For individual patients and their reproductive outcome, the size of abdominal incision, laparoscopy, laparotomy or even vaginal surgery seems to be less important than ovarian functionality. Therefore, every surgeon should apply the method he can best perform with the goal of preserving as much ovarian tissue as possible.

It is generally thought that laparoscopy is superior to laparotomy in the management of benign adnexal cysts as it is associated with shorter hospital stay, less post-operative pain, a better cosmetic outcome and a faster recovery. However, minilaparotomy or the vaginal approach also requires no sophisticated equipment or very specialised training but utilises basic, classical techniques and is a patient-friendly technology. In situations where laparoscopic ovarian cyst enucleation is technically not possible, laparatomy is still a safe technique.

A comparison of the laparoscopic and laparotomic approach regarding outcome, infection, pain and consecutive fertility revealed an advantage of laparoscopy over laparotomy, especially in terms of perioperative morbidity and post-operative pain [42]. Operating time and intraoperative complications were similar for both approaches. At present, laparoscopy should definitely be considered the gold standard for the management of benign adnexal disease. Intraoperative spillage can be avoided in both laparoscopy and laparotomy. The transvaginal resection of ovarian cysts is only performed by some specialists [43].

Tubal pathology in benign cases, such as ectopic pregnancies, sacto or pyosalpinx, should be surgically treated without lacerating or extirpating the ovary in women of reproductive age. Adnexectomy in cases of ectopic pregnancy is usually not indicated and must be left as tubectomy in specific cases [44].

9.3.2 Ovarian Dysfunction and Amenorrhoea

During the reproductive age, the normal cyclic function of the ovary is characterised by recruitment of the follicular cohort, selection of the dominant follicle, ovulation with consecutive corpus luteum formation, corpus luteum function and the final regression of the corpus luteum. In this cycle, the central nervous system, the limbic system, the hypothalamus, the hypophysis and the ovary are partners. Disturbances of these interactions lead to ovarian dysfunction with follicular maturation disturbances, inadequate ovulation and inadequate functioning of the corpus luteum. The resulting bleeding abnormalities (poly-, oligo- or

amenorrhoea and also pre, intra and post-ovulatory bleeding) have to be treated separately.

The 1973 WHO classification of ovarian dysfunction still gives the best general idea of diagnostic techniques and therapy [45]. According to this classification, amenorrhoea may be the consequence of an ovarian insufficiency (group 2b), an anatomically caused amenorrhoea (group 4), hyperprolactinemia (groups 5 and 6) or a non-increase in gonadotropins (group 1). The pathophysiology reveals a lack of stimulation of the hypophyseal gonadotropin secretion. Groups 3 and 7 comprise patients with hypergonadotropic ovarian insufficiency.

Anovulation can be defined as absence of ovulation without follicular rupture and no follicles persisting after an initial period of growth. In primary anovulation, ovulation has never commenced. In secondary anovulation, there is an ovulatory period, followed by subsequent anovulation. In anovulation, a peak in LH and FSH is missing and there is a continuous rather low oestradiol and progesterone production. Cyst formation in the ovary frequently prevents the development of ovulatory follicles by compression of the ovarian cortex [25]. In anovulation, the basal body temperature curve is constant, without rise. Using ultrasound, absence of growth in one of the ovarian follicles during the cycle can be observed. Also, there is often an associated atrophic endometrium.

Anatomical problems involved in follicular growth in PCOS can be operated using laparoscopic surgery by a large wedge resection or follicular puncture using a monopolar needle. Ovarian drilling creates large holes which do not allow follicular fluid to continue to accumulate in the unruptured follicles. Alternatively, anovulation can also be treated by endocrine stimulation, such as clomiphene, HMG/HCG or FSH/HCG stimulation, under the continuous observation of oestradiol and progesterone levels and careful ultrasound measurements of follicular growth. In anovulation with single or double-chamber ovarian cysts, the cyst is resected entirely and the ovarian bed is carefully coagulated, if necessary. Ultrasound denaturation or laser coagulation may also be applied. Ovarian cysts and endometriomas have to be totally resected and removed from the abdomen in an endobag. Unilateral or bilateral ovariectomy is advisable in cases of borderline ovarian lesions, bilateral adnexectomy, hysterectomy, omentectomy and lymphadenectomy in cases of ovarian cancer [46].

9.3.3 Benign and Malignant Ovarian Transformations

Benign ovarian transformations are treated by laparoscopy and have been discussed in Sect. 9.2.3. The incidence of ovarian cancer is influenced by country of origin, race and age. The highest percentages are observed in industrialised, the lowest in non-industrialised countries. Multiple factors are discussed for the development of ovarian cancer comprising environmental factors, rubella exposure, coffee, fat, vitamin consumption, number of children, oestrogen replacement therapy, oral contraceptives, tubal ligation, hysterectomy, BRCA1 and 2 mutations and others.

A continuous oral contraceptive uptake may reduce the risk of developing ovarian cancer. The safety of long-term menopausal hormonal replacement therapy is debated. Even tubal ligations and hysterectomies are said to have a protective effect against borderline lesions and ovarian cancer. The most frequent ovarian cancer is the epithelial ovarian cancer compared to the non-epithelial ovarian cancer = germ cell tumours. Radical surgery, including lymphadenectomy, is the treatment of choice for ovarian cancer, followed by chemotherapy, immune therapy and anti-hormonal therapy.

Preoperative investigations include expert ultrasound examination, abdominal and vaginal; CA125 determination, MRI, bone scan or CT scan. Karyotypes should be obtained in all premenarchal girls with ovarian tumours as tumours often arise from dysgenetic gonads.

9.3.4 Polycystic Ovarian Syndrome

The PCO syndrome cannot be defined as a unique entity as various heterogeneous forms of morphology and clinical symptoms are described. The common endocrine increased LH concentrations in serum and a shift of the LH/FSH ratio towards LH are known. Further characteristics are the hyperandrogenism and hyperinsulinemia following an increased peripheral insulin resistance. This disease has been the subject of multiple genetic studies and is fairly well known at the present time. Chronic anovulation, amenorrhoea, hyperinsulinemia and increased insulin resistance are often treated with weight-loss strategies; metabolic treatment with metformin, clomiphene, GnRH agonists and antagonists as well as laparoscopic ovarian drilling. The genetically caused enzyme deficiencies of the adrenal androgen biosynthesis are not yet fully clarified.

With a prevalence of more than 5 %, PCOS is one of the most common diseases in young women. It is defined by the combination of oligo or amenorrhoea, clinical or biochemical hyperandrogenism and the exclusion of pituitary, adrenal or other ovarian disorders.

Polycystic ovaries PCO are associated with the syndrome but are not very specific for the diagnosis. The most common complaints are hirsutism, infertility and obesity although even very slender patients can be affected. Many patients are found to be insulin resistant, associating PCOS with the metabolic syndrome and implicating a risk to develop its sequelae. The consideration of insulin resistance has established insulin sensitisers as a new option for the treatment of PCOS. The older concept of wedge resection or ovarian drilling to remove mechanical compression of normal ovarian tissue by fluid-filled cysts and edematous tissue is still considered a method of treatment.

Laparoscopy offers the possibility of releasing the ovarian capsule and the retended fluid by ovarian drilling which can be performed with monopolar or bipolar electricity, laser or ultrasound. Ovarian drilling is a surgical treatment not accepted by everyone. We personally find it well indicated in ultrasound images with typical “string of pearls” cysts [25]. The number of holes to be drilled

(between 5 and 30 on each side) depends on the size of the ovary and the number of follicular cysts. Pure monopolar cutting current with 80 W should be used for the drilling. Careful continuous rinsing with Ringer's lactate prevents post-surgical adhesion formation.

Metformin increases insulin sensitivity, reduces glucose uptake and inhibits glucose synthesis. In obese women, metformin supports weight loss and improves menstrual cyclicity with increased ovulation rates. With metformin therapy, serum testosterone decreases and symptoms of hirsutism significantly improve. In ovarian stimulation, metformin improves response to clomiphene or FSH with increased pregnancy rates. Some studies suggest a positive effect of metformin, even on early pregnancy, leading to reduced abortion rates. Metformin should be taken for at least 3 months at a dose of 2–3 × 500 mg or 2 × 850 mg daily. This sequence is especially recommended for obese patients with peripheral insulin resistance although even lean patients can benefit from this therapy.

Various combination treatments, including oral contraceptives and metformin as well as ethinyl oestradiol and metformin, have been proposed. A significant effect of the combination of oral contraceptives and metformin together with androgens and SHBG has not been found. However, the combination of metformin with the intermittent application of ethinyl oestradiol and cyproterone acetate seems to improve the symptoms of androgen excess in cases of PCOS. As metformin is currently not yet approved for the treatment of PCOS, it is not given on a wide scale in Germany. The complex and differential diagnosis of PCOS requires a close interdisciplinary cooperation of gynaecologists, endocrinologists and dieticians. Surgical treatment with ovarian drilling and wedge resection stands side by side with endocrine treatment and the necessary weight loss in obese patients. Molecular genetic findings on the origin of PCOS have not yet led to any practical therapeutic treatment modalities but have given some insight into the genetic background of the disease [47].

9.4 Summary and Conclusions

9.4.1 Infertility, Ovarian Stimulation Within ART

It is generally thought that laparoscopy is a leading technique in the management of benign adnexal cysts as it is associated with shorter hospital stay, less post-operative pain and faster patient recovery. Studies comparing conventional laparotomy and laparoscopy for the management of benign adnexal cysts report significant differences in favour of laparoscopy in terms of post-operative pain, length of hospital stay and post-operative recovery of the patient. Ovarian stimulation and follicular puncture increase the ovarian metabolism and thus may lead to an earlier termination of growth of oocytes from immature follicles in comparison to non-treated ovaries. Ovarian stimulation itself is central to any artificial reproductive technology as it allows the possibility of injecting or pairing metaphase II oocytes with the corresponding spermatozoa or single sperm. If contraception and consecutive anovulation have taken place for 20 years, as the patient approaches

menopause the number of remaining follicles with the potential for ovulation is increased [41].

9.4.2 Ovarian Dysfunction, Amenorrhoea and Contraception

According to the WHO classification for ovarian insufficiency and amenorrhoea, only groups 2, 4 and 5 are difficult to treat. Patients in groups 2 and 5 are usually responsive to ovarian stimulation; group 5 patients should be given dopamine agonists after exclusion of a hypophyseal tumour. Patients in all other groups can be stimulated for ovulation induction. The patients in group 3 are the real problem.

9.4.3 Ovarian Surgery, Benign and Malignant Transformations

Ovarian surgery in women of reproductive age requires excision only in cases of benign proliferative swellings and cyst formations resistant to endocrine therapy. In cases of malignant transformations, a resection of the gonads is required. In malignant transformations, a rapid and swift spread within the local lymphatic drainage takes place. For this reason any malignant transformation of the ovary requires radical surgical resection including both ovaries, uterus, omentum and the pelvic and paraaortic lymph nodes. The spread of ovarian cancer with small local lesions in the ovary (stage IA) into the paraaortic lymph nodes, even with only one positive lymph node, transforms the stage to a FIGO stage IIIB which requires additional chemotherapy. Stage IA can be cured by performing the necessary radical surgery alone. Laparoscopic ovarian surgery seems to be the method of choice in benign cases, particularly as surgery can be performed under higher magnification. Laparoscopic surgery should only be performed after adequate training, with the necessary care and surgical skill. If possible, adhesion prevention should be carried out at the end of the procedure.

9.4.4 Polycystic Ovary Syndrome and Conservation of Ovaries at the Time of Hysterectomy

Equivalent therapeutic options for the treatment of PCOS are laparoscopic ovarian drilling and hormonal therapy, such as clomiphene or FSH combined with metformin or ethinyl oestradiol plus cyproterone acetate combined with metformin. The main argument **in favour** of taking out the ovaries at the time of hysterectomy before the age of 65 is absence of the possibility of malignant transformation. The main argument **against it** is an increased risk for death through coronary heart disease and infarction. While there is an ongoing discussion whether or not the ovaries should be removed together with the uterus in younger postmenopausal women, there seems to be an agreement that in women 65 years and older the

ovaries should be taken out because the risk of malignant transformations seems to further increase.

9.4.5 Preservation of Fertility

As ovulation plays a central role in female well-being and reproductive life, much effort is taken to preserve fertility in patients at risk of losing ovarian function due to potentially sterilising therapies. While the cryopreservation of embryos after ART is quite effective, results obtained with different oocytes cryopreservation techniques have been disappointing, particularly those obtained with slow-cooling procedures. A rapid flash-freezing technique known as vitrification has re-kindled interest in oocyte freezing. Certain modifications, especially minimising the volume of storage fluid, have resulted in markedly improved pregnancy rates with vitrified thawed oocytes [21, 48]. An increasing number of well-trained and educated professional women are planning pregnancy at advanced maternal age. The techniques discussed above may be used to postpone pregnancy without increasing the genetic risks associated with advanced maternal age.

9.4.5.1 Fertiprotect

Radiological treatment and chemotherapy often leave females with POFafter a successful cancer treatment. This can be prevented in many haematopoietic and extragenital malignancies by pre-cancer treatment with oocyte, embryo or ovarian tissue freezing, and in genital as well as other cancers sometimes by transposition of ovaries up to the pelvic brim out of the field of radiation. Fertiprotect is a group of European fertility experts working together with oncologists to preserve the fertility of females and males in specific cases.

9.4.5.2 Ovary-Conserving Surgery

In patients of reproductive age with benign ovarian tumours, particular attention should be paid to inflict as little damage as possible to the ovary during the operation in order to preserve as much ovarian fertility and follicular reserve as possible. Therefore, laparoscopic surgery has become a widely accepted standard. However, in cases of malignancy, immediate radical gonadectomy, hysterectomy, omentectomy or lymphadenectomy may have to be performed. There is some consensus that conservation of ovaries at the time of hysterectomy may be preferable for patients up to 65 years of age. However, a family history of malignant ovarian tumours, the patient's genetic disposition and the patient's wishes have to be taken into account before a decision can be made [41, 49].

9.5 Future Outlook

Molecular genetic mechanisms of ovarian malignant transformations will allow the diagnosis of ovarian cancer at an early stage. A combination of microarray technology, biochemical investigation, improved ultrasound imaging and computer software will allow a risk calculation and therefore make screening programs possible. Surgery will only be performed laparoscopically. Pelvic and paraaortic lymph nodes can be assessed by laparoscopy. Human ovaries with follicular development and oestrogen/progesterone production will always be in the focus of assisted reproductive techniques. However artificial gamete production derived from either somatic or embryonic pluripotent stem cells will become available a pregnancy will be able to be started without oocytes of the individual patient. Donor oocytes can already be fertilised in vitro and embryos transferred into the uterine cavity of a patient without ovaries under exogenous hormonal stimulation.

9.6 Focus

- All dominant preovulatory follicles are already selected for the pool of germ cells at 24 weeks of gestation.
- Ovulation stands in the centre of female well-being and reproductive life.
- Ovarian stimulation within ART has to be performed knowledgeably, carefully and appropriate to the patient's endocrine reaction. Damage to the ovary by ovarian stimulation, which can easily be assessed by the hormonal reaction of the patient, has to be prevented. The ovarian overstimulation syndrome should be avoided.
- Contraceptive methods without ovulation inhibition are preferable. If ovulation inhibitory methods in the form of mono-, bi- or triphasic hormonal tablets are applied, a continuous intermediate ovarian hormonal production monitoring should be carried out every 2–3 years. If the patient does not menstruate in the contraceptive pause, she should cease any anti-ovulatory treatment. The cause of amenorrhoea has to be treated according to the final diagnosis. Ovarian surgery for benign alterations has to be performed with the utmost care by laparoscopy; in only a few cases is laparotomy indicated. As much as possible of germ cell production should be preserved. Ovarian cysts have to be carefully enucleated and the remaining regenerative tissue should only be coagulated using monopolar electricity in cases of severe bleeding or when the cyst has not been taken out totally.
- Should an ovarian malipnoma be encountered, immediate radical gonadectomy, hysterectomy, omentectomy and lymphadenectomy have to be performed.
- It is agreed that conservation of ovaries at the time of hysterectomy is preferable for the patient up to the age of 65; however, all signs of malignancy in the family and in the patient have to be carefully considered before such a decision is taken.

- The PCOS is genetically well defined. Equal treatment options include laparoscopic ovarian drilling and metformin combined with various contraceptive regimens.
- In patients of reproductive age with benign ovarian tumours, particular attention should be paid to inflict as little damage as possible to the ovary during the operation in order to preserve as much ovarian fertility and follicular reserve as possible.
- Artificial oocyte production may play an important role within human reproduction. Ethical comments to this statement are not given in this chapter. Pluripotent stem cells can be derived from embryos or somatic cells.

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Ovulation Induction: Adverse Effects

10

Joseph G. Schenker

Ovulation dysfunction is one of the most common causes of reproductive failure in infertile couples. The prevalence of this disorder in infertile women is about 30–40 %.

In order to appreciate the methods of inducing ovulation, a basic understanding of the endocrinology of the menstrual cycle is essential. Failure of synthesis or release of hypothalamic LHRH or the gonadotropins FSH and LH according to the normal pattern of the menstrual cycle will result in failure of ovulation with or without cessation of menses.

10.1 Principles of Ovulation

1. To induce ovulation, FSH is necessary in early phase of cycle to recruit and select follicles.
2. For growth and maturation, both FSH and LH are necessary and usually take 4–6 days.
3. Daily increase in follicular diameter, during the active phase, is by 1.5–2 mm/day.
4. Serum estradiol levels should be about 200–300 pg/ml per growing follicle of 16 mm.

J.G. Schenker (✉)
Department Obstetrics Gynecology, Hadassah Medical Centre, Hebrew University, Jerusalem, Israel
e-mail: schenker@cc.huji.ac.il

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10.2 Clomiphene Citrate

The first clinical trials of ovulation induction were carried out in 1961 with MER-25, a close structural analog of clomiphene, Greenblatt et al. [1] were the first to report the successful induction of ovulation and pregnancies following clomiphene therapy. Clomiphene is chemically related to chlorotrianisene (TACE), which is a weak estrogen. Structurally, it is related to the potent synthetic estrogen diethylstilbestrol. Clomiphene may exist in either the *cis* or the *trans* configuration, the former being significantly more potent. Structural similarity to estrogen allows Clomiphene citrate (CC) to bind to estrogen receptors (ER) throughout the reproductive system. However, in contrast to estrogen, CC binds nuclear ER for an extended period of time and ultimately depletes ER concentrations by interfering with the normal process of ER replenishment

Clomiphene citrate remains the first-line therapy for ovulation induction in anovulatory patients who are not estrogen deficient. It is a simple, cheap treatment, almost devoid of side effects, and yields ovulation in 70 %, pregnancy in 30 %.

Patients refractory to standard CC treatment may ovulate in response to combined treatment regimens: Clomiphene/hCG, Clomiphene/Estrogens, Clomiphene/Corticoids, Clomiphene/Hmg, and Clomiphene/Metformin.

10.2.1 Complications

Multiple Gestations

Ovarian hyperstimulation syndrome (OHSS): Mild and moderate are common, severe is rare [2].

Congenital Anomalies: There is no evidence that CC treatment increases the risk of birth defects.

Cancer: Some reports demonstrated increase incidence of breast cancer and borderline ovary tumors [3, 4].

10.3 Letrozole: Aromatase Inhibitors [5]

Letrozole may be effective alternative to Clomiphene Citrate. It less inhibits estrogen synthesis, thereby causing enhanced GnRH pulsatility and consequent FSH and inhibin stimulation. This results in normal or enhanced follicular recruitment without the risk of multiple ovulation and OHSS. Letrozole has a very short half-life and, therefore, is quickly cleared from the body. For this reason, it is less likely to adversely affect the endometrium and cervical mucus. Combination of letrozole and FSH enhances follicular recruitment while reducing the amount of FSH needed for optimal stimulation.

10.3.1 Side Effects

Similar to Clomiphene, most of these are minor and temporary in nature. They include hot flashes, blurred vision, nausea, bloating sensation, and headache. Serious side effects are rarely seen. One of the side effects is the possibility of multiple pregnancy. Long-term use of letrozole is not recommended.

10.4 Hyperprolactinemia

Hyperprolactinemia of different etiology results in anovulatory cycles. In 1983, Ben-David and Schenker [6] suggested a possibility of a transient preovulatory rise in PRL levels.

That lasted for 2–3 days and coincided with estradiol (E) peak. In their study, 94 % of patients showed as this transient rise and 40 % conceived within 3 months of bromocriptine treatment.

10.5 Bromocriptine

Bromocriptine is an ergot medication that works by helping to restore the balance of a certain natural substance (dopamine) in the brain. It also prevents the release of certain hormones (growth hormone and prolactin). Bromocriptine can lower these hormone levels, but it does not cure the causes of the increased levels.

10.5.1 Side Effects

Nausea, constipation, dizziness, drowsiness, loss of appetite, vomiting, diarrhea, headache dizziness, syncope and symptomatic hypotension.

10.6 Other Dopamine Agonists

Several other compounds have been shown to decrease prolactin levels by binding with dopamine D2 receptors with greater affinity than bromocriptine.

The advantage of most of the newer dopamine agonists is the convenience of once a day dosage due to longer half-life.

10.6.1 Pergolide

Pergolide is a synthetic ergoline which lacks the peptide side chain of bromocriptine. It has been used in treatment of microadenomas for up to 5 years without any significant side effects or complications.

Many studies have shown the effectiveness and tolerance of pergolide over bromocriptine. It was found to be as efficacious as bromocriptine in decreasing prolactin levels, reducing galactorrhea and breast tenderness and resumption of normal menses.

10.6.2 Cabergoline

Cabergoline is a long acting dopamine receptor agonist with high affinity of D2 receptors and low affinity for D1, alpha adrenergic or 5HT and serotonin receptors. The estimated half-life is between 63 and 65 h, which is responsible for the prolonged prolactin lowering effect. It was found that cabergoline decreased prolactin levels more rapidly after a single dose as compared to bromocriptine.

10.7 Replacement Therapy using Gonadotropins

LH and FSH from animal sources were obtained in the 1930s. However, in clinical practice, it is only human gonadotropins, not available until the 1950s, which have proved clinically useful.

10.7.1 Heterologous Gonadotropins

The heterologous gonadotropin preparation, which has been most widely used, is equine serum-gonadotropin (pregnant mares' serum, PMS) being placental in origin. Its activity is largely follicle stimulating with insignificant luteinizing activity. In large doses, it may produce ovarian hyperstimulation, but its biggest disadvantage is its ability to produce antihormones with cross-reaction to human gonadotropins [7].

10.7.2 Human Pituitary Gonadotropins

Human pituitary gonadotropin (HPG) consists essentially of a mixture of FSH and LH with a predominantly FSH action extracted from cadaveric pituitaries. The disadvantage of the biological preparation of HPG was its short supply [8].

10.7.3 Human Menopausal Gonadotropins [9]

The gonadotropins FSH and LH are excreted in urine in a bioactive form and this excretion rises rapidly after the menopause with the reduction of ovarian steroid negative feedback. Thus, menopausal urine has proved clinically the most useful source of gonadotropins [9]. Human menopausal gonadotropins (Hmg) has a

predominantly FSH action with LH supporting effect and is commercially available as Pergonal (Serono and Searle) and Humegon (Organon).

Hmg is not usually successful alone as this therapy simply stimulates follicular development and an ovulatory surge of LH is required; this may be provided by Human chorionic gonadotropin (hCG).

The biological properties of hCG are very similar to LH, being capable of inducing ovulation after a follicle has been developed, converting it to a corpus luteum.

10.8 Recombinant Human FSH [10])

Recombinant DNA technologies were introduced in the early 1990s for the production of recombinant human FSH (r-hFSH) with the insertion of alpha and beta-FSH subunits into genetically engineered mammalian cells. The advantage of this technology is that the manufacture of r-hFSH is independent of urine collection, ensuring the consistent availability of biochemically very pure FSH preparation with minimal batch to batch variation.

There is some evidence that r-hFSH preparations have clinical advantages over Hmg or highly purified uhFSH. Several studies have demonstrated significant advantages for r-hFSH in terms of efficacy as assessed by the number of oocytes retrieved as well as efficiency judged by FSH consumption and the duration of treatment. Pregnancy rates were marginally higher after r-hFSH than after u-hFSH.

10.9 GnRH [11]

The main objectives of controlled ovarian stimulation (COH) for Assisted Reproductive Techniques (ART) are: hypophyseal activity suppression, multiple follicle growth stimulation, and ovulation induction. By suppressing hypophyseal activity, it is possible to prevent untimely LH surge and allow the appropriate development of the leading follicle.

10.9.1 GnRH-Agonist

GnRH-agonist (GnRH-a) administration is used for patients undergoing IVF. These properties of GnRH-a have been applied in clinical practice with two main regimens of administration.

10.9.2 The Long-Term GnRH-a Protocol

Both pituitary and ovarian desensitization are induced by GnRH-a administration in the early follicular or midluteal phase of the cycle preceding the planned IVF. Once

desensitization is obtained, ovarian stimulation with gonadotropins is started and GnRH-a injection is continued until hCG is administered. In clinical practice, the long-term protocol is the most traditional and widely used regimen, probably because it is more convenient for programming.

10.9.3 The Short-Term GnRH-a Protocol

This regimen takes advantage of the initial rise (flare-up) of serum gonadotropins on follicular recruitment and of the subsequent pituitary desensitization induced by daily agonist administration. Gonadotropin administration is started in the early follicular phase. Several adjustments to this protocol have been suggested: a shorter period of GnRH-a administration, for 3 days (ultrashort protocol) or for 7 days, on the assumption that suppression of the endogenous LH surge may be obtained through a very short course of GnRH-a administration.

10.9.4 GnRH Antagonists

In initial clinical studies, GnRH antagonists were used to prevent a premature LH surge during the menstrual cycle and, subsequently, during ovarian stimulation for IVF. GnRH antagonists are synthetic analogs of GnRH that compete with endogenous GnRH for pituitary binding sites. Clinical advantages of GnRH antagonists over GnRH agonists are the absence of the initial stimulation of gonadotropin release (flare-up effect) and, as a consequence, a more direct, immediate and reversible suppression of gonadotropin secretion, which allows their use without the need for a desensitization period.

There are two regimens using GnRH antagonists.

Multiple-Dose GnRH Antagonist Administration. In this protocol, daily injections of low-dose antagonist are given from day 6 of ovarian stimulation using exogenous gonadotropins, which is when multifollicular development and estradiol secretion may trigger an endogenous LH surge.

The optimal daily dose is 0.25 mg. The short half-life of the antagonist with this dose requires a daily administration up to the time of hCG administration. Indeed, this dosage is able to adequately prevent the endogenous LH surge before hCG administration and simultaneously maintain a residual basal LH secretion compatible with a high rate of estradiol secretion, mature oocyte collection, and pregnancy.

Single-dose GnRH antagonist administration. The injection of a single and large dose of GnRH antagonist in the late follicular phase has proved to be effective in postponing the spontaneous LH surge.

10.9.5 Advantages of GnRH Antagonists Over GnRH-a in ART

1. Short, simple, and convenient method of stimulation which is well tolerated by the patient.
2. The antagonists are safer as there is:
   - No initial flare-up
   - No symptoms of estrogen deprivation
   - Minimal local reactions
   - Decreased risk of OHSS.
3. Immediate reversibility.
4. Reduced dose of gonadotropins.
5. Clinical results of IVF cycles are comparable.
6. Decrease in the overall cost of treatment.

The main complications of ovarian stimulation are OHSS and Multiple Pregnancies.

10.10 Ovarian Hyperstimulation Syndrome [12]

OHSS is characterized by massive transudation of protein-rich fluid (mainly albumin) from the vascular space into the peritoneal pleural and to a lesser extent to the pericardial cavities. The intensity of the syndrome is related to the degree of the follicular response in the ovaries to the ovulation inducing agents. OHSS is still a threat to every patient undergoing ovulation induction.

The following are two types of severe OHSS:

(I) Early, which occurs in response to hCG trigger within 5–7 days of ovulation;
(II) Late, which is caused by the rising hCG hormone levels produced by the placenta in conception cycles.

10.10.1 Classification of OHSS

Schenker and Weinstein [2] divided OHSS into three main categories—mild, moderate, and severe syndrome.

10.10.1.1 Mild Hyperstimulation

Chemical hyperstimulation is a very common accompaniment of ovulation induction. The mild form of OHSS presents as a sensation of abdominal heaviness, tension, swelling, and pain. The physical findings are bilateral ovarian enlargement by multiple follicular and corpus luteum cysts; the ovaries may be up to 6 cm in diameter. In recent years, mild hyperstimulation has become more common with superovulation in ovulatory women participating in the various kinds of assisted reproduction programs. Occasionally, the cyst may rupture or undergo torsion. This often presents a difficult problem in the differential diagnosis between a ruptured cyst, torsion of adnexa, and an ectopic pregnancy.

10.10.1.2 Moderate Hyperstimulation

In cases of moderate hyperstimulation, the abdominal discomfort is more pronounced. Gastrointestinal symptoms, such as nausea, vomiting, and (less frequently) diarrhea, are present. There is some weight gain and an increase of abdominal circumference. The ovaries are enlarged to 12 cm in diameter, and some ascitic fluid is detected by ultrasonography. Most patients will have mode OHSS within 10 days of hCG administration—early OHSS. In nonconception cycles, the symptoms may appear later due to placental secretion of hCG, especially in multiple gestation—late OHSS. OHSS is a self-limiting process in nonconception cycles, the symptoms disappear by onset of menstruation, but regression of the ovarian can take 2–4 weeks and sometimes even longer.

10.10.1.3 Severe Hyperstimulation

Severe OHSS is a serious iatrogenic complication of ovulation induction in an otherwise healthy woman. The clinical manifestations may include pleural effusion, pericardial effusion, hypovolemia, impairment of renal function, electrolyte imbalance, disturbance in liver function, thromboembolic phenomena, shock, tension ascites, and adult respiratory distress syndrome (ARDS).

The condition of a patient with severe OHSS improves within several days when she is correctly treated, and when conception does not occur. The large ovarian cysts gradually subside after the abrupt appearance of clinical symptoms of hyperstimulation. The presence of ascites is a major sign of the capillary leak phenomenon present in OHSS. There is a direct connection between the intensity of capillary permeability and the severity of OHSS, as has been shown in our experimental model intraperitoneal pressure exceeds the normal intraluminal pressure of the abdominal vena cava, the inferior vena cava is compressed, and blood flow in the interior vena cava is reduced. During these pathological changes, there is reduced preload to the heart, leading to decreased cardiac output and impairment of renal and respiratory function.

The most serious complications of OHSS are thromboembolic phenomena, both arterial and venous. Thromboembolic events on arterial side were the common cause of death. The mechanism of thromboembolism in the course of OHSS mainly the arterial one were explained by us as result of increased permeability of blood vessels in response to excessive vasoactive substances of ovarian origin, and vasoconstrictive effects of some other agents of ovarian origin, which lead to hemoconcentration and hypovolemia with resultant arterial hypotension gonadotropin administration, increased supraphysiological concentrations of 17β-estradiol following ovulation induction, which may be a risk factor in patients with inherited thrombophilias. Arterial events are predominantly cerebrovascular accidents, usually occurring concurrently with the onset of OHSS. Venous thromboses occur several weeks later and are mostly reported in unusual yet specific sites such as large veins of the upper extremities and neck.

Hepatocellular and cholestatic changes have been noted with and without conception. Several factors may account for these changes including increased estrogen levels and increased vascular permeability.

