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Frontiers in Gynecological Endocrinology

Volume 2: From Basic Science to Clinical Application

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Frontiers in Gynecological Endocrinology

Volume 2: From Basic Science to Clinical Application

Springer

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

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ISSN 2197-8735 ISSN 2197-8743 (eBook)
ISBN 978-3-319-09661-2 ISBN 978-3-319-09662-9 (eBook)
DOI 10.1007/978-3-319-09662-9
Springer Cham Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014956923

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Contents

Part I

Adolescent Gynecology

Disorders of the Menstrual Cycle During Adolescence

1

George K. Creatsas and Maria Creatsa

Menstrual disorders are a common problem in young girls. Table 1.1 presents the menstrual disorders during adolescence among 790 cases treated in our institution.

1.1 Dysfunctional Uterine Bleeding (DUB)

DUB (Table 1.1, A) is a painless endometrial bleeding that is prolonged, excessive, and irregular and not attributable to any underlying structural or systemic disease.

The etiology of DUB, during adolescence, arises out of continuing maturation of the hypothalamus [1–3]. In the USA the definition of DUB refers to anovulatory bleeding. 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 demonstrable pelvic disease, complication of pregnancy, or systemic disease. DUB can be either ovulatory or anovulatory [4].

A shift in the ratio of prostaglandins (PGs) and especially of the endometrial vasoconstrictor (PGF2a) to the vasodilator (PGE2) and an increase in total endometrial PGs have been demonstrated in ovulatory DUB patients [1, 5].

Diagnosis is made by the clinical history and the clinical examination, followed by the necessary laboratory tests, the pelvic ultrasonography, the endocrinological examination, and occasionally hysteroscopy and/or laparoscopy. DUB differential diagnosis includes pregnancy complications; neoplasms of the genital system; genital tract infections; endocrinopathies; treatment with various, several medications; trauma; coagulation disorders; and chronic systemic diseases.

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*,
ISGE Series, DOI 10.1007/978-3-319-09662-9_1

Table 1.1 Menstrual disorders during adolescence

Menstrual disorders	Incidence %
A. DUB	381 (48.2 %)[a]
B. Amenorrhea	180 (22.8 %)
C. Oligomenorrhea	165 (20.9 %)
D. Dysmenorrhea	64 (8.1 %)
Total	790 cases

[a]Personal data

The disease is classified in three groups as follows: group 1, mild hypermenorrhea (hemospherin (Hb) and hematocrit (Hct) within normal limits); group 2, moderate hypermenorrhea (Hb 9–10 g and no signs of anemia); and group 3, severe hypermenorrhea (Hb less than 8 g). The management depends on the severity of the disease and includes: the use of combined oral contraceptives (COCs,) progestogenic compounds followed by COCs, nonsteroidal anti-inflammatory drugs, transfusion, iron supplements, and reassurance [6–8].

1.2 Amenorrhea

Amenorrhea (Table 1.1, B) is classified as primary or secondary. Primary amenorrhea (PA) is the absence of menstruation in 16-year-old girls who have already developed secondary sexual characteristics or in 14-year-old girls who have no secondary sexual characteristics development. Especially for the second group, the term "late puberty" is preferable. Secondary amenorrhea (SA) is the absence of menstruation for 6 months. For adolescents with formerly regular cycles, SA is defined as the absence of menses for more than three subsequent periods [1, 5].

WHO classifies PA in three groups as follows: group I, no evidence of endogenous estrogen production, normal or low follicle stimulating hormone (FSH) levels, normal prolactin (PRL) levels, and no evidence of a lesion in the hypothalamic-pituitary region; group II, evidence of estrogen production and normal levels of PRL and FSH; and group III, which involves cases with elevated FSH serum levels indicating gonadal failure.

Table 1.2 presents the etiology of PA and SA.

Delayed puberty (DP) is presented as PA and is defined as the absence of onset of puberty by >2 SD later than the average age, i.e., >14 years in females [2, 8].

Congenital uterovaginal anomalies includes: obstruction of the genital tract and absence of the uterus or/and the vagina [9, 10].

Several endocrine disorders may also be the cause of PA or SA. Table 1.3 presents the causes of hypothalamic amenorrhea [2]. The pituitary causes of amenorrhea are: (a) Tumors: prolactinomas, other hormone-secreting pituitary tumors, nonfunctional tumors (craniopharyngioma) metastatic tumors. (b) Space-occupying lesions:

Table 1.2 Etiology of PA or SA

1. Delayed puberty (PA)
2. Congenital uterovaginal anomalies (PA or SA)
3. Endocrine disorders (PA or SA)
4. Premature ovarian failure (PA or SA)
5. Chromosomal anomalies (PA or SA)
6. Stress and psychological problems (PA or SA)

Table 1.3 Causes of hypothalamic amenorrhea

1. Dysfunctional	Stress
	Exercise
	Nutrition and pseudocyesis
2. Other	Isolated gonadotropin deficiency, Kallmann syndrome, idiopathic hypogonadotropic hypogonadism
	Infections, chronic debilitating disease
	Tumors (craniopharyngioma, germinoma, hamartoma, Langerhans cell histiocytosis, teratoma, endodermal sinus tumor, metastatic carcinoma)

empty sella syndrome, arterial aneurysm. (c) Pituitary necrosis: postpartum pituitary necrosis (Sheehan syndrome), panhypopituitarism, and systemic inflammatory diseases (sarcoidosis, hemochromatosis) [2, 8].

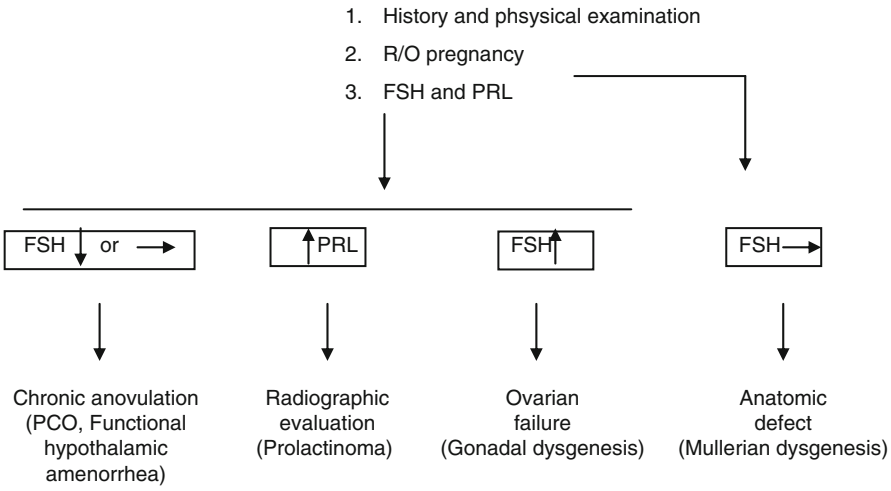
Hyperprolactinemia is associated with decreased estradiol concentrations and amenorrhea or oligomenorrhea. In cases of persistent hyperprolactinemia, after ruling out primary hypothyroidism, a magnetic resonance imaging of the pituitary is indicated.

The premature ovarian failure (POF) is usually a cause of SA. In patients with POF who are sexually active, we would strongly consider using the combined oral contraceptives (COCs) as hormone replacement therapy. COCs may be more socially acceptable to a young woman. However, we always counsel all sexually active girls regarding the correct use of condoms to prevent sexually transmissible diseases. In adolescent women with POF, a karyotype should be also obtained to rule out sex chromosome translocations and the presence of a Y chromosome, which is associated with an increased risk of gonadal tumors.

Amenorrhea due to chromosomal anomalies may be primary of secondary. In these cases the possibility of gonadal dysgenesis, pseudohermaphroditism, and other pathologies, as mentioned above, should be ruled out.

Amenorrhea may also be due to stress, anorexia, or exercise. According to the practice committee of the American Society of Reproductive Medicine, the evaluation of PA is indicated when there has been a failure to menstruate by age 15 in the presence of normal secondary sexual development (2 SD), above the mean of 13 years or within 5 years after breast development, if that occurs before age 10 or if there is a failure of breast development by age 13 (2 SD above the mean of 10 years) [4, 11].

Table 1.4 Suggested flow diagram aiding in the evaluation of amenorrhea [11, 12]



Further to the previous reported investigations, Table 1.4 presents the suggested flow diagram for the evaluation of amenorrhea.

The management of amenorrhea during adolescence depends on the etiology of the symptom. In any case treatment should be started as soon as possible.

1.3 Oligomenorrhea

Oligomenorrhea during adolescence is usually due to the polycystic ovarian syndrome (PCO). Symptoms of hyperandrogenism in adolescent girls are usually due to the PCO syndrome.

The management of oligomenorrhea during adolescence is mainly related to the management of PCO syndrome using also the new generation COCs.