Severe OHSS is characterized by an extraparenchymal restrictive type of pulmonary dysfunction, attributed to intra-abdominal or pleural fluid accumulation, which limits descent of the diaphragm and expansion of the thoracic cage. This may induce uncoordinated lung ventilation and atelectasis with subsequent ventilation–-perfusion mismatch and hypoxemia. The clinical picture may deteriorate further because of pulmonary infection, pulmonary thromboembolism, or ARDS, all of which have distinct clinical, radiographic, and blood gas characteristics [13].

Hypoalbuminemia, a well-established feature of OHSS, is caused by leakage of albumin to the third space we determined globulin concentrations in the plasma and ascitic fluid of patients with severe OHSS from the time of admission until convalescence. Our studies demonstrated severe OHSS are at increased risk for infection due to leakage of gamma globulins from intravascular space [14].

10.10.2 Incidence

The incidence and severity of OHSS vary with the different clinical conditions in which ovulation is induced in anovulatory patients or ovulatory patients hyperstimulated and treated by assisted reproductive technology. In anovulatory women treated with different preparations for induction of ovulation, the incidence of mild hyperstimulation is 5–10 % of cycles. The incidence in women treated by assisted reproduction is 2–4 % of moderate OHSS and 0.1–0.5 % of severe OHSS.

10.10.3 Risk Factors

Several risk factors were reported to be associated with OHSS: young age (<35 years), polycystic ovary-like patients, asthenic habitus, pregnancy, and hCG luteal supplementation. Different protocols for ovarian stimulation in ART cycles affect the incidence and the severity of the syndrome. Ovarian stimulation results in high serum estradiol (E), multiple follicles (>35), and ultrasonic ovarian "necklace" sign. Data from sequential ultrasonographic measurements of follicles during induction of ovulation show a strong positive correlation between the total number of follicles (all sizes) and the occurrence of OHSS. Higher number of immature follicles (under 12 mm in diameter), small follicles (12–14 mm), and large follicles (>18 mm) were observed on the day of hCG administration in patients who developed OHSS.

Women with PCO disease are at increased risk of developing OHSS; therefore, it is of primary importance to diagnose PCO disease before induction of ovulation.

In spite of this data, there are no clear predictive risk factors for the development of OHSS. Stepwise logistic regression showed that early OHSS was predicted by the number of oocytes retrieved and the E2 concentration on the day of hCG administration. Late OHSS was predicted by the number of gestational sacs on ultrasound after embryo transfer but not by the number of oocytes or E2.

10.10.4 Pathogenesis of OHSS

There is a continuous effort to find the exact factors responsible for the increased vascular permeability, which was shown in our experimental model such as histamine, serotonin, prostaglandins, and prolactin, and variety of other substances were implicated in the past. However, only scant data support an important role for any of these factors.

The following factors were studied:

Histamine. It was found in animal model that OHSS could be blocked in rabbits by administration of antihistaminic preparations. In animals treated with antihistamine, a more rapid regression of the hyperstimulated ovaries was observed than in a control group. Although these animal studies had promising results, later studies demonstrated no difference in histamine levels between rabbits in whom OHSS was induced and controls [15].

Estrogens. Abnormally high levels of various steroids, estrogens in particular, are found in ascitic fluid and serum in cases of OHSS following Hmg-hCG ovulation induction. Thus, it is not a surprise that estrogens were implicated as a possible triggering factor that eventually increases capillary permeability. On the other hand, it is known that the administration of high doses of estrogens do not, by themselves, produce clinical hyperstimulation. Moreover, Meirow et al. [16] showed that induction of ovulation without elevation of estrogens may lead to OHSS.

Prostaglandins. Experiments in animal models set out to determine whether prostaglandins are the "active substances" playing a role in the development of this syndrome. It was demonstrated in early experiments on an animal model that Indomethacin, a blocker of prostaglandin synthesis, can prevent the fluid shift associated with the ascites, pleural effusion, and hypovolemia seen in this syndrome [17]. Moreover, other animal studies showed that in the presence of OHSS, ascites formation is not effectively suppressed by Indomethacin. In the clinical setting, Indomethacin was used as a therapeutic measure in cases of severe OHSS with variable results. Therefore, the role of prostaglandins in triggering the pathological processes of OHSS was not proved.

Renin–Angiotensin System. Increased vascularity as well as increased capillary permeability at the time of ovulation is an important part of the angiogenic response in the follicle. The angiogenic properties of human follicular fluid combined with high prorenin, high plasma renin-like activity, angiotensin II-like immunoreactivity, and angiotensin-converting enzyme (ACE) raised the hypothesis on the possible involvement of renin–angiotensin system in the pathogenesis of OHSS through new vessel formation and increased capillary permeability. The involvement of a locally activated renin–angiotensin–aldosterone cascade has been implicated as a possible cause of the severe form of the syndrome through neovascularization and increased

capillary permeability rate through endothelial cells in vitro. Plasma renin activity and aldosterone in patients with ovarian hyperstimulation and demonstrated was studied by us. The results showed the pattern of plasma renin activity in Hmg hyperstimulated cycles is characterized by a mid-luteal peak which declines to normal in the late luteal phase in nonconceptual cycles, whereas a sustained elevation of plasma renin activity occurs in conceptual cycles. A direct correlation between the magnitude of plasma renin activity and the severity of OHSS was established [18].

According to this concept, the increased capillary permeability present in OHSS is due to the involvement of the renin–angiotensin system and the synthesis of prostaglandins in the ovaries. However, although the renin–angiotensin system may explain some of the characteristics in OHSS such as vasoconstriction as well as several other signs, it is not clear whether this system triggers the cascade leading to OHSS or merely is a secondary reactional feature.

Vascular Endothelial Growth Factor. It was found by us and others that VEGF is responsible for the significant increase in the capillary permeability in OHSS [19]. VEGF, also known as vascular permeability factor (VPF), can provoke extravascular fluid accumulation, hemoconcentration and elevated plasma concentration of von Willebrand factor all known complications of OHSS. VEGF is a potent vasoactive protein with a remarkable permeability enhancing capacity that is approximately 1,000 times that of histamine. Elevated levels of VEGF were found in the serum of patients who developed severe OHSS. Follicular fluid VEGF was found to be 100-fold greater than serum or peritoneal fluid 36 h after hCG administration. Abramov et al. [19] investigated the role of VEGF in OHSS. Samples of therapeutic paracentesis were collected from severe OHSS patients. They found that VEGF is the major capillary permeability factor in OHSS ascites since adding specific antibodies against VEGF (rhVEGF) was able to neutralize 70 % of capillary permeability activity. Several other evidence for the key role of VEGF in the pathogenesis of OHSS were also found. High concentration of this substance was found in ascites from OHSS patients. Lately, dynamic changes of VEGF levels in the ascitic fluid of patients with severe OHSS were reported. Moreover, it was found that VEGF is hCG trigger for OHHS.

Human Chorionic Gonadotropin. Severe OHSS is depended on either exogenous administration of hCG or endogenous pregnancy-derived hCG. It is administered during ovarian stimulation for both triggering ovulation and for luteal support. It is well known that hCG administration is critical for the development of OHSS. This iatrogenic syndrome cannot be totally prevented by GnRH substitution for hCG and inducing endogenous LH surge.

10.10.5 Treatment

Mild OHSS usually does not require any active form of therapy other than observation and maintenance of hydration by the oral route. Moderate grade OHSS requires close observation and, in most instances, hospitalization, since patients may rapidly undergo a change of status, particularly when conception occurs, and it may become severe with subsequent complications; thus, vigilant observation is required. Patients with severe OHSS require immediate hospitalization and treatment.

During hospitalization, meticulous monitoring of hemodynamic stability is required by restoration of the depleted intravascular volume. Large volume crystalloid infusion is recommended. However, these patients must be closely monitored, as this can result in sequestration of fluid in the third space. Since no treatable single causative mechanism has been found for this syndrome, therapy has remained conservative and supportive, aimed at refilling the arteriolar vasculature, mobilizing fluids from the third space back to the intravascular tree, maintaining circulatory hemodynamics, and preventing hemoconcentration.

We have previously shown that severe OHSS is characterized by leakage of albumin (with a molecular weight of 69 kD) as well as IgG and IgA (with molecular weights of 150 kD and 180 kD, respectively) to the abdominal cavity. Since IgM, which has a molecular weight of approximately 900 kD, did not leak at all, and since IgA leaked much less than IgG and albumin, we suggested that molecular human albumin, however, is considered the most "physiologic" solution for this purpose and is probably the most common one used. Its popularity may be attributed to publications that reported a benefit of prophylactic administration of human albumin before and immediately after oocyte retrieval in women at high risk for severe OHSS. However, some recent reports could not reproduce these results and found no significant benefit of human albumin therapy in prevention of severe OHSS.

We compared human albumin with 6 % hydroxyethyl starch, a powerful, high-molecular-weight colloid currently used to treat other states of intravascular volume depletion, such as burns and hemorrhagic or septic shock. It was proved that 6 % hydroxyethyl starch has advantage over albumin [20].

Tension ascites with oliguria calls for paracentesis. Impending renal failure and unrelenting hemoconcentration require intensive care and possibly dopamine drip. Heparin should be added for thromboembolic phenomena, whereas surgical intervention should be reserved for ovarian torsion, rupture of cysts, or ectopic (heterotopic) gestation. Therapeutic termination of an existing pregnancy may be lifesaving when all other measures have failed, making both patient and physician face extremely difficult decision with vast psychological consequences for the patient.

10.10.6 Prevention [21]

The key to the primary prevention of OHSS during ovarian stimulation is individual approach recognizing risk of the patient to develop OHHS. Several measures can be employed to prevent OHSS. There are, however, numerous reasons why even with the most careful and painstaking preventative measures, OHSS cannot be eliminated.

Monitoring of induction of ovulation is the most reliable method in the prevention of OHSS. Measurable parameters, which more or less accurately reflect follicular maturation, are used to monitor ovulation induction since direct observation is impossible.

Clinical evaluation is important, and such methods as cervical scoring may be used as adjuvant methods of evaluation. Determining the cervical score reflects indirectly the total estrogen activity. Serum estrogen values have established their effectiveness in monitoring induction of ovulation.

Estrogen monitoring has effectively reduced OHSS with clinical symptoms necessitating hospitalization. Higher levels of 17β-estradiol are reached in induced cycles to achieve the optimal pregnancy rate. However, we and others have observed OHSS with peak plasma estradiol levels of >2,000 pg/ml, hCG should be withheld.

An additional factor that may serve as a warning sign is the slope of rise of the plasma estradiol level. If values are more than doubling during 2 or 3 days (steep slope), then this should be regarded as a serious warning sign and hCG withheld in that cycle. In assisted reproductive programmers, hCG should be withheld when estradiol levels are >3,000 pg/ml.

We and others have demonstrated that there is a linear correlation between the follicular diameter and estradiol levels in plasma in normal ovulatory cycles. However in induced cycles, where there is more than one dominant follicle and several maturing follicles, there is a poor statistical correlation between the ultrasonographic ovarian morphology and the plasma oestradiol level.

In assisted reproductive of ovarian stimulation, the following manipulations and interventions during the treatment cycle have been used:

(a) Withholding hCG—cancelling of cycle—As OHSS is associated with hCG, terminating the ovulation cycle by cancelling the hCG trigger in the presence of several risk factors for OHSS is the most effective technique to prevent OHSS. hCG induces the production of VEGF, the primary mediator of OHSS. It is usually reserved for patients at high risk of OHSS and those with total loss of cycle control. Cancelling a cycle has an economic and psychological effect on the patient.

(b) Rescue of overstimulated cycles—coasting—withholding exogenous gonadotropins and postponing the hCG trigger until a patient's E2 level has declined. Coasting leads to the selective regression of the pool of immature follicles, thereby reducing the functioning granulosa cell mass available for luteinization and resulting in a decline in vasoactive substances involved in the pathogenesis of OHSS, including VEGF. Coasting has been shown to reduce

the incidence of OHSS in high-risk patients but affecting cycle outcome. Coasting results in lower pregnancy rates.

(c) Aspiration of follicles—has a protective effect with a decline in hormonal levels being noted. This may account for the reduced incidence of OHSS, but this approach does not offer complete protection against the development of OHSS.

(d) Albumin—Potential benefit of intravenous (IV) albumin at the time of oocyte retrieval to prevent OHSS was reported. An early Cochrane review clearly showed a benefit associated with the administration of IV albumin at the time of oocyte retrieval in patients at high risk of OHSS, with no effect on pregnancy rate. Recent studies found that while there was no statistical benefit regarding the rate of OHSS, it may reduce pregnancy rates.

(e) Dopamine agonist—A therapeutic strategy to prevent OHSS development is to use a dopamine agonist in order to benefit from its established action of inhibiting phosphorylation of VEGFR2 and preventing increased vascular permeability. It reduces the early onset of OHSS, without causing any effect in pregnancy, implantation, and miscarriage rate [21].

(f) Cryopreservation—Embryo cryopreservation is an effective method of OHSS prevention. Recently, it has been showed that emergency vitrification of embryos has been successful for the prevention of OHSS in high-risk women.

(g) The use of a GnRH agonist to trigger final follicle maturation in stimulated cycles of hyper responders was associated with a favorable reproductive outcome and no incidence of OHSS. The rate of multiple pregnancies nevertheless was found to be uncontrollably elevated, raising serious concerns regarding the safety of this protocol in standard clinical practice [22].

(h) Preovulatory LH surge triggering by agonist instead of the conventional hCG. However, patients receiving a GnRHa trigger had poor clinical outcomes, with a reduced likelihood of pregnancy and an extremely high early pregnancy loss rate, which was attributed to luteal phase insufficiency, despite standard luteal phase support with progesterone.

10.10.7 Multiple Pregnancy

The frequency of multiple gestation has increased as a result of the relatively widespread use of induction of ovulation and ART. The overall multiple pregnancy rate for ART is 22–28 %, most of which are twins (20 %), triplets (4 %) and, occasionally, higher-order gestations.

The medical and social problems associated with multiple pregnancies have been recorded. There is an increased frequency of maternal complications together with higher perinatal morbidity and mortality [23]. It is now common for women who are carrying a pregnancy of high order, even of triplets, to have the number of fetuses reduced to two or one by selective abortion of the excess fetuses. In order to prevent the need for selective termination, the number of embryos transferred into

the uterus should be limited to one or even two. Some countries have already regulations that limit the number of embryos transferred into the uterus.

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Premature Ovarian Insufficiency and Its Fertility Implications

11

Michael Savvas and Haitham Hamoda

11.1 Terminology

Premature menopause is defined as the complete loss of ovarian function occurring before the age of 40 and is a diagnosis that is usually made retrospectively when a woman presents with oestrogen deficiency symptoms, amenorrhoea of more than 1 year, an elevated FSH and reduced serum oestradiol.

Premature ovarian failure or premature ovarian insufficiency is that phase when there is some loss of ovarian function associated with impaired fertility and impaired hormone production. While a woman may have normal periods and be able to conceive, this phase is often associated with some degree of infertility and irregular menstrual cycles. There is no agreed precise definition of POI and it may be regarded as the initial phase of a continuum that ultimately results in premature menopause.

11.2 Causes

There are many causes of premature ovarian insufficiency (Table 11.1), but in the majority of cases the cause remains unknown. An increasing number of young women and girls are surviving cancer treatment and there is, therefore, a growing number of women with iatrogenic ovarian failure. It is estimated that 5 % of women will experience the menopause by the age of 45, 1 % before the age of 40 and 0.1 % before the age of 30.

M. Savvas (✉) • H. Hamoda
The Assisted Conception Unit, King's College Hospital, London, UK
e-mail: Mike.savvas@nhs.net

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Table 11.1 The causes of premature ovarian insufficiency

Causes of POI
Idiopathic
Iatrogenic
Auto-immune
Genetic
X Chromosome abnormalities
Familial genetic causes
Viral infection

11.3 Clinical Presentation

Women with premature ovarian insufficiency may present with oligo or amenorrhoea in association with climacteric symptoms, hot flushes or night sweats. Sometimes these symptoms first become apparent when a woman discontinues the oral contraception pill in order to try for a pregnancy. In many cases, the diagnosis is made by the fertility specialist, when investigating a woman with infertility but normal menstrual cycles. The blood test may reveal an elevated FSH, reduced oestradiol or an abnormally low AMH. Indeed, it is likely that many cases of unexplained infertility are in fact due to undiagnosed premature ovarian failure.

11.4 Clinical Symptoms

The symptoms of premature ovarian infertility include irregular periods, amenorrhoea and the typical menopausal symptoms.

In the long term, women with premature ovarian insufficiency are also at risk of osteoporosis, heart disease and there is also an associated increase in overall mortality (Table 11.2).

The most distressing symptom of premature ovarian failure is often loss of fertility with 54 % of women reporting this as the most distressing consequence of their diagnosis [1].

11.5 Pregnancy After Premature Ovarian Insufficiency

It is thought that around 5 % of women with this diagnosis will go on to conceive but this is variable, a younger woman with a diagnosis is more likely to conceive than a woman in her late 30s with the same diagnosis. There is no effective intervention to enhance the likelihood of spontaneous or natural conception. One study [2] has shown that 24 % of women with premature ovarian insufficiency experienced intermittent ovarian function and 4 % went on to conceive. The vast majority of those who conceived did so in the first year indicating that the longer the period of amenorrhoea, the less likely it is that a woman will conceive naturally. Women who present with premature ovarian failure and primary amenorrhoea are

Table 11.2 Symptoms and long term consequences of premature ovarian insufficiency

Symptoms
Vasomotor
Psychological symptoms
Sexual dysfunction
Reduced cognitive function
Long-term consequences
Osteoporosis
Heart disease
Increased overall mortality

also very unlikely to conceive as compared to those who present with secondary amenorrhoea.

The average age at which women give birth has been rising in the recent decades and in the UK the average age of a woman having giving birth is 29.7 years with nearly half of women being over the age of 30 (Fig. 11.1). The average age of first birth is currently 27.9 compared to 26.6 in 2001 (Office for national statistics 2013). An increasing number of women who have delayed having children will therefore not be able to do so due premature ovarian insufficiency occurring in the third or fourth decade of life.

11.6 Predicting POI

Most women are aware of the biological advantages in having children earlier but are prevented from doing so because of complex economic, educational and social factors.

Many women, therefore, wish to be reassured or at least want to know the state of their ovarian function and how much longer they have before their fertility is significantly reduced. The clinical history, assessment of ovarian reserve and response to ovarian stimulation may be used for this.

11.6.1 Clinical History

The clinical predictions tend not to be very helpful as there may already be some degree of decline of ovarian function before this is suspected clinically as when a woman presents with a history of oligomenorrhoea associated climacteric symptoms. A history of autoimmune disease, particularly Addison's and autoimmune thyroiditis may also increase the likelihood that a woman will develop premature ovarian failure.

Family history can sometimes be helpful particularly if the mother or any older sisters had an early menopause.

A recent study from Denmark revealed that women whose parents had an early menopause were more likely to have reduced AMH and antral follicle count.

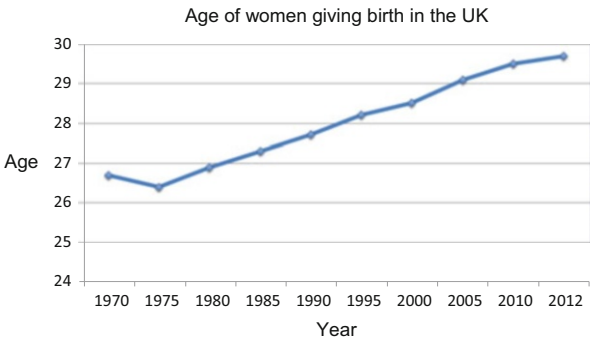

Fig. 11.1 The mean maternal age at time of giving birth. Adapted from National Statistics Office (2012)

Interestingly, there was no significant association with elevated FSH, serum oestradiol or ovarian volume [3].

11.6.2 Assessment of Ovarian Reserve

Ovarian reserve can be defined as the size of the ovarian follicle pool as associated with the quality with the oocytes. These naturally decline with age resulting in reduced fertility. Fertility specialists employ a number of methods to assess ovarian reserve as a way of predicting outcome to treatment, in particular in predicting response to ovarian stimulation and therefore helping decide on the appropriate dose of FSH to be used for stimulation. Assessment of ovarian reserve is typically carried out in the early follicular phase FSH. An elevated FSH indicating some degree of ovarian failure. Antral follicle count has also been used, however, its reliability is very much operator dependent. Recently, AMH has been used and appears to be more reliable than FSH or AFC. A further advantage is that AMH can be carried out at any time during the cycle; however, while ovarian reserve tests are useful in predicting response to ovarian stimulation, they cannot predict menopause because follicular atresia does not occur as a constant and uniform rate. It has been suggested that the rate of decline in AMH rather than absolute AMH levels may be useful in predicting the age of the menopause [4]. However, this is of limited clinical value as the average age of women in this study was 41 and the shortest time interval required was 3.5 years. These findings may therefore not hold for younger women and in any case a 3.5-year interval makes it impractical as a test for women wishing to predict the time of the menopause.

11.6.3 Poor Ovarian Response to Stimulation

A history of poor response to ovarian stimulation is a further indicator of increased risk of ovarian failure.

Nikolaou et al. [5] reported that women who had poor response to ovarian stimulation were likely to develop menopausal symptoms within 7 years. Lawson et al. reported that poor ovarian response was a stronger predictor of ovarian failure than an elevated FSH [6].

11.7 Fertility Treatment

Treatment with donor eggs remains very successful with very good pregnancy rates. The difficulty with this treatment, however in many countries, remains the lack of donors; this issue is discussed elsewhere in this publication.

A further aspect of the treatment is oocyte (or embryo) cryopreservation; it is widely used for women prior to cancer treatment and there is an increasing demand for social egg freezing.

11.7.1 Egg Freezing

Egg freezing was first carried out more than 25 years ago. However, in recent years, the success rate of egg freezing has improved with the introduction of vitrification or fast freezing, which is a technique that avoids ice formation within the cell. A recent study has shown that the pregnancy rate using fresh eggs is not better than that of using frozen eggs from donors with pregnancy rates of around 50 % in both groups. It must be pointed out however that in this study the egg donors in both groups were very young at 26 year so age [7].

11.7.2 Social Egg Freezing

There is increasing demand for social egg freezing. One of the largest reports from Brussels [8] reported that the mean age of women who store eggs for social reasons was 37. The reason for this presumably is that women in their middle to late 30s who realise that they will not be having children in the very near future are wishing to preserve fertility as an insurance policy. The majority of women in this report indicated that they expected never to have to use these frozen eggs. However, experience of thawing is limited, particularly in this age group and only one woman thawed her treatment with frozen/thawed eggs. She was 39 and unfortunately did not conceive. There is more experience with post-chemo therapy and the success here is likely to be related to the woman's age and health prior to any chemo or radiotherapy. Data regarding the successful thawing of fertility treatment for women who have chemotherapy is lacking due to the fact that women who freeze eggs prior to chemotherapy may not be in a position to undergo fertility treatment until many years later.

11.7.3 Ovarian Tissue Freezing

More recently, there have been reports of successful ovarian tissue freezing with autologous transplantation. However, very few pregnancies have occurred with this treatment and this remains experimental. The advantages, however, are obvious in that a large number of oocytes can be stored, whereas oocyte preservation will only be applicable for a limited number of eggs.

11.7.4 Fertility Chemo Protection

GnRH treatment prior to chemotherapy has been proposed as a way of reducing the likelihood of ovarian damage and a recent Cochrane review confirms that this can reduce the likelihood of amenorrhoea and increase the likelihood of spontaneous ovulation. However, there does not appear to any increase in the incidence of pregnancy [9].

11.8 Conclusion

Loss of fertility is often the most distressing consequence of premature ovarian insufficiency and premature ovarian menopause and indeed this diagnosis may first be identified by infertility specialists. As women delay motherhood, an increasing number of women with this diagnosis will require fertility treatment. There is an increasing demand for social egg freezing but while the results of freezing donor eggs is encouraging, there is little data regarding the outcome of social egg freezing where women are usually older. Women needing chemotherapy or radiotherapy may benefit from pre-treatment with Gonadotropin Releasing Hormone. As yet there is no reliable predictor of POI.

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Premature Ovarian Insufficiency: Strategies to Preserve Good Health and Fertility

12

Nick Panay

Premature ovarian insufficiency (POI) remains poorly understood and under-researched [1]. It describes a syndrome consisting of early cessation of periods, sex steroid deficiency, and elevated menopausal levels of the pituitary hormones FSH and LH in women below the age of 40. POI can be primary (spontaneous POI) or secondary (induced by radiation, chemotherapy or surgery). Controversy persists over nomenclature with terms such 'premature ovarian failure/dysfunction and 'primary ovarian insufficiency' still in usage.

POI has been estimated to affect about 1 % of women younger than 40, 0.1 % under 30 and 0.01 % of women under the age of 20. However, as cure rates for cancers in childhood and young women continue to improve, it is likely that the incidence of prematurely menopausal women is rising rapidly [2]. Recent data from Imperial College London suggest that the incidence of POI may be significantly higher than originally estimated. Cartwright and Islam [3] studied 4,968 participants from a 1958 birth cohort. They found that 370 (7.4 %) had either spontaneous or medically induced POI. Smoking and low socioeconomic status were predictive of POI and poor quality of life (SF 36) was twice as common in POI. The incidence of POI also appears to vary according to the population studied. It appears to be significantly higher, >20 %, in some Asian populations (personal communication from Indian Menopause Society).

In the past, the focus of medical care has been on improvement of survival rates. Very little attention has been given to the maintenance of quality of life in the short term and to the avoidance of the long-term sequelae of a premature menopause. One of the main reasons for this has been the bias of economic expenditure and medical endeavour to the prolongation of life (e.g. cancer treatments) rather than towards optimising quality of life in cancer survivors. Should this trend continue we are in danger of creating a population of young women who have been given back

N. Panay (✉)
Queen Charlotte's & Chelsea and Chelsea & Westminster Hospitals, Imperial College London, Du Cane Road, TW9 3BU London, UK
e-mail: nickpanay@msn.com

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the gift of life but left without the zest to live it to its full potential. Maintenance of postmenopausal health is also of paramount importance if we are to minimise the economic impact on society in this and future generations.

Causes of spontaneous POI include idiopathic (no known cause), genetic, autoimmune and infective. The typical presentation of spontaneous POI is erratic or complete cessation of periods in a woman younger than 40 years, which may or may not necessarily be accompanied by symptoms. These symptoms may not be typical vasomotor in nature and include mood disturbances, loss of energy and generalised aches and pains. Our data and data from others [4–6] indicate that the next most disturbing aspect of POI after the loss of fertility is the adverse impact on sexual responsiveness and other psychological problems.

Thus, women with POI require integrated care to address physical, psychosocial and reproductive health as well as preventative strategies to maintain long-term health. However, there is an absence of evidence-based guidelines for diagnosis and management. POI is a difficult diagnosis for women to accept, and a carefully planned and sensitive approach is required when informing the patient of the diagnosis. A dedicated multidisciplinary clinic separate from the routine menopause clinic will provide ample time and the appropriate professionals to meet the needs of these emotionally traumatised patients. At the West London Menopause Centres, we have restructured our services and created a dedicated clinic for the POI patients. Counselling at this stage should include explanation that remission and spontaneous pregnancy can still occur in women with spontaneous or medical POI. Specific areas of management include the provision of counselling and emotional support, diet and nutrition supplement advice, hormone replacement therapy and reproductive health care, including contraception and fertility issues. There is an urgent need for large-scale long-term randomised prospective studies to determine the optimum routes and regimens of hormone replacement therapy. Outcome measures should include short-term symptoms, vasomotor, urogenital and psychosexual and the long-term effect on cardiovascular, cognitive and skeletal health.

12.1 Predictive Tests

As a minimum, the initial investigation of patients presenting with erratic periods, for which pregnancy should be excluded, include measurement of serum follicle-stimulating hormone (FSH), oestradiol and thyroid hormones. If FSH is in the menopausal range in a woman younger than 40, the test should be repeated along with oestradiol for confirmation as levels can fluctuate.

Evaluation of other hormones of ovarian origin, such as inhibin B and anti-Müllerian hormone (AMH), and the ultrasonographic estimation of the antral follicle count are also being used to predict ovarian reserve. Some studies suggest that the precise age of menopause transition can be predicted through the use of these biomarkers; this requires confirmation, especially in POI [7–9]. In the long term, the polygenic inheritance of a risk for spontaneous POI will be unravelled and banks of genes will be tested to give an individual the precise risk of suffering POI.

12.2 Counselling and Emotional Support

Women diagnosed with POI go through a very difficult time emotionally. The condition has been associated with higher than average levels of depression. Loss of reproductive capability is a major upsetting factor and this does not depend on whether the woman has already had children or not. Professional help should be offered to help patients cope with the emotional sequelae of POI. Adequate information should be given in a sensitive manner, including information about National self-support groups for POI, such as the Daisy Network in the UK (http://www.daisynetwork.org.uk).

12.3 Hormone Replacement Therapy

Young women with spontaneous POI have pathologically low oestrogen levels compared to their peers who have normal ovarian function. The global consensus on hormone therapy [10] and updated 2013 IMS recommendations [11] state that in women with POI, systemic hormone therapy is recommended at least until the average age of the natural menopause (51 years).

Hormone therapy is required not only to control vasomotor and other menopause symptoms but also to minimise risks of cardiovascular disease [12], osteoporosis [13] and possibly Alzheimer's dementia [14], as well as to maintain sexual function. There is no evidence that the results of the Women's Health Initiative study (a study of much older women) apply to this younger group. Hormone replacement therapy in POI patients is simply replacing ovarian hormones that should normally be produced at this age. It is of paramount importance that the patients understand this in view of the recent press on HRT. The aim is to replace hormones as close to physiological levels as possible.

Since spontaneous ovarian activity can occasionally resume consideration should be given to appropriate contraception in women not wishing to fall pregnant. Although standard oral contraceptive pills are sometimes prescribed, they contain synthetic steroid hormones at a greater dose than is required for physiological replacement and so may not be ideal. Low dose combined pills may be used to provide oestrogen replacement and contraception, although they are less effective in the prevention of osteoporosis and induce less favourable metabolic changes [15, 16]. The progestogen intrauterine system may also be offered in those who choose HRT and require contraception.

In our experience, the choice of HRT regimen and the route of administration vary widely among patients. In the absence of better data, treatment should therefore be individualised according to choice and risk factors. Where libido is a problem, testosterone replacement should be replaced, especially in surgically menopausal women. Although there is an absence of licensed androgenic preparations which can be used, off-label use of physiological female doses of transdermal testosterone appears efficacious and safe.

To complement the role of HRT for the long-term prevention of osteoporosis, supplementary intake of adequate dietary calcium (1,000 mg/day) and vitamin D (800–1,000 IU/day) should be encouraged, as should weight bearing exercises. The use of complementary therapies and non-oestrogen-based treatments such as bisphosphonates, strontium ranelate or raloxifene for the prevention of osteoporosis in women with POI has not been studied.

12.4 Fertility

Women with POI are not necessarily sterile unless surgically menopausal. There is however only a 5 % chance of spontaneous conception. Hence, women for whom fertility is a priority should be counselled to seek assisted conception by IVF using donor eggs or embryos. Future advances in the research of stem cells may make it possible for some women with POI to achieve pregnancy with their own oocytes [17]. Until such a time, oocyte/embryo donation remains the only real chance for these women to achieve pregnancy by assisted conception. Another family building option that should be discussed is adoption.

12.5 POI Registry

We urgently need to determine the scale of the POI problem, initially by the trawling of data from all clinics that manage women with POI. The data will undoubtedly demonstrate extreme variations in management and deficiencies will emerge. Armed with this information departments of health can then be petitioned to provide appropriate funding for the setting up of multidisciplinary units for the management of the particular psychological and physical needs of women with POI.

In the absence of prospective randomised controlled data, there is a need for high-quality observational data. There have been calls for a database/registry from our and other units to provide this information [18, 19].

Individual centres generally do not have sufficient exposure to women with POI to gather sufficient observational or RCT data to give meaningful results on disease characterisation and long-term outcomes. Cooper et al. make the point that fragmented research leads to fragmented patient care [19]. We are in total agreement that without definitive research, we are left to advise women with POI using inappropriate postmenopausal practice guidelines that are based on a different patient population.

The problems we need to overcome in setting up this database include a lack of established standards and design, quality of data, consistency of recruitment criteria, etc. Also, there has to be agreement as to the nature and quantity of the sample size required e.g. inclusion of women with iatrogenic POI as well as spontaneous. The collaborative effort of a cohort of international centres specialising in POI management can overcome many of these limitations.

It is vital that there is a sense of collective ownership of the data and any publications resulting from the research. We are currently in the process of data entry field modification through regular workshops with key collaborators to refine data capture fields and propose areas of data analysis and publication.

The potential benefits of such a database are many. It could be used to create not only an information database but also a global bio bank for genetic studies, with an ultimate goal of defining the specific pathogenic mechanisms involved in the development of POI e.g. unravelling the polygenic inheritance mechanism.

The database would have the potential to define and characterise the various presentations of POI along the lines of the STRAW + 10 Guidelines for natural menopause. The STRAW + 10 collaborators in their recent paper state that special groups, such as POI, warrant urgent attention for staging of reproductive aging [20]. It could also be used to further refine the role of biomarkers such as anti-Mullerian hormone to precisely predict the course and timing of natural and early ovarian insufficiency [7–9].

There is a desperate need to determine long-term response to interventions such as the contraceptive pill, hormone therapy and those not receiving treatment. This is particularly important in women with rare causes and hormone-sensitive cancers where randomised trials are unlikely to be ever performed.

Regarding treatment, questions which urgently need to be answered include, does the type of HRT matter, body identical versus other types of HRT, oral versus transdermal oestrogen, dosage of oestradiol, progesterone versus retroprogesterone versus androgenic progestogens and impact of androgens, on both short-term quality of life and long-term outcomes. The database will also give the opportunity for the role of unproven fertility interventions in POI to be studied such as DHEA, and the use of ultra low dose HRT and the contraceptive pill to suppress FSH levels to facilitate ovulation of any remaining oocytes.

As is the case with a number of other centres, we have been collecting data from our cohort of women with POI for a number of years (over 500 subjects to date) [21]. The next step is to amalgamate these data with those of our colleagues globally. We have already had verbal agreement from more than 30 international experts in POI who would be willing to contribute to such a database. An online website is currently being designed. All collaborators will have the opportunity to offer their views on ultimate database structure and data entry fields before real-time data entry commences in late 2013. The concept of the database has already been launched at the 15th World Congress of Gynecological Endocrinology 2012 and the 9th European Congress on Menopause and Andropause 2012 to the universal approval of experts and delegates [22, 23].

12.6 Conclusion

POI affects many young women globally. These women have unique needs that require special attention. There is an urgent need for standardised terminology and evidence-based guidelines upon which to establish the diagnosis and manage this

difficult condition. These guidelines must be drawn up from population specific data to have any relevance. An international POI registry has the potential to provide such information. The problems and limitations of a disease database/registry can be minimised with adequate consensus, communication and collaboration. We hope this will ultimately lead to better understanding of the condition and the development of guidelines for the strategic optimisation of health and fertility in POI.

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Treatment with Donor Eggs

13

Michael Savvas, Haitham Hamoda, and Monica Mittal

13.1 Introduction

Treatment with donor eggs is a highly successful treatment option for women with Premature Ovarian Insufficiency (POI) and is also indicated for those who have had unsuccessful IVF due to poor response to ovarian simulation or have repeated implantation failure. It may also be indicated in cases where the woman is known to be a carrier of an inherited disorder.

This treatment requires careful assessment of the Donor as well as the Recipient and her partner.

13.2 Assessment of Donors

In the UK, the law requires that the donor is altruistic although reasonable expenses may be claimed, up to a maximum of £750. The donors need to be healthy and between the ages of 18 and 35 years of age. All potential donors are carefully assessed to exclude any inheritable conditions. A detailed medical history is obtained to assess the potential donor's health and exclude any familial conditions which may be genetic. All potential donors undergo a number of investigations (Table 13.1). The potential donor is screened for blood-borne viruses to avoid the risk of transmission to the recipient or the foetus and are carried out at the first visit and repeated again just before treatment is commenced. The screening for Haemoglobinopathies and Tay–Sachs is carried out in the appropriate racial groups.

The donor's ovarian reserve is also assessed with an Antral Follicle Count and biochemically with measurement of FSH LH and E2 in the early follicular phase of the cycle though increasingly the AMH is used instead.

M. Savvas (✉) • H. Hamoda • M. Mittal
The Assisted Conception Unit, King's College Hospital, London, UK
e-mail: Mike.savvas@nhs.net

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Table 13.1 Donor screening test

HIV
Hepatitis B
Hepatitis B
Hepatitis C
Syphilis
Blood group
Karyotype
Cystic fibrosis
Chlamydia
N. gonorrhoeae
Sickle cell anaemia
Thalassaemia
HTLV
Tay–Sachs

In addition to this, we write to the General Practitioner of all potential donors asking them to confirm that there is no relevant medical history.

The process involved is fully explained to the patient and in particular and the risks involved are discussed. This includes possible side effects of the drugs including the risk of Ovarian Hyperstimulation Syndrome and the potential risks associated with the egg collection procedure.

All women seeking to be egg donors are also required to see a specialist counsellor at which time the woman's reason for wishing to be a donor explored and the legal implications are explained.

13.3 Assessment of the Recipient

Before the recipient can proceed with treatment, she will need to be assessed very carefully. The Human Fertilisation and Embryology Authority (HFEA), the body that regulates this form of treatment in the UK, requires that the welfare of any children born as a result of this treatment must be considered. This involves taking a detailed medical history and the potential recipient and her partner are required to complete a form, which specifically enquires about any medical, social or psychological issues that may impact on the quality of parenting.

The potential recipients and her partner receive counselling where the implications of embarking on this treatment are discussed and the legal position regarding parenthood is explained. In the UK, the woman who gives birth and her husband will be the legal parents. If the recipient is unmarried, her male partner can be the legal further if he consents to his partner undergoing treatment and signs the relevant documents. Similarly, if the recipient is in a same sex relationship, her partner will be the legal "second parent" if they are in a civil partnership. If not in a civil partnership, her partner can still be the second parent if the relevant forms are completed.

The egg recipient can receive non-identifying information about any donor such as hair colour, eye colour, height and ethnicity. She can also receive a copy of the pen portrait written by the donor primarily for the use of the donor-conceived child.

Prior to commencing treatment, the recipient usually undergoes a "dummy cycle" where she is given 6 mg Oestradiol orally an ultrasound scan is performed after 10 days to assess endometrial thickness; we aim to achieve a thickness of 8 mm or more. If the endometrial thickness is inadequate, the dose or duration is increased. In this way, the appropriate dose and duration of Oestradiol required to achieve optimal endometrial thickness is determined and allows us to synchronise the recipient's endometrium with the timing of the donor's egg collection.

13.4 The Law

In the UK, donors have no legal rights or obligations towards any children born as a result of their donated eggs; however, they can be told whether any children were born as a result of the donation, the sex and the year in which they were born.

In accordance with HFEA Code of Practice, we encourage patients to tell their children that they were conceived with donor gametes. Donor anonymity was removed in 2005 and their identity can be revealed to donor-conceived people once they reach the age of 18. Only the donor-conceived person can initiate contact with the donor, the donor cannot be given the identity of the recipient or the donor conceived person.

Donor anonymity was removed in response to the need for donor-conceived people to know their genetic origin as this may have an important role in the formation of their personal identity. Studies have shown that concealment of such information could have a detrimental effect on individuals' familial and social relationships, particularly if that information is later discovered in an unplanned manner [1].

When donor anonymity was removed in 2005, there was much anxiety that this would lead to a marked reduction in altruistic donors. However, the number of egg (and sperm) donors has continued to rise since 2005 (Fig. 13.1) though the absolute numbers are relatively small. Similarly, in Sweden when a change in the law in 1985 removed sperm donor anonymity, there was an initial reduction in donor numbers although numbers subsequently increased to their original levels [2].

The absolute number of donors in the UK is small and is inadequate to meet current demand. Many women who require treatment with donor eggs cannot find an anonymous altruistic donor and instead find their own donors from within their family or circle of friends while others seek treatment overseas. Some women may opt for egg sharing, where a woman who is undergoing IVF/ICSI for a male factor diagnosis agrees to share her eggs and the recipient subsidises her treatment. We have concerns about this form of treatment because we feel that women who require such treatment are vulnerable and may choose to share their eggs simply to enable themselves to get "free or subsidised treatment". We also have concerns that the

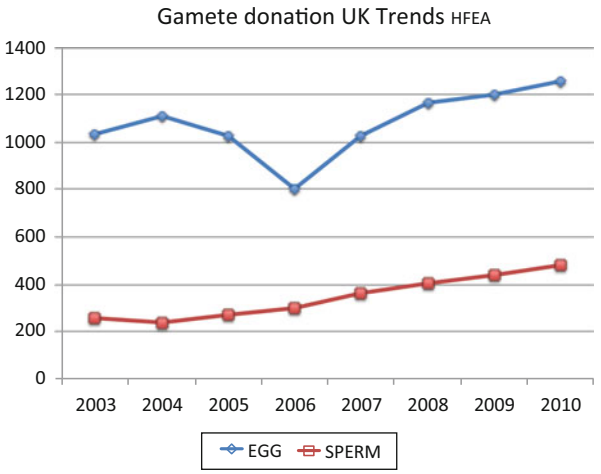

Fig. 13.1 The number of egg and sperm donors in the UK since 2003

donor may have profound issues to cope with if she failed to get pregnant while the recipient was successful.

13.5 The Process

Stimulation protocols vary but the donor usually undergoes pituitary downregulation with a GnRH analogue starting on day 21 of the preceding cycle, a baseline down regulation scan is performed and then stimulated with FSH, the dose being calculated on the basis of her age and ovarian reserve. Transvaginal Egg collection is usually carried out under intravenous sedation. The eggs are then fertilised with the recipient's partner's sperm. The recipient commences progesterone usually in the form of vaginal pessaries (Cyclogest 400 mg bd) on the day the donor undergoes egg collection. Embryo transfer is increasingly performed at the blastocyst stage and any surplus embryos can be cryopreserved for future use.

Alternatively, the eggs can be frozen so that they can be thawed and fertilised at a later date. The advantage of freezing eggs is that it is more convenient and reduces the likelihood of cancelling a cycle if there is any problem with the recipients. A further theoretical advantage is that it allows eggs to be quarantined until viral tests have been carried out. Though there have been no recorded cases of viral transmission with donor eggs, the techniques of egg freezing has improved in recent years with introduction of vitrification, where the eggs are frozen rapidly thus avoiding the formation of intracellular water crystals that can damage the egg. In recent years, the results from vitrified donor egg treatment have improved and have been shown to be as successful as when using fresh eggs [3].

13.6 Obstetric Outcomes

Women who conceive with donor eggs have a higher incidence of bleeding in the first trimester, pre-eclampsia and small-for-gestational age. There has also been reported a significantly increased rate of caesarean section [4].

It has been reported that the age of the recipient does not affect the rate of implantation; however, a more recent study indicates that the implantation rate is reduced if the recipient is 45 five years or older [5]. Other factors that can affect implantation rate include smoking and the presence of hydrosalpinx. The effect of weight is unclear, but a recent study indicated that the implantation rate is significantly reduced if the BMI of the recipient is greater than 35 [6].

13.7 Conclusion

Donor egg treatment is becoming increasingly popular and highly successful; however, access to this treatment is limited by the shortage of donors. The improvement in egg freezing techniques and the establishment of egg banks may prove helpful.

Better outcomes are achieved if the recipient is less than 45 years of age, is a non-smoker and has a normal BMI. These pregnancies tend to have a higher incidence of pre-eclampsia, antepartum haemorrhage and small-for-gestational age.

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Part IV

Quality of Life and Sexual Health

Hypoactive Sexual Desire Disorder

14

Johannes Bitzer

14.1 Definition

DSM IV defines Hypoactive Sexual Desire Disorder (HSDD) as:

- Persistent or recurrent deficiency (or absence) of sexual fantasies and desire for sexual activity
- Causes marked distress or interpersonal difficulty
- Cannot be better accounted for by other factors (e.g. medical or psychiatric illness, drug of abuse and medication)

HSDD is not only associated with general personal distress but also has a specific negative impact on a woman's relationship and her partner.

16 premenopausal women and 20 postmenopausal women with HSDD or decreased sexual desire who participated in five focus groups reported:

Impact on self

Women felt "sad", "distressed", "frustrated", "annoyed", "guilty", "confused" and "bothered" about their decreased sexual desire.

Women "wanted to want sex."

Impact on relationship

Women experienced issues with trust, changes in intimacy and often had sex to appease partners.

This is a shortened and adapted version of a publication in the Journal of Sexual Medicine.

J. Bitzer (✉)
Department of Obstetrics and Gynecology, Women's Hospital, University Hospital Basel, Spitalstrasse 21, 4031 Basel, Switzerland
e-mail: JBitzer@uhbs.ch

A.R. Genazzani and M. Brincat (eds.), *Frontiers in Gynecological Endocrinology*, ISGE Series, DOI 10.1007/978-3-319-03494-2_14,

Impact on partner
Women perceived that they induced feelings of rejection and frustration in their partners.
Many partners understood towards the woman's decreased desire.

14.2 Trying to Understand Desire and Lack of Desire

As a largely subjective experience, sexual desire may or may not be accompanied by externally observable changes in sexual behaviour.

14.2.1 General Factors Which Constitute Desire

Sexual desire can be described as a composite experience consisting of different elements:

- Drive (Biological component)
- Motivation (Cognitive component)
- Responsiveness to sexual stimuli (Response component)

Drive can be considered as an internal force (appetite and energy) that pushes an individual to do something. It is usually viewed as an instinct, with inborn patterns of reaction.

Motivation for sexual activity is a more complex psychophysiological phenomenon and is much more linked to cognitive processes, which are typically characterised by the concept of incentive or reward. Motivation for sexual activity may reflect a desire for sexual pleasure, intimacy, pleasing the partner, feeling desired, emotional or narcissistic satisfaction or motives not related directly to sexual desire or behaviour (e.g. financial gain).

Responsiveness to sexual stimuli refers to the ability of sexual stimuli to induce sexual desire, arousal, sexual behaviour and sexual pleasure in an individual. This component is certainly a mixture of a physical reactivity (possibly having to do with sensitisation of receptors or neurochemical systems) and cognitive processes (reward expectations, personal value system, etc.).

We can distinguish "drive" as an internal factor that pushes an individual to do something from the "incentive" as an external factor that pulls an individual towards it.

Applied to sexual behaviour, hormonal factors around ovulation push women towards sexual thoughts and behaviours, whereas the appealing features of an individual or situation would pull women towards interacting sexually with that person or in that situation.

14.2.2 Models of Understanding Desire Disorder

After the description of the sexual human response by Masters and Johnson with the phases of excitement, plateau and orgasm and the addition of the desire phase by Kaplan in a linear model of the human sexual response, it has been questioned whether this "classical model" describes the sexual experience of women.

Basson described a circular model in which the above-mentioned three dimensions of sexual drive, motivation and responsivity are integrated in a circular process in which desire is part of the flow of sexual activity, but not necessarily the first, or initiating step. There may be spontaneous desire or other motives to become sexually active or responsive to sexual stimuli. This may lead to sexual arousal, which may trigger or enhance desire, thus leading to an increase in sexual activity, arousal and sexual interaction that result in orgasm and other states of emotional reward (feelings of fulfilment, relief, etc.). In turn, such experience is thought to increase desire as an internal state of "wanting sex".

In this model, the three elements described above are found in reciprocal interaction. "Spontaneous desire" is a drive dimension; "Various motives" describe a motivational dimension; and "Response" to "sexual stimuli" corresponds to the receptivity dimension.

Other models of understanding sexual desire have been developed:

14.2.2.1 The Incentive-Motivation Model

In contrast to Freud's understanding of drive as an inborn instinct which needs to be satisfied to reduce inner tensions this model focuses on the individual adequacy of the sexual stimulus to induce desire. Desire as sexual motivation and action is created when an external adequate stimulus meets with an internal readiness to respond.

14.2.2.2 The Push–Pull Model

The underlying hypothesis is that there are two dynamic forces acting together which "produce" a feeling of desire.

One is a "*pushing factor*" that comprises the internal energy that pushes a person towards sexual expression and activity. This force includes inborn instinct, hormonal activity, innate or learned sexual preferences and other internal elements.

The "*pulling factor*" includes the attraction or incentive that pulls a person towards sexual activity. This includes the sex appeal of the partner and/or the situation, expected reward, sexual feedback and reinforcement from the partner. This model gives desire a biographical dimension that spans an individual's experience and memory.

14.2.2.3 The Excitation/Inhibition Model

Several authors have pointed out that desire is the result of a dynamic interaction between physiological and brain mechanisms of excitation and inhibition, thus providing a dual control mechanism of sexual behaviour. The turn on/turn off balance is driven or steered by excitatory forces which are the result of specific

prosexual physiological and organic mechanisms that activated by appropriate psychosocial and sociocultural events on one hand, and by inhibitory forces which are also the result of specific inhibitory physiological and organic mechanisms driven by antisexual psychosocial and sociocultural events.

These models suggest that HSDD may result from hypofunctional excitation, hyperfunctional inhibition or some mix of the two.

The biological basis for this dual response is estimated to be the following:

Steroid hormones have mainly a priming effect for the brain to respond to various neurotransmitters and increase receptivity to sexual stimuli.

Sexual excitation neurotransmitters

Brain noradrenaline systems underlie sexual arousal, whereas brain dopamine systems (incertohypothalamic and mesolimbic) that link the hypothalamus and limbic system activate attention and incentive motivation.

Melanocortin systems in the brain activate desire, and oxytocin systems activate preference behaviour.

Sexual inhibition neurotransmitters

Brain opioid systems that underlie pleasure and reward, endocannabinoid systems that induce sedation and serotonin systems that induce satiety are activated during periods of sexual inhibition. These systems blunt the ability of excitatory systems to be activated by appropriate sexual incentives.

All dual control models stress the adaptive nature of excitatory and inhibitory processes to respond to the environment.

- The adaptive nature of sexual excitement would drive individuals to seek out sex partners for reproductive or reward purposes.
- The adaptive nature of sexual inhibition would guard again situations that threaten the individual including chronically stressful life events.

14.3 Prevalence

Overall, the prevalence of desire complaints ranges from 10 to 40 % depending on the study methodology, participants and geographic location/culture. When the term “distressed” is considered, prevalence of desire/arousal complaints drops by at least half, although those rates increase when the term “bothered” is used.

Low desire increases with age but low desire + distress decreases with age.

14.4 Aetiology and Pathogenesis

The best approach to distressing low desire is the multidimensional perspective of the biopsychosocial model of understanding human sexuality as the result of an interaction between biological, psychological and social factors. From this perspective, a large variety of factors may contribute to low desire.

14.5 Biological and Biomedical Factors

14.5.1 Hormones and Endocrine Changes During the Life Course of the Woman

Ovarian steroid hormones are involved on central and peripheral processes as part of female's sexual physiology and biology. Oestrogen can be regarded as permissive or receptive signal and testosterone is not only important for desire in men but also in women.

- **Oestrogens:** Increases in self-reported sexual desire are highest in women during ovulation when oestradiol levels peak. Oestradiol acts mainly on ER alpha in the female brain, with highest concentrations of oestradiol measured in the hypothalamus and the preoptic area. Increased oestrogen action increases vaginal blood flow (VBF), while a decreased concentration diminishes VBF. The mechanism by which this occurs is related to oestrogen stimulation of the release of vasoactive substances such as nitric oxide by endothelial cells, which induces vasodilatation.
- **Progestins:** In rats and other animals, progestins like progesterone facilitate solicitations and lordosis. However, progesterone treatment to hypogonadal pre- or postmenopausal women does not facilitate measures of desire.
- **Androgens:** Testosterone interacts with androgen receptors with highest concentrations in the substantia nigra/ventral tegmental area, the hypothalamus and the preoptic area. Testosterone is also the primary precursor for oestradiol biosynthesis in the brain; indeed, the testosterone concentration in the brain is 7–10 times higher than the oestrogen concentration, with the highest ratio of testosterone versus oestradiol in the preoptic area. The effects of testosterone are difficult to distinguish from those of oestradiol, and combined replacement therapy using both steroids generally results in a better enhancement of sexual desire than either steroid alone.

Women experience typical transitional periods in their life which are characterised by changes in ovarian steroid hormones. These are natural experiments to better understand the role of these hormones in real-life situations for the sexual desire and activity of women.

- **Menopause transition:** The menopausal transition has been associated with a decline in desire and subjective arousal among women. HSDD as the most frequently reported sexual problem in women, ranging from 15 to 25 % in premenopausal women to 40–50 % in postmenopausal women. Although the

role of hormones as isolated factors is controversial, well-designed longitudinal studies have shown an increase in sexual dysfunction with a major negative impact on desire and a correlation with the decline in oestrogen. It must be noted, however, that the decline in circulating oestrogens is correlated with an increase in dyspareunia and lubrication difficulties. Those could lead secondarily to diminished desire or avoidance of sexual activity.

- **Postpartum period:** The postpartum period is associated with high sustained levels of prolactin and oestradiol that may induce inhibitory feedback on brain mechanisms that excite sexual desire. Accordingly, reports indicate that a woman's interest in sexual activity changes after childbirth. A substantial proportion of women (range: 47–57 %) interviewed at 3-month postpartum noted a decreased interest in sexual activity. However, decreased desire during this period could also be attributed to fatigue, pain and concern over injury. Despite any changes in desire, more than 80 % of women resume sexual activity by 6-week postpartum. Similarly, in female rats the postpartum period is associated with high oestradiol and prolactin levels, and a complete avoidance of sexual activity with males. Those levels decrease precipitously after weaning or removal of pups and sexual activity is resumed when cyclic hormonal rhythms are re-established.
- **Oral contraceptives:** Combined oral contraceptives containing ethinyl oestradiol increase SHBG titres and thus decrease available free testosterone. This could contribute to a lack of desire and subjective arousability [83]. Due to the fact that oral contraceptives are linked to myriad psychological and biological actions, some of which may have a positive impact on sexuality (e.g. reduce anxiety about unwanted pregnancy, diminish dysmenorrhoea, attenuate acne, etc.), it is very difficult to discern the clinical effect of the decrease of free testosterone in users of some oral contraceptives and clinical studies have been inconclusive some reporting decreased desire, some no change in desire and others increased sexual desire.

14.5.2 Diseases and Drug Use

A large number of clinical conditions and medications can lead to decreased sexual desire.

The three most important factors are major depression, cancer and medication

- **Major depression:** Major depression is the most important clinical condition having an impact on desire. This disorder or group of disorders has a complex pathogenesis and certainly is not defined and determined by purely neurotransmitter dysregulation. It is now generally accepted that there is a neurobiological component which is characterised by altered functions, especially of the noradrenergic and serotonergic systems.
- **Cancer:** Malignant diseases, especially in the urogenital region, may have various negative consequences for the female patient's sexual function and thereby affect indirectly or directly desire. The disease itself and the subsequent

surgery and radiation can lead to destruction of sexual organs, as occurs in vulvar, vaginal, uterine and ovarian cancers. These are often accompanied by disfigurement of the body that impacts negatively on sexual self-image.

- **Medications:** Both prescription and over-the-counter medications have the capability to alter arousal, desire and orgasm. The mechanisms can be divided into central nervous, peripheral nervous, neurovascular and neuromotor, endocrine and local. Any medication that alters blood flow (e.g. antihypertensives), affects the CNS (e.g. psychotropics) or dries the skin or mucous membranes (e.g. antihistamines) may disrupt normal sexual function.

One of the major classes of medications that impacts sexuality is the selective serotonin reuptake inhibitors (SSRIs), frequently used to treat depression in both pre- and perimenopausal woman. The risk/benefit ratio with use of these agents is based on individual need and response. When depression is severe, SSRIs may allow a short-term increase in sexual activity by treating the underlying process. However, in many patients, chronic therapy can diminish sexual desire and alter or eliminate arousal and orgasm. The mechanisms for this inhibition may be through decreased dopamine transmission (leading to increased prolactin levels), or by stimulation postsynaptic serotonin receptors that blunt sexual arousal and desire. Stimulation of 5-HT1b, 5-HT2 and 5-HT3 receptors appears to inhibit sexual desire.

14.5.3 Others

Other frequent contributing factors are Lower Urinary Tract Disorders and Diabetes

- **Urinary Incontinence**: Prevalence rates from 0.6 to 64 % are reported. In a case–control study, women with urinary problems had significantly more incidents of low desire, arousal difficulties and pain.
- **Diabetes:** The predominant symptoms are largely arousal based, including arousal dysfunction and decreased lubrication in women. No statistical significant difference in desire was found compared with the control groups used in those studies.

Neurological diseases often have a direct impact on the neuroregulation of the female sexual physiology. Their impact on desire is mainly indirect

- **Spinal cord injuries, MS and neuromuscular disorders:** There is a direct impact of these disease states on the neuromuscular and neurovascular elements of the sexual response. These mechanisms are very prominent in neurological diseases like MS, spinal cord injuries, etc. The effect on desire is in general indirect, and mediated by arousal disorders and pain.
- **Parkinson's disease, Dementia and Schizophrenia:** It is known that hypothalamic sexual centres are connected to central nervous neurotransmitter pathways and may be therefore influenced by disturbances of dopaminergic, serotonergic, adrenergic and GABAergic action. Examples of this are the disturbances occurring in patients with Parkinson's disease, dementia and various psychiatric diseases. The changes can result not only in decreased desire but also in

increased desire and hypersexual behaviour (e.g. as occurs in patients with decreased frontal lobe function in dementia). Sexual dysfunction is estimated to affect 30–80 % of patients with schizophrenia and is a major cause of poor quality of life.

- **Pituitary tumours and Hyperprolactinaemia:** The main mechanism is supposedly the inhibitory impact of elevated prolactin on the dopaminergic system although dopamine acts as a prolactin inhibitory factor, and decreased dopaminergic function in general may lead to HSDD and hyperprolactinaemia by two different mechanisms.

14.6 Individual Psychologic Factors

A large number of psychological factors can lead to low sexual desire.

These factors can be subdivided in those which have occurred in the past (predisposing and indirect factors) and those which are still now contributing to the symptom (maintaining and immediate factors).

Predisposing, Indirect Factors

- **Negative early environment:** Bad quality of attachment to parents and caregivers can predispose to negative internal scripts of sexuality and sexual pleasure.
- **Sexual abuse and emotional neglect in childhood:** One of the sequelae of this experience is low desire and sexual aversion disorder.
- **Traumatic experiences during puberty:** Negative sexual experiences and especially humiliation and offense may have harmful long-term consequences also in reducing motivation for being sexually active.

Maintaining, Immediate Factors

- **Perceived distress:** Distress may induce physiological responses like cortisol increase, which may counteract testosterone secretion and thus contribute to low desire in addition to cognitive distraction and anxiety which may accompany chronic stress and thus counteract sexual desire.
- **Distraction:** Distraction has been shown to be detrimental to female sexual function, especially subjective arousal and desire linked with sexual arousal.
- **Performance anxiety (concerns) and anxious apprehension:** For women, there is a large array of sexual concerns (worries about pleasing her partner, fear of partner rejection, fear of pregnancy and STIs, unease related to the ability to reach orgasm, etc.) which may induce performance anxiety.
- **Expectations (Anticipation) of a negative experience:** Low self-esteem combined with anticipation of negative outcomes may diminish the receptivity for erotic and sexual cues.

- **Body image self-consciousness:** Negative or insecure concepts and concerns about the body may lead to inhibition and sexual desire.

14.7 Relationship Factors

There is a close link between relationship and sexual satisfaction, which may indirectly impact sexual desire.

- **Partner's sexual dysfunction*:*** Sexual dysfunction of the male partner, especially erectile dysfunction and premature ejaculation, has a negative impact on the female partner's desire.
- **Duration of the relationship and routine:** Habituation and routine may contribute to the fact that the duration of relationship is inversely correlated to sexual desire and arousal.
- **Communication deficits:** Difficulties in the ability to express sexual needs, wishes and fears between partners are often an immediate and direct factor, which impacts negatively on a woman's desire to engage in sexual activity.

14.8 Sociocultural Factors

14.8.1 Diagnosis

Due to the lack of objective criteria, the importance of subjective experience, and the multifactorial aetiology of HSDD, it is necessary to use a diagnostic pathway that takes those characteristics into account.

14.8.1.1 Initiation

A physician–patient discussion about sexual problems is likely very different from one about blood pressure:

– It can be uncomfortable for both physician and patient.
– There is no real example of an "ideal" conversation.
– There is a lack of clarity regarding definition, assessment and objective measures.

The challenge of talking appropriately with patients about sex needs to be met because sexual problems:

– Are highly prevalent.
– May affect overall well-being and self-image more than many other conditions.

Most patients feel a sense of relief when they understand that their sexual problems are common. Therefore, it is the responsibility of the physician to initiate the conversation and to use appropriate communication skills. Communication skills include the use of open questions, encouragement, generalising and normalising the issue of sexuality.

14.8.1.2 The Narrative: Understanding the Individual Profile of HSDD

The narrative describes the story of the patient in her own words. It allows the physician to get inside into the world of the patient (her feelings and thoughts) by listening to the content, the words used, the tone, the phrasing, the pauses, etc.

The physician must be able to understand the **individual profile of the desire problem** and the **multifaceted phenomenology** of each individual case.

Several aspects of the desire problem should be attended to with great care:

- **Dimensions:** This refers to the internal comparison a woman makes regarding her desire problem. Is it less desire compared to the partner's desire? Less than in past experience? Less than she might perceive other women's to be? Less than some internal ideal of desire that she might have?
- **Elements and composition**: Which parts of the desire experience are affected, such as internal (cognitive and emotional elements example fantasies, daydreams, feeling sexy and feeling sexual appetite) or external behavioural elements (active seeking of sexual stimuli and/or sexual activity with or without partners).
- **The distress caused by the low desire**: This can be elucidated by asking the patient what the impact of low desire is on her individual mental well-being, the relationship and her general quality of life?

14.8.1.3 Differentiating Questions

After understanding the individual profile of the HSDD, the physician needs to differentiate clinical subtypes. The following subtypes are of importance and can be differentiated by questions:

A) Has this lack of interest in sex always been there? Was it different before? When did you consider your desire was sex good for you?
   Subtype: Primary (lifelong) versus secondary (acquired)
B) Did the loss of desire develop gradually or occur abruptly?
   Subtype: Gradually developing versus related to specific events
C) According to your experience, is the lack of desire related to specific situations? Are there situations in which you feel desire and interest in sex? Is the lack of desire related to your partner, for example, does your partner have sexual difficulties like premature ejaculation or ED, or is the lack of desire related to specific behaviours of your partner, such as a lack of adequate stimulation? Is it related to the appearance or attractiveness of your partner, or some other difficulty (e.g. level of communication) with your partner?
   Subtype: Generalised or situational
D) When you engage in sexual activities do you have difficulties getting aroused (emotionally and physically)? Do you have difficulties experiencing orgasm? Do you feel pain when you masturbate or have sexual intercourse?
   Subtype: Single or combined

14.8.1.4 The Descriptive Diagnosis of HSDD

The descriptive diagnosis of HSDD describes the dimensions, elements, the degree of bother or distress, the possible combination with arousal disorder, orgasmic

disorder, sexual pain disorder and distinguish between primary versus secondary, global versus situational, gradually developing versus abrupt beginning and single versus combined disorder.