1.4 Dysmenorrhea

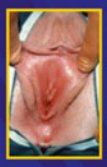
Dysmenorrhea is a common problem in adolescence. It is presented as a painful menstruation (organic disease, congenital anomalies, and endometriosis). Usually pain starts along with the start of bleeding and lasts for 48–72 h. Dysmenorrhea is characterized as primary (PD) when no organic disease is present and as secondary when a pelvic pathology is documented. PD is more frequent in adolescence and usually starts after ovulation. COCs and PG synthetase inhibitors are the most frequently used agents for the management of PD [12].

1.5 Clinical Cases

CASE 1

- Adolescent 14 years old
- Primary amenorrhea
- No sexual intercourse
- Normal secondary characteristics
- No pelvic pain
- Uterus and vagina absent

Diagnosis: Syndrome Mayer Rokitansky Kuster Hauser
Surgery: Creatsas vaginoplasty



Uterovaginal aplasia Pretreatment

Post treatment

CASE 2

- Adolescent 16 years old
- Primary amenorrhea
- Short stature
- Breast tanner I
- Karyotype XO

Diagnosis: Gonadal dysgenesis
Management: Hormone replacement therapy

CASE 3

AGE: 14 years old, height: 1.49m, weight: 54kg, BMI: 24.3

Severe Uterine Bleeding

Menarche	**13 years old, no rmal menstrual pattern**
Medical & family history	**Free**
Laboratory investigation	**HCT: 21%, Hb: 6.0 gr %**
Blood pressure	**110/60 mmHg**
Hormonal profile	**Elevated TSH and anti-TPO**
Pelvic ultrasound	**Ovarian volume (L-R): 6cc, 6.5cc**
	Microfollicular ovarian morphology

Diagnosis: Abnormal uterine bleeding due to hypothyroidism (Hashimoto thyreoiditis)

Treatment: Admission to hospital, blood transfusion, COCs until bleeding stops, then decrease dose within 4 days to 1/day continuous use for 30 days, approximately iron supplement, endocrine assessment for thyroid disease.

CASE 4

- **18 years old.**
- **Secondary dysmenorrhea**
- **Gynecological examination: Pelvic mass 10 cm x 14 cm - right andexa, confirmed by the pelvic US and the magnetic resonance imaging**
- **CA 125:102 ng/ml**
- **Other laboratory and hormonal tests: normal**

- ***Diagnosis: Endometriosis, confirmed by laparoscopy and the histopathological examination***
- ***Management: Excision of the mass and cauterization of other pelvic endometriotic lesions. Use the new generation 17 β estradiol COCs for six months.***

Conclusion

Menstrual disorders are a common problem during adolescence. Information and consultation should be provided to the young girl and the family about normal menstruation and menstrual disturbances. Prevention and early treatment should be provided by specialized gynecologists, preferably in pediatric and adolescent gynecological centers.

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PCOS and Insulin Resistance (IR): From Lifestyle to Insulin Sensitizers

2

Alessandro D. Genazzani, Susanna Santagni, Erika Rattighieri, Elisa Chierchia, Giulia Despini, Alessia Prati, and Federica Ricchieri

2.1 Introduction

According to the Rotterdam criteria, elaborated by the European Society of Human Reproduction and Embryology (ESHRE) and by the American Society for Reproductive Medicine (ASRM), polycystic ovary syndrome (PCOS) is defined by at least two of the three following criteria:

1. Clinical signs of hyperandrogenism or biochemical hyperandrogenemia
2. Oligo-/amenorrhea and chronic anovulation
3. Ultrasonographic evidence of at least one polycystic ovary and exclusion of other relevant diseases (i.e., hyperprolactinemia, thyroid diseases, androgen secretion tumors, and adrenal dysfunction hyperplasia) [1]

This evolution was relevant because it permitted the inclusion of women with PCOS who were excluded by previous NIH criteria [2]: those with polycystic ovaries affected by hyperandrogenism and ovulatory cycles or chronic anovulation and normal androgen levels.

Recently, the Androgen Excess and PCOS Society considered PCOS as an androgen excess disorder in biosynthesis, utilization, and/or metabolism of androgen in women [3].

PCOS occurs in as many as 8–10 % of women of reproductive age [4] with onset manifesting as early as puberty [5].

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_2

The syndrome has strong association to infertility, hyperinsulinemia, insulin resistance (IR), impaired glucose tolerance, dyslipidemia, android fat distribution, and obesity. Approximately 60 % of women with PCOS are obese. IR is found in 40 % of normal weight women with PCOS and nearly all overweight women both with and without PCOS [6], but IR is not routinely assessed when diagnosing or treating PCOS. The IR can be treated by insulin sensitizers and/or with diet and exercise before and during fertility treatment and pregnancy. The IR is not currently diagnosed or treated routinely and the effect of treatment is undocumented. Treatment of IR in young women may reduce the risk of diabetes and CV complications later in life. Moreover, a detailed understanding of the importance of IR in female reproductive health and reproduction could lead to new treatment strategies and improved pregnancy and life birth rates for PCOS patients. The PCOS is a multigenic condition where the phenotype is modulated by external lifestyle factors. The risk of adults developing metabolic disease, particularly obesity, hypertension, diabetes, and CVD, is probably influenced by events during embryonic development and fetal and neonatal growth [7]. The risk of diseases during later life may be determined by events or conditions experienced by the mother even before pregnancy occurs.

The IR and hyperandrogenism are associated with altered coagulation and fibrinolysis leading to endothelial dysfunction, vascular chronic low-grade inflammation [8], and atherothrombosis [9]. In PCOS both normal and elevated concentrations of plasminogen activator inhibitor type-1 (PAI 1), an indicator of endothelial dysfunction and of a prothrombotic state, have been found [10]. Other biomarkers such as fibrinogen, coagulation factor VII, coagulation factor VIII, von Willebrand factor, tissue-type plasminogen activator, urokinase-type plasminogen activator (u-PA), and activated partial thromboplastin time have been studied in PCOS and the results are conflicting [11]. Increased high sensitivity C-reactive protein (hs-CRP) is associated with PCOS, cardiovascular disease, overweight, or lean PCOS [12] and IR [13].

In vitro fertilization (IVF) outcomes in PCOS patients have the same live birth rate as control IVF patients [14]. PCOS patients with IR, measured by homeostatic model assessment of insulin resistance (HOMA-IR), had a significantly lower maturation rate of their immature oocytes compared to those with normal IR [15].

Hyperandrogenism and hyperinsulinemia affect follicular microenvironment, resulting in reduced ovarian development of immature oocytes. Moreover, in PCOS patients, significant abnormalities are observed at the earliest stages of folliculogenesis. However, it is unclear which molecules are responsible for the abnormal regulation during early folliculogenesis. It has been reported that some growth factors and sex steroids may have a role in aberrant folliculogenesis in PCOS [16].

A number of growth factors, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), insulin-like growth factor I (IGF 1), and epidermal growth factor (EGF), localize within growing follicles and regulate important aspects of folliculogenesis [17].

The hepatocyte growth factor (HGF) and c-Met-mediated epithelial mesenchymal mechanisms are important for follicle development [18]. HGF was reported as a growth factor that controls several key functions, including the regulation of growth

and differentiation of ovarian follicles. It has been reported that the HGF/c-Met signalling modulates every major component of folliculogenesis, including steroidogenesis, the growth of theca and granulosa cells, and apoptosis of granulosa cells [19]. Nevertheless, it is currently unknown whether the HGF/c-Met signalling is involved in the development of immature oocytes in PCOS.

In one study [20], the levels of HGF in serum and in follicular fluid and the mRNA expression of c- Met in granulosa cells were slightly higher in patients with PCOS than in normal patients taken as control, and the same study showed that the increase in serum HGF levels after hCG treatment was similar in the PCOS patient and in control group with no PCOS assessment. Higher levels of HGF in serum and in follicular fluid and the increased c-Met expression in granulosa cells were important for the maturation and fertilization of oocytes, and the increased c-Met expression in granulosa cells might be a marker for the fertilization of oocytes [20].

In relation to PCOS and pregnancy, several studies indicate that women with PCOS have increased risk of adverse obstetric outcomes [21], with an increased risk of preeclampsia, pregnancy-induced hypertension, gestational diabetes, and preterm birth. Whether an increased risk of pregnancy complications has been related to PCOS, an increased BMI or fertility treatment is not fully understood.

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 [22]. On such genetic predisposition, environmental factors may play a key role, such as peculiar lifestyle, type of food, living condition, and also the impact during the intrauterine growth [23].

2.2 The Impact of Obesity on the Features of PCOS Patients

Although the pathogenesis of PCOS is complex and fully understood, insulin resistance and obesity are proposed to be key metabolic defects in its etiology [24].