14.8.1.5 Exploring Conditioning Factors

The multifactorial aetiopathogenesis of HSDD is well documented in the literature.

Two major groups of conditioning factors can be distinguished, which have to be elucidated by history taking:

A) Biomedical factors which can be subdivided into diseases, drugs and hormones.
B) Psychosocial factors which can be subdivided into individual psychological factors, relationship factors, sociocultural and economic factors.

The gynaecological examination should include:

- Vulva: check for labial and clitoral structure and morphology (agglutination, etc.), check for atrophy, lichen, inflammation, check for painful points in vestibulum.
- Vagina: check for atrophy, ph, signs of infection, descensus, cysto and rectocele
- Pelvic floor: check for hypertonicity of pelvic floor muscles, muscular insufficiency, ability to voluntary contract pelvic floor muscles
- Uterus: check for fixed retroflexion, painful sensations especially of uterosacral ligaments and fibromas
- Adnexal region: painfulness on examination and adnexal masses

Ultrasound examinations to assess uterine adnexal pathology are also recommended.

Usually, there is no indication for **laboratory investigation**. Oestrogen deficiency can be detected by history and physical exam. Androgen deficiency can be detected by history and checking into the combination of symptoms. I think we need to add other blood test that can be recommended if indicated as glucose, thyroid hormones, prolactin and maybe more specialised as FSH, LH? What about blood pressure is that also on the list? However, I agree that the message should be that blood tests are taken when there is a clinical indication, not routinely.

14.8.1.6 The Explanatory Comprehensive Diagnosis

The biopsychosocial assessment should be summarised and organised in two major dimensional lines as an explanatory diagnosis.

A) Biological, psychological, relational and sociocultural factors
B) Approximate direct and distant indirect factors.

In each dimension, there are factors that have a direct immediate impact on sexual function: for example, on the biological level, this may be drugs or hormonal changes; on the psychological level, these can be ignorance, performance anxiety, distraction; on the level of the relationship, it maybe the partner's way of stimulating or partner's dysfunctions. Distant indirect factors are those that date back in the life story of the patient but still have an impact like previous operations (biological level), early neglect and abuse (psychological level), previous traumatic experiences in relationships (relational level) and education (sociocultural level).

14.9 Therapeutic Options

14.9.1 Basic Counselling

Basic counselling comprises several elements as given below:

- It gives the patient the opportunity to talk about her own sexuality. Through active listening the patients will feel accepted and understood and may get emotional relief (**Catharsis effect**).
- Information can be disseminated about frequency of problems, differences and similarities between female and male sexuality, knowledge about sexual physiology and anatomy (**Psychoeducation**).
- Counselling can increase knowledge and dispel myths and misinformation about human sexuality (**Empowerment**).

14.9.2 Hormonal treatments

Hormone replacement therapy is indicated for the following:

- HSDD with a clinically significant drive deficiency component
- Medical conditions leading to hormone deficiency states
- Menopause transition and aging
- Hormonal contraception
- Add-back therapy in patients with mixed aetiology

A large majority of studies show positive effects of hormone replacement therapy in different aspects of female sexual function and sexual satisfaction.

Clinical trials with **testosterone therapy** in women with HSDD have shown treatment efficacy in:

- Surgically menopausal women treated with oestrogen and progesterone
- Naturally menopausal women treated with oestrogen and progesterone
- Surgical and natural menopausal women without oestrogen and progesterone treatment and in premenopausal women

Tibolone had beneficial effects on HSDD in two studies [117, 118].

DHEA has not proven effective in controlled studies. There are, however, interesting results indicating that DHEA and DHEAS may serve as important precursors for androgen production, and thus substitution with these substances may correct some subclinical deficiencies in testosterone levels.

14.9.3 Centrally Active Drugs

These would be indicated for women with HSDD in whom no major endocrine or psychosocial factors contribute to low desire. Although no drugs have yet been approved for the specific treatment of HSDD, some are used off-label to promote sexual desire in women suffering from HSDD.

One is the antidepressant bupropion [121], which can increase arousability, responsiveness and sexual desire in women with major depression. This drug blocks the reuptake of dopamine and acts as a noradrenergic and cholinergic receptor antagonist, which may augment the activation of excitatory systems in the brain for sexual desire.

Several drugs are currently undergoing clinical trials for the treatment of HSDD.

- The melanocortin agonist drug bremelanotide [122] promotes dopamine release in the preoptic area of the hypothalamus and has shown initially promising results in men and women. But unexpected cardiovascular side effects have led to the stop of further research with this drug.
- Flibanserin, a drug that acts at serotonin receptors to reduce the inhibitory influence of serotonin, showed partial efficacy and would have been an interesting venue for the pharmacological treatment of low desire. The FDA asked the producer to provide further evidence about efficacy and risks which led to a situation in which the drug was not registered for this indication.

14.9.4 Psychotherapeutic Interventions

Psychotherapy is indicated when there is ambivalent motivation to be sexually active with a partner, but in which the partner does not suffer from sexual dysfunction and both partner and patient are motivated to fix the problem. The lack of desire may stem from interpersonal relationship issues, lack of knowledge and experience with sexual pleasure, low sexual self-esteem, patterns of sexual activity that have become "routine", etc. The treatment of HSDD by psychotherapeutic interventions is not well documented as far as evidence-based medicine requirements are concerned. Although the sensate focus therapy of Masters and Johnson was reported to be successful, it had limited outcome measurements assessed in the short term. It is not clear how long the therapeutic effect lasted, or whether it translated well from the therapeutic environment back to the patients' home environment. There is only one randomised controlled trial in the past 6 years, in which group cognitive behaviour therapy was shown to improve HSDD in 74 % of women [124]. More recent studies have reported good efficacy in treating both sexual arousal and desire disorders in women using elements of mindfulness, meditation and yoga in addition to psychotherapy [129]. It is likely that therapeutic approaches must be tailored to the particular subtype of HSDD along with the particular needs of the patient. It is also likely that drug therapy in conjunction with psychotherapy will be beneficial for many patients, especially if the psychotherapeutic intervention can build upon a faster amelioration induced by the drug effect.

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Quality of Life and Sexual Health in Breast Cancer Survivors

15

Johannes Bitzer

15.1 Definitions of Quality of Life

There are many definitions of the quality of life depending on the perspective which is taken (economic, political, medical, psychological, etc.). WHO has given over the course of time different definitions:

- "*individuals' perception of their position in life in the context of the culture and value systems in which they live in relation to their goals, standards and concerns*" (WHO 1993)
- "*Complete physical, mental and emotional wellbeing*" (*2000*)

A newer definition defines the health-related quality of life as the impact of the health condition (disease) on physical and psychological functioning (Fig. 15.1).

To simplify and to have a practical approach, we suggest a definition which takes into account the subjectively experienced needs of an individual and the degree to which these needs are satisfied (Fig. 15.2).

This definition allows or changes on both sides (needs and fulfilment of needs) to reestablish a new balance. The impact of breast cancer and its treatment on the life of the patient comprises many dimensions and almost all aspects of life:

Physical symptoms: Pain, fatigue, immobility, hair loss, etc.
Emotions: Fear, anxiety, depression, tension, loss of self-esteem and body image changes
Social, financial and professional stress: Changes in professional roles
Family: Roles and interaction pattern
Problems with the medical system: Lack of time, change of physicians, communication problems, etc.

J. Bitzer (✉)
Department of Obstetrics and Gynecology, Women's Hospital, University Hospital Basel, Spitalstrasse 21, 4031 Basel, Switzerland
e-mail: JBitzer@uhbs.ch

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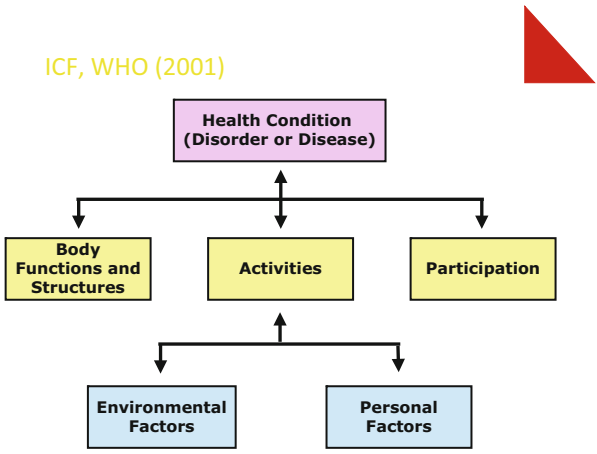

Fig. 15.1 Definition of quality of life

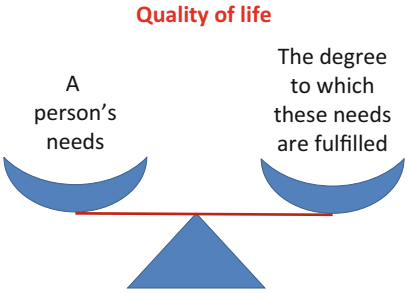

Fig. 15.2 Quality of life

Existential and spiritual challenges: Confrontation with death and searching sense

Sexual life: Loss of desire, pain, fear of losing the partner, etc.

Specific stressors for breast cancer patients are:

- Threat to femininity and female Identity
- Sexual life impairment
- Premature menopause
- Premature infertility
- Role changes
  - Housewife, mother, partner, professional and cancer
- Culturally defined gender roles

The first reaction to the diagnosis of the disease is similar in many patients as:

- Shock, numbness and disbelief
- Desperate and hopeless
- Mixed mood state with dysphoria, irritability and fear depressive states
- Loss of appetite and sleeping disorder
- Difficulty to concentrate
- Intrusive thoughts

Symptoms usually regress during a 7–14-day period

15.1.1 The Stress Response: General Aspects

Different levels of the longer lasting stress response can be distinguished as:

Emotional reactions
- Anxiety and fear
- Death, depression disfigurement disability and dependence
- Loss of control, anger, shame, helpless and hopeless

Cognitive reactions
- Threat to life
- Blame
- Punishment
- Loss
- Injustice
- Destruction
- Chaos
- Non-sense

Behavioural response
- Becoming a patient
- Acting out
- Help seeking behaviour
- Withdrawal
- Social isolation
- Passivity
- Aggressive behaviour

Physicians should notice and understand the individual stress response to help patients with adaptation difficulties to look for changes in their coping pattern.

The individual response to the disease will depend on the person's defence and coping mechanisms.

Defence mechanisms are semi-conscious or even unconscious psychological reactions and include suppression, denial, isolation, projection, displacement, etc.

Coping mechanisms are emotional expression, humour, cognitive reframing, finding sense, getting information, optimism, sublimation, etc.

These mechanisms will depend on the patient's personality, previous life events, education, social support and belief symptoms.

If the defence and coping mechanisms cannot help to create a new psychological balance in the patient, psychiatric morbidity may occur (Table 15.1).

Table 15.1 Psychiatric morbidity of cancer patients

Prevalence	
Anxiety disorder	Screening 50 %, interview ca. 30 %
Depression	Screening 50 %, interview 15 %
Adaptation disorder	Screening and interview ca. 50 %
Post traumatic stress disorder	Screening or interview ca. 30 %
Other symptoms: Sleeping disorder (20–70 %), Fatigue (20–35 %), Cognitive impairment (20–75 %)	

If general counselling and a helpful therapeutic relationship are not enough, more specific interventions should be proposed.

There is a vast literature on psychological interventions.

More than 10,000 empirical studies are published in the literature.

Last major Meta-analysis with more than 18,400 studies showed a summary of those interventions, which are very well evaluated. The following interventions lead to an increase in the quality of life of those cancer patients who ask for or use these psychotherapeutic possibilities:

- Group therapy
- Supportive psychotherapy
- Cognitive-behavioural therapy
- Exercise and body-centred approaches

A prerequisite for efficacy is the willingness of the patient to work in a psychotherapeutic setting which includes the readiness to accept help.

15.2 Sexual Health and Breast Cancer

There is a dialectic relationship between sexuality and cancer: Sexuality is commonly associated with life, love, joy, passion, etc. and cancer is for many of us synonymous with destruction, death, loss and sadness. This antinomy is reflected in typical irrational health beliefs, which can be found not only among breast cancer patients but also among physicians.

- Sex is something luxury which does not have any place in the serious fight for survival. Sexual life is no more possible in the diseased body or may even be harmful for that body.
- Losing one part of sexual function means that the entire sexual life has to be given up.
- Intercourse and sexuality are identical.
- Being able to have intercourse defines sexual identity.

In these rather destructive health beliefs the concept of sexuality is reduced to intercourse or the physiology of the human sexual response. It is however necessary that we are reminded as physicians and that we remind our patients that there are several dimensions to the sexual life of an individual. Besides the genital response, sexuality has to do with one's identity (being a woman or being a man), with

emotional intimacy (feeling close and feeling understood), with body image (being in accordance with the body, feeling beautiful and attractive), and last but not least with the potency of reproduction (with for a child and feeling fertile).

15.2.1 Sexual Dysfunction in Women with Breast Cancer

The prevalence of sexual dysfunction has proven to be high in breast cancer patients in several studies.

- Anderson found severe and long-lasting sexual dysfunctions among 50 % of patients.
- In another study, hypoactive sexual desire disorder was observed in 64 % of cases, 42 % suffered from problems with lubrication, 38 % reported dyspareunia and 30 % had difficulties reaching orgasm. More than half of the women indicated that they had problems to accept their body.
- In a longitudinal study, it was found that the quality of life diminishes during the diagnostic and the primary therapeutic phase but recovers with time. Only sexual life suffers a persistent deterioration.
- In a case–control study with women after breast cancer and under chemotherapy, all domains of sexual function were significantly inferior to controls. Multivariate analysis showed that vaginal dryness was an important variable influencing and modifying all the other domains of the sexual experience and explaining a large proportion of the difference between patients and controls.
- Concerning the types of surgery, Bukovitch found that there was a considerable diminution of sexual satisfaction in women after mastectomy and breast-conserving surgery without a significant difference between the two groups. In both groups, the acceptance by the partner was considered either better than before the operation or the same like before. The only difference was that 58.3 % of patients after mastectomy reported difficulties with their body image, while this affected only 44.9 % among patients with breast-conserving therapy.

Chemotherapy seems to have a deleterious effect on sexual function not only during treatment but also up to 3 years after treatment and this mainly in premenopausal women.

Tamoxifen alone does not show negative effects among women beyond 50 years, while zoladex and the combination of LHRH with tamoxifen lead to negative effects on sexual function.

Looking at variables that have an influence, Speer found in his study that patients had low scores in all domains of sexual function except desire and that there was no correlation between the degree of sexual dysfunction and the type of cancer or plasma values of testosterone. The distress linked to the relationship was the most important variable to explain arousal problems, orgasm difficulties, satisfaction and sexual pain.

In most studies age, relationship difficulties, and depression were the important factors contributing to sexual dysfunction of the patients.

In another study, Greendale found that two among three sexual domains were influenced by the quality of the relationship, vaginal dryness, sociocultural factors and hot flushes. Other factors were related to only one domain of the sexual experience: Age, the time since diagnosis, breast conservation, presence of comorbidities, urinary incontinence, body image, plasma values of bioavailable testosterone, LH and SHBG [1–9].

15.2.2 Breast Cancer and the Relationship: Risk Factor or Resource for Healing

The disease represents a huge challenge to the couple and as has been shown before the quality of the relationship is a predominant factor for the sexual life of the patient. To better understand the complex changes for the couple, it is useful to have a look at the different changes the patient has to cope with:

- Overcome the fear of death
- Integrate the surgical or other physical changes into her body image
- Reestablish self-confidence and confidence in her body
- Cope with the recurrent pain episodes and the fatigue
- Cope with menopausal symptoms
- Overcome phases of depression and exasperation
- Accept a certain reduction in activities and physical and mental fitness

All these efforts are experienced by the partner and are accompanied by him or her. This means that there is a fundamental restructuration of the relationship. For clinical purposes, we can distinguish several axes on which the couple has to redefine and reestablish a functional balance.

15.2.2.1 Axis Autonomy Versus Independence

This axis describes the hierarchic or power dimension in a relationship. The female patient has at least for a while to accept a diminution of her autonomy and an increase in dependence on the partner. As a reaction to this, the partner has to respond to this change with an increase in involvement and care, which may need a redefinition of roles. For the couples in whom the autonomy of the woman was an essential part of her self-esteem, these changes may lead to aggressive reactions by the patient and misunderstandings among the partners.

15.2.2.2 Axis Symmetry Versus Complementarity

There are couples in whom the completion of daily tasks, the social positions, and the competences are equally distributed and symmetric and other couples in whom there is much more asymmetric complementarity. The disease may demand a reorganisation of tasks and competences and a flexible adaptation. For couples with rigid symmetry or complementarity, this may present a crisis to which they are not used or for which they have to develop new patterns of interaction.

15.2.2.3 Axis Closeness Versus Distance

The physical change and the changes in physical and mental well-being can at different moments in the same patient lead to an increased need for emotional closeness or sometimes may create a need for more distance and being on her own. Couples who are unable or unused to modify closeness and distance and who are either very close or very distant are at risk to exaggerate the pre-existing pattern like getting into an symbiosis on one hand or an alienation on the other hand.

Taking into account these complexes, it becomes evident that the interaction of the couple may become very difficult with a lot of possible misunderstanding and communication problems.

In the first place, pre-existing conflicts can be reactivated by the disease and get a new importance in this crisis.

Second, the patient feels threatened and searches a new internal balance and to some degree a new definition of herself, a "partially new" identity.

Third, the partner has often a lot of ambivalent feeling fluctuating between empathy and frustration, between hope and guilt and between care and aggression. He too has to find a new internal balance for himself.

Finally, both of them often are afraid of the changes and the outcome of redefining their relationship.

15.2.3 How Can We Help?

The main task to facilitate the talk about sexuality and to help patients and couples understand the impact of the disease on their sexual life.

We propose the following steps:

1. **Define together with the patient or the couple the sexual problem and the consequences**:

   Ask actively about the actual sexual experience by giving a general introduction:

   - *In many patients the disease or the treatment you are having impacts on their sexuality. How is your experience*?

   Help the patient to describe the sexual problem in terms of desire, arousal, orgasm, pain, and general satisfaction:

   - *Did or do you observe any change in your sexual desire or interest, in sexual fantasies or activities*?
   - *Do you have difficulties in getting sexually aroused*?
   - *Does the vagina not feel wet enough*?
   - *Do you have difficulties to experience an orgasm*?
   - *Do you feel pain during intercourse or masturbation*?

2. **Assess the pre-existing characteristics of the patient's sexual experience and behaviour and body image**:

   - *How would you rate the importance of sexuality in your life before the onset of the disease*?
   - *Have you would you rate your enjoyment of sexuality at that time*?

- *Did you experience any of the following sexual difficulties* (*Loss of interest*, *difficulty to reach orgasm*, *arousal difficulty*, *etc.*)?

3. **Assess the pre-existing level of physical and psychological well-being**:
   - *What diseases did you suffer from before the onset of the actual illness*?
   - *How would you rate your physical and psychological well-being before*?
4. **Assess the disease-specific impact on sexuality following the 9D mammogram**:
   - Danger (Threat)
     How does the patient experience the threat of the disease to her or his life?
   - Destruction
     Does the disease or treatment have a direct impact on the integrity of sexual organs?
   - Disfigurement
     Does the disease lead to a change in the body's outer appearance with a possible negative emotional impact?
   - Disability and pain
     Is the disease causing chronic pain and motor disability which may impact on the patient's capacity to enjoy the bodily expression of her sexuality?
   - Dysfunction
     Does the disease lead to an impairment of the sensorimotor and sensovegetative innervation of the physiological processes involved in the human sexual response?
   - Dysregulation
     Does the pathophysiology of the disease have an impact on the neurobiological and neuroendocrine processes involved in the central or peripheral regulation of the sexual response cycle?
   - Disease load
     Is the disease accompanied by an impairment of intimate physical mechanisms like micturition and defecation?
   - Drugs
     What is the impact of the drugs used for the treatment of the disease?

4. **Assess the patient's and partner's response to the disease**:
   - *How would you describe your actual state of mind* (*mood*)?
   - *What are the greatest difficulties you encounter in living with the disease*?
   - *How do you cope and what are the things that help you in confronting the disease*?
   - *What was and is your partner's reaction to the disease*?
   - *Have you observed a change with respect to your sexual needs*?
   - *What about your partner*?

Summarizing this information will allow to define together with the patient and the partner the sexual problem and help them understand the impact of previous life experiences, disease-specific factors, and the way of coping with the disease on the sexual life of both.

15.2.4 Therapeutic Plan

After having established a comprehensive explanatory diagnosis, treatment option should be discussed with the couple.

The first question refers to the individual objectives regarding change:
"What is good and valuable in your sexual life and what should remain as it is?"
"What should change in your sexual life and how would you notice that change has taken place?"
"Are there different levels of objectives like ideal scenario, good enough scenario and acceptable scenario?"

All couples need basic sexual counselling.

The contents of this general session should be the following:

- Information and education about the sexual problem, its medical name and prevalence
- Information and education about the biological, psychological and social factors contributing to the problem along the line of the diagnostic pathway explaining general predisposing and maintaining factors and disease-specific factors using the 8 Ds
- Education about possible gender differences in response to disease, stress, and sexual difficulties
- Discussion of the individual's and couple's concept of sexuality and love
- Discussion of possible new definitions and orientations and new needs with respect to love and sexuality

For many patients in the clinical setting, this psychoeducational intervention is not only helpful but also may be sufficient as a first step and basic sexological care.

15.2.4.1 Individualised Sexological Treatment

There are basically two groups of therapeutic options physicians should have knowledge about:

(a) Medical interventions:

These include local oestrogen for dyspareunia (see above), antidepressants without negative impact on desire and lubricant and change of oncological therapies in consultation with the oncologist. Other possible approaches include PDE 5 inhibitors in patients with arousal problems, oxytocin nasal spray (desire and orgasm).

Testosterone replacement is very controversial and has not yet been integrated into treatment programs.

Finally, physical therapy may be very helpful to reduce pain (e.g. lymphoedema)

Patients should be informed about the efficacy, possible side effects, and risks of these interventions in relation to their individual problems. They can then take an informed decision regarding specific treatment options, which usually need a multidisciplinary approach with close collaboration between the attending physician and the therapist trained in sexology.

(b) Psychological interventions:

The mainstay is based psychological interventions. These include supportive psychotherapy, interpersonal psychotherapy, Couple therapy, Coping counselling and Specific Sex Therapy (Sensate focus, Sexual aids, etc.).

15.2.4.2 Example Couple Therapy

Couple therapy can provide help for the patient.

- The patient has often to learn how to express and verbalise her emotions in a way that allows a dialogue with her partner.
- She has to become aware of her requests and exigencies she has towards her partner and the environment and how to put this into words and phrases.
- She has to rebuild her body image and find out what her sexual wishes are, what has changed, and what has remained the same.

Couple therapy can provide help for the partner.

- He has to determine for himself the significance and importance of his partner's disease for him.
- What is he going to lose? Which are the changes he is afraid of or he feels threatened by? What role do feelings of guilt play for him and how is he handling these feelings? Which are possibly controversial feelings and internal conflicts he has as a reaction to the disease of the partner?
- He has to redefine his relationship to the damaged body of his partner, of his emotions and his feelings and behaviour. He also has to redefine his sexuality and the couple's sexuality.

Couple therapy can provide help for the couple.

One of the largest difficulties lies in the need for open communication. The physician can help to open up and maintain such a dialogue which will develop through different phases with ups and downs, with good and bad feeling and with learning processes for both. The major functions of this moderated dialogue are catharsis, "putting negative feelings and conflicts on the table", increasing insight and mutual understanding, defining the roles, defining the problems to be resolved and searching for solutions.

Systemic questions put forward by the physician can catalyse this dialogue:

- What do you think your partner should change in her/his behaviour and what do you think that he/she should maintain?
- According to your experience what are the consequences of the disease for your partner's sexual life?
- What do you think are the consequences for your relationship?
- What do you think can be changed and what has to be accepted?
- What are impossible and possible solutions?

This moderation can catalyse a constructive communication between the partners and thus help that the relationship becomes a healing resource and not an additional stressor or risk factor.

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Part V

Hormone and Pregnancy

Thyroid Disorders and Pregnancy: Diagnostic and Therapeutic Proposal

16

Andrzej Milewicz, Anna Brona, Diana Jędrzejuk, and Felicja Lwow

Thyroid function changes in pregnancy. Thyroid volume increases by 10 to 20–40 % (more in iodine deficiency regions). The total T4 and T3 production increases by about 50 % (with simultaneous requirements for iodine). TSH concentrations fall during pregnancy, especially in the first trimester, because hCG cross-reacts with TSH receptors on the thyroid gland. The lowest serum TSH level is observed in 10 week of pregnancy. At the same time (between 7 and 11 weeks gestation), serum hCG level is highest. Serum TSH level increases gradually throughout pregnancy.

In 10–20 % of pregnant women, in the first trimester, increased thyroid antibodies titer with normal TSH levels are found. In 16 % of them, TSH level will exceed 4.0 mlU/l by third trimester. 33–50 % of pregnant women with thyroid antibodies will develop postpartum thyroiditis. There are no indications for thyroid antibodies screening; however, TPO antibodies estimation should be considered in pregnant women in first trimester or those who are planning pregnancy.

During pregnancy, free thyroid hormones concentrations should be carefully interpreted. The tests based on antigen–antibody reaction may provide lower than real results, especially in second and third trimesters, because serum TBG concentrations rise and lead to increase in circulating total T_4. Albumins concentrations decrease and dilution of serum is present. Free fatty acids concentrations rise. Rare effect of drugs administered during pregnancy (i.e., heparins) may be present. In some women in the advanced stages of pregnancy, free thyroxin level is observed to drop (by 10–30 %). In ambiguous cases, 150 %

A. Milewicz (✉) • F. Lwow
Department of Health Promotion, Faculty of Physiotherapy, University School of Physical Education, Paderewskiego 35, Wroclaw 51-612, Poland
e-mail: andrzej.milewicz@umed.wroc.pl

A. Brona • D. Jędrzejuk
Department of Endocrinology, Diabetology and Isotopes Therapy, Wrocław Medical University, Pasteura 4, Wrocław 50-367, Poland

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value of standard upper range of normal total thyroid hormones concentrations for nonpregnant women may be applied.

TSH screening should be regarded before and during pregnancy. TSH routine determination is indicated in women planning pregnancy. TSH routine determination is also indicated in women in 4th–8th week of pregnancy. TSH evaluation is recommended before conception in women taking medicines influencing concentration of thyroid hormones (metformin). It is advisable to define and apply referential TSH values, which are specific for pregnancy particular trimesters in the particular population and laboratory. If it is impossible, values not higher than 2.5 mIU/l should be adopted as standard TSH upper range.

TPO antibodies estimation is recommended in pregnant women or those planning pregnancy with concomitant autoimmune diseases, positive history of autoimmune diseases, TSH >2.5 mIU/l, thyroid ultrasound pointing at thyroid autoimmune disease regardless TSH result, positive history of miscarriages or preterm deliveries, after postpartum thyroiditis, and in those who are or were treated for infertility.

Determination of serum TRAb is recommended in hyperthyroid patients diagnosed for the first time during pregnancy. It is also recommended at the end of second trimester (before 22nd week of gestation) in the case of fetal or neonatal hyperthyroidism during previous gestations, current antithyroid drug therapy due to Graves' disease, pregestation treatment (thyroidectomy or 131I treatment) due to Graves' disease—including also euthyroid and hyperthyroid patients, previously increased TRAb titer and presence of fetal inexplicable tachycardia or fetal goiter detected on ultrasound.

Thyroid imaging is used in some situation. Thyroid ultrasound in pregnancy is indicated in the following cases: dispersed or nodular goiter or its suspect, abnormal results of hormonal tests or thyroid antibodies tests, and in pregnant women from thyroid cancer risk group. The examination should be performed in patients with increased TRAb titer or/and treated by antithyroid drugs. It should be performed for the first time in 18th–22nd week of gestation and preferably repeated every 4–6 weeks. Active or subsided Graves' disease as well as antithyroid drugs treatment are indications for fetal thyroid ultrasound. It should be performed at the end of second trimester (18th–22nd week) and should be repeated every 4–6 weeks if there are any clinical indications.

16.1 Thyroid Disorders and Pregnancy

Hyperthyroidism and hypothyroidism are the main causes of thyroid disorders in pregnancy. Thyroid diseases affect up to 4 % of all pregnancies (0.1–0.4 % hyperthyroidism, 2–3 % hypothyroidism).

16.1.1 Hyperthyroidism

Graves' disease is the most common cause of autoimmune hyperthyroidism in pregnancy. It affects 0.1–1.0 % of all pregnancies (of these 0.4 % clinical and 0.6 % subclinical). More frequent than Graves' disease as the cause of thyrotoxicosis is the syndrome of gestational hyperthyroidism defined as "transient hyperthyroidism, limited to the first half of pregnancy characterized by elevated FT4 or adjusted TT4 and suppressed or undetectable serum TSH, in the absence of serum markers of thyroid autoimmunity". It is diagnosed in about 1–3 % of pregnancies, depending on the geographic area and is secondary to elevated hCG levels. It may be associated with hyperemesis gravidarum. Other conditions associated with hCG-induced thyrotoxicosis include multiple gestation (TSH suppression is observed in 67 % of pregnant women with hCG concentration >200,000 IU/l, and in 100 % with hCG concentration >400,000 IU/l; since hCG concentrations are higher in multiple pregnancies than in singleton pregnancies, the downward shift in the TSH reference interval is greater in twin pregnancies than in singleton pregnancies), hydatidiform mole, or choriocarcinoma. In previously healthy pregnant woman, in whom TSH value is found below lower range of referential values, fT3 and fT4 evaluation is indicated, and TSH should be checked in second trimester. Treatment is not necessary. Thyroid ultrasound is required and in ambiguous cases. TRAb titer should be determined.

Multiple gestation patients with nonrestrained vomiting or gestational trophoblastic disease are especially predisposed to pregnancy induced thyrotoxicosis. In this group of patients, FT3, FT4, and TSH and even TRAb antibodies should be determined as well as thyroid ultrasound is indicated. Antithyroid drugs administration may be considered only when the symptoms of hyperthyroidism are very aggravated in mother. In most women, FT4 level normalizes in 15th week and TSH in 19th week. Incorrectly controlled hyperthyroidism may lead to: miscarriages, preterm deliveries, small birth weight, stillbirths, mother's thyroid storm, and her congestive heart failure. Differentiation between gestational hyperthyroidism and other reasons for thyrotoxicosis is very critical as they require different procedures.

Diagnosis of hyperthyroidism during pregnancy creates sometimes some difficulties, because of nonspecific symptoms of hyperthyroidism: tachycardia, increased sweating, nervousness, tremor, and weight loss, which are typical symptoms for pregnant women without any thyroid disease. Specific symptoms of thyroid disease like goiter, thyroid ophthalmopathy, pretibial edema, lower TSH (depends on trimester of pregnancy; 0.01–0.3), proximal myopathy, weight loss in women without vomiting and with good appetite, and increased TRAb titer are necessary for diagnosis of hyperthyroidism in pregnant women.