Obesity and abdominal obesity are common in PCOS with 10–50 % of women with PCOS having a BMI above the acceptable range of 19–25 kg/m^2 [25]. Both these enhance the features of insulin resistance and are associated with reproductive dysfunction including menstrual irregularity, increased serum androgens and luteinizing hormone (LH), infertility, and complications during pregnancy and childbirth [26, 27].

There is considerable evidence that a key etiologic feature of PCOS is the presence of insulin resistance, which is present in the majority of women with PCOS, although its severity varies between lean and obese women [28].

Insulin resistance is defined as the inability of insulin to exert its physiological effect. It is manifested peripherally (at the tissues level) or centrally (at the liver level) through a reduction in the ability of insulin to lower plasma glucose. This can be demonstrated as impaired insulin-stimulated glucose uptake and suppression of lipolysis at the muscles or adipose tissue, hepatic glucose overproduction, and suppression of glycogen synthesis. The mechanism implicated in the etiology of insulin resistance includes elevated levels of plasma free fatty acid, cytokines such as tumor

necrosis factor alpha and interleukin 6, leptin, resistin, and the peroxisome proliferator-activated receptor gamma (PPAR gamma) [29].

The gold standard for detecting insulin resistance is the euglycemic clamp technique, where a constant infusion of insulin is maintained and glucose infusion is adjusted to maintain euglycemia [30].

At steady state, the insulin-mediated glucose disposal rate can be calculated by the amount of infused glucose representing that taken up by tissues. Using the euglycemic clamp technique, both lean and obese women with PCOS had significantly lower rates of insulin-mediated glucose uptake than weight-matched controls of comparable age, thus indicating greater insulin resistance [31]. Obesity and PCOS had additive and deleterious effects on insulin sensitivity. Other studies of insulin resistance in PCOS support the additive role of obesity on the level of insulin resistance seen [32].

The impact of insulin in the presence of obesity in PCOS is particularly notable in high rates of glucose intolerance and diabetes seen in obese women with PCOS [33]. Glucose abnormalities may be detected by measurement of the fasting glucose; however, this method may be less sensitive in obese women with PCOS. A significant number of women with PCOS demonstrating glucose intolerance on a 2 h glucose challenge will have normal fasting glucose level according to the American Diabetes Association (ADA) criteria [33, 34].

Evidence exists that an android body fat distribution (i.e., a central distribution of body fat) induces higher risk of cardiovascular disease and diabetes than does a gluteofemoral fat distribution [34, 35]. In particular, visceral adipose tissue exhibits functional differences in comparison to subcutaneous adipose tissue when studied in vitro [36]. Production of adipocyte-associated cytokines, such as adiponectin and leptin, as well as inflammatory markers such as IL6, varies between the two adipocyte compartments [37]. Under conditions of visceral fat accumulation, these compartmental differences may contribute to the association between visceral fat and insulin resistance [38].

Women with PCOS tend to accumulate fat in a central distribution as demonstrated by increased waist-to-hip ratio [39]. In PCOS, this increase in visceral fat is associated with a worse metabolic profile, with higher fasting insulin levels, dyslipidemia, and higher serum androgen concentrations [40]. Central fat mass correlates with serum levels of inflammatory markers such as C-reactive protein, independently of age and total fat mass as reported in a recent study on PCOS and BMI-matched controls [41]. Modest alterations, therefore, in the visceral fat compartment may produce a significant impact on metabolic parameters.

The predominant underlying risk factor for development of metabolic syndrome is abdominal obesity and likely represents a consequence of insulin resistance. Patients with 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, dyslipidemia, and hypertension, and an increased risk for cardiovascular disease and diabetes [42]. The prevalence of metabolic syndrome in PCOS ranges from 33.4 to 47.3 % in published trials [43].

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 [44].

The risk factors for MS are as follows:

- Waist circumference >88 cm
- Elevated triglycerides >150 mg/dL (>1.7 mmol/l)
- Reduced HDL cholesterol <50 mg/dL (<1.29 mmol/l)
- Elevated blood pressure untreated >130 mmHg systolic or >85 mmHg diastolic
- Fasting plasma glucose >100 mg/dL (over 5.6 mmol/l) or previous diagnosis of type 2 diabetes mellitus

Women with PCOS have lower HDL levels, higher LDL to HDL ratio, and higher triglyceride levels than healthy eumenorrheic women. 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 [9], probably related to the insulin resistance and/or to the higher free testosterone plasma level [45].

The impact of metabolic syndrome on the presence of cardiovascular morbidity in PCOS has not been studied; as metabolic syndrome is recognized as a significant risk factor for cardiovascular disease in the general population, obese women with PCOS with metabolic syndrome would appear to be at increased risk as well [46]. Such risk has also been demonstrated to be higher in postmenopausal women, previously demonstrated to be PCOS during fertile life [47].

2.3 Endocrine Profile of PCOS Patients

PCOS is characterized by increased ovarian and adrenal androgens, increased luteinizing hormone (LH) levels, high estrogen levels (mainly estrone) due to extraglandular conversion from androgens, lower levels of sex hormone binding protein (SHBG), and higher levels of insulin, the latter often present in overweight or obesity. Hyperandrogenism is a key feature of the syndrome, although it is not constant [48]. It is mainly of ovarian origin with an adrenal contribution, since a certain percentage of PCOS women might show a mild steroidogenetic defect in adrenal glands (such as for 21-hydroxylase) or just a higher adrenal hyperactivation due to stress [49].

Androstenedione and testosterone are the markers of androgen secretion from the ovary, whereas dehydroepiandrosterone sulfate (DHEAS) is the best markers of adrenal secretion. The 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 patients [50].

Hyperandrogenism correlates positively with insulin resistance, and obesity worsens insulin resistance. Additionally, obesity is associated with lower concentrations of SHBG that is the major binding protein for testosterone. Normally, less than 3 % of testosterone circulates as unbound in the serum. The presence of hyperandrogenism reduces the hepatic synthesis of SHBG and leads to a relative excess of free circulating androgens. In PCOS, hirsutism usually occurs with decreased SHBG levels and obesity [51].

Moreover, estrone plasma levels, a weak estrogen with biological activity 100 times less than estradiol, are increased as the result of peripheral conversion of androstenedione by aromatase activity. Excess of estrone leads to a hyperestrogenic state, and this might predispose patient to endometrial proliferation and to a higher risk for endometrial cancer [52].

Compared to normal women, women with PCOS had an accelerated LH pulse pattern. However, when obese women with PCOS were studied in comparison to lean PCOS women, an attenuated pattern of LH secretion was noted in the obese women. Twenty four hours mean LH concentrations have also been noted to be lower with increasing BMI in obese women [53].

Overall obesity appears to exert a significant, although modest, impact on hyperandrogenism in PCOS, mediated primarily via impact on free hormone concentration. There is also evidence of attenuation of LH secretion with obesity resulting in a lower LH to FSH ratio. Hirsutism is reported more frequently in obese women with PCOS, consistent with the impact of higher free androgen concentration.

A great percentage of PCOS patients are overweight to severely obese, and any excess of weight can induce a reduction of peripheral tissue sensitivity to insulin, thus inducing the compensatory hyperinsulinism. Hyperinsulinemia might be central in the pathogenesis of the syndrome because it can induce higher ovarian androgen production and anovulation [54], sustained also by the abnormal LH secretion, with a higher frequency of menstrual abnormalities than in normoinsulinemic PCOS patients [55]. 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 [56].

2.4 Lifestyle Modification in PCOS Treatment

One of the primary goals of treatment in PCOS is the normalization of serum androgens and restoration of reproductive function; however, the presence of metabolic disturbance has become a prominent feature of the disease that may interfere with long-term health.

In non-PCOS subjects, weight loss and exercise reduce insulin resistance, plasma lipids, and blood pressure. In PCOS, therapeutic use of insulin sensitizing agents normalizes hyperinsulinemia and hyperandrogenism. However, management of lifestyle factors, where possible, is preferable to pharmacological management because of potential costs, side effects, and long-term maintenance. Metabolic abnormalities are significantly increased by obesity in PCOS, with high prevalence rates of impaired glucose tolerance and diabetes as well as dyslipidemia.

In PCOS, caloric restriction improves insulin sensitivity measured through euglycemic clamps, fasting glucose/insulin ratios, homeostasis model assessment (HOMA), OGTT stimulated insulin, and fasting insulin. Weight loss in obese women with PCOS has been demonstrated to reduce hyperlipidemia, in particular total cholesterol and triglycerides levels and plasminogen activator inhibitor-1 (PAI-1) activity, a marker of impaired fibrinolysis and atherothrombosis [57]. Weight loss also decreases ovarian cytochrome P450 c17 alpha activity and reduces basal adipocyte lipolysis.

Pasquali et al. studied obese PCOS women undergoing a hypocaloric diet with or without metformin administration [58]. A 12.3 % reduction in visceral fat was noted in those treated with diet alone versus 2.5 % reduction in subcutaneous fat. This suggests that there is a great sensitivity to reduction in the more metabolically active visceral component of adipose tissue with energy restriction.

Weight reduction in PCOS women improves insulin sensitivity as measured by euglycemic clamp studies [59]. Both insulin values of a 2 h oral glucose tolerance test [60] and fasting insulin parameters [61] have been shown to improve with weight reduction in PCOS patients.

Hyperandrogenism is one of the defining characteristics of PCOS and it is a relevant target for treatment in PCOS women. Hirsutism, a common clinical sign of PCOS, has been noted to be worsened in obese PCOS patients [62]. Serum testosterone and free androgen index are also increased in these types of patients [63]. Pasquali et al., after 3 months of treatment, did not show any change in sex steroid concentration in obese PCOS women [64].

In contrast, other studies, have demonstrated improvements in serum androgens or in SHBG levels, with decrease in free testosterone levels [65], and improvement in hirsutism [66]. Although altered gonadotropin secretion has been demonstrated in PCOS, studies evaluating weight loss have not demonstrated restoration of normal gonadotropin secretion. No improvements in LH pulsatility were found after weight loss as shown by Guzick et al. [61].

Van Dam et al. [67] studied women with PCOS after short-term dietary restriction with 24 h frequent sampling. They demonstrated an increased LH basal and pulsatile secretion, although they did demonstrate a 23 % reduction in serum testosterone. Overall these data indicate that reductions in androgens observed after weight loss may not be mediated by changes of pulsatile gonadotropin secretion but perhaps through other mechanisms such as changes in insulin sensitivity at the pituitary level.

Modest weight loss has been shown to have a significant effect in improving menstrual cycles and ovulation in PCOS [61]. There are no randomized data on the impact that modest weight reduction has on the live birth rate, either with pregnancies resulting from spontaneous ovulation or in response to fertility treatment. Lifestyle modification also reduces the long-term risk of diabetes, heart disease, and possible endometrial cancer in PCOS women.

Useful changes include the following: dietary modification with reduction in calories by limiting daily intake to 1,400 kcal with low daily intake of simple and complex sugar and increased in protein intake, low intake of sugary drinks, avoid snacking between meals, and increase intake of low glycemic index fruits and

vegetables. Other important lifestyle modifications are smoking cessation, moderate alcohol/caffeine intake, and regular moderate daily exercise (at least 30 min a day at the very least).

Some studies [68] have shown that lifestyle changes (in this case, intensive exercise with a goal of over 150 min/week of activity) resulting in weight loss reduced the risk of type 2 diabetes [69]. 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 to engage in regular exercise. Their lifestyle changes to achieve pregnancy will improve and the risks during pregnancy will be reduced. A healthier lifestyle will also reduce their long-term risk of diabetes, hypertension, dyslipidemia, and cardiovascular diseases. 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 counselled about diet and exercise. Pharmacological intervention could be combined with this approach as appropriate, but the abovementioned studies suggest that lifestyle modification is the first-line treatment.

2.5 Use of Insulin Sensitizer Agents and Inositol in PCOS Treatment

The logic for use of insulin sensitizer drugs, such as metformin, to treat PCOS patients is the fact that about 45–65 % of these patients have been demonstrated to have insulin resistance and a compensatory hyperinsulinemia that negatively affect ovarian function in terms of steroidogenesis and follicular recruitment and maturation [21].

Excess insulin increases androgen concentrations blocking follicular maturation and increasing cytochrome P450 c17a activity, a key enzyme in the synthesis of both ovarian and adrenal androgens [21]. 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 [21].

The use of metformin might be suggested when abnormal insulin sensitivity is diagnosed [70]. Metformin reduces hepatic glucose production from 9 to 30 % 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 [21]; the recovery of normal ovulatory function is probably due to the direct action of metformin on the ovarian tissues and to the metformin-induced normalization of the ovarian steroidogenesis with normal feedback on the pituitary gland, lowering LH secretion and restoring LH pulse secretion. Metformin improves ovarian and adrenal steroidogenesis; in fact, insulin plays specific modulatory roles on these two glands that have the same enzymatic pathways [71].

The use of insulin sensitizers do not reduce hyperandrogenism better than oral contraceptive [72], 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 [73]. Other metabolically active hormones such as 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.

In the last years, a higher attention has been given to the role of inositol-phosphoglycan (IPG) mediators of insulin action [74], 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. PCOS patients have high urinary clearance of DCI [75] and that metformin administration in obese PCOS patients improves the release of DCI-IPG mediator [76].

DCI is synthesized by an epimerase that converts myo-inositol into DCI and, depending on the specific needs of the two molecules, each tissue has a typical conversion rate [77]. Considering that ovaries never become insulin resistant and being MYO administration able to induce regular menses in both lean and obese hyperinsulinemic PCOS patients [74], a possible modulatory role of MYO on the insulin-mediated endocrine effects has been hypothesized [74]. 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 patients with PCOS improving ovarian function and decreasing hyperandrogenism [78]. Such studies suggested the putative presence of a defect in the insulin signalling pathway in which DCI-PG is the mediator of insulin action, thus contributing to the pathophysiology of the insulin resistance of PCOS [75]. Besides DCI, MYO has been reported to be greatly correlated to ovarian function [79] and oocyte quality in patients undergoing IVF procedures, independently from circulating plasma levels [80]. Such data support a specific role also for MYO on gonadotropin-induced ovarian function [81] though not confirmed by others [75].

MYO administration has been demonstrated to modulate insulin sensitivity in overweight PCOS patients improving all hormonal parameters and improving insulin sensitivity [74, 81]. The daily dosage of 2 g in the morning has been reported to be effective in hyperinsulinemic obese PCOS patients with fasting insulin levels above 12 mU/ml [81]. Such insulin level seems to be a putative cutoff that suggests when MYO administration might give higher chances of success not only on hormonal parameters but also on hyperinsulinemia and insulin sensitivity [81].

In conclusion, PCOS is a complex syndrome, with hormonal and metabolic aspects, and the therapeutical approach for PCOS patients needs 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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Polycystic Ovary Syndrome: From Contraception to Hormone Replacement Therapy

3

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3.1 Introduction

Polycystic ovary syndrome (PCOS) is a very peculiar disease and is one of the most frequent endocrine disorders in women as it occurs in as many as 8–10 % of women of reproductive age [1, 2]. For many years, there has been no agreement on the criteria on which to base the diagnosis of PCOS. This was probably a consequence of the heterogeneity of the syndrome, but also depended on the absence of clear pathogenetic mechanism(s) [3].

At first, the 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) [4]. 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 [5]. A few years later the diagnostic criteria were expanded and PCOS was considered to be present when at least two of the three features were diagnosed: oligo- or anovulation, clinical/biochemical hyperandrogenism, and polycystic ovaries as assessed by ultrasound examination [6]. This evolution was relevant because it permitted the inclusion of women with PCOS who had been excluded by previous criteria: those with polycystic ovaries affected by hyperandrogenism and ovulatory cycles, or chronic anovulation and normal androgen levels. After assessing this, we then have to clarify that PCOS is completely different from PCO. PCO means

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_3

polycystic ovary and refers only to the morphological aspect of the ovary at ultrasound examination. Indeed, PCOS can be found in many other dysendocrinopathies such as hyperprolactinemia, thyroid dysfunction, and stress-induced amenorrhea.

3.2 Endocrine Profile of PCOS

Polycystic ovary syndrome is characterized by higher plasma concentrations of ovarian and adrenal androgens, increased luteinizing hormone (LH) levels, high estrogen levels (especially estrone) owing to extraglandular conversion from androgens, lower levels of sex hormone-binding globulin (SHBG) and higher levels of prolactin and insulin, the latter often in the presence of excess weight or obesity.

Although the pathogenesis of PCOS is still controversial [7–9], PCOS typically shows elevated LH and normal or relatively low follicle-stimulating hormone (FSH) secretion; thus, almost 50–60 % of PCOS patients show a high LH:FSH ratio (>2.5) [7, 8], an exaggerated LH response to gonadotropin-releasing hormone (GnRH) stimulation test [7, 8] and a higher frequency of LH pulsatile release from the pituitary [4, 7, 8, 10], which induces higher stimulation of theca cells and excess androgen secretion, as well as impaired follicular development [4].