Treatment of hyperthyroidism in pregnancy comprises antithyroid drugs and thyroidectomy. Antithyroid drugs [methimazole (MMI) and propylthiouracil (PTU)] are the drugs of first choice. The great concern with the use of antithyroid drugs are side effects—rare cases of embryopathy associated with MMI and the risk of acute hepatic failure associated with PTU. Starting doses are 5–15 mg for MMI, and 50–300 mg for PTU. PTU is postulated to be restricted to first trimester. Other exceptions to avoiding PTU are patients with MMI allergy and management

of thyroid storm. Hepatotoxicity may occur at any time during PTU treatment. Monitoring hepatic enzymes during administration of PTU should be considered. In the second trimester, change for MMI is recommended. At the initial stage of treatment, follow-up should be continued every 2 weeks. After restoration of euthyroid state, control tests should be continued every 2–4 weeks. FT4 concentration should be maintained in the upper range of reference values characteristic for gestation. The "block and substitute" treatment (LT4 and antithyroid drug combination) is forbidden.

Thyroidectomy is indicated in second trimester only in the case of antithyroid drugs severe side effects, the necessity of high doses or/noncooperative patient with uncontrolled hyperthyroidism. Subclinical hyperthyroidism should not be treated. 131I treatment during breast feeding is absolutely forbidden. Cordocentesis for estimation of umbilical blood thyroid hormones concentration should be performed only in the case of inability to diagnose fetal thyroid disease on the basis of clinical history or when the result may influence the treatment.

Hyperthyroidism is associated with following adverse pregnancy outcomes: preeclampsia (OR 1.78), superimposed preeclampsia (OR 3.64), preterm birth (OR 1.81), and intensive care unit admission (OR 2.08). Fetal and neonatal risk related to mother's hyperthyroidism are fetal hyperthyroidism, neonatal hyperthyroidism, fetal and neonatal hypothyroidism, and central (secondary) hypothyroidism.

There are no contraindications for breast feeding in hyperthyroid patients if MMI dose does not exceed 20 mg/day, and PTU 300 mg/day. The drugs should be taken after breast feeding and 3-h break should be preserved before the next one [1–4].

16.1.2 Hypothyroidism and Pregnancy

Clinical hypothyroidism is characterized by TSH >2.5 mIU/ml and decreased FT4 or TSH >10 mIU/ml independently of FT4 concentration. Subclinical hypothyroidism means TSH within the range 2.5–10 mIU/ml and normal value of FT4. Subclinical hypothyroidism is related to neurocognitive defects, increased risk of miscarriage and obstetric complications. In women with previously diagnosed hypothyroidism, in preconception period, TSH concentration value should be maintained at the level below 2.5 mIU/l, preferred value—at about 1.0 mIU/l (in order to reduce the risk of TSH elevation during the first trimester). After pregnancy confirmation, L-Thyroxin dose should be increased by 30–50 %. After change of L-Thyroxin dose, TSH concentration control is needed every 4 weeks. After delivery, pregestation L-Thyroxin dose should be adjusted and TSH should be checked after 4–6 weeks. There is no contraindication for breast feeding in patients treated with L-Thyroxin.

L-Thyroxin therapy is indicated for patients planning pregnancy with TSH concentration value between 2 and 2.5 mlU/l and standard upper range for the particular laboratory, especially when TPOAb titer is increased.

In the case of diagnosis of clinical hypothyroidism, normal TSH and free thyroid hormone concentration should be resumed. Subclinical hypothyroidism diagnosed during pregnancy should also be treated. There is no evidence for advantageous treatment of isolated hypothyroxinemia in second and third trimester of pregnancy. Adequate iodine prophylaxis should be administered. Hypothyroidism is associated with following adverse pregnancy outcomes: preeclampsia (OR 1.47), superimposed preeclampsia (OR 2.25), gestational diabetes (OR 1.57), preterm birth (OR 1.34), induction (OR 1.15), cesarean section, both preterm and after spontaneous labor (OR 1.31), and intensive care unit admission (OR 2.08) [1–4].

16.1.3 Thyroiditis and Pregnancy

Chronic autoimmune thyroiditis should be considered before pregnancy. In women planning pregnancy, in whom TSH exceeds the value of 2.5 mlU/l, TPOAb titer should be estimated. In women planning pregnancy, in whom TPOAb titer is elevated, TSH concentration should be monitored every 6 months.

Patients, especially predisposed to postpartum thyroiditis, are these with increased TPOAb titer and the history of postpartum thyroiditis or diabetes type 1. In this group, TSH measurement is indicated in 6 week, 3, 6, and 12 months after delivery. In thyrotoxic phase in the course of postpartum thyroiditis, antithyroid drugs administration should be avoided. In hypothyroid phase, L-Thyroxin should be administered and TSH concentration should be maintained <2.5 μlU/ml—preferable value is below 2.0 μlU/ml. After 1-year treatment with L-Thyroxin may be abandoned [1–4].

16.1.4 Nodular Goiter and Pregnancy

The prevalence of nodular goiter increases with gestations number (in iodine insufficiency areas). Increase of existing thyroid nodules size during pregnancy may occur. Pregnancy is the risk factor of new thyroid nodules formation. Indications for fine-needle aspiration in pregnant women are the same as in general population. Thyroid gland biopsy may be performed regardless of stage of pregnancy. In case of fine-needle aspiration sample is suspicious for thyroid cancer, there is no indication for L-Thyroxin treatment. Pregnant woman with nodular goiter should supplement their diet with standard prophylactic doses of iodine [1–4].

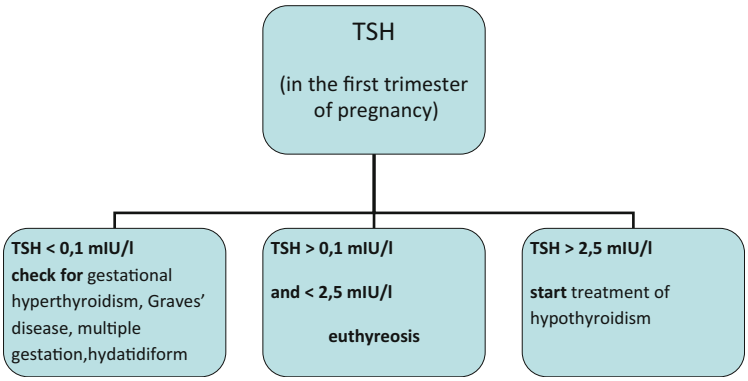

Fig. 16.1 First trimester screen algorithm

16.2 Thyroid Carcinoma and Pregnancy

Diagnosis of thyroid carcinoma in pregnancy requires fine-needle biopsy. In case of advanced carcinoma process, surgery should be considered irrespectively of gestational age. In other cases, surgical procedures may be postponed until postpartum period. Surgery for follicular (well-differentiated thyroid) carcinoma should be performed in postpartum period. In women treated pharmacologically during pregnancy (surgery for well-differentiated thyroid carcinoma deferred after postpartum), L-Thyroxin should be administered in order to maintain TSH concentration of 0.1–1.5 mIU/l. In women with previously treated thyroid cancer, the level of TSH suppression depends on preconception evidence of residual or recurrent disease [1–4].

16.3 Thyroid Function and Fertility

In patients preparing for assisted reproduction, temporary TSH increase is observed and it lasts till the end of 1st trimester—small doses of L-Thyroxin are proposed. There is no equivocal indication for L-Thyroxin use in euthyroid women (TSH below 2.5 mIU/l) with the presence of thyroid antibodies and miscarriages in medical history or/and treated for infertility in the past. In women suffering from endometriosis and/or ovarian dysfunction as well as in women preparing for treatment of infertility with the use of assisted reproduction technologies, thyroid function should be assessed and thyroid antibodies should be estimated [1–4].

16.4 Conclusions

Serum levels of TSH and FT3, FT4 depend on trimester of pregnancy. In hyperthyroidism (adenoma toxicum and Graves' disease) in the first trimester PTU and in the second trimester MMI therapy is recommended. In hypothyroidism, L-Thyroxin

treatment is recommended in dose adjusted to the severity of disease. Breast feeding is not contraindicated in women treated for hyper- or hypothyroidism (Fig. 16.1).

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The Role of Progesterone in the Prevention of Preterm Labour

17

Jean Calleja-Agius and Mark Brincat

17.1 Introduction: Endocrinology and Immunology of Parturition

Hormonal interactions are indispensable to control the establishment of pregnancy, foetal development, and even the process of parturition [1]. The placental progesterone, along with other hormones, act as allocrine factors, being produced by one organ and used by another, to modify the maternal environment and satisfy the needs of the growing foetus.

Parturition is divided into different phases depending on the contractile activity of the myometrium. The initial phase is termed "Phase 0" (quiescence), wherein the myometrium is relaxed and relatively insensitive to stimulatory uterotonics (substances that regulate myometrial tone and contractility) such as prostaglandins and oxytocin. Instead relaxatory uterotropins and uterotonics, such as progesterone, β-adrenergic agents, prostacyclin (PGI_2), relaxin, CRH, nitric oxide, work to maintain pregnancy. Generally, all these regulatory factors activate adenylyl cyclase and increase intracellular cAMP [1].

Parturition begins at the transition from "Phase 0" to "Phase 1", when the myometrium gains response to uterotonics and starts to contract forcibly and rhythmically. This is made possible by progesterone withdrawal and an increase in oestrogen drive [2]. Also, the myometrium is transformed by the expression of genes known as contraction-associated proteins (CAPs), which upregulate gap junctions between cells, ion channels, uterotonin receptors and enzymes [3]. The progesterone withdrawal and oestrogen activation are not mediated by changes in the levels of these hormones but rather by the myometrial responsiveness to these

J. Calleja-Agius • M. Brincat (✉)
Department of Obstetrics and Gynaecology, Mater Dei Hospital, Birkirkara, Malta
e-mail: jean.calleja-agius@um.edu.mt; brincatm@maltanet.net

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hormones [4]. Progesterone responsiveness depends on the activity of nuclear prostaglandin receptors (nPRs). PR-B is a principal ligand-dependant transcriptional modulator of progesterone responsive genes, which mediates relaxatory actions. Conversely, PR-A represses the transcriptional activity mediated by PR-B. In fact, it is the PR-A/PR-B expression ratio, which determines progesterone responsiveness, and it is hypothesised that progesterone withdrawal is mediated by an increase in this ratio [5]. With regard to oestrogen, the two major subtypes of receptors are ERα and ERβ [6]. ERα is drastically increased at term with the onset of labour, and it is directly associated with Cx43 expression (oestrogen-responsive CAP gene), thereby causing the functional oestrogen activation. Conversely, ERβ is not influenced by the onset of labour [7].

"Phase 2" (active labour) is then initiated by the increase in the levels of prostaglandins and the increased sensitivity of the myometrium to the prostaglandins and oxytocin. This is characterised by rhythmic contractions, which become progressively more forceful. These contractions propel the foetus forward toward the birth canal, and eventually dilate the softened cervix so that the foetus and the placenta are both delivered [1]. The main prostaglandins involved are PGE2 and $PGF_{2\alpha}$, which are produced by intrauterine tissues, mainly the amnion, chorion, decidua and myometrium [8]. The rate limiting step of prostaglandins production is catalysed by cyclooxygenase, COX-1 and COX-2, enzymes [9]. The prostaglandins are metabolised by prostaglandin dehydrogenase (PGDH), which irreversibly converts PGE2 and $PGF_{2\alpha}$ to inactive forms. The actions of prostaglandins are mediated by specific prostanoid receptors [10]. The other important mediator, oxytocin, is the most potent and specific stimulant of uterine contraction and is used to induce labour and treat postpartum haemorrhage. It is produced during pregnancy by the amnion, chorion and decidua [11]. Despite its potency, it is generally not regarded as being involved in the initiation of labour [12].

"Phase 3" begins after the placenta is expelled. The myometrial contractions are sustained in order to constrict the spiral arteries and minimise post-partum haemorrhage. Finally, the uterus returns to menstrual state by myometrial cell apoptosis and atrophy. The cervix also returns to its closed and rigid state [1].

In pregnancy, immunological suppressor activity is carried out by T regulatory (Treg) cells that increase in number when progesterone levels are high. Treg cells influence other cells through cytokines, which may influence the survival and growth of the foetoplacental unit [13]. Cytokines are also produced by the reproductive tract such as the uterine epithelium and trophoblast. Suppression may also be mediated by a soluble factor that is related to transforming growth factor-β (TGF-β) and by Prostaglandin (PGE2) by decidual cells and macrophages. All these cytokines and factors may inactivate lymphocytes [14, 15].

During pregnancy, the maternal immune system must protect the mother against any infections and tumours but at the same time must protect the foetus from any harmful immunological effects. This occurs by an altered T-helper 1 and T-helper 2 (TH1/TH2) cytokine balance [16].

The establishment of pregnancy, successful foetal development and parturition is achieved by hormonal interactions between the mother, placenta and foetus [1]. In addition, it is essential that there must be well-coordinated interactions between the maternal innate immune system and the trophoblast. The trophoblast and maternal immune system protect the foetus and mother against infectious microorganisms by acting in synchrony. Potentially dangerous molecular signatures are first identified by the trophoblast and then the maternal immune system responds in a coordinated way. The success of a pregnancy depends on good communication between the trophoblast and maternal immune system [17]. Cytokines, which can be elaborated with or without the involvement of the immune system, are involved in this communication [18]. The type of cytokines is very important in the success of pregnancy and it varies between implantation, early and late pregnancy and parturition [19]. There are mutual interactions between the closely related endocrine and immune systems. The steroid hormones and cytokines act as mediators and messengers to achieve a successful pregnancy [20]. An imbalance in hormones or cytokines can cause problems in pregnancies such as preterm birth, as well as miscarriage, pre-eclampsia and intrauterine growth retardation (IUGR) [21–24].

17.2 Preterm Labour

Preterm delivery refers to birth occurring before 37 completed weeks or 259 days of gestation [25]. In cases of uncertainty about the gestational age only, foetal weight becomes valuable in determining preterm birth, with a threshold of 500 g. However, this method is rather inaccurate since viable neonates born after 24 weeks may be less than 500 g due to IUGR and some unviable neonates may weigh more than 500 g [17]. Preterm births may be classified as "spontaneous", which may occur either with intact membranes or with PPROM. Otherwise, preterm births are classified as "indicated/iatrogenic", meaning that preterm labour is induced or elective caesarean section is performed due to obstetric complications such as pre-eclampsia, IUGR, multiple pregnancies or chorioamnionitis [17]. A significant proportion of infants born preterm develop one or more related complications, some of which require life-long care [26].

17.2.1 Common Pathway of Parturition

Preterm labour results from pathological processes which trigger some or the entire components characteristic of the normal physiologically activated pathway seen in term labour, with the critical difference being a smaller gestational age [27]. These characteristics include increased uterine contractility, cervical changes and membrane rapture [28]. Labour is characterized by a drastic change from "contractures", which refer to several minutes of myometrial activity with moderate increase in intrauterine pressure, to "contractions" which are short episodes of dramatic

increase in intrauterine pressure [29]. Various cervical changes which have been described include softening which begins in early pregnancy, ripening which involves a decrease in the concentration of collagen and dispersion of collagen fibrils and dilation which may be described as an inflammatory process with influx of macrophages and neutrophils accompanied by matrix degradation [30, 31]. Membrane rupture normally occurs in preparation for delivery and involves the degradation of foetal fibronectin (fFn) at the chorion–decidual interface. However, PROM may also occur due to amnion epithelial apoptosis and localized inflammation [32].

The common pathway is a term defined as the anatomical, physiological, biochemical, endocrinological, immunological and clinical events occurring at term or preterm within the mother and/or the foetus [33–35]. These events are mostly notable in the uterine component, but extrauterine components are also involved in this pathway. Many scientific research led prostaglandins, a lipid compound, to be considered the primary mediators of the most important changes associated with the onset of labour, including myometrial contractility, cervical ripening and membrane activation [36]. Prostaglandins production is stimulated by an increasingly high oestrogen/progesterone ratio at parturition [2]. This then leads to an increase in the intracellular calcium concentration of uterine smooth muscle cells by upregulating sarcoplasmic and transmembrane calcium fluxes. Prostaglandins also increase contractility by upregulating transcription of oxytocin receptors, gap junctions and prostaglandin receptors (EP and FP) [37]. A second effect of this lipid compound is to stimulate the foetal membrane and the cervix to synthesis MMPs, which are involved in membrane rapture and cervical ripening [38]. Thirdly, increased expression of progesterone receptor isoforms (PR-A/PR-B) is made possible by prostaglandin (PGE2 and $PGF_{2\alpha}$) to induce a functional progesterone withdrawal [39].

17.3 Aetiological Mechanisms of Spontaneous Preterm Birth

Preterm birth is regarded to be a "syndrome", implying that it has multiple aetiologies with a combination of signs and symptoms creating the characteristic clinical presentation of the mother [40]. It is believed to be of multifactorial origin, since certain causes of preterm birth, such as micro-organisms, are attributed to an environmental influence and cause inflammation under genetic control [17]. The main mechanical processes that have been implicated in preterm birth syndrome are intrauterine infection, inflammation, uteroplacental ischaemia and haemorrhage, maternal and foetal stress, uterine over distension, cervical disease, endocrine disorders, allergic phenomena and abnormal allogenic recognition [17].

The main hormone implicated as having an influence on the process of preterm parturition is progesterone. This hormone performs a number of critical functions in order to maintain pregnancy, including gap junction downregulation, cervical ripening inhibition and downregulation in chemokine production. Therefore, any abnormalities in its function may lead to preterm birth. Evidence has shown that a

"functional progesterone withdrawal" occurs in intrauterine tissue, in both term and preterm parturition, creating a change in the ratio of oestrogen and progesterone that triggers components of the common pathway of parturition [41].

17.4 Prevention and Management

Many methods have been employed in an attempt to predict preterm delivery, but to date, they are of limited clinical use. Without this knowledge, preventative measures would be useless. However, different techniques have been and are still being developed to prevent the problem in those females at high risk of experiencing preterm birth [42]. The fact that the exact mechanism of the disease is not yet understood makes it difficult to provide successful diagnostic tests and successful prophylactic and/or treatment methods [17]. Obstetricians in clinical practice often face the dilemma of how to manage an established preterm labour. The physician should always balance the risks to both mother and foetus of delivering the baby prematurely against the risk of trying to prolong the pregnancy. Treatment is aimed either at preventing the initiation of myometrial contractility or at preventing cervical dilatation.

17.4.1 17-a-Hydroxy Progesterone

The corpus luteum serves as a source of steroid hormones, mainly progesterone, for the first trimester, corresponding to approximately the first 13 weeks of gestation. However, the placenta then takes over in the second and third trimesters and remains the major source during most of the pregnancy by acting in concert with the mother and the foetus [2]. Progesterone is an important hormone produced by the placenta, which plays the indispensable role of maintaining pregnancy. Progesterone production involves the transport of low-density lipoprotein (LDL) cholesterol from the maternal compartment into the placental compartment where it is converted first to pregnenolone and then to progesterone in a rapid and efficient manner [43]. As shown in Fig. 17.1, the process requires the cholesterol desmolase P450scc (cholesterol side-chain cleavage) and 3β-hydroxysteroid dehydrogenase (3β-HSD), which are expressed in the human placenta. This process of steroidogenesis terminates with progesterone because the fact that the human placenta lacks 17α-hydroxylase and 17,20-lyase (whose activity is mediated by a single enzyme called P450c17), which allows the formation of glucocorticoids and androgens in the adrenal cortex [1, 2].

This "progestational" hormone prevents rejection of the conceptus by the immune system and is responsible for the maintenance of pregnancy. This is possible since progesterone blocks the maternal immune responses to foreign antigens through suppression of T-lymphocyte cell-mediated responses [44]. Table 17.1 shows the effect of progesterone on the myometrium.

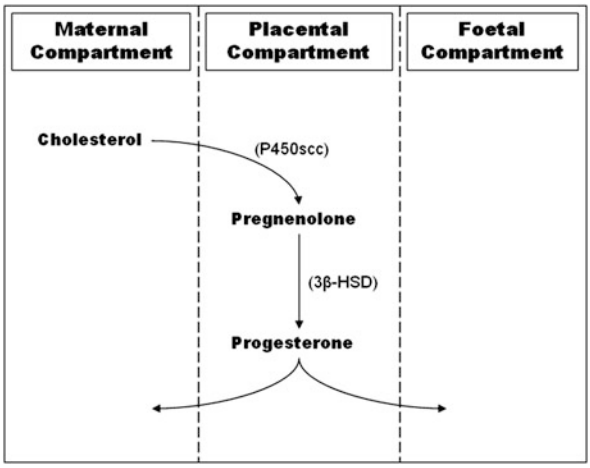

Fig. 17.1 Biosynthetic pathway of placental progesterone

Table 17.1 Actions of progesterone on the myometrium

Decreases conduction of contractions
Increases threshold for stimulation
Decreases spontaneous activity
Decreases number of oxytocin receptors
Suppresses the inflammatory cascade
Acts as a calcium antagonist
Inhibits T lymphocyte development
Promotes expression of prostaglandin EP2 receptor
Prevents formation of gap junctions
Administration of progesterone antagonists stimulates onset of labor in women at term

17-a-Hydroxy progesterone has also been documented to be a successful drug in the prevention and in decreasing the rate of recurrent preterm labour [45]. Progesterone increases cAMP which maintains quiescence by promoting the uptake of calcium into the sarcoplasmic reticulum [46]. In a randomized study from Brazil, a daily 100 mg progesterone vaginal suppository decreased the incidence of preterm delivery from 28.5 % (placebo group) to 13.8 %. Delivery prior to 34-week gestation was reduced from 18.5 % to 2.7 % [47].

A systematic review and meta-analysis of individual patient data investigated the use of vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity [48].

In total, 5 trials were included, which involved *775 women and 827 infants*. Vaginal Progesterone (dose range 100–200 mg daily) showed significant reduction in the rate of preterm birth $<$ 33weeks and was also of benefit $<$35 weeks and $<$28 weeks. This study shows that vaginal progesterone used prophylactically reduces the risk of preterm birth and the neonatal morbidity and mortality in women with a short cervix ($<$25 mm).

Another recent systematic review and indirect comparison meta-analysis has been carried out on the use of vaginal progesterone versus cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, singleton gestation and previous preterm birth. Four studies were included where treatment using vaginal progesterone versus placebo was compared in 158 patients. Five studies were also included where cerclage was compared versus no cerclage in 504 patients. Both interventions were associated with a statistically significant reduction in the risk of preterm birth less than 32 weeks of gestation and composite perinatal morbidity and mortality compared with placebo/no cerclage. Adjusted indirect meta-analyses did not show statistically significant differences between vaginal progesterone and cerclage in reducing preterm birth or adverse perinatal outcomes. In conclusion, both vaginal progesterone and cerclage are equally efficacious in the prevention of preterm birth. However, selection should be on an individual basis.

A UK-based randomised controlled trial (OPPTIMUM) is being carried out to provide further evidence on the effectiveness of vaginal progesterone for prevention of preterm birth and improvement of neonatal outcomes in selected groups of women with singleton pregnancy at high risk of preterm birth [49]. Additionally, it will determine whether any reduction in the incidence of preterm birth is accompanied by improved childhood outcome.

Dydrogesterone in high-risk pregnancies showed comparable preterm delivery rates 7.9 % vs. 7.1 % as the control population (Muscat Baron et al., unpublished data). Seventy-six women with bad obstetric history and/or problematic current high-risk pregnancies taking 10 mg TDS–QDS dydrogesterone for the first 34 weeks of pregnancy. 26 women were on low-dose aspirin and 6 were on heparin 5,000 iu bd. These were compared to 140 normal pregnant controls.

Initial data suggests that in high-risk pregnancies dydrogesterone may be a useful adjunct to prevent preterm delivery.

17.5 Conclusion

Preterm birth is a very important health problem since it is a leading cause of perinatal mortality and morbidity. Perinatal mortalities and morbidities may be significantly decreased if preterm labour can be predicted early enough and treated accordingly. Many aetiologies and mechanisms that lead to preterm birth are better understood. This understanding is leading to the identification and evaluation of a number of novel markers as predictors of SPB. Since SPB is multifactorial, it is highly unlikely that a single test can be found that is a reliable and accurate predictor of SPB. Currently, fFn, ultrasonographic measurement of cervical length and obstetric history are used to predict SPB in women at highest risk. However, there is no biological marker that is recommended as a universal test among asymptomatic women for the prediction of SPB. The right direction for future research may be to try to combine a number of biological markers and produce a multi-marker test for the prediction of SPB.

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Part VI

Ovarian Ageing and Menopause

Therapeutic Management of the Menopausal Transition

18

Giulia Palla, Stefania Spina, Guja Bernacchi, Elena Cecchi, Silvia Di Bello, Silvia Pisaneschi, Magdalena Montt Guevara, Adrian Campelo, and Tommaso Simoncini

18.1 Definitions

Reproductive age in women is characterized by several different phases, which constitute a unique endocrinologic continuum. It starts with the beginning of fertile life, with regular, cyclic menses, typical of ovulatory cycles, and it ends with a concluding menstrual period, due to final ovarian senescence, indicated as the menopause.

An important moment in this complex process is represented by the menopausal transition (MT), the time period in the late reproductive years, which usually begins with menstrual irregularity and persists until 1 year after last menses. The menopausal transition typically starts in the late 40s or early 50s and continues for about 4–7 years.

To better understand the complexity of woman's transit through menopause and also to simplify the nomenclature, Souls and other proposed the Stages of Reproductive Aging Workshop (STRAW) in 2001 [1].

The STRAW classification divides reproductive and postreproductive life into several periods; each one is different for the age range and duration time. The main event is the final menstrual period, FMP. Five stages are before FMP and two stages are after. Stage −5 represents the early reproductive period, stage −4 the reproductive peak, and stage −3 the late reproductive period. Stage −2 refers to the early menopausal transition (MT) and stage −1 to the late MT. In the early menopausal transition (stage −2), menstrual cycles are still regular, but the interval between cycles typically becomes shorter (7 or more days different from normal). Compared with younger women, FSH levels increase, and serum estrogen levels may be elevated in the early follicular phase. Regular ovulatory cycles may be alternated

G. Palla • S. Spina • G. Bernacchi • E. Cecchi • S. Di Bello • S. Pisaneschi • M. Montt Guevara • A. Campelo • T. Simoncini (✉)
Division of Obstetrics and Gynecology, Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, Pisa 56100, Italy
e-mail: tommaso.simoncini@med.unipi.it

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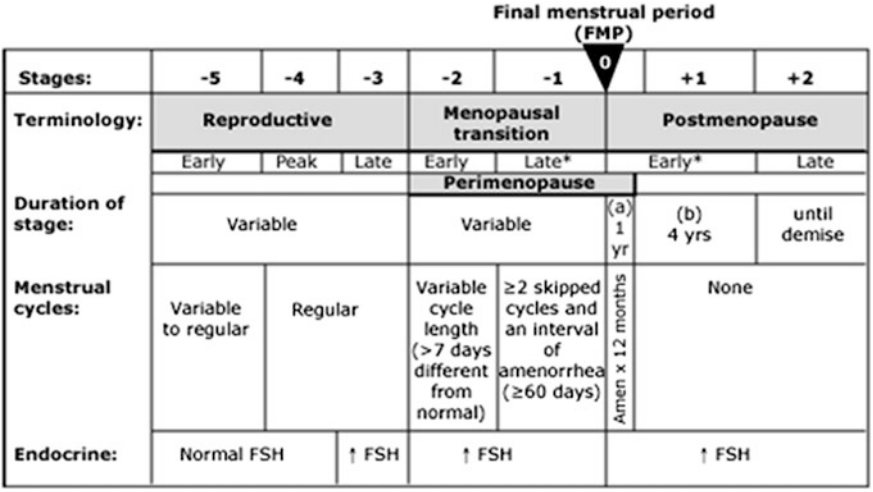

Fig. 18.1 The STRAW staging system (adapted from Soules, MR et al., Fertil Steril 2001)

to anovulatory cycles during this transition. The late menopausal transition (stage −1) is defined by two or more skipped menses or at least one interval of amenorrhea longer than 60 days, since the periods of anovulation become more and more frequent [1].

Stage +1a refers to the first year after FMP, stage +1b identifies the years two to five postmenopause, and stage +2 refers to the later postmenopausal years until demise (Fig. 18.1).

18.2 Physiological Changes

Menopausal transition is a physiological event in woman life; nevertheless, at this period, women complain about new, unexpected, and annoying symptoms; their bodies are at the mercy of intense hormonal changes, and, in addition, there is evidence of increased risk for developing depression and mood swings, due to both hormonal alterations and awareness of aging and its consequences.

Thus, menopausal transition may have a significant impact on personal, family, and professional aspects of life.

For this reason, one of the main points is to guarantee to women the best quality care from physicians during menopause, based on good communication, enough time to visit and to discuss their worries, giving information and resources to explain the basis of their physical and psychological symptoms.

In the recent past, growing evidence suggests that menopause is a primary central nervous system event, in which the aging process is probably triggered by a central pacemaker in the hypothalamus, or/and in higher brain areas, in combination with changes in several peripheral organs (ovaries and adrenal cortex) [2,

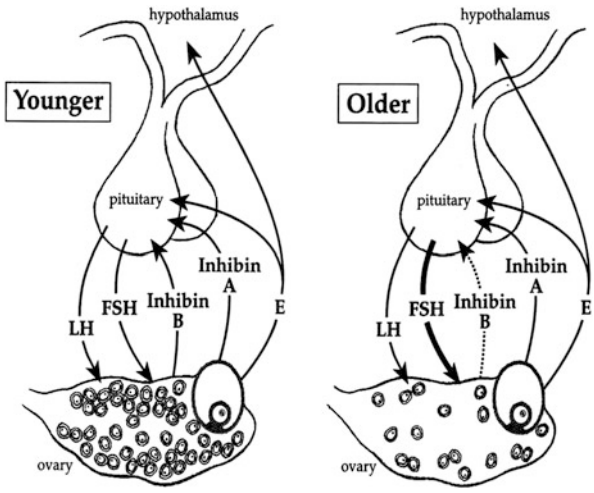

Fig. 18.2 Endocrine consequences of follicle depletion

3]. This hypothesis comes from several experimental models in animals that show that ageing in the brain is associated with altered hypothalamic neurotransmitter control. In addition, getting closer to the final menstrual period, hypothalamic regulation of GnRH secretion appears desynchronized, with hormonal release at maximal frequency and amplitude and impaired gonadotropin secretory rhythm. This phenomenon starts in the late reproductive stage and in the early menopausal transition and it corresponds, clinically, with still regular menses and normal estrogen level, but levels of progesterone, Anti-Mullerian Hormone (AMH), inhibin B begin to decrease slightly [4] (Fig. 18.2).

The Melbourne Women's MidLife Health Project (MWMHP) and related studies have underlined that the first endocrine event, followed by the onset of menstrual irregularity, is not the increase in FSH, as stated in the past, but it is the decrease of inhibin B concentration at follicular phase, without any substantial increase in FSH and any change in estradiol or inhibin A [5]. In addition, based on the prospective determination of the moment of final menses (FMP), it has been shown that estradiol levels begin to fall and FSH levels to rise only about 2 years before FMP [6].

Nowadays, we think that the early menopausal transition begins with first menstrual irregularities and, simultaneously, inhibin B and AMH reduction due to declining follicles. As a consequence, serum FSH levels start to rise, even if estradiol levels are quite stable, but reduced amounts of progesterone are found during luteal phase [7].

In the late menopausal transition, the menstrual irregularities increase, at the same time serum FSH and estradiol are markedly variable within different cycles, with irregular ovulation.

An important aspect is that both hypothalamus and pituitary show a reduced sensitivity to estrogens and a variable loss of positive and negative feedbacks of estrogens on synthesis and release of LH. Moreover, FSH and LH in peri- and

postmenopause appear to be hyperglycosylated, thus giving them prolonged half-life. This contributes to the increased FSH and LH levels and seems to be associated to decreased biological effects.