Androgen excess is a classic feature of the syndrome, although it is not constant [7] and is a great part of ovarian production with an adrenal contribution, as a certain percentage of PCOS patients may show a mild steroidogenetic defect in the adrenal glands (such as for 21-hydroxylase) or merely greater adrenal hyperactivation owing to stress [11]. Androstenedione and testosterone are the best markers of ovarian androgen secretion, while dehydroepiandrosterone sulfate (DHEAS) is the best marker of adrenal secretion. Most testosterone is derived from peripheral conversion of androstenedione and from direct ovarian production. In addition, the adrenal glands contribute in part to testosterone, although in hyperandrogenic PCOS the main source of androgens is usually the ovaries. As cytochrome p450c17 is the androgen-forming enzyme in both the adrenal glands and the ovaries, whatever changes or increases its activity triggers the pathogenic mechanism underlying hyperandrogenism in PCOS [4]. In addition, in the presence of 5α-reductase, testosterone is converted within the cell to the more biologically potent androgen dihydrotestosterone. Excess or normal 5α-reductase activity in the skin determines the presence or absence of hirsutism [12]. Additionally, estrone plasma levels, a weak estrogen with biological activity 100 times less than estradiol, are increased as a result of the peripheral conversion of androstenedione by aromatase activity, which is more active in PCOS than in healthy controls, while estradiol levels are normal or low because of the frequent anovulatory cycles. All this results in a chronic hyperestrogenic state with the reversal of the estrone:estradiol ratio that may predispose to endometrial proliferation and to a possible increased risk of endometrial cancer [13, 14]. Another relevant aspect is the fact that normally less than 3 % of testosterone circulates as unbound in the serum. In fact, most circulating androgens are bound to SHBG, and thus biologically inactive. Any condition that decreases the levels of SHBG (such as an excess of circulating androgens) inducing reduced

hepatic synthesis, leads to a relative excess of free circulating androgens. In PCOS, hirsutism usually occurs with decreased SHBG levels and obesity [4].

In addition, androgen excess may both directly and indirectly induce alterations in glucose metabolism, and ultimately be an additional cause of abnormal insulin sensitivity. Androgens may directly inhibit peripheral and hepatic insulin action. In fact, testosterone could induce insulin resistance in women with PCOS, acting on the post-binding signal, in particular by reducing the number and efficiency of glucose transport proteins, such as the type 4 glucose transporter (GLUT-4), especially in muscle and fat tissues [15]. It has also been reported that women with central obesity, typical of obese PCOS sufferers, have higher free androgen levels and exhibit significantly higher levels of insulin insensitivity than weight-matched controls and show increased free fatty acids [4].

3.3 PCOS, Brain and Abnormal Steroid Milieu

On the basis of what has been reported above, it is clear that in PCOS patients aesthetic problems such as acne, seborrhea and hirsutism can be terribly common and invalidating and their occurrence is simply related to the excess of androgens due to the abnormal ovarian function/regulation, which leads to chronic anovulation.

In most of these cases the only real solution is the use of a contraceptive pill. This choice is not merely related to the fact that normal menstrual cyclicity has to be re-established, but also to the fact that the clinical signs that PCOS patients show are invalidating, mainly from a psychological point of view. This aspect is quite complex; however, at its basis there are not only subjective complaints. but also greater vulnerability due to the impaired production of endogenous neurosteroids.

Indeed, it has been recently reported that patients suffering from menstrual disturbances (oligo- or amenorrhea) have a higher chance of experiencing changes in mood and behavior, anxiety and depression [16–18] and that such impairments are to a great extent related to the reduced ability to secrete active neurosteroids, such as allopregnanolone, inside the brain. Usually, estradiol, progesterone and DHEAS are the steroids that as inductors or substrate permit the regular synthesis of allopregnanolone. Whatever dysfunction of the ovarian function occurs, the steroid milieu is impaired and consequently the biosynthesis of neurosteroids to. Recently, we reported that in obese hyperinsulinemic PCOS patients, the absence of adrenal response in terms of allopregnanolone secretion to adrenocorticotropic hormone (ACTH) stimulation was restored under metformin administration [19], thus suggesting that on the basis of the frequently observed sexual dissatisfaction [16–18], as well as a high degree of occurrence of a depressive state [20] in PCOS, there is a lack of or an impaired synthesis of neurosteroids from the adrenal gland and/or by the brain. Moreover, being PCOS anovulatory in a higher rate with normal or abnormal menstrual cyclicity, high androgens and relatively low estrogens induce lower SHBG production, thus permitting a higher amount of free circulating androgens. On the other hand, low estrogens and no progesterone or very low progesterone due to anovulation determine low synthesis of neurosteroids in the brain.

It is quite clear that impairment of ovarian function affects various compartments and systems and the putative suggestion of the use of a contraceptive pill deserves consideration in blocking the abnormal ovarian function and reducing androgen production on the one hand and increasing the estrogenic milieu at the liver level, thus promoting SHBG synthesis.

3.4 Estrogen–Progestin Preparations and PCOS

In general, we can say that all combined estrogen–progestogen preparations are able to more or less solve the clinical complaints of any PCOS patient. This is because such preparations block the ovary, suppress androgen production and improve SHBG synthesis, thus reducing the circulating free androgens that are biologically effective on the target tissues such as skin, sebaceous glands and hair follicles [21, 22].

As it is well known that the estrogenic compound of the contraceptive pill (i.e. ethinyl estradiol) only has ovariostatic activity (no direct antiandrogenic effect); the antiandrogenic action has to be modulated by the progestogen compound. At present there are four progestogens with specific antiandrogenic activity: cyproterone acetate, dienogest, drospirenone and chlormadinone acetate [21]. Cyproterone acetate is the progestogen with the highest antiandrogenic activity; although it induces a relatively higher rate of side effects such as cephalea, all the others induce similar positive effects [22]. Contraceptive pill administration not only improves the clinical signs of the androgenization, it also normalizes the ovarian size and morphology, which are typically impaired in PCOS patients [23]. As an additional effect, estrogen–progestogen preparations protect against both follicular and corpus luteum cyst occurrence [22].

The efficacy of contraceptive preparations with regard to the signs of hyperandrogenism (i.e. acne, hirsutism, seborrhoea and alopecia) is determined as a function of time, as the biological evolution of the skin and of all its annexes is approximately 110–120 days. This means that the youngest cells of the epithelium become old and superficial in around 4 months. Whatever the contraceptive pill administered, the minimum treatment period has to be 4–5 months, possibly up to 12 months. Better results are obtained when such pills are administered for longer periods and/or coupled with antiandrogen compounds such as flutamide [24] or finasteride.

Most clinicians agree on the fact that the treatment of dysendocrinopathy of PCOS greatly supports the psycho-emotional recovery of almost all PCOS patients. Moreover, the use of the contraceptive pill for long periods of time protects the patient from being a victim of the recrudescence of hyperandrogenism and the diseases it induces, mainly chronic anovulation and infertility. In fact, the use of the estrogen–progestogen preparation has been reported to improve the chance of conception [25] and there is no difference in this kind of beneficial protective effect on ovarian function between the progestin-only pill and combined oral contraceptives. After 12 months of discontinuation of the treatment in order to conceive, the conception rate was 95–99 % in those using the pill versus 70–81 % for those

patients using depot medroxyprogesterone acetate (DMPA) injections or Norplant (levonorgestrel implants) [25].

If the rationale is correct and all the data we have with regard to PCOS are true [26], environmental and genetic factors induce PCOS and mark that patient as "affected" up to the postmenopausal period. This means that predisposition to all the clinical problems is quiescent up to the moment when the patient undergoes treatment and aging (more or less evident) will occur soon after discontinuation.

As during the perimenopausal and postmenopausal transition there is a relevant modification of the endocrine profile in all women, those who have had PCOS during fertile life are more predisposed to having severe symptoms such as those related to behavior, mood, sleep, anxiety, and those related to metabolism, in particular insulin resistance and compensatory hyperinsulinemia. The menopausal transition induces, as a natural event, insulin resistance that, together with the hypoestrogenism and the lack of progesterone, induces a greater tendency toward increasing body weight. There are convincing data that this metabolic link has to be considered relevant when discussing the menopause with our ex-PCOS perimenopausal patients [27].

The menopausal transition may substantially worsen a previously not perfect metabolic condition. Since both estrogens and progesterone are able to modulate the glucose metabolism, as soon as the perimenopausal modifications of the ovarian function take place and within a few months/years the menopause begins [28, 29], abnormalities of the metabolic pathways may be more relevant than expected if during fertile life abnormal metabolic function(s) were present, such as insulin resistance with excess weight or obesity.

Although it cannot be generalized, the use of hormone replacement therapy is crucial and important at the moment of the menopausal transition, ensuring that the patient has no contraindications. It is relevant to maintaining an adequate steroidal milieu so that biological pathways, in particular the metabolic ones, are not crushed by the overlapping phenomena of menopause plus aging [30].