With advancing age, there is a level change in adrenal steroid production, with decline in dehydroepiandrostenedione sulfate and androstenedione. Also, the production of sex hormone-binding globulin (SHBG) decreases after menopause with an increased level of free or unbound estrogen and testosterone. This higher amount of androgens lead to an increased conversion rate of androstenedione to estrone, a weaker estrogen compared to estradiol, due to an increase of aromatase activity in adipose tissue, which characterizes the aging process [8, 9].

All those hormonal changes are accompanied together with a rapid depletion of ovarian follicles, which starts in the late 30s and early 40s and goes on until the point in which the ovary is virtually empty of follicles.

During early menopausal transition, the endometrium shows the features of the fertile period, since ovulatory cycles are still prevalent. After that, during the later stage of menopausal transition, anovulation is frequent, and the endometrium exhibit estrogen's effect when unopposed by progesterone. Accordingly, proliferative changes or disordered proliferative changes are frequently found by endometrial biopsy samples.

18.3 Clinical Signs

The clinical signs during menopause transition are menstrual irregularities, vasomotor symptoms, sleep disruption and mood alterations, urogenital complaints, and sexual dysfunction.

As stated, altered bleeding pattern is one the most common signs during menopause: menses may be irregular in more than 50 % of women during this period [10]. This is linked to anovulation and progesterone deficit, which cause variable periods of relative hyperestrogenism that turn into breakthrough bleedings (irregular spotting), oligomenorrhea, and late cycles.

Nevertheless, in all women, regardless of menopausal status, the etiology of irregular bleeding should be thoroughly investigated.

Even if hormonal dysfunctions are frequent reason of bleeding in this period of life, endometrial hyperplasia, estrogen-sensitive neoplasms (leiomyomas and uterine polyps), should always be considered. Moreover, also pregnancy can be a reason of late cycles, since many women in their 40s quit using contraception, with the false conviction of not being fertile anymore.

Malignant precursors of endometrial cancer (complex endometrial hyperplasia with or without atypies) become more common during menopausal transition, and endometrial biopsy is needed to exclude malignancy. Endometrial cancer should be suspected in any woman in menopausal transition with abnormal uterine bleeding.

Vasomotor signs are early symptoms, often present intermittently during early perimenopause and become more common during late transition phase and during

early-postmenopause. They afflict 75 % of women and usually disappear within 1–5 years, even if sometimes they persist beyond 70s.

They have been described as sudden feeling of heat to the trunk and face that quickly generalizes to the rest of the body. The duration is between seconds to 2–3 min. This change is mainly noticeable in the fingers and toes, where skin temperature can increase up to 10 °C [11]. Sweating starts on the upper body and it relates closely in time with an increase in skin conductance.

Hot flushes are usually associated to palpitations and often followed by shivering and anxiety.

Cardiovascular changes that occur during hot flushes have been deeply examined.

During hot flushes, an increase in systolic blood pressure has been described [12]. In addition, an increase in the heart rate (up to 15 beats per minute) is present, simultaneously with peripheral vasodilatation and sweating.

Temperature decreases 0.1–0.9 °C due to heat loss from increased peripheral vasodilation, after about 5 min from the beginning of the hot flush. Skin temperature slowly returns to normal and, whether the heat loss and sweating is significant enough, women may experience chills [13].

Hot flush could be 1–2/day up to 30–40/day, more frequent at night, with obvious consequences on sleep.

The pathophysiology of vasomotor symptoms is linked to dysfunction of central thermoregulatory centers in the hypothalamus. In particular, the medial preoptic area of the hypothalamus represents the thermoregulatory nucleus; it is influenced by estrogen withdrawal and neurotransmitters concentration, in particular norepinephrine, dopamine, serotonin, and β-endorphin [14]. Norepinephrine is supposed to be the main neurotransmitter responsible. When changes in core body temperature, even very subtle, happen in the woman, norepinephrine lowers the setpoint in the thermoregulatory nucleus. This is followed by the activation of heat loss mechanisms, mainly vasodilation, and increased blood stream to the skin and sweating, associated with hot flushes [15]. Interestingly, those changes are contemporary to LH pulses. After that, there is a loss of body heat and shivering takes body temperature back to normal.

Freedman and colleagues [16] have found a decrease in hypothalamic α2-adrenergic receptors related to estrogen withdrawal. The decline in presynaptic α2-adrenergic receptors causes increased norepinephrine levels, thereby provoking vasomotor symptoms.

A similar mechanism is probably activated by a reduced opioid tone and decreased serotonin levels, associated to loss of estrogens, related to menopause.

Sleep dysfunctions are due mostly to hot flushes and nocturnal sweats, which determine repeated awakening and chronic insomnia. This has been found by a cohort study in which women with a greater incidence of hot flushes are expected to experiment poor sleep more frequently, than women with fewer vasomotor symptoms [17]. Hot flushes are more frequent during early phases of sleep, while REM sleep is associated with reduced frequency. The most common complaints reported are difficulties in sleep onset and sleep maintenance, which determine

daytime fatigue, mood lability, irritability, and short-term memory difficulties [18]. Moreover, other sleep disorders become more common in perimenopause and postmenopause, such as sleep–apnea syndrome and restless leg syndrome.

Also, anxiety and depressed mood contribute to sleep disruption. These clinical signs are common during perimenopause, mostly represented by irritability, nervousness, elevated anxiety, rapid mood swings, and depressive symptoms [19]. It has been described an increased risk of major depressive episode during menopausal transition that reduces after menopause. The predisposing factors are personal history of depression, PMS, postpartum depression, which can mix with other predisposing factors typical of this stage. During this period, women can experience family modifications (as empty-nest syndrome, divorce, or widowhood), problems with partner and loss of fertility, changes in social role, such as retirement and unemployment. In addition, personal or parents' health problems can worsen the situation. However, the entity and the way of expression of mood and cognitive symptoms are clearly culture specific. In Western, beauty and youth are deeply emphasized by society, thus an elderly women can experiment a sense of loss, worthlessness, and impotence.

It has been suggested also a biological explanation of those signs, due the hormonal fluctuations. During early menopausal transition those modifications are responsible, in part, for this affective instability. In addition, it has been found that surgical menopause induces mood changes because of the quick hormonal loss.

A key component of the emotional distress during menopausal transition may be due to high and erratic estradiol levels. Ballinger and colleagues [20] have shown that stress hormones increases (and probably stress-related symptoms) are physiologically associated to relative hyperestrogenism, typical of menopausal transition. On the other hand, clinical studies also suggest that lack of estrogens, typical in women after menopause, may be related to cognitive dysfunction, such as the progression of brain degenerative diseases (Alzheimer's disease or Parkinson's disease), and the hypothesis that estrogen administration to postmenopausal women might decrease the progression of these conditions is enduring [21].

Also, the lack of progesterone could be involved in this process. Progesterone is needed for the production of allopregnanolone, a neurosteroid involved in the regulation of brain function. Different exogenous mediators, such as progesterone, allopregnanolone, and DHEA, but also exogenous (benzodiazepines, imidazopyridines, ethanol, and barbiturates) act on GABA receptor, regulating cellular excitability, network synchronization, and synaptic plasticity, thus provoking changes in mood, emotional state, and affectivity.

Urogenital symptoms are important aspect to consider during menopausal transition. Since vaginal, urethral, and bladder trigone are sensitive to estrogens, estrogen withdrawal determines thinner vaginal mucosa, with pale or petechial aspect and loss of mucosal folds. The reduction in glycogen and increase in pH up to 6.0–7.5 cause the growth of endogenous bacteria and this is followed by vaginal dryness, itching, bleeding, and dyspareunia. Those symptoms are present in 20 % of the women during late menopausal transition and 50 % 3 years after menopause.

Another problem reported by women is urinary incontinence, both stress and urge urinary incontinence. The main predisposing factors are the presence of a thinned urethral mucosa, which favor urine leaks, ascending infections and colonization by yeasts and bacteria, which often become recurrent. Those modifications contribute to sexual dysfunction: the loss of elasticity and the atrophy are accompanied by a decreased blood flow to vagina and vulva, decreased lubrication due to vaginal dryness. All those factors cause pain and difficult intercourse [22]. If those signs are mainly linked to estrogen withdrawal, also androgen deficit is responsible for decreased sexual interest, with a loss of libido, fantasies, and motivation, but also linked to reduced trophism and innervation of vulva and introitus. Moreover, an altered body image and reduced motivation can worsen the situation. Weight gain and fat deposition in abdomen are common in women during menopausal transition, which not only contribute to reduced self-esteem and tendency to depressive symptoms but also increase the probability of developing insulin resistance, diabetes mellitus, hypertension, and cardiovascular disease [23, 24].

18.4 Therapeutic Challenges in Menopausal Transition

During MT, physicians should guide the therapy on controlling the bleeding and the vasomotor symptoms, acting on anxiety/mood swings and improving the sexual function. Choosing the treatment in perimenopause is challenging because few randomized controlled trials have been published.

Based on the idea that menopause and perimenopause are characterized by similarly low estrogen levels, it is common practice to treat perimenopause with estrogens or oral contraceptives. This choice comes from extrapolating data from postmenopausal women and from clinical experience. To treat perimenopausal symptoms like those of menopause, however, ignores the different hormonal background between the two, mainly the higher estrogen levels and the fluctuations in hypothalamic–pituitary ovarian feedback in perimenopause.

Estrogen treatment could lead to heavier flow, getting worse mood swings, and more breast tenderness. Instead, simple actions are often quite effective. Explanation about perimenopausal hormone changes and the distinctive clinical signs accompanying them, giving idea of the perimenopause timeline, could all be very useful instruments [25].

In addition, light aerobic, continued physical exercise, increased calcium and vitamin D intake, healthy eating habits, relaxation training, and meditation can all be beneficial. These simple and everyday recommendations can help the majority of perimenopausal women. However, the 20 % are supposed to need additional therapy.

The control of cycles is a hard battle, because OCs are often contraindicated in this age group, because of the high number of women aged > 35 and smokers. Age and smoking are the major risk factors for myocardial infarction in women who

may consider the OC. The increasing prevalence of obesity, high blood pressure, and diabetes in population are also important contributing factors.

Moreover, HRT could be ineffective due to the irregularity of ovarian activity.

Progesterone supplementation can be a good strategy, but it is difficult to be timed efficiently over the long term. Cyclic or daily oral micronized progesterone can help with heavy flow, hot flushes, breast tenderness, and sleep.

LNG-loaded IUD gives good results but may not be accepted. Also, endometrial ablation techniques could be an alternative, but it requires hospital stay, anesthesia and it is not possible in presence of myomas present.

Vasomotor symptoms also need frequently a well-rounded approach [26]. As stated above, OCs are often contraindicated. Even if administration of a minimal amount of estrogens is effective (25–50 mcg patches, transdermal gels or 1 mg estradiol daily usually sufficient) and does not alter cycle, this requires endometrial surveillance in long-term therapy. Thus, this could be considered a temporary measure to be replaced by standard HRT in postmenopause. In addition, a LNG-loaded IUD can be used as an add-back therapy, giving the possibility to use estrogens more liberally.

Again, some behavioral modification, like avoiding drinking caffeine and alcohol, living in cool environment, and wearing lighter clothing, may be favorable. Herbal medicines or acupuncture may offer some relief, although it has not been found much medical evidence to support these therapies. Some antidepressants (SSRIs and SSNIs) and other medicines that act on the central nervous system (clonidine and gabapentin) are also helpful strategy for hot flushes. They may also be a good choice for women with sleep or mood disturbances.

Vaginal symptoms could be faced by using local or systemic hormones, often in low dose, if need in addition to vaginal lubricants and moisturizers, typically applied prior to sexual activity [27].

In regard to sexual dysfunction, first step is to provide enough estrogen levels, usually with transdermal estrogens, in order to avoid increasing SHBG. If androgens are reduced, tibolone, oral DHEA (10–50 mg/die), or transdermal Testosterone (300 mcg/die) could be efficiently used.

18.5 Conclusions

Menopausal transition is a period of intense changes and most women experience perimenopausal symptoms and seek for medical help.

A good counseling, to provide patient-specific education and consultation, in addition to personalized therapy, based on needs, symptoms, and hormonal status, are the guiding principles for the best management in MT.

Last but not least, each moment in a woman's life can be the starting point to quit smoking, start physical activities, and have a healthy and balanced diet. Having a healthy menopause to get a healthy life.

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Menopause-Related Changes in the Musculoskeletal System, Cartilages and Joints

19

Jean Calleja-Agius and Mark Brincat

19.1 Introduction

Osteoporosis and related fractures are a significant concern for the global community. As the population continues to age, morbidity and mortality from fractures due to osteoporosis will likely continue to increase. The menopause has been shown repeatedly to have a negative effect on the connective tissue in the bone matrix. Such an effect is prevented and in some cases reversed with oestrogen therapy. Studies show that oestrogen prevents osteoporosis partly by inhibiting bone resorption. Selective oestrogen receptor modulators (SERMs) act through oestrogen receptors and are agonists for bone and antagonists for breast and uterine tissue. A new approach to menopausal therapy is the tissue selective oestrogen complex or the pairing of a selective oestrogen receptor modulator with oestrogens. Novel bone-targeting oestradiol delivery systems have the potential to improve the safety profile of oestradiol in the treatment of osteoporosis.

19.2 Bone

Postmenopausal osteoporosis is a silent systemic progressive disease characterised by a decrease in bone mass per unit volume. This condition compromises the physical strength of the skeleton and increases the susceptibility to fractures on minor trauma. The imbalance between bone formation and bone resorption is known to be responsible for postmenopausal bone loss. Oestrogen deficiency contributes to bone loss by increasing the production of proinflammatory cytokines by bone marrow and bone cells. Clinical and molecular evidence indicates that oestrogen-regulated cytokines exert regulatory effects on bone turnover implicating their role as being the primary mediators of the accelerated bone loss at menopause.

J. Calleja-Agius • M. Brincat (✉)
Department of Obstetrics and Gynaecology, Mater Dei Hospital, Birkirkara, Malta
e-mail: jean.calleja-agius@um.edu.mt; brincatm@maltanet.net

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At menopause, bone turnover increases, and may remain high for up to 25 years after the last menstrual period [1]. Bone turnover is controlled by a complex interrelationship of a number of factors, including oestrogen, progesterone, testosterone, Vitamin D, corticosteroids, thyroid hormones and retinoids [2]. Oestrogen alone has a known beneficial effect on reducing bone fractures and limiting bone loss. A number of studies have shown the positive effect of progesterone on bone proliferation and inhibition of bone resorption [3–6]. However, another study showed no difference between progesterone and placebo in terms of any difference in markers of bone resorption [7]. Consequently, large-scale randomised controlled trials are necessary to determine the role of progesterone alone in the prevention or treatment of osteoporosis [8]. Oestrogen and progesterone alone could have distinct yet complimentary roles in maintenance of bone [9–11].

19.3 Intervertebral Discs

Each intervertebral disc is composed of high collagen content and glycosaminoglycans. Intervertebral discs are responsible for 20 % of the spinal column height and allow flexion and extension of the back and also act as "shock absorbers" of the spinal column. This may have an important role on osteoporotic compression fractures [12].

With the ageing process, there is a change in collagen type [13], with a more profound difference with increasing years since menopause [14]. The collagen Types I, III and VI predominate at the expense of collagen Types II, IV and IX. There is also a significant decrease in glycosaminoglycans and elastin in the aged intervertebral disc [15]. The comparison between a normal and an aged intervertebral disc is shown in Fig. 19.1a, b.

The lumbar intervertebral disc height has been shown to be significantly higher in the premenopausal group (height of three lumbar discs 2.16 $\pm$ 0.1 cm) and hormone-treated group (disc height 2.2 $\pm$ 0.12 cm), compared to the untreated postmenopausal women (disc height 1.86 $\pm$ 0.06 cm) ($p < 0.0001$)[14]. This has been confirmed by another study on a bigger cohort. The premenopausal women and hormone-treated women had disc heights of 2.01 $\pm$ 0.09 cm and 2.15 $\pm$ 0.08 cm, respectively, the latter results being significantly higher than the untreated postmenopausal group (height of three lumbar discs 1.82 $\pm$ 0.06 cm) and the osteoporotic fracture group (1.58 $\pm$ 0.1 cm) ($p = <0.0001$) [14].

These results may be due to the effect that the menopause has on the connective tissue components of intervertebral discs. This may lead to loss of the shock-absorbing properties of the intervertebral disc and an altered discoid shape, influencing the occurrence of osteoporotic vertebral body fractures [16]. After menopause, intervertebral disc space shows a progressive decrease that almost entirely occurs in the first 5–10 years since menopause, suggesting that the decline in oestrogen level may rapidly change connective tissue metabolism in the intervertebral discs [17].

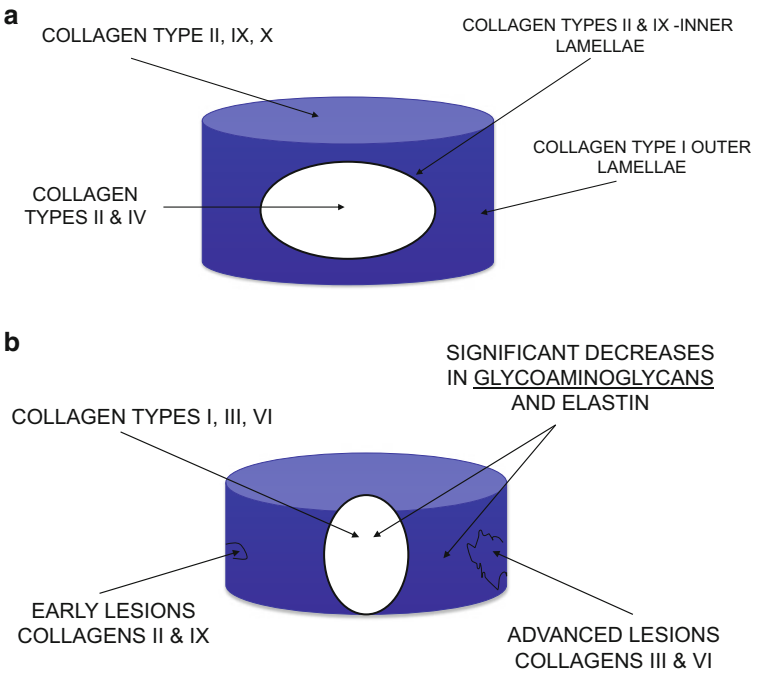

Fig. 19.1 (**a**) Normal intervertebral disc, (**b**) Aged intervertebral disc

19.4 Muscle

In menopause, there is a decline in muscle mass and strength ensues when serum oestrogen declines. Oestrogen improves muscle strength. The underlying mechanism involves oestrogen receptors to improve muscle quality rather than quantity [18].

Hormone therapy attenuates exercise-induced skeletal muscle damage in postmenopausal women. Postmenopausal women not using hormonal therapy experience greater muscle damage [19].

19.5 HRT-Where Do We Stand?

In the wake of the WHI trial, many dilemmas have yet to be resolved regarding the use of HRT in postmenopausal women. Several factors may have contributed to the widely different conclusions of the WHI trials in comparison to the observational studies.

WHI included two randomised double-blind, placebo-controlled investigations of unopposed oestrogen (0.625 mg of conjugated equine oestrogen, CEE) alone for women with a prior hysterectomy [20] and of combined oestrogen–progestin (the

progestin component consisted of 2.5 mg of medroxyprogesterone acetate, MPA) for women with a uterus [21]. The combined HRT arm of the WHI was stopped in May 2002 after a mean of 5.2 years follow-up, because the test statistic for invasive breast cancer exceeded the stopping boundary and the global index statistic supported risks exceeding benefits [22]. The conclusions from the study at that time were that the risks of coronary heart disease, stroke and pulmonary embolism were significantly increased in the intervention group, the risks of hip fracture and colorectal cancer were reduced and the mortality risk was unchanged [21].

The oestrogen-alone arm of the WHI study was stopped in February 2004, 1 year earlier than planned, due to excess stroke. It was concluded that CEE alone increases the risk of stroke, reduces the risk of hip fractures and does not affect the risk of cardiovascular heart disease in postmenopausal women with prior hysterectomy over an average of 6.8 years. There was a possible reduction of breast cancer risk, but this required further investigation [20].

The potential side effects and risks involved in taking HRT may be reduced by using lower HRT doses; minimising or eliminating systemic progestogens; using non-oral routes in some women; and initiating HRT in symptomatic women near menopause. When HRT is initiated near menopause for symptom control, there may be additional benefits including reduced fracture and cardiovascular risk. These benefits outweigh the risks, which are not significantly raised in women under age 60 years. As long as their therapy and risks are assessed on an individual basis and each patient is aware of the risks, older women with continuing symptoms should not be denied HRT [23].

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Is It Safe to Prevent and Treat Postmenopausal Osteoporosis?

20

John C. Stevenson and Thomas E. J. Stevenson

20.1 Introduction

Postmenopausal osteoporosis is the commonest metabolic bone disease affecting more than half of women by the end of their lives. Loss of ovarian function at the menopause results in increased bone turnover with excessive resorption leading to bone loss, disruption of the underlying micro-architecture, and hence fractures. Prevention or reversal of bone loss will help preserve the micro-architecture and reduce the risk of fracture. A number of therapeutic options are available to help achieve this, and techniques such as bone densitometry are available to identify those individuals at high risk for future fracture who would warrant such treatments. Since the major underlying cause of postmenopausal osteoporosis is the loss of bone resulting from oestrogen deficiency, hormone replacement therapy (HRT) with oestrogen, and if necessary a progestogen, is a logical approach to prevention and treatment. Many studies had shown that HRT was an effective treatment for the prevention of postmenopausal bone loss [1, 2] and fractures [3, 4], and its additional benefits on menopausal symptoms and the cardiovascular system made it an obvious first-line treatment for postmenopausal women. HRT was equally effective with different routes of administration [1], and it had become apparent that lower doses than those originally used were also effective [2]. But following the initial publication of the preliminary data from a large randomised clinical trial of HRT, the Women's Health Initiative (WHI), in 2002 [5] followed by the publication of a large observational questionnaire study of HRT, the Million Women Study (MWS),

J.C. Stevenson (✉)
National Heart and Lung Institute, Imperial College London, Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, London SW3 6NP, UK
e-mail: j.stevenson@imperial.ac.uk

T.E.J. Stevenson
Department of Surgery, Frimley Park Hospital NHS Foundation Trust, Portsmouth Road, Frimley, Surrey GU16 7UJ, UK
e-mail: tstevenson@doctors.org.uk

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in 2003 [6], the European Committee for Proprietary Medicinal Products (CPMP) was asked to examine safety concerns about the use of HRT for osteoporosis prevention. The European Union's Heads of Agencies then issued new recommendations from an ad hoc expert group of the European Agency for the Evaluation of Medicinal Products (EMEA) that for the prevention of osteoporosis in women with an increased risk of fractures the benefit–risk balance of HRT with different kinds of oestrogens and oestrogen–progestogen combinations is, on the basis of available evidence, not favourable. Hence, HRT would not be the first-line treatment for this indication. This recommendation was swiftly adopted by regulatory authorities worldwide. But are these safety concerns about HRT robust, and are the available alternative osteoporosis therapies any safer? We now compare the efficacy and safety of the current therapeutic options for postmenopausal osteoporosis.

20.2 Hormone Replacement Therapy

The WHI demonstrated that one specific HRT with oestrogen alone [7] or oestrogen–progestogen [8] is effective in reducing all fractures at classical osteoporotic sites in postmenopausal women without established osteoporosis. However, it purported to show major safety issues [5], with increases in coronary heart disease, stroke, venous thromboembolism and breast cancer. Subsequent publications of the full data showed that the vascular safety issues were very much dependent on age at initiation of the HRT and also on the presence or absence of medroxyprogesterone acetate [9]. Since a fixed dose of oestrogen was used in the study, for those initiating HRT below age 60 years this was a suitable dose, but for those initiating HRT above age 70 years this was an inappropriately high dose. Not surprisingly, cardiovascular harm was only seen in those initiating HRT above age 70 years. In those initiating HRT below age 60 years, non-significant reductions in coronary events were seen which became significant in oestrogen-alone users during long-term follow-up [10]. These findings have been confirmed by a subsequent longer-term randomised trial in early postmenopausal women [11] and by meta-analysis [12]. Stroke risk was not increased in this age group nor was venous thromboembolism with oestrogen-alone although it was with combined HRT [13]. Breast cancer incidence was not significantly increased with oestrogen–progestogen when appropriate adjustment for confounding variables was made [14], and the incidence was reduced with oestrogen-alone [15]. Thus, the safety concerns originally raised have not proved to be substantiated in women initiating HRT at the usual age of below 60 years.

20.3 Tibolone

Tibolone is a synthetic molecule with oestrogenic, progestogenic and androgenic properties which is used to relieve menopausal symptoms. Its effect on bone density is similar to HRT and it has been shown to reduce the incidence of vertebral fractures [16]. There have been insufficient data to demonstrate any effect on hip fracture prevention. Tibolone has some adverse metabolic effects on lipids and lipoproteins. It also increases insulin resistance. It may increase the risk of stroke, and its effect on breast cancer risk is unclear, with a decrease in incidence seen in healthy women but an increase in recurrence in breast cancer survivors [17].

20.4 SERMs

Selective oestradiol receptor modulators (SERMs) have both oestrogenic and anti-oestrogenic activities depending on the target tissue. Thus, the SERMs have an oestrogenic effect on the skeleton, albeit weaker than oestrogen itself, and an anti-oestrogenic effect on the endometrium and the breast. Raloxifene has been shown to reduce the incidence of vertebral fractures in postmenopausal women with and without osteoporosis, but it does not reduce the incidence of hip fracture [18]. Lasofoxifene [19] and bazedoxifene [20] have been shown to reduce the incidence of vertebral fractures in postmenopausal osteoporotic women, and additionally lasofoxifene reduces the incidence of non-vertebral fractures. Ospemifene has positive effects on bone turnover [21], but definitive fracture studies have not been reported. Most SERMs tend to increase vasomotor symptoms in postmenopausal women, and there is an increased risk in venous thromboembolism similar to that seen with oral oestrogen.

20.5 Bisphosphonates

These are stable analogues of pyrophosphate which bind to bone and inhibit osteoclasts. They are powerful anti-resorptive agents that are administered either orally or intravenously. They have been shown to reduce vertebral and hip fractures in osteoporotic women, although their effectiveness for fracture prevention in non-osteoporotic women is not as clear. Alendronate is given as a once weekly oral dose, whereas risedronate and ibandronate are given as a monthly oral dose. Ibandronate can also be given as an intravenous injection every 3 months, and the most potent bisphosphonate to date, zoledronate, is given as an annual intravenous infusion [17]. However, these drugs are associated with serious adverse effects. The gastric irritation commonly seen with daily administration has been largely circumvented by the less frequent dosing regimens. Atrial fibrillation has been reported with oral bisphosphonate use and is more common with intravenous administration [22]. Osteonecrosis of the jaw is also seen more commonly with intravenous bisphosphonates, particularly in cancer patients, and almost always

follows dental extractions [23]. Although an increased risk of oesophageal cancer with oral bisphosphonates was reported by the MWS investigators [24], other population studies have not confirmed this [25]. Both oral and intravenous bisphosphonates can induce inflammatory eye disease, mainly uveitis and scleritis [26]. With long-term bisphosphonate use, increasing numbers of femoral fragility fractures have been reported. These are usually sub-trochanteric transverse fractures, which occur with minimal trauma [27]. They are presumably the result of accumulation of fatigue damage caused by oversuppression of bone turnover resulting in lack of normal skeletal maintenance in susceptible individuals. As yet, it is not possible to predict reliably which patients are susceptible, although the fractures may be preceded by pain in the thigh and characteristic cortical beaking may be seen on radiograhs [28]. Finally, it must be remembered that these drugs have long skeletal retention times, and it is possible that new and serious adverse effects could emerge in the very long term. For this reason, caution should be taken if their use is considered in the non-elderly, and primarily they should be regarded as a treatment for the elderly osteoporotic woman.

20.6 Strontium Ranelate

Strontium is a divalent cation that is given as a salt for the treatment of osteoporosis. It acts as an anti-resorptive agent and is claimed to also have anabolic effects on bone formation. However, this latter action, whilst shown in animal models, has not been demonstrated unequivocally in humans. Strontium has been shown to reduce fracture incidence in both the spine and the proximal femur in postmenopausal women with osteoporosis, but there is no evidence for the primary prevention of osteoporosis in non-osteoporotic women [29]. Strontium ranelate has been associated with gastrointestinal side effects and was also shown to be associated with an increased risk of venous thromboembolism, and with a severe drug rash with eosinophilia and systemic symptoms (DRESS), which may prove fatal [30]. Most recently, the EMEA has issued a restriction on the use of strontium ranelate because of an associated increase in serious cardiac disorders, including myocardial infarction [30].

20.7 Calcitonin

Calcitonin is a peptide hormone secreted by the thyroidal C cells. It acts directly on osteoclasts to reduce both activity and numbers and is thus an anti-resorptive hormone. Synthetic human, salmon and eel calcitonins have been developed for clinical use, but salmon calcitonin is the most potent and has been used most extensively. It was previously administered by subcutaneous injection but can now be given by intranasal spray. It has been shown to prevent postmenopausal bone loss in the spine but not the hip [31]. A randomised clinical trial of postmenopausal osteoporotic women showed a significant reduction in vertebral fractures but

not hip fractures [32]. The study results were unusual in that they showed no effect of 100 IU daily, a significant effect of 200 IU daily, but no effect of 400 IU daily. The main drawback to its use, besides its lack of protection against hip fracture, had been its cost. However, a recent review of its safety data by the EMEA found an increased association in cancers generally with its use, and the nasal spray has now been withdrawn from use. The biological plausibility for this finding has yet to be elucidated.

20.8 Teriparatide/PTH

Parathyroid hormone (PTH), or its recombinant 1–34 fragment teriparatide, has a direct effect on osteoblasts to stimulate bone formation. They have been shown to increase bone mass and reduce vertebral fracture incidence in postmenopausal osteoporotic women, but a significant reduction in hip fracture has not as yet been demonstrated [33]. Both peptides are given daily as a subcutaneous injection and hypersensitivity reactions have been reported, as has transient hypercalcaemia. An increase in cortisol secretion has been reported. PTH has been shown to induce osteosarcoma in experimental animals, but there is as yet no report of this occurring in humans. One of the major drawbacks to teriparatide or PTH is the high cost of treatment, with the monthly cost being more than 140-fold higher than oestrogen or alendronate [17].

20.9 Denosumab

Denosumab is a monoclonal antibody to receptor activator of nuclear factor κ-B ligand (RANK-L). RANK-L is a signal from the osteoblast that increases osteoclastic activity, and thus blocking this signal with the antibody reduces this activity quite profoundly. Denosumab is administered every 6 months by subcutaneous injection and has been shown to reduce significantly the incidence of both spine and hip fractures in postmenopausal osteoporotic women [34]. No data have been presented for its effects in non-osteoporotic women. A main side effect of this treatment has been an increased risk of infections, presumably due to the fact that RANK-L is also used as a signal in the immune system. Increased muscle pain and increased cholesterol have also been reported [35]. Because it is such a potent antiresorptive agent, both osteonecrosis of the jaw and atypical femoral fractures have also been seen with longer-term use, similar to those found with bisphosphonates.