In conclusion, lifestyle, good and healthy eating, and the right amount of physical exercise are relevant in PCOS patients during fertile life, with or without the use of oral contraceptives, but when menopausal transition takes place all of the above need to be coupled with adequate hormone replacement therapy to counteract the higher risk of menopausal PCOS sufferers in facing higher rate of diseases, mainly cardiovascular diseases and diabetes.

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Management of Adolescent Hyperandrogenism

4

Charles Sultan, Laura Gaspari, and Françoise Paris

4.1 Introduction

Androgen excess during puberty produces a variety of clinical signs and symptoms that must be appropriately recognized, evaluated, and treated. Acne, hirsutism, and obesity are outward signs of androgen excess, and they therefore must be considered as more than cosmetic concerns. The body image component of sexual identity and peer interactions are critical for the evolving personality. Timely medical intervention may prevent health sequelae and contribute to psychological well-being.

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_4

4.2 Definition

Hyperandrogenism (HA) must be considered in an adolescent with [1]:

- Severe acne
- Hirsutism
- Menstrual irregularities
- Abdominal obesity
- Masculinization of the body habitus
- Clitoromegaly

The management of an adolescent girl with HA has three main goals:

1. To eliminate the severe causes of HA, such as ovarian/adrenal tumors and the nonclassical form of congenital adrenal hyperplasia (NCCAH).
2. To diagnose polycystic ovarian syndrome (PCOS) as early as possible in order to begin antiandrogen therapy without delay and put into place long-term strategies to prevent obesity and insulin resistance.
3. To distinguish the so-called "physiological" HA of puberty, which will resume within one to 2 years from an endocrine cause. During pubertal development in the girl, plasma testosterone (T) rises from 0.1 to 0.5 ng/ml, while the sex hormone-binding globulin (SHBG) level drops from 3 to 1 nmol/l. This increased free plasma T is reinforced by both the physiological insulin resistance that occurs during puberty and the increase in insulin-like growth factor 1 (IGF-1) that parallels the pubertal growth spurt and growth hormone hyperproduction. All these events contribute to the so-called "physiological" HA, which is often associated with the multifollicular ovaries observed on pelvic ultrasonography (US).

4.3 Causes of Hyperandrogenism in Adolescent Girls

In the peripubertal period, HA may be due to the following (Fig. 4.1, Table 4.1):

- Ovarian disorders, such as PCOS, hyperthecosis, ovarian tumors, and enzymatic defects such as 17-keto-reductase deficiency
- Adrenal disorders, such as NCCAH, Cushing's disease, or adrenal tumor

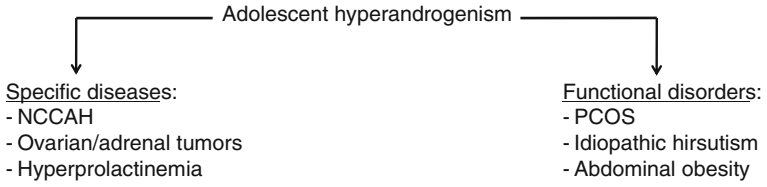

Fig. 4.1 Diagnostic approach to adolescent hyperandrogenism

Table 4.1 Causes of adolescent hyperandrogenism

1. Polycystic ovarian syndrome
2. Idiopathic hirsutism
3. Nonclassical congenital adrenal hyperplasia
4. Obesity
5. Transient/idiopathic hyperandrogenism
6. Adrenal: ovarian tumors
7. Hyperprolactinemia
8. Drugs

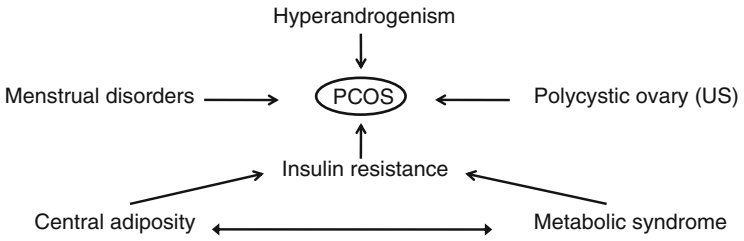

Fig. 4.2 Pathophysiology of PCOS

- A mixed origin, such as hyperprolactinemia, stress, anorexia nervosa, and elite sport
- A peripheral origin, such as obesity or idiopathic hirsutism

For the last 15 years, we have managed a cohort of 178 adolescent girls with HA in our pediatric endocrinology clinic. The causes of HA were as follows: PCOS (34 %), NCCAH (15 %), abdominal obesity (10 %), idiopathic hirsutism (9 %), elite sport (10 %), anorexia nervosa (6 %), transitory HA (11 %), 46,XY disorder of sex development (46,XY-DSD) (3 %), hyperprolactinemia (2 %), and endocrine tumors (1 %).

4.3.1 PCOS During Puberty

The long-term sequelae of PCOS are well known and continue to present challenges for endocrinologists and gynecologists, who need to make early diagnoses (in the pubertal period) so that these teenagers can be promptly treated both symptomatically and prophylactically. The striking trend toward adolescent obesity should reinforce our responsibilities. Menstrual irregularities in adolescents in the early postmenarcheal years can be an early sign of PCOS. In obese adolescents who subsequently develop glucose intolerance, there is an overall clinical impression that PCOS has become a prevalent cause of hyperandrogenism and menstrual disorders.

There is currently no consensual definition of adolescent PCOS [2]. We propose to define PCOS in the adolescent as the combination of four of the following criteria comprising the PCOS diagnosis (Fig. 4.2):

- Clinical HA: persistent and severe acne and hirsutism (Ferriman score >10)
- Oligo- or amenorrhea persisting 2 years postmenarche
- Biochemical evidence of HA: T >50 ng/ml, along with dysovulation (LH/FSH ≥2)
- Insulin resistance and hyperinsulinemia: visceral adiposity, acanthosis nigricans, and impaired glucose tolerance
- Polycystic ovarian morphology on ultrasound

There are several clinical expressions of PCOS during adolescence [3]:

- Postmenarcheal PCOS, the most common expression.
- Premenarcheal PCOS.
- Familial PCOS.
- PCOS that occurs in adolescents previously diagnosed with central precocious puberty (CPP).
- PCOS that occurs in adolescents previously diagnosed with intrauterine growth retardation (IUGR) and/or precocious pubarche.
- Early metabolic expression: hyperinsulinism and insulin resistance are present in early puberty.
- In certain elite sports, we have observed PCOS-like symptoms in a significant percentage of adolescent athletes (50 % vs 22 % in the control group) [4].

We propose screening for PCOS in all adolescents with oligo- or amenorrhea that persists 2 years after menarche, with particular attention given to those girls presenting obesity and a history of IUGR, premature pubarche, CPP, or familial history of PCOS.

Diagnosis of PCOS should be based on several criteria (Fig. 4.2):

1. Medical history
   - Birth weight (high or low)
   - Ethnic origin
   - Family history
   - Adrenarche = premature pubarche?
   - Lifestyle factors
2. Physical examination
   - Degree and type of acne
   - Degree and type of hirsutism
   - Fat distribution (WHR: >70)
3. Laboratory evaluation
   - Androgens: T, DHEAS
   - 17-OH progesterone
   - LH (±FSH)
   - Fasting glucose/insulin
4. Radiologic imaging
   - Transabdominal US

The aims of treatment are to regulate menses and improve androgenic concerns as well as lifestyle issues. The treatment is based on the following:

- Lifestyle intervention and weight loss, both of which have been found to be beneficial in many areas.
- Antiandrogens (cyproterone acetate, Androcur*: 50 mg/day, day 1–day 20) and natural estrogens (Provames*: 2 mg/day, day 1–day 20).
- Oral contraceptive pills (OCP), if contraception is needed.
- Insulin sensitizers (metformin: 500 mg × 3/day) have been proven useful for regulating menses, inducing ovulation, and normalizing weight [5].

4.3.2 Non-classical CAH

Individuals with non-classical CAH (NCCAH) typically present in late childhood, adolescence, or adulthood with signs and symptoms of excessive androgen production. The prevalence of NCCAH ranges from 0.1 to 0.26 %, but it occurs much more frequently among Ashkenazi Jews (prevalence 1–2 %).

Many women with NCCAH are relatively fertile, but the success rate of women seeking pregnancy is in the range of 60–70 %. This heightened risk of subfertility may be due to ovulatory dysfunction, inadequate endometrial maturation, or impaired embryo implantation secondary to the elevated progesterone levels.

The diagnosis NCCAH is sometimes difficult. Random 17-OH progesterone measurements may show values within the normal range [6]. The gold standard today therefore remains the ACTH stimulation test, which should identify 17-OH progesterone >1,500 ng/dl at the end of the test.

Genetic testing is helpful for diagnosis, especially to identify those individuals with compound heterozygous mutations, and for genetic counseling. Since two thirds of NCCAH women show compound heterozygosity, the predicted incidence is 1 out of 360.

The molecular genetic investigation of individuals with NCCAH has shown that the most common finding is compound heterozygous mutations with a different mutation on each allele:

- Seventy percent of NCCAH: Val 281 Leu (50–82 % loss of 21-OHase).
- Other missense mutations: P30L, P4535, and R339H.
- The phenotype reflects the residual activity of the milder mutation.

Many patients with NCCAH are asymptomatic and thus are not in need of treatment [7].

The symptomatic patients are often prepubertal girls with premature pubarche, girls with accelerated growth velocity and bone age, and adolescents with hirsutism (60 % of cases), oligomenorrhea (53 %), and persistent acne (30 %).

The aims of treatment for NCCAH in adolescents and young women are the following:

- Regularization of the menstrual cycle
- Prevention of progressive hirsutism (acne)
- Improved fertility

NCCAH management includes:

- OCP alone, which is useful in oligomenorrheic, hyperandrogenic adolescents and women not seeking fertility
- Antiandrogens
- Glucocorticoids

4.3.3 Idiopathic Hirsutism

Idiopathic hirsutism (IH) is defined by evidence of clinical HA contrasting with normal androgen levels and no menstrual dysfunction [8]. IH is considered as a hypersensitivity to androgens (short CAG repeat lengths on the androgen receptor in target cells). The current diagnosis of IH should be one of exclusion.

Its prevalence ranges between 10 and 15 % in certain ethnic groups (e.g., of Mediterranean origin).

4.3.4 Obesity

Several studies have suggested that abdominal obesity is linked to HA in peripubertal girls. In addition, peripubertal obesity has been associated with variable degrees of insulin resistance. Compensatory hyperinsulinemia can then increase ovarian and/or adrenal androgen production and lower SHBG, both of which increase free plasma T concentration [9, 10].

In some girls, HA impairs the sensitivity of the GhRH pulse to negative feedback, leading to a persistently rapid GnRH pulse and elevated LH, which maintain or worsen HA.

4.4 Patient Evaluation

The first visit begins with a thorough medical history and careful physical examination. Certain clinical symptoms should draw the clinician's attention toward serious disease, such as:

- Rapidly progressing hirsutism
- Symptoms of hypercorticism
- Galactorrhea

In most situations, the symptoms of hyperandrogenism are mild, such as hirsutism and acne.

The laboratory investigations are limited to evaluation of plasma T, 17-OH progesterone, and basal plasma LH and FSH; in some situations, however, investigation should include an ACTH stimulation test and/or genetic analysis, along with pelvic US [11, 12].

Conclusions

1. Hyperandrogenism should be the concern of all health professionals who treat adolescents.
2. Adolescents with hyperandrogenism are at increased risk for metabolic complications, cardiovascular disease, and infertility.
3. Intervention may prevent or reduce major health sequelae and can contribute to psychological well-being.

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Prevention of Adolescent Pregnancies

5

George K. Creatsas

5.1 Introduction

Adolescent sexuality and reproductive health refers to adolescent pregnancies, termination of undesired pregnancies, contraception for adolescents, prevention and treatment of sexually transmitted diseases (STDs), and other gynecological pathologies [1].

Worldwide data presents that 56 % of girls and 73 % of boys have had sexual intercourse before the age of 18. Worldwide 27 % and in developed countries 7.5–10 % of adolescent women get pregnant. 52 % of adolescents use noneffective contraception, and 31 % of adolescents used no contraception at first intercourse, mostly those who had just met their sexual partner [2–4].

The adolescent pregnancy rate is as high as 97/1,000 women aged 15–19. Approximately 49 % of these pregnancies are unintended (45/1,000 women unintended pregnancy rate in the USA, the highest of industrialized nations). From the patients who had an unintended pregnancy only 42 % used contraception [5].

Adolescence special needs for contraception are related to the frequency of sexual intercourse, STDs, the fear of consultation, and the inadequate information provided to teenagers and the family. 31 % of adolescents used no contraceptive method at first intercourse, mostly those who had just met their sexual partner [2, 3].

Table 5.1 presents the contraceptive methods (CMs) used during adolescence.

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_5

Table 5.1 CMs for adolescents

Hormonal	Nonhormonal
COCs	The condom
Emergency contraception	The double dutch method *(COCs and condom)*
LARCs	Others[a]
Injectable contraception	Sponge and diaphragm
IUDs	Abstinence
Implants	Withdrawal
Patches	Periodic sexual intercourse
Vaginal rings	

COCs combined oral contraceptives, *LARCs* long-acting reversible contraceptive methods, *IUDs* intrauterine devices
[a]Not recommended

Table 5.2 Noncontraceptive beneficial effects of 17 β-estradiol COCS

Ovarian cysts, premenstrual tension, ectopic pregnancies
Endometrial, epithelial ovarian cancer and colorectal cancer
Menstrual disorders: dysfunctional uterine bleeding, dysmenorrheal oligomenorrhea
Endometriosis
Pelvic inflammatory disease, dyspareunia, chronic pelvic pain
Bone mass
Polycystic ovarian syndrome: acne and hirsutism
Lipid and carbohydrate profile, thyroid, hemostatic and inflammation makers, liver function
Ovarian stimulation (pretreatment)

5.2 Oral Contraceptives

Among the new generation COCs, those with estradiol or estradiol valerate together with the new progestagenic compounds are recommended [6].

If COCs are used properly, their failure rate is less than 1 %, while the typical failure rate is approximately 3 % in adults and 5–15 % in adolescents [6, 7]. On the other hand the noncontraceptive benefits of the new generation COCs should be emphasized to improve compliance during adolescence (Table 5.2) [8, 12].

The COCs side effects are the most commonly reported reasons why adolescents discontinue this method. COCs users discontinued their use because of sexually transmitted infections, the fear for breast and cervical cancer, as well as the venous thromboembolism.

Teens should be advised that COCs are only effective if taken regularly. Another contraceptive method should be followed if more than two consecutive pills are missed in any menstrual cycle. In any case, sexually active adolescents always should be advised to use condoms, even while taking COCs.

5.3 The Condom

The condom should be consistently used during adolescence preferably in combination with COCs (the double dutch method) as a method of providing complete protection against unwanted pregnancies and STDs. The condom is easily available and inexpensive, presents no side effects, and has an effectiveness of up to 88% [13].

5.4 Emergency Contraception

The emergency contraceptive methods are listed below [13–14]:

- The combined "estrogen and progestin" emergency contraception (EC) kit. The kit contains four tablets of ethinyl estradiol and levonorgestrel.
- The progestin-only product. Two tablets of levonorgestrel, to be taken 12 h apart.
- A single dose of RU-486 – mifepristone. A progesterone blocker, which acts as an abortifacient given within 72 h of coitus with nearly of 100 % success rate.
- A 19-nor-progestagenic derivative given within 5 days after coitus, acting as endometrial progestagenic modulator.

The situations that call for the use of EC are:

- No contraception used
- Condom breakage, slippage, or incorrect use
- Three or more consecutive missed COCs
- Progestogen-only pill (minipill) taken more than 3 h late
- More than 2 weeks late for a progestogen-only contraceptive injection
- Breakage, dislodgment, tearing, or early removal of a diaphragm or a cervical cap
- Failed coitus interruptus
- Failure of a spermicidal tablet
- Expulsion of an intrauterine device
- Miscalculation of the periodic abstinence method
- Sexual assault (woman not protected by a contraceptive method) [10, 11]

5.5 Long-Acting Reversible Contraceptives

LARC's (Table 5.1) are very useful methods for the prevention of adolescent pregnancies. LARC's are also recommended for the prevention of unwanted pregnancies in young women with special needs.

5.5.1 The Injectable Contraception

The injectable contraception (DMPA depot-medroxyprogesterone acetate) is an effective contraceptive agent and it is given intramuscularly every 12–13 weeks. The failure rate is 0.3 % [15].

5.5.2 The Levonorgestrel IUDs

The levonorgestrel IUDs cause reversible atrophy of the endometrium. The new mini IUDs are preferable.

5.5.3 The Implants

"The implants" is an alternative method not recommended for adolescents. The effective life varies from 6 to 84 months [16–17].

5.5.4 The Patch

The contraceptive patches have a convenient application schedule: "3 weeks ON, 1 week OFF." Its delivery system offers continuous doses of estrogen and progesterone. It is also not in common use by adolescents.

5.5.5 The Vaginal Ring

The contraceptive ring has also a convenient schedule of 3 weeks IN 1 week OUT. The ring delivers combined-continuous doses of estrogen and progesterone. The pregnancy rates are decreased. A backup contraception is needed if the ring is removed for more than 3 h. The side effects and the bleeding profiles are comparable to COCs [13, 18]. Merki-Feld and Hund [19] reported the main advantages of Nuvaring ® mentioned by a young group of users.

Conclusions

Consultation for adolescents should be provided by the family and health-care professionals in pediatric and adolescent gynecological units and family planning centers. Adolescents spend 17–20 h per week viewing TV or Internet. Numerous studies illustrate the television's powerful influence on adolescents sexual attitudes and beliefs, while the Internet predisposes to early sexual activity [20].

The future goals for the new contraceptive methods are the safety and their long-acting effect, the efficacy the protection against STDs, as well as the reversibility and the accessibility of the method.

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Transsexualism: Endocrine Aspects

6

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Harry Benjamin, the father and establisher of transsexualism, tried to describe this phenomenon as *terra incognita* or *noli me tangere* (1966), trying to explain that many doctors were blinded in the presence of a new undescribed and undiagnosed disorder [1]. Ira Pauly described one hundred transsexuals from 13 countries [2].

6.1 Definition

In everyday practice two sexes are mentioned: male and female. However, there are four different types of sex:

- Gonadal (presence of ovaries or testis)
- Chromosomal (46,XX or 46,XY)
- Phenotype (female or male)

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_6

Table 6.1 Some etiological hypotheses of transsexualism

Effects of gonadal steroids on the hypothalamus during gonadal formation [4]
Disorders of androgen to estrogen conversion [5]
Receptor disorders
Aromatase changes [6]

- Psychic (feeling of being woman or man)

In a case of transsexualism, gonadal, chromosomal, and phenotype sex are of one type, and, psychic sex is the opposite. In such a situation, transsexualism can be classified under pseudohermaphroditism.

Male-to-female transsexuals (MFTs) have testis, a 46,XY karyotype, a male phenotype and a feeling of being female. Female-to-male transsexuals (FMTs) have ovaries, a 46,XX karyotype, a female phenotype and a feeling of being male.

Gender dysphoria is characterized by suffering from a strong, persistent discomfort between the biological sex and the experienced expressed gender with significant impairment in interpersonal, familial, social, professional and other important areas of functioning [3].

Persons with gender dysphoria want to have the secondary sexual characteristics of the opposite sex. Transsexual identification is permanently present. The disorder is not a part of some other disorder or disease.

6.2 Etiology

Until now, the etiology of transsexualism has been unknown. There are some hypotheses (Table 6.1) and many scientific centers in the world are working on the discovery of an etiological cause of transsexualism.

Gender identity is developed as a result of the interaction between the developing brain and gonadal steroids from the 8th to 12th gestational week. Swaab and Hofman [7] found a gender-specific difference between the volume of the suprachiasmatic nucleus and the nuclei striae terminalis. The latest studies from Prince Henry's Institute in Australia implied a longer androgen receptor gene, leading to less effective circulating testosterone, undermasculinization and a brain more similar to a female brain in MFTs. This study was criticized by the fact that in some other disorders with changes in androgen receptors no similar changes in psychic gender were found. Trying to make a contribution to examining the etiology of transsexualism, our team provided data on finger lengths in transsexuals [8].

6.3 Incidence

Since 1966, many studies have referred to the incidence of transsexualism. The ratio between MFTs and FMTs has varied, depending on surgeons' willingness to perform the operation. Because male-to-female surgery is less complicated, there have been more MFTs. In countries with highly specialized surgeons, such as Serbia, the

Table 6.2 Incidence of transsexualism around the world

Author	Year	Country	Ratio MF:FM
Benjamin	1966	USA	6:1
Eklund	1988	Netherlands	3:1
Godienski	1988	Poland	1:5.5
Ross	1981	Australia	9:1
Garrels	2000	Germany	1.2:1
Vujovic	2009	Serbia	1:1

number of transsexuals has been the same (male-to-female and female-to-male) [9]. In Table 6.2, the incidence of transsexualism is shown.

In some studies, the number of patients was too small. In human biology the incidence of many disorders is the same in males and females and it would be difficult to explain such a high difference in ratio, except with some technical details regarding the operations.

6.4 Diagnosis

A team of three highly educated psychiatrists in the field of sexual disorders confirm the diagnosis after 1 year or more of follow-up. They have to exclude many psychiatric disorders such as transvestitism, homosexuality etc. After that the endocrinologist examines the patient, detects the karyotype and carries out hormonal analysis. It is necessary to take blood samples in MFTs for follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol, progesterone, testosterone, SHBG, 17 OH progesterone, free thyroxine, thyroid-stimulating hormone (TSH), and cortisol. In FMTs on day 7 of the menstrual cycle (for those younger than 30 years of age) blood samples are taken for FSH, LH, prolactin, estradiol, testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS), 17 OH progesterone (to exclude congenital adrenal hyperplasia), fT4, TSH, cortisol and on day 21 progesterone is measured. According to these results endocrine diseases mimicking transsexualism can be excluded such as androgen-secreting tumors, congenital adrenal hyperplasia, pseudohermaphroditism of other different origins, and some other endocrine diseases, such as thyroid and adrenal gland diseases. A complete internal examination and an ultrasound of the gonads (ovaries or testis) and breasts are obligatory.

After confirming diagnosis from the endocrine point of view therapy regarding the characteristics of the opposite sex can be initiated. Sperm of MFTs can be frozen if desired and FMTs can store their follicles in case they want to have a biological child later on.

6.5 Therapy

The aim of the therapy is to help a patient to look like a person they feel that they can depend upon to provide normal sexual function and work abilities, and to determine the dosage of the therapy individually.

Table 6.3 Changes in symptoms and signs during therapy for male to female transsexuals (MFTs)

Month	Symptoms and signs
1	Breast enlargement, areola pigmentation, higher pitch voice
3	Loss of erection and ejaculation, softer skin, strength decrease, more sensitive, loss of typical male libido
6	Sex hair loss, changes in waist to hip ratio
12	Significant reduction of sex hair, more prominent female sex characteristics

Table 6.4 Progesterone effects in MFTs

Decreases the number of estradiol receptors
Higher affinity for androgens receptors
Stimulates 17 beta dehydrogenase (conversion of estradiol to estrone)
Antimineralocorticoid effects
Sedative and anxiolytic effect
Stops spermatogenesis at the level of spermatogonia
Seminal tubule atrophy
Decreases Leydig cell number

6.5.1 Male to Female Therapy

Before the operation and 6 months later oestradiol ampoules at 10 mg are given intramuscularly within a 7- to 10-day interval with ciproterone acetate (50 mg daily orally). Micronized progesterone is added 7 days a month (100 mg) after 6 months of therapy. From 6 months after the operation estroprogestagen therapy is initiated orally and it is necessary to continue throughout life. Ciproterone acetate is reduced to 25 mg, according to hirsutism status. The effects of estrogen, progestogen and antiandrogen therapy on body shape is shown in Table 6.3. There are many reasons for adding progesterone (Table 6.4).

6.5.2 Therapy for FM Transsexuals

Testosterone ampoules are initiated in a dose of 250 mg every 2 weeks. It is safer than the oral route because it is lifelong therapy. Testosterone can also be advised in the form of transdermal and sublingual implants. Alkalizing forms are contraindicated. Dihydrotestosterone gel (non-aromatizable to estradiol) is advised for local treatment on the clitoris (Table 6.5). After 12 months of therapy the expert team of psychiatrist, endocrinologist and surgeon gives a final conclusion and suggestion regarding the operation. Later on, transsexuals have twice-yearly endocrinological checkups. Our team follows up transsexuals for 20 years.

There was an equal number of MFTs and FMTs. FMTs were not smaller than control women, which is consistent with other studies [10, 11]. Males were 12 cm taller on average. Mostly, they finished secondary school. By profession MFTs are usually models, musicians, dancers, or waiters, while FMTs may be want to be

Table 6.5 Dynamic of clinical changes during testosterone therapy for female to male transsexuals (FMTs)

Month	Symptoms or signs
1	Acne, tenderness in the inguinal, increased libido, increased strength
6	Menstruation loss, deepening voice, clitoral enlargement
9	Increase of bitrochanteric circumference 4–7 cm, clitoris length 4 cm
12	Decreased breast volume, spread of sexual hair, more typical masculine phenotype

Table 6.6 Possible unwanted effects of hormone therapy in transsexuals

Male to female transsexual	Female to male transsexual
Thromboembolism	Hypercholesterolemia
Hyperprolactinemia	Hepatocyte hyperplasia
Depression	Liver adenoma
Hypertrophy of the prostate	Liver carcinoma
Myocardial infarction	Calculous cholecystitis
Breast carcinoma	

hairdressers. Their mother's average age was 20–25 years and their father's 26–30 years. Mothers were mostly housewives and fathers were soldiers or policemen