20.10 Calcium/Vitamin D

Calcium supplements, with or without vitamin D, are frequently given as adjuvant therapy in the treatment of osteoporosis, but are usually not effective when given alone. While they have been shown to reduce hip fracture incidence in elderly

Table 20.1 Fracture reduction efficacy and monthly costs of available treatments for osteoporosis

Treatment[a]	Vertebral fracture (%)	Hip fracture (%)	Cost per month (£)[b]
HRT (E alone)[c]	−38	−39	1.34
HRT (E + P)[c]	−34	−34	2.17
Oral bisphosphonates	−55	−51	0.91
IV bisphosphonates	−70	−41	21.12
Tibolone	−45	n.s.	10.36
SERMs[c]	−35	n.s.	19.86
Strontium ranelate	−24	−43	27.08
PTH/teriparatide	−64	n.s.	271.88
Calcitonin	−33	n.s.	95.76
Denosumab	−68	−40	30.50

Adapted from [17] with permission
[a]The cheapest agent in each treatment group that has fracture efficacy data has been selected
[b]Costings from British National Formulary (August 2013)
[c]Study population not selected as being osteoporotic

women with vitamin D deficiency [36], they do not appear to reduce fracture incidence in non-institutionalised postmenopausal women [37]. Although they are considered safe, they increase the risk of renal calculi [37] and have been associated with increased cardiovascular events [38].

20.11 Conclusions

Various treatment options are available with fairly similar efficacies but widely varying costs (Table 20.1). It has become quite clear that the initial safety concerns raised over 10 years ago about HRT having major adverse effects have not been substantiated, and the risks of HRT are actually extremely small. It has also emerged that the alternative therapies all carry their own risks which are as significant, if not more so, than those of HRT. For prevention of postmenopausal osteoporosis, it is obvious that HRT should again become first-line therapy, and the regulatory authorities must act to correct their advice. There are several therapeutic options for the treatment of established postmenopausal osteoporosis, and the choice of agent will depend on the balance of their risks against their benefits.

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Menopause, Aging, Pelvic Organ Prolapse, and Dysfunction

21

Silvia Pisaneschi, Giulia Palla, Stefania Spina, Guja Bernacchi, Elena Cecchi, Silvia Di Bello, Magdalena Montt Guevara, Adrian Campelo, and Tommaso Simoncini

21.1 Introduction

The pelvic floor is a complex of units involved in many undertakings that go further than the support of pelvic organs. Pelvic floor dysfunction affects on several functions such as micturition, defecation, and sexual activity. Urinary incontinence (UI), female pelvic organ prolapse (POP), sexual dysfunction, chronic obstructive defecation syndrome (OFD), and constipation are just a few of the many facets of pelvic floor dysfunction, and their incidence increases dramatically with age and menopause.

21.1.1 POP: Definition, Signs, and Symptoms

According to the definition of a joint report by the two leading urogynecological societies, POP [1] is defined as "any descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix) or the apex of the vagina (vaginal vault or cuff scar after hysterectomy)". Typical manifestations of POP are vaginal bulging, vaginal bleeding, pelvic pressure, discharge and infection, and low backache. Prolapse of organs toward the vagina (urethra, bladder, small intestine, colon, or rectum) often makes it necessary to digitally replace the prolapse or to apply manual pressure, e.g., to the perineum (splinting), the vagina, or rectally (digitation) to assist micturition or defecation.

Clinical POP can be identified in 31.8 % of postmenopausal women. Yearly incidences of cystocele, rectocele, and uterine prolapse have been estimated as 9.3, 5.7, and 1.5 cases per 100 women, respectively, 3 (Table 21.1).

S. Pisaneschi • G. Palla • S. Spina • G. Bernacchi • E. Cecchi • S. Di Bello • M. Montt Guevara • A. Campelo • T. Simoncini (✉)
Division of Obstetrics and Gynecology, Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, Pisa 56100, Italy
e-mail: tommaso.simoncini@med.unipi.it

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Table 21.1 Prevalence and incidence of POP on the basis of different definitions of POP

Study	Definition of POP	Prevalence	Incidence
Swift [2]	Pelvic organ prolapse quantification	6.4 % stage 0 43.3 % stage 1 47.7 % stage 2 2.6 % stage 3	
Hendrix [3]	Women's Health Initiative grading system (grades 1, 2, or 3)	Any prolapse: 41.1 % Cystocele: 34.3 % Uterine: 14.2 % Rectocele: 18.6 %	
Handa [4]	Women's Health Initiative grading system (grades 1, 2, or 3)	Cystocele: 24.6 % Uterine: 3.8 % Rectocele: 12.9 %	(Grades 1, 2, or 3) Cystocele: 9.3/100 Women-years Uterine: 1.5/100 Women-years Rectocele: 5.7/100 Women-years
Nygaard [5]	Pelvic organ prolapse quantification	2.3 % stage 0 33 % stage 1 63 % stage 2 1.9 % stage 3 25.6 % based on leading edgeR0	
Bradley [6]	Pelvic organ prolapse quantification	23.5–49.4 %	
Rortveit [7]	Patient symptoms past 12 months (not confirmed by examination)	5.7 %	
Nygaard [8]	Affirmative to "Do you experience bulging or something falling out you can see or feel in the vaginal area?"	2.9 %	

21.1.2 Urinary Incontinence (UI): Definition, Signs, and Symptoms

A realistic description of UI recently provided by the International Continence Society [4] is: "the burden of any uncontrollable leakage of urine". This annotation, although correct, needs further examination: as on the type, the frequency, the severity, and the precipitating factors. Social impact and also hygiene plays an important part on quality of life. Once we have established that the individual seeks help a clinical approach is needed to assess the severity of the leakage.

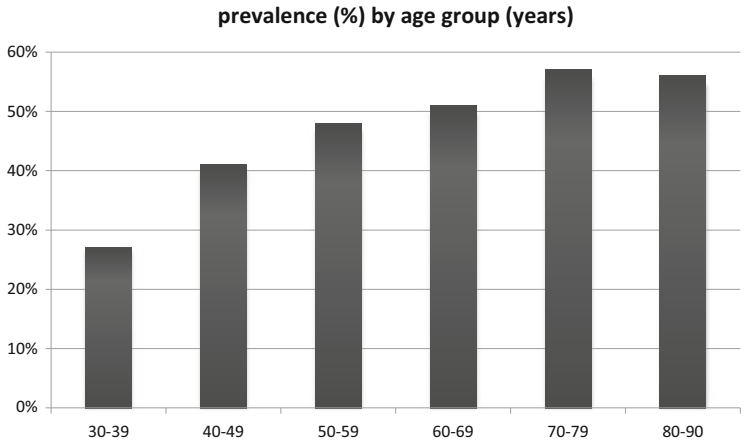

Fig. 21.1 Prevalence of urinary incontinence by decade of life (Adapted from Melville JL, Katon W)

The relentless increase of UI cases goes along with aging [9, 10] (Fig. 21.1). 31.7 % of US Women over the age of 80 have clinically significant UI, compared with women aged 40–59 years, showing a prevalence of 17.2 % [8].

21.1.3 Chronic Constipation: Definition, Signs, and Symptoms

Chronic constipation is a common disorder that heavily affects quality of life [11]. Frequent causes of chronic constipation are slow transit constipation and dyssynergic defecation. Irritable bowel syndrome is also associated with pelvic floor dysfunction, and particularly with hypertonic levator ani muscle and pelvic pain syndrome. Secondary causes are: low physical activity, inappropriate diet, constipating drugs (Table 21.2) or metabolic, neurological, endocrine, psychiatric or connective diseases, which are all frequent problems in older individuals [12]. Anatomical disruption of the entire pelvic floor or limited to the bowel (e.g., intussusception, rectocele, internal or external rectal prolapse) and reduced rectal sensation are also common in aging individuals [13]. This can include the consequences or complications of surgical procedures on the pelvis and the perineum [14].

The most referred symptoms are infrequent defecation, straining at defecation, hard or lumpy stools, sensation of incomplete defecation or anorectal obstruction, and need for manual maneuvers to facilitate bowel movements [15]. These symptoms are the basis of the most common diagnostic criteria to define constipation, the so-called Rome III criteria for functional constipation (Table 21.3). The prevalence of chronic constipation is approximately 16 % in adults overall and 33 % in adults older than 60 years and it is more common in women (F:M = 1,5:1)

Table 21.2 Drug associated with constipation in elder people

Common
Antacids
Anticholinergics
Antidepressants
Antihistamines with antimuscarinic properties
Antispasmodies
Calcium channel blockers
Calcium supplement
Diuretics
Neuroleptics with antimuscarinic properties
Opiate analgesics
Oral iron
Less common
Anticonvulsants
Antiparkinsonian drugs
Nonsteroidal anti-inflammatory drugs

Table 21.3 Rome criteria for functional constipation

Diagnostic criteria[a]
1. Must include two or more of the following:
(a) Straining during at least 25 % of defecations
(b) Lumpy or hard stools in at least 25 % of defecations
(c) Sensation of incomplete evacuation for at least 25 % of defecations
(d) Sensation of anorectal obstruction/blockage for at least 25 % of defecations
(e) Manual maneuvers to facilitate at least 25 % of defecations (e.g., digital evacuation, support of the pelvic floor)
(f) Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

and increases with age. However, about 50 % of community-dwelling elderly report constipation with an estimated prevalence up to 74 % in nursing homes [16, 17].

21.1.4 Sexual and Pelvic Floor Dysfunction

Most of the symptoms associated to these conditions have devastating effects on sexual function, due to dyspareunia or chronic pelvic pain, to the modified self-image associated to the change in the appearance of the genitalia, or to the loss of urine or feces associated with attempted coital activity [18].

21.1.5 Function and Dysfunction of the Pelvic Floor

Pelvic floor looseness depends on injury of the muscles and on the progression of pelvic floor weakening. Connective tissue degradation [19], pelvic denervation [20], devascularization, and anatomic modifications [21] all create a decline in mechanical strength and dyssynergic pelvic floor function, predisposing to prolapse [22].

Several muscles, essential for the support and function of female pelvic structures, constitute the pelvic floor complex. The levator ani is the floor of the pelvis; it is composed of three different parts: the pubococcygeus, the puborectalis, and iliococcygeus muscles. The main part of the levator ani is the pubococcygeus, which extends from the pubis toward the coccyx. Behind the anorectal junction there are the two parts (right and left) of the puborectalis, which coordinate a muscular sling. The smallest part the levator ani is the iliococcygeus.

In women with normal pelvic statics, smooth muscle fibers in the anterior vaginal wall are organized in tight bundles orientated in circular and longitudinal order, whereas in women with POP the vaginal muscularis presents a decline of overall smooth muscle amount, fewer, smaller, and disorganized bundles [23].

Levator ani injury has an established role in the pathophysiology of prolapse but does not explain all pelvic organ prolapses. 30 % of women with prolapse show no sign of muscle injury on MRI: highlighting the fact that the process includes other factors as well [24, 25]. The failure in this chain of events of one of the structural elements of the pelvic floor complex, e.g., the levator ani, results in overloading all other mechanical components (connective tissue and smooth muscle) which will eventually fail as well. On the other side, connective tissue abnormalities and smooth muscle alterations may represent the leading event in the development of prolapse [26].

Pelvic connective tissues are structured into a fascial sheet which covers the pelvic floor muscles and forms ligaments that connect pelvic organs to the bony pelvis [27]. Female pelvis has architectural characteristics, which allows for delivery of fetuses with increasing head diameters and upright standing and walking. Parallel to this evolutionary modification, connections of fascial structures to the pelvic sidewalls have progressively grown, suggesting a central role in the stabilization of the pelvic viscera of connective tissue [28]. Qualitative and quantitative alterations in collagen content and structure and in genes related to collagen remodeling in women with genital prolapse and stress urinary incontinence have been identified, which may represent individual predisposing factors for these conditions [29, 30].

Vessels are important for the function of the pelvic floor, as well, particularly for urinary function [31]. Large veins are located near the urethra, forming a spongious body. Intravascular pressure in this venous web determines a mechanical pressure on the urethra, working as seal and contributing to urinary continence [32], since it contributes for at least one-third of urethral pressure [33]. Indeed, incontinent postmenopausal women have less vessels in the periurethral tissue and a reduced blood pressure in these vessels [34].

21.2 Menopause and Aging: Impact on Pop and UI

The lower urinary and female genital tracts are strictly related and both derive embryologically from the urogenital sinus. 50 % of postmenopausal women complain of urogenital symptoms [35]; these appear after the menopausal transition and worsen with time. Dyspareunia, dysuria, frequency, nocturia, incontinence, and recurrent infections [36] are all facilitated by estrogen withdrawal.

Estrogen receptors (ER) are present in the epithelial tissues of the urethra, bladder, trigone, vaginal mucosa, and in the support structures of the uterosacral ligaments, as well as in levator ani muscles and pubocervical fascia [37]. Estrogen is involved in the increase of cell maturation index of these epithelial structures. It has been demonstrated that alterations in the ratio of estrogen receptor α (ERα) to ERβ may be related to the development of stress urinary incontinence [38]. Synthesis and metabolism of collagen in the genital and urinary tract is under the control of estrogens [39], which also increase the number of muscle fibers in the detrusor muscle and in the urethral muscles [40].

A hypothesis is also that estrogens influence micturition through the neurologic control in the central nervous system, changing the density of sympathetic nerve fibers in the pelvis and the central and peripheral synthesis of neurotrophins, although this set of actions is not completely understood [41].

Progesterone receptors are also expressed in the lower urinary tract, even if with less density than estrogen receptors [42]. It has been noticed that progesterone has adverse effects on female urinary tract function [43], since it is linked to an increase in the adrenergic tone, provoking a decreased tone in the ureters, urethra, and bladder. This could be the reason why urinary symptoms worsen during the secretory phase of the menstrual cycle, and progesterone may be responsible for the increase in urgency during pregnancy, although the precise mechanism is not fully figured out.

Notwithstanding all of the above, the role of menopause on pelvic floor dysfunction is unclear. Neither menopausal status [44] nor the length of hormone deficiency [3] has been clearly associated to the risk or severity of POP.

In spite of the evidence indicating generally positive effects of estrogens on the urogenital tract, there is no evidence supporting the use of estrogen therapy for the prevention or treatment of POP or UI in climacteric women [45]. In particular, available evidence does not show a beneficial effect of the use of estrogen therapy, both local and systemic, on stress urinary incontinence. On the other hand, recent studies underline that local estrogen therapy is effective for the treatment of urge urinary incontinence, overactive bladder and it can reduce the recurrence of urinary tract infections [46]. In women with overactive bladder symptoms, neuromodulatory effects by estrogens could be beneficial, as estradiol reduces the amplitude and frequency of spontaneous detrusor muscle contractions [47].

21.3 Aging and Constipation

In women aged <50 years paradoxical contraction or lack of relaxation of the pelvic floor muscles seem to be the most frequent causes of obstructed defecation. On the opposite, during aging more complex changes in the structure and function of the gastrointestinal tract, usually in the colon and in the anorectal region may develop and determine impaired bowel habits and evacuation mechanisms. Constipation is a problem that very often is related to older people, but should not be considered as a "physiological" consequence of aging. Constipation in the elderly has rarely one single cause and it is frequently secondary to emerging diseases or drugs (Table 21.2).

Aging is associated with loss of neurons (cholinergic neurons and interstitial cells of Cajal) in both the myenteric and submucosal plexus. Some studies indicate that delayed colon transit time occurs with aging. However, more recent publications underline that in healthy elder individuals, in the absence of comorbidities, there are no significant changes in the gut transit time. In any case, it is noted that in small groups of elderly patients an increased absorption of water could lead to the production of harder stools and consequently to difficulty in evacuation.

The adequate perception of rectal, anal, and perianal region is of importance in order to have a normal defecation. However, elderly people may need to have larger volumes of bowel content to stimulate rectal sensation and promote a normal defecation [48].

Changes in the anatomy of the anal canal, external anal sphincter atrophy, and internal anal sphincter degeneration have been associated with aging as much as tissue atrophy resulting in reduced distensibility. All of these could explain why aging [49] predisposes to alterations of defecatory function.

Injury of pudendal nerves can also play a role in the onset of constipation (i.e., obstructed defecation) in the elderly, particularly in women. In this condition, an abnormal perineal descent is frequently observed, causing a prolapse of the anal canal or of the anterior rectal mucosa with a consequent alteration of rectal emptying [50]. A recent study [51] seems to confirm this concept. In a group of 334 women with obstructed defecation, after eliminating the confounding effect of vaginal delivery from the risk factors, the authors find that rectocele, intussusception, rectocele associated with intussusception, rectocele associated with mucosal prolapse, and grade III enterocele/sigmoidocele increase with age.

21.4 Conclusion

Pelvic floor in women is a highly complex and vulnerable structure. Injuries, pregnancy, functional modifications, and aging of the pelvic floor structures all contribute to pelvic organ prolapse and the related symptoms. These symptoms are extremely common in aging individuals, creating a substantial discomfort and impairing a comfortable quality of life. Since POP and incontinence often develop

at the time of the menopausal transition, when women already face important problems that impact on their quality of life, it is important to identify and manage appropriately these problems. Even if consensus is not available, some of the hormonal interventions that can be considered in menopausal women can also positively affect some of the symptoms that are generated by POP, such as pelvic pain, sexual dysfunction, or urinary incontinence. Pathophysiology of pelvic organ prolapse, urinary incontinence, and bowel dysfunction is different in each patient. Finding the cause is the start of a successful treatment.

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The Influence of Sex Steroids on Affairs of the Heart

22

John C. Stevenson and Marie O. Gerval

22.1 Introduction

There is a gender difference in coronary heart disease (CHD); women develop the disease at a later age than men. The overall incidence in women is similar to that of men, but premenopausal women are relatively immune from the disease. Following the menopause, the incidence of CHD in women steadily increases and eventually matches that seen in men. This is a strong indication that female sex hormones may have a protective role, since other risk factors for CHD are the same in both men and women [1]. This concept is supported by the fact that premature menopause leads to premature CHD [2]. We discuss the evidence for the biological plausibility that estrogen has a beneficial effect on the cardiovascular system, and examine the observational and randomized clinical trial data for a beneficial effect of hormone replacement therapy (HRT) on CHD.

J.C. Stevenson (✉)
National Heart and Lung Institute, Imperial College London, Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, London SW3 6NP, UK
e-mail: j.stevenson@imperial.ac.uk

M.O. Gerval
Department of Gynaecology, Chelsea and Westminster Hospital NHS Foundation Trust, Fulham Road, London SW10 8NH, UK

Royal Brompton and Harefield NHS Foundation Trust, London SW3 6NP, UK
e-mail: m.gerval@imperial.ac.uk

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22.2 Biological Effects

22.2.1 Metabolic Effects

Estrogen has profound effects on metabolic risk factors for CHD as well as having direct arterial actions [3]. It lowers total cholesterol by reducing LDL cholesterol levels, an effect that is not impeded by progestogen addition, and also increases HDL cholesterol. Both these actions are considered beneficial in reducing CHD risk. These effects are dose dependent and are greater with oral than with transdermal administration [4]. The increases in HDL cholesterol are reduced or reversed by the addition of androgenic progestogens. Oral estrogen increases triglycerides, but this effect is also reduced or reversed by the addition of androgenic progestogens. In contrast, transdermal estradiol lowers triglycerides, again an action that should reduce CHD risk [5].

Insulin resistance is a pivotal disturbance in the metabolic syndrome and increases the future risk of both CHD and diabetes mellitus type 2. Estrogen has beneficial effects on glucose and insulin metabolism, producing a reduction in insulin resistance. This effect is more pronounced with oral than transdermal estrogen, but it is impeded by the addition of androgenic progestogens [6]. Nonandrogenic progestogens, such as oral micronized progesterone and dydrogesterone, do not have this unwanted effect [7].

HRT has an overall neutral effect on body weight, although a combination of estradiol with drospirenone causes a reduction. Central fat distribution is closely linked to insulin resistance and the metabolic syndrome, and hence increased CHD risk, and menopause results in an increase in this central fat [8]. However, HRT helps to reverse the menopausal changes in body fat distribution, with a reduction in central fat accumulation.

Oral estrogen has effects on hemostasis. Although it decreases the levels of certain clotting factors such as fibrinogen and factor VII, and decreases levels of the antifibrinolytic PAI-1, it is associated with an increase in coagulation activation [9]. Thus oral estrogen is associated with an increase, albeit transient, in venous thromboembolism (VTE). This adverse effect may be avoided by the use of nonoral estrogen, or reduced by using low doses of oral estrogen.

22.2.2 Direct Arterial Effects

Estradiol receptors are widely distributed throughout the vasculature, and estrogen can have both genomic and rapid nongenomic actions. Estrogen causes vasodilatation through a number of mechanisms [3]. It acts on the vascular endothelium, increasing endothelial nitric oxide synthase (eNOS) levels and therefore increasing production of NO, a potent vasodilator [10]. NO is involved in the regulation of blood pressure, platelet function, inhibition of vascular smooth muscle proliferation, and expression of adhesion molecules. Estrogen also reduces the release of endothelin-1, a potent vasoconstrictor [11]. Both oral and transdermal estrogen

reduce levels of cell adhesion molecules, suggesting an anti-inflammatory effect on blood vessels [12]. Estrogen inhibits calcium channels [13] and activates BKCa channels [14] to increase vasodilatation and improve arterial function. Estrogen, and certain progestogens, reduces angiotensin-converting enzyme (ACE) activity, again beneficial for cardiovascular health [15].

Abnormal deposition and remodeling of vascular extracellular matrix is involved in the pathogenesis and progression of atheroma, and normalization of these processes may inhibit atherogenesis. Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are key to these processes, and they have been implicated in the development of cardiovascular disease. Estradiol increases MMP activity in a dose-dependent manner [16]. Small increases in MMPs effected by low doses of estrogen may help normalize vascular remodeling, whereas high doses of estrogen may result in large increases in MMPs and may result in excessive remodeling, with disruption of existing atheromatous plaques. Thus, the dose of estrogen at initiation of therapy may be crucial in determining whether there is benefit or harm to the vasculature.

22.3 Observational Studies

Epidemiological studies have consistently shown an association between postmenopausal HRT use and reduction in cardiovascular disease, primarily CHD. The largest study, the Nurses Health Study, showed around a 40 % reduction in the incidence of CHD. This became apparent soon after initiation of therapy and persisted for up to 10 years of use [17]. Concerns are raised about the findings of observational studies as they are not randomized and can thus be influenced by a healthy user bias. Women who choose to take HRT are fitter and healthier and less likely to have CHD risk factors than those who do not take HRT. However, due to the large size of these studies, statistical adjustments can be made to account for any differences in confounding variables such as CHD risk factors, and such adjustments made no difference to the findings of the study. Observational studies of women with CHD have also shown an association between HRT use and reduced incidence of events. In a study of almost 2,500 women with previous myocardial infarction or documented atherosclerosis, there was a significant reduction in recurrence of major CHD events with either estrogen alone or estrogen–progestogen in up to 20 years follow-up [18]. In accordance with this, an observational study of postmenopausal women being admitted with an acute myocardial infarction showed that women who were on HRT at the time had a significantly better survival rate than those not on HRT [19]. An observational study of 1,280 postmenopausal women who participated in randomized clinical trials of HRT or placebo of 2–3 years duration around the age of 50 years and who took no subsequent HRT found a significant reduction in cardiovascular death in those originally allocated to HRT compared with those allocated to placebo during up to 15 years follow-up [20].

22.4 Randomized Trials

A series of animal studies using cynomolgus macaques demonstrated that intervention with HRT at the time of menopause resulted in a significant reduction of dietary-induced atheroma compared with placebo, but a delay in initiating HRT caused a loss of this effect [21–23]. This led to the "timing hypothesis" which suggests a window of opportunity for a number of years immediately after the onset of menopause to initiate HRT and obtain cardiovascular benefit. This theory is supported by the results from a variety of clinical trials. A study of a modest dose of oral estradiol 1 mg daily given to healthy women in the early postmenopausal period resulted in a reduction in atheroma progression compared with placebo [24]. In contrast, a study of elderly women with established CHD given conjugated equine estrogens at a relatively high dose (for their age) of 0.625 mg daily showed no difference in atheroma progression compared with placebo [25]. This could have been due either to the timing of initiation of therapy, or the dose at initiation, or both. The KEEPS trial compared the effects of a modest dose of conjugated equine estrogens (0.45 mg) with a standard dose of transdermal estradiol (50 mcg) on carotid and coronary atheroma progression over 4 years in women in the early postmenopause [26]. Neither treatment resulted in any difference from placebo. The WHI randomized trials compared conjugated estrogens (0.625 mg day), alone or combined with medroxyprogesterone acetate (2.5 mg daily), and placebo in over 27,000 postmenopausal women aged between 50 and 79 years of age [27, 28]. They initially reported a significant increase in coronary events with combined estrogen/progestogen [27], but subsequent publications showed that this was not significant [29, 30]. The estrogen-alone arm showed a nonsignificant reduction of coronary events with estrogen [31]. However, a clear effect of age at initiation of therapy was seen, with those aged below 60 years or within 10 years of menopause showing a trend to reduced CHD and reduced mortality. The trend ($p = 0.02$) for CHD reduction with proximity of the menopause was not statistically significant because the authors set the significance level at 0.01 in this publication, although not in prior or subsequent publications [30]. In those women initiating estrogen-alone therapy below age 60 years, there was a significant reduction in coronary interventions and a significant reduction in a composite endpoint of myocardial infarction, coronary intervention, and death [31]. In this group of women, a post-hoc study of coronary calcification showed a decrease of 20–40 % in calcified plaques in those previously allocated to estrogen compared with those previously allocated to placebo. In those women who were more than 80 % compliant with their therapy, the reduction in calcified plaques was 50–60 % [32]. In an 11-year follow-up, those women who had initiated therapy below age 60 years and completed an average 7 years estrogen-alone treatment had a significant reduction in coronary events compared with those allocated to placebo [33]. In agreement with these findings, a meta-analysis of the pooled results of over 39,000 postmenopausal women from 23 randomized clinical trials showed a significant reduction in myocardial infarction or death in women initiating HRT aged below 60 years or within 10 years of the onset of menopause compared with women initiating HRT aged above 60 years or beyond 10 years of

the onset of menopause [34]. The Danish Osteoporosis Prevention Study (DOPS) was a smaller randomized clinical trial but with a much longer treatment duration and follow-up [35]. Women who were on average 7-month postmenopause were randomly allocated to treatment with oral estradiol, with or without cyclical norethisterone acetate, or no treatment. The study was stopped after 10 years and an observational follow-up conducted for a further 6 years. There was a significant reduction in the primary composite endpoint of myocardial infarction, admission for heart failure, or death in those using HRT compared with the nonusers. The strengths of this study were that a different HRT to that of WHI was used, and the follow-up was longer. The limitations were that the number of events was extremely small due to the young age of the women, a total of only five myocardial infarctions in the randomized trial (one on HRT) rising to 16 in the observational follow-up (five on HRT).

Secondary prevention trials have largely failed to show a benefit of HRT on CHD outcomes. The Heart and Estrogen/progestogen Replacement Study (HERS) randomized almost 2,800 postmenopausal women with established CHD to treatment with conjugated equine estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg or placeboa [36]. No overall benefit or harm was shown after 4-year follow-up, although there appeared to be an initial increase in events followed by a later decrease. Concerns were raised that the dose of estrogen was too high for the age of the women (mean 67 years) [37]. A similar pattern of events was seen in the small Papworth HRT atherosclerosis study (PHASE), which used transdermal estradiol, with or without norethisterone acetate [38]. But again the dose of estradiol 80 μg was inappropriately high for the age of the patients. In contrast, studies using a lower dose of oral estradiol 1 mg daily showed nonsignificant reductions in events during the first 12 months [39, 40].

22.5 Conclusions

The totality of the data on HRT for the primary prevention of CHD points to a beneficial effect when treatment is initiated in the early postmenopause. Secondary prevention studies have simply highlighted how important is the dose at initiation in older women, and this seems to be a crucial fact. As yet there is no established indication for the use of HRT solely for the prevention of CHD. Nevertheless, its use should be considered in women at increased risk for CHD as part of their overall management. The age of the woman initiating HRT is of paramount importance, as the dose appears crucial in determining whether there may be benefit or harm.

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Reproductive Depression and the Response to Oestrogen Therapy

23

John Studd and Rossella E. Nappi

23.1 Introduction

It is probable that the first quantitative account of the incidence of depression in women and men came from Charles Dickens [1] who went through the books of St. Luke's hospital for the insane reporting in his journal Household Words the increase of admission for depression in women. He claimed that this increase in depression occurred particularly in "women of the servant class" thus indicating the effect of both gender and social deprivation on mental illness. The excess of depression in women compared with men can be the result of social and environmental factors but most convincingly it occurs at times of hormonal fluctuation and is a result of these endocrine changes.

23.2 Reproductive Depression and Ovarian Hormones

Depression in women commonly occurs at times of hormonal changes [2], most commonly seen with depression in the premenstrual days. There is also a peak of depression in the postnatal months, often following a pregnancy characterised by a good mood with less depression. Later in life, depression occurs at its most severe in the 2 or 3 years before the periods cease in the menopausal transition. Together, these three components of premenstrual depression, postnatal depression and climacteric depression with its probable endocrine aetiology mostly influenced by changes in ovarian hormones are best termed "Reproductive Depression" as originally suggested by Nappi et al. [3]. This name gives emphasis to the fact that it is a

J. Studd (✉)
London PMS and Menopause Centre, 46 Wimpole St, London W1G8SD, UK
e-mail: studd@me.com

R.E. Nappi
Department of Obstetrics and Gynaecology, Research Centre for Reproductive Medicine, University of Pavia, Pavia, Italy

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hormone-mediated mood change, which may well be most effectively treated by correction of these hormonal changes [4, 5].

These peaks of depression often occur in the same woman. The typical story is one who has mild-to-moderate PMS as a teenager, which may become worse with age with fewer good days per month. When pregnancy occurs, they are normally in a good mood throughout pregnancy in spite of possible common problems such as nausea, pre-eclampsia or other obstetric complications. After delivery, they develop postnatal depression for many months and it is at this point that women often have their first "nervous breakdown". They are treated with various antidepressants which are barely effective. When the periods return the depression becomes cyclical and more severe but improves with subsequent pregnancies. They still have cyclical depression in their 1940s and the depression becomes worse in the 2 or 3 years of the menopause transition [6]. If they develop vasomotor symptoms of flushes and sweats, they may be given oestrogens which will cure these symptoms and usually often helps the depression.

With this history in mind, it is important to realise that hormone responsive depression cannot be diagnosed by any blood test. Too frequently, women who believe that their depression is related to her hormone visit their family doctor, their gynaecologist or psychiatrist who measures their hormone levels, which are normal and the association with hormonal changes is dismissed. These are all premenopausal women who will have normal FSH and oestradiol levels, which may not be optimal for the individual but they are normal. It is a huge mistake to exclude hormone responsive depression because of normal blood levels [2]. The clue to the diagnosis is in the history and even then psychiatrists will often regard the association of depression with periods and postpartum changes as irrelevant.

23.3 Premenstrual Depression

Most women will be aware of physical and mood changes a day or two before the periods which indicates that they are premenstrual but this is not a severe abnormality. Perhaps 10 % of women suffer severe premenstrual syndrome for 10–14 days a month with severe depression, behavioural changes, anxiety, aggression, loss of energy, loss of libido and somatic symptoms of headaches, abdominal bloating and mastalgia.

The American Association of Psychiatrists in their DSM IV publication has termed this premenstrual dysphoric disorder. The word dysphoric strongly indicates a psychiatric origin of a condition we can now view as incorrect. The motive behind this renaming by psychiatrists is one done for a reason of territory and of course reimbursement in the American system. "Ovarian Cycle Syndrome" would be a better name as it clearly establishes the cyclical and hormonal aetiology of the condition and the fact that the ovary being the architect of these changes [7], but this has not found favour with psychiatrists involved in the treatment of "PMDD".

This most common component of reproductive depression is an endocrine problem due to the hormonal changes that occur following ovulation and it is

logical that effective treatment should be one which suppresses ovulation and suppresses the ovarian hormonal changes (whatever they are) that produce the cyclical symptoms of the premenstrual syndrome. The most logical and easiest way to suppress ovulation is the birth control pill [8], but these women are usually progesterone/progestogen intolerant [9] and hence the birth control pill even when taken "back to back" will suppress cycles and even suppress bleeding if taken back to back but they may have depressive and somatic symptoms most of the time without having the usual 10–14 good days a month that even the most severe cases enjoy.

Suppression of ovulation by transdermal oestradiol in the form of oestradiol patch 200 mcgs twice weekly has been shown to be effective [10] and transdermal oestrogen in the form of oestradiol gels, Oestrogel 2 measures daily or Sandrena 2 g/day will also be effective. It is necessary to give cyclical progestogen by some route to prevent endometrial hyperplasia, but it is common for the PMS symptoms to reoccur during these days; hence, a minimum duration of progestogen is recommended for the first 7 days of each calendar month with a withdrawal bleeding occurring on about day 10 of each calendar month. Alternatively, a Mirena IUS is usually very effective although perhaps 10 % of women do have absorption of the D-norgestrol and suffer almost continuous PMS symptoms [11]. These symptoms disappear within 24 h of the removal of the Mirena IUS.

Alternatively, ablation of ovulation by the use of GnRH analogues is most effective [12] and indeed is a useful diagnostic tool if a hysterectomy and bilateral salpingo oophorectomy is contemplated [13]. There is a risk of distressing menopausal symptoms and even osteopenia so add-back HRT is essential if prolonged treatment is required. This will usually be in the form of transdermal oestradiol and cyclical oral progestogen [14], which may produce a return of PMS symptoms or the insertion of a Mirena IUS. Using Livial as Add Back is an effective way of avoiding bleeding and progestogenic side effects [15].

Women with severe PMS who respond partially to treatment because of progestogenic side effects or bleeding problems should be offered a hysterectomy and bilateral salpingo oophorectomy. A hysterectomy alone is not effective because the ovaries will still produce the cyclical hormonal changes and the cyclical symptoms although menstruation has been abolished the cyclical symptoms have not.

There are now many studies showing the very beneficial effect of surgery and long-term replacement therapy for the most severe PMS [16, 17]. This is a further example to indicate that the condition is endocrine and not psychiatric.

The great danger to women with severe PMS who do not respond to antidepressants is that they are given a higher dose then a second or third antidepressant, which also do not work. By then they can be labelled as bipolar disorder and the scene is set for mood stabilising drugs, antiepileptics and even electroconvulsive therapy. After 10 or more years of this therapy, it is difficult but not impossible to wean them off these psychotropic drugs by transdermal oestradiol, which they should have had in the first place. The clues of course are in the history.

There are eight vital questions to diagnose PMS and to exclude bipolar disorder [18]:

1. Relating earlier depressive episodes to the menstrual cycle
2. The relief of depressive symptoms during pregnancy
3. The recurrence of depression postpartum
4. Premenstrual depression on menstruation recurs after delivery
5. The premenstrual depression becoming worse with age blending into the menopausal transition
6. Often the co-existence of somatic symptoms such as menstrual migraine, abdominal bloating or cyclical mastalgia
7. These patients usually have seven to ten good days per month
8. Although depression can be cyclical they rarely have highs.

23.4 Postnatal Depression

The seriousness of this condition cannot be overstated as both the mother and the child can be in great danger. It occurs in 10 % of healthy women and can last for months or years. It is not the "baby blues" occurring in the week after delivery. It is usually treated with varying success with antidepressant drugs, psychotherapy or admission to mother and baby units, but once again the association with profound, abrupt hormone changes after childbirth should point to a hormonal aetiology. Prolonged breast feeding which is associated with lower oestradiol levels often produces more severe and prolonged depression.

Depression has been reproduced experimentally in women with a history of postnatal depression by creating a pseudo pregnancy with excess doses of oestradiol and progesterone, which is then suddenly discontinued [19]. Depression occurred in women with a history of postnatal depression but not in the women in the study without a previous history of postnatal problems. Transdermal oestradiol is effective in the treatment of postnatal depression even in those women who have inadequately responded to antidepressants [20]. Unfortunately, psychiatrists rarely use this therapy preferring antidepressants, psychotherapy or admission to mother and baby units. Formerly, progesterone and progestogen have been recommended, but there is no evidence that they are effective. On the contrary, studies have shown them to be ineffective, and the Cochrane report has agreed that oestrogen improves mood and postnatal depression and norethisterone makes depression worse [21].

23.5 Climacteric Depression

There are many reasons why women become depressed around the time of menopause. Hot flushes and sweats produce insomnia and social embarrassment, headaches are troublesome and the vaginal atrophy producing dyspareunia, recurrent cystitis together with loss of libido are enough to cause some depression. These typical symptoms of oestrogen deficiency can easily be treated with routine HRT and the low mood associated with these problems of sexuality and sleep are improved [2]. However, there is another type of depression not associated with

characteristic menopausal symptoms in the 3 or 4 years before the periods cease in the so-called menopausal transition [22]. This is the depression that occurs usually in the absence of vasomotor symptoms or vaginal dryness and has been shown in many studies to be responsive to oestrogens, both oral oestrogens and transdermal oestrogens [23, 24]. In fact, the evidence for the benefit of oestrogens on perimenopausal depression is more convincing than the beneficial effects in the depression of the postmenopausal woman [25]. This treatment is best done by transdermal oestrogens in the form of gels or patches continuously with cyclical progestogen if the woman has a uterus [2]. Gynaecologists are aware that depression occurring in *most* perimenopausal women respond well to oestrogens given for the depression or associated symptoms although most psychiatrists are unaware of this because they do not use oestrogens. Antidepressants would be there first choice therapy.

23.6 Hysterectomy

It may seem odd to include a section of hysterectomy, but there is much evidence from psychiatrists that depression is less common after hysterectomy [26]. In spite of this virtually all newspaper and magazine articles on this subject stress the belief that hysterectomy causes profound depression, loss of sexuality and marital breakup. The reverse is true. In younger women having persistent cyclical depression as well as other cyclical problems of bleeding, pain and cyclical headaches, hysterectomy with bilateral oophorectomy will usually cure these problems. In the specific case of premenstrual depression in those women with progestogen intolerance, hysterectomy with bilateral oophorectomy and replacement of oestradiol and testosterone have been shown in all studies to be beneficial [27]. Thus, a well-conducted hysterectomy for the correct indication should be seen as a life-enhancing produce and may also remove the need for progestogen and the 4 % of women who die of cancer of the ovary, cervix and uterus should be seen as a life saving as well as a life-enhancing procedure [28]. This should not be seen as a radical last choice—or never choice option.

23.7 General Principles of Hormone Therapy for Reproductive Depression

The use of transdermal oestrogens is recommended to suppress ovulation in women with premenstrual syndrome, or in correcting the profound oestrogen decrease with postpartum depression. It should be the first choice therapy in perimenopausal women with depression whether they have associated vasomotor symptoms or not. But such therapy does not exclude the combined therapy with antidepressants [29]. Most studies looking at hormone responsive depression have used transdermal patches or implants, but there is no reason why oral oestrogen should not be effective although the appropriate studies have yet to be published. However,

transdermal oestrogens are preferable because they do not invoke hepatic coagulation factors and are not associated with the higher rates of venous thromboembolism of oral estrogens. The preferred regimen would be oestradiol patches 200 mcgs twice weekly or oestradiol gels 2–4 g daily throughout the month. Cyclical gestagen in women with a uterus should be used for the first 7 days of each calendar month which would produce a scanty withdrawal bleed on approximately day 10 of each calendar month.

The monthly progestogen duration has been reduced from the orthodox 14 days as these women with depression are usually progestogen intolerant and there is now mounting evidence that the major side effects of HRT are related to the progestogen component.

For the women with libido and energy problems which often coexist with depression and treatment by antidepressants, testosterone can be added in the form of testosterone gel in the appropriate dose. This would be approximately 10 % of the average male dose which in practical terms would be one-quarter of a sachet of Testogel alternate days or a quarter of a tube of Testim alternate days. 100 mg testosterone pellets would be ideal, but at the time of writing they are no longer available.

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Body Identical Hormone Replacement

24

Nick Panay

24.1 Introduction

The adverse outcomes seen in WHI [1] were mainly due to an overdosage of hormones in a relatively elderly population. However, fundamental differences exist between conjugated equine oestrogens and 17 beta-oestradiol and between medroxyprogesterone acetate and natural progesterone. It is likely that these differences also contributed to the adverse outcomes in WHI, which were contrary to the cardiovascular benefits seen in previous observational trials. Recent studies of cardiovascular risk markers in younger women have been designed using predominantly oestradiol and natural progesterone (transdermal and oral) as the primary interventions. This chapter reviews the effects that body identical oestradiol and progesterone can have, both in the physiological environment and also when replaced as transdermal oestradiol and micronised oral progesterone.

24.2 What Are Bio-identical Hormones?

"Bio-identical hormones" are precise duplicates of oestradiol, oestriol, oestrone, progesterone, DHEA and testosterone as synthesised by the human ovary and adrenal. However, this is a marketing term and bios is a Greek term referring to "life". A more accurate way to refer to these hormones is "body identical" [2]. This chapter focuses on the possible differential effects of transdermal oestradiol and micronised progesterone. Although androgens have a vital role to play in hormone replacement, there is general agreement that testosterone should be delivered non-orally in a physiological formulation and dosage.

N. Panay (✉)
Queen Charlotte's & Chelsea and Chelsea & Westminster Hospitals, Imperial College London, Du Cane Road, TW9 3BU London, UK
e-mail: nickpanay@msn.com

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24.3 Why Is There Controversy?

Compounding pharmacies market their own unregulated bio-identical products promoted in a number of countries by high-profile celebrities. Some practitioners prescribing these compounded preparations claim to be able to calculate the precise level of each deficiency from salivary hormone levels and then replace the precise amount using oestrogen, progesterone and testosterone delivered by lozenges or creams. This practice is not supported by evidence for efficacy nor safety. In reality, imbalances of oestrogen and/or progesterone can lead to problems such as endometrial hyperplasia. It is high time the regulatory authorities took this issue seriously and introduced a statute to prevent these unregulated products from being freely sold on the open market. The US Senate are passing a bill on bio-identical hormones to bring these products under Food and Drug Administration (FDA) regulation. The North American Menopause Society (NAMS) is concerned about pharmacy compounders who operate as manufacturers without following Good Manufacturing Practices. NAMS have called for the manufacturers of body identical hormones to register with the FDA. Bulk chemicals should be identified and checked for quality and purity. Standard information should be provided on risks and benefits of the product. There should be appropriate investigation and reporting to the FDA of adverse events potentially related to the drug.

24.4 Are There Any Differences Between Bio-identical and Non Bio-identical Hormones?

The most significant difference, in terms of biological effect, is with the progesterone component. The synthetic analogues of progesterone, i.e. progestins/progestogens were developed to make the hormone available orally before the process of micronisation had been developed. Unfortunately, in addition to binding to the progesterone receptor, many of these compounds also bind to the glucocorticoid, mineralocorticoid and androgen receptors. This binding can lead to unwanted side effects such as unfavourable glucose metabolism, fluid retention, acne and weight gain [3]. The progesterone molecule binds primarily to the progesterone receptors to produce the desired effect in the endometrium, i.e., secretory transformation. There is some weak binding to the mineralocorticoid receptor, but here there is an antagonistic effect which gives it mild diuretic properties. Progestogens and progesterone bind to the progesterone receptors in the central nervous system. Both can lower mood through stimulation of the neurotransmitter gamma amino butyric acid (GABA); whereas progesterone has a mild sedative effects through its intermediate metabolites, progestogens tend to cause anxiety and irritability [4].

Synthetic forms of oestradiol, e.g. valerate are cleaved at an early stage during GI absorption leading to delivery of bio-identical oestradiol. The biological effects of conjugated equine oestrogens are complex and have still not been fully evaluated.

24.5 Does the Route of Administration Make a Difference?

There are some fundamental differences between oral and transdermally administered oestradiol due to the avoidance of first pass hepatic metabolism. In theory, transdermal delivery manifests in a more physiological systemic effect; factors of coagulation are not activated and neither is the renin–angiotensin–aldosterone cascade, thus minimising the risk of venous thrombosis and hypertension [5].

24.6 Effect on the Cardiovascular System

Micronised progesterone has several properties, which facilitate a neutral or positive effect on the cardiovascular system. There appears to be a neutral effect on lipid and glucose metabolism and on vascular tone. Thus, the beneficial effects of oestrogen are not attenuated as they are with some synthetic progestogens such as MPA which can blunt the increases in HDL [6]. Progesterone also has beneficial effects by preventing the growth and movement of cells involved in the formation of arteriosclerotic plaques and relaxes arterial smooth muscle via enhancement of nitric oxide from the endothelium. Conjugated equine estrogens lead to greater increases in triglycerides than 17 beta-oestradiol, but it is unclear how significant this is as far as cardiovascular disease risk is concerned.

New randomised trials, such as KEEPS [7] and ELITE, have been designed to study bio-identical hormones in the expectation that there will be a more favourable effect on cardiovascular risk markers. In both studies, micronised progesterone has been used as progestogenic opposition. Preliminary data from KEEPS reported at NAMS in October 2012 showed a significant improvement in quality of life with no significant effect on carotid intima media thickness, coronary calcium scores and lipids and insulin resistance. The final ELITE study report is due in 2014.

24.7 Effect on Venous Thromboembolic Risk

There are differential effects of transdermal oestradiol and micronised progesterone on the cardiovascular system. There is lack of a procoagulant effect of transdermal oestradiol with absence of thrombin generation and resistance to activated protein C. This may result in primary prevention benefits for myocardial infarction and diabetes, though larger studies would be desirable to confirm this. The type of progestogen seems to negate even the route of administration of oestrogen. Observational data suggest that the use of progesterone-derived progestogens may modulate the increased risk conferred by oral oestrogen. There was no modification of venous thromboembolic (VTE) risk regardless of route of oestradiol administration with an odds ratio of 0.9 (CI 0.6–1.15) in the E3N study [8] and an odds ratio of 0.7 (CI 0.3–4.9) in the ESTHER study [9].

24.8 Endometrial Protection

Although consistent endometrial protection was shown with micronised progesterone in the PEPI trial [10], is it adequate if used orally? In the EPIC cohort, more endometrial cancers occurred overall in sequential combined HRT users: HR 1.41 (CI 1.08–1.83) but particularly in oestradiol/micronised progesterone users: HR 2.42 (CI 1.53–3.83) [11]. There was a significant reduction in risk in continuous combined users with an HR of 0.24 (CI 0.08–0.77).

A possible explanation is that there was less compliance in micronised progesterone users because there were two separate components to their HRT which had to be complied with.

24.9 Effect on the Breast

Micronised progesterone stimulates the 17 beta hydroxysteroid dehydrogenase transformation of oestradiol into less potent oestrone E_1. E_1 competes poorly with oestradiol E_2 for binding to the oestrogen nuclear receptor and diffuses out of the target cells more easily than E_2. In addition to this, progesterone has a pro-apoptotic effect on breast epithelial cells—this is in contradistinction to the effects of androgenic progestogens, such as medroxyprogesterone acetate, which have a proliferative effect [12].

Do the laboratory/animal data translate into clinical benefits? Data from the E3N Cohort Study would suggest so. Established in 1990 with 98,995 women from a health insurance scheme covering French teachers, born 1925–1950 it is part of the European Prospective Investigation into Cancer and Nutrition (EPIC). Oestrogen–-progesterone combination HRT was associated with a significantly lower relative risk (neutral for "ever use" of HRT) than for other types of combined HRT (RR 1.7–2.0). The increased risk appeared to apply preferentially to oestrogen receptor (ER) positive carcinomas and to affect both ductal and lobular carcinomas [13]. However, subsequent analyses of the data from EPIC showed that if HRT was initiated less than three-year post-final menstrual period, more than 5 years use of HRT was associated with an increased risk of breast cancer, even in oestradiol and micronised progesterone users [14].

It has also been argued that possible preferential use of oestradiol and progesterone in overweight women could explain lack of association with breast cancer as in WHI [15]. Another factor needing consideration is that oral micronised progesterone is poorly absorbed; the weak effect may take longer to increase risk of breast cancer. Finally, how do we explain no increase in risk of breast cancer in the Danish Osteoporosis study with the androgenic progestogen norethisterone acetate; this may be due to the small size of the study group but follow-up was long term (16 years) [16]. There is clearly a need for further prospective randomised studies using oestrogen–progesterone combinations to confirm these data [17].

24.10 Global Consensus [18] and IMS Recommendations [19]

The recent global consensus is that the use of custom compounded bio-identical hormone therapy is not recommended [18]. The IMS recommendations [19] state the following:

Natural progesterone and some progestogens have specific beneficial effects that could justify their use besides the expected actions on the endometrium.

Progestogens may not be alike in regard to potential adverse metabolic effects or associated breast cancer risk when combined with long-term oestrogen therapy.

24.11 Conclusions

There is evidence that replication of the physiological hormonal environment with transdermal oestradiol and natural progesterone can maximise the benefits and minimise the side effects and risks of hormone therapy. It is time we moved away from the notion, often propagated by epidemiologists and the media, that HRT products have a single class effect. However, regulated bio-identical products must not be confused with unregulated products from compounding pharmacists. In order to avoid confusion, the editors propose that regulated products should be referred to as "body" rather than "bio" identical. The published data thus far suggest that differential effects can be achieved by the use of body-identical HRT in comparison to synthetic non-body-identical HRT. Further data from larger studies on major cardiovascular and breast endpoints are required to confirm these effects. In the interim, the logical approach would be to continue to prescribe individualised HRT regimens from the whole pharmacopeia according to the evidence base and IMS recommendations [19], taking into account each woman's risk profile.

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Postmenopause and Ageing: The Concept of Personalized Therapy

25

Tommaso Simoncini, Silvia Pisaneschi, Stefania Spina, Guja Bernacchi, Silvia Di Bello, Elena Cecchi, Paolo Mannella, and Andrea R. Genazzani

25.1 The Menopause

The climacteric is the consequence of the withdrawal of estradiol and progesterone due to the cessation of the cyclical ovarian function. This hormonal change affects a large series of bodily targets, causing atrophy of tissues, metabolic modifications along with psychological and sexual changes that are variably experienced by women. The first signs include the typical vasomotor symptoms, nocturnal sweats, and the psychological instability. Soon after these first manifestations, atrophic changes and metabolic and body composition changes develop. Changes in the lipid profile and in body fat distribution and quantity are associated with estrogen deprivation, and lead to a change in the metabolism of climacteric women towards a "male" status. The skeletal system is heavily affected in most individuals with an accelerated bone loss that can lead to osteopenia or to overt osteoporosis. The function of the cardiovascular system is also affected by the changes in circulating sex steroids, with enhanced atherosclerotic degeneration. Circumstantial evidence indicates that the central nervous system may be affected in the long term, with an increased risk for neurodegenerative diseases, such as dementia.

25.2 Hormone Replacement Therapy

Associations of estrogens with or without a progestin represent the most effective therapies for climacteric symptoms, but recent findings have opened a debate that has not yet settled, on the safety of these therapies, particularly in regard to breast cancer and to cardiovascular disease (CVD).

T. Simoncini • S. Pisaneschi • S. Spina • G. Bernacchi • S. Di Bello • E. Cecchi • P. Mannella • A.R. Genazzani (✉)
Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, Pisa 56126, Italy
e-mail: argenazzani@tiscali.it

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25.2.1 Cardiovascular System

Several long-term observational studies suggest that hormone replacement therapy (HRT) prevents CVD in postmenopausal women. The conclusion of all these trials is that HRT reduces the risk of coronary heart disease (CHD) of about 40 %. This has been largely confirmed by the main prospective clinical trial available so far, the Women's Health Initiative [1] showing that women receiving estrogens soon after the menopause are protected in the long term from CVD.

The potential cardioprotective actions of estrogen indeed depend on the levels of preexisting CVD at the time of therapy initiation [2]. For example, the ERA clinical trial reported that women with preexisting atherosclerosis receive no benefit on the progression of carotid atherosclerosis by estrogen replacement [3]. Thus, while estrogen may protect against the development of atherosclerosis, it does not appear to be protective against existing atherosclerosis. Studies in women with low CVD risk concur with this. Indeed, in the WHI, those women who started HRT early after the menopause, probably having less developed CVD, showed better cardiovascular outcomes [1]. However, the vast majority of the women included in the WHI trial had a severely diseased vasculature due to the age and to the large prevalence of cardiovascular risk factors (obesity, high cholesterol, and hypertension) and this explains the failure of this trial in showing overall cardiovascular benefits with HRT in women over 60 years of age.

25.2.2 Bones

Osteoporosis is characterized by reduced bone mass that leads to reduced bone quality and resistance, and consequently to an increased risk of fractures. Osteoporosis is a very common condition in postmenopausal women causing significant morbidity and reduced quality of life.

Circulating estradiol has a protective effect on the bones, reducing skeletal remodeling through many mechanisms: reduction in activation of bone metabolic units, enhanced survival of osteoclasts, and improved efficiency of gastrointestinal calcium absorption and renal calcium conservation [4].

By increasing bone mineral density, HRT is the best (and more physiological) protective therapy against osteoporosis and fractures in postmenopausal women.

In the double-blind Postmenopausal Estrogen/Progestin Intervention (PEPI) trial and in the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial, women treated with estrogen or estrogen/progesterone therapy had a significant increase in the BMD vs. the placebo group, in which a loss of bone mass was observed [5]. Prospective randomized studies confirm these results. In the Women's Health Initiative study (WHI), there was a clear reduction in the risk of fractures among women receiving continuous combined CEE plus MPA or the estrogen alone therapy [1].

25.2.3 Cognitive Function

Because of the presence of ERs throughout the brain, estrogen effects are also widespread and affect brain structure and function and provide neuroprotection against oxidative stress via an antioxidant effects [6]. Moreover, estradiol, in vitro, promotes the breakdown of the β-amyloid precursor protein preventing the accumulation of β-amyloid. There exists, then, a biological plausibility for the clinical hypothesis that estrogen helps to maintain cognition in women and prevents or delays the development of neurodegenerative disorders.

Observational studies in which the treatment is started in the early postmenopausal period show a decreased risk for Alzheimer's disease with treatment [7]. In contrast with these results, the Women's Health Initiative Memory Study (WHIMS) showed a nearly doubling of the risk for all-cause dementia [8]. One explanation for this discrepancy is that late initiation of hormone therapy (after 65 years), as in the WHIMS study may not be effective in preventing neurodegeneration and may instead precipitate vascular dementia, whereas an early use confers benefit [2, 9].

While the prevention of Alzheimer's disease with HRT is still to be established it seems that the initiation of hormone therapy in patients aged 65 or more may increase the risk of impaired cognitive function.

25.2.4 Breast Cancer

Breast cancer is the most common cancer in women in the Western countries. Estrogens have clear proliferative activity on breast cancer cells in vivo and in vitro [10], so it may be biologically sound that prolonged exposure to estrogens increases the risk of breast cancer. However, it is not clear if exposure to estrogens has any effect on cancer development per se. Most of the currently available evidence suggests that cancer transformation may not be related to estrogens exposure, but that once this primal event takes place, then estrogens may promote tumor growth and eventually spread. On the other side, progestins have traditionally been seen as protective against breast cancer development despite the absence of a strong biologic rationale for an antiestrogenic effect of progestins on the breast.

Correlation between HRT use and breast cancer risk has been studied in many epidemiological studies. A large meta-analysis published on the Lancet in 1997 indicated that the risk of breast cancer is increased in women using HRT and increases with increasing duration of use [11]. This excess risk is reduced after HRT cessation and disappears within 5 years [11]. Recently, the WHI study reported a 26 % increase in the relative risk of breast cancer for combined estrogen–progestogen when compared with a placebo [1]. However, the parallel arm of the WHI study investigating the effect of the administration of estrogens alone showed no increase of breast cancer, with a trend toward a reduction of the risk [1]. This study, along with the long-term analysis of the Nurse's Health Study, in general indicates that the impact on the incidence of breast cancer of HRT is limited and associated only with very long administrations [12]. In addition, recent

trials call for new research to better understand the role of progestins, showing that based on the compound, the risk of breast cancer changes [13].

25.2.5 Endometrial Cancer

The vast majority of all endometrial malignancies occur mostly in perimenopausal and early postmenopausal women. The pathogenesis is in part linked to a prolonged and excessive exposure to endogenous or exogenous estrogens, not balanced by the cyclical production of progesterone. The risk of endometrial cancer is not clearly related with the dose but with the duration of unopposed estrogen exposure, as long-term administration correlates with fivefold higher risk [14]. HRT with estrogen alone increases endometrial cancer risk, whatever the type and the dose of estrogen and the route of administration [14]. Progesterone has a well-known antiestrogenic effect on the endometrium. The addition of a progestogen to the estrogen replacement therapy (ERT) is then mandatory to avoid the risk of endometrial cancer, contrasting the stimulation of the endometrium by estrogens. To this extent, in the presence of a progestin, endometrial cancer risk is decreased either with cyclic or continuous HRT. Cyclic regimens including more than 10 days of progestogen exposure per month appear to provide maximum protection [15].

25.2.6 Colorectal Cancer

Colorectal carcinoma is a leading cause of illness and death in the Western countries, being the second most common cancer in women after breast cancer [16]. There is strong evidence to show that the incidence of colorectal carcinoma can be significantly reduced by HRT. A meta-analysis of 18 epidemiological studies of HRT and colorectal cancer showed a 20 % reduction of colon and rectal cancer risk in women who had ever taken HRT compared with those had never taken HRT [16]. In addition, the WHI trial showed a significant reduction in colon cancer risk in HRT users. The possible biological explanation of this reduction of risk include effect of sex steroids on bile acid metabolism and direct effects on the colonic epithelium [17].

25.3 Other Therapies

Other molecules have been studied as alternatives to standard replacement therapy with sex steroid hormones.

25.3.1 Tibolone

Tibolone is a synthetic steroid that is rapidly converted to two metabolites with estrogenic activity and to a third metabolite characterized by a mixed progestogenic/androgenic activity [18]. Tibolone controls hot flushes, sweating, mood symptoms and is effective in improving libido, due to its androgenic component [19].

25.3.1.1 Cardiovascular System

Cardiovascular clinical outcomes from randomized controlled trials are not available yet. Surrogate endpoint studies for arterial disease and venous thromboembolic disease are inconclusive with regard to benefit or risk [20].

25.3.1.2 Bones

Randomized, controlled studies show that tibolone increases bone mineral density and reduces fracture risk. These beneficial effects are seen over long-term treatments [21] (over 10 years) and both in early and late postmenopausal women as well as in women with established osteoporosis.

25.3.1.3 Breast Cancer

The Million Women Study reported an increased risk of breast cancer in women treated with tibolone, although this was significantly less than that seen with combined therapies with estrogens and progestins [22]. However, this study has many biases, including the likely selective prescription of tibolone to women at higher risk of breast cancer, due to the assumption that this compound could be less active on the breast respect to standard HRT. The combined analysis of randomized clinical studies on tibolone indicates no increase in risk of breast cancer development compared with placebo. Tibolone treatment is associated with a reduction of proliferation and a stimulation of apoptosis in normal breast cells that is possibly attributable to the impact of this compound on the activity of estrogen-metabolizing breast enzymes [23]. However, the LIBERATE has shown increased risk of relapse in breast cancer survivors receiving tibolone to treat menopausal symptoms [24].

25.3.1.4 Endometrial Cancer

The metabolization of tibolone is tissue selective, and the conversion to the progestogenic metabolite is particularly active in the endometrium. Investigation of endometrial histology in women treated with tibolone shows no hyperplasia and a high level of atrophic endometrium, indicating no proliferative effect of this molecule [25].

25.3.2 Phytoestrogens

Phytoestrogens are biologically active compounds found in certain plants in high concentrations. They have a chemical structure similar to that of estradiol and the

ability to bind to ERs exerting variable estrogenic and antiestrogenic effects [26]. Many clinical studies have been conducted to assess the effects of phytoestrogens on postmenopausal syndrome but while some studies report a modest benefit compared to placebo, others do not [27].

25.3.2.1 Cardiovascular System

In vitro, genistein, a phytoestrogenic molecule, stimulates the synthesis of nitric oxide from endothelial cells [28]. Clinical trials demonstrate that consuming 25–50 g/day of soy protein is effective in reducing LDL cholesterol by approximately 4–8 % [29] and the Framingham Offspring Study reports that a high intake of phytoestrogens in postmenopausal women is associated with a favorable metabolic cardiovascular risk profile [30]. The beneficial effects of phytoestrogens on CVDs need, anyway, to be confirmed.

25.3.2.2 Bones

Some observational epidemiologic studies reported that soy proteins and phytoestrogens are beneficial for bone mass in postmenopausal women [31]. Only few randomized trials have been conducted on this issue, but recent trials seem to confirm that phytoestrogens are effective against postmenopausal bone loss [32]. However, the optimal dosage and the component responsible for the favorable effects are still unclear.

25.3.2.3 Cognitive Function

The effects of phytoestrogens on the central nervous system in humans are poorly understood.

Scattered reports suggest a beneficial effect of phytoestrogens on memory, but the evidence on this issue is insufficient.

25.3.2.4 Breast Cancer

To date, several studies have been performed to assess the direct relation between the individual dietary intake of soy products and the risk of breast cancer, but none of them reported statistically significant breast cancer reductions. Recent data indicates that surrogate markers of breast cancer risk, such as mammographic breast density, are not altered by phytoestrogens [33], supporting the view that this class of compounds may act differently from standard hormonal therapies on the breast.

25.3.2.5 Endometrial Cancer

The reports on the effect of phytoestrogens on endometrial cancer are limited. In the Hawaii's multiethnic population, soy intake has been related to reduced endometrial cancer risk [34]. Similar data have been found in non-Asian women in San Francisco [35].

25.3.3 Raloxifene

Raloxifene is a nonsteroidal Selective Estrogen Receptor Modulator (SERM). This compound induces estrogenic or antiestrogenic actions depending on the tissue. Raloxifene is not effective on vasomotor symptoms that can even be worsened during raloxifene administration, therefore making it an unsuitable agent for the treatment of symptomatic menopausal women.

25.3.3.1 Cardiovascular System

While previous trials suggested potential reduction of cardiovascular events in postmenopausal women receiving raloxifene [36], the publication of the Raloxifene use for the Hearth (RUTH) trial has instead shown no reduction of cardiovascular events [37]. However, this compound is active in vascular cells, where in general it behaves like an estrogen, possibly inducing protective effects [38, 39].

25.3.3.2 Bones

Raloxifene acts as a powerful estrogen on the bone, where it prevents bone loss and provides an effective treatment for osteoporosis [40].

25.3.3.3 Breast Cancer

The large Study of Tamoxifen and Raloxifene (STAR) trial indicates that raloxifene administration to postmenopausal results in a clinically relevant reduction of breast cancer risk that is comparable to that achieved with tamoxifen [41].

Newer SERMs with partially different characteristics are currently under development by the pharmaceutical industry and many of these compounds are in advanced clinical development.

25.4 Conclusions

In conclusion, while all the available therapies for early postmenopausal symptoms or for the prevention of the consequences of the long-term estrogen deprivation have specific risk/benefit ratios, clinical selection is the key to maximize the advantage for each patient. Overall, the safety profile of hormonal preparations is extremely reassuring, and the big claims of carcinogenetic actions of these drugs are not justified.

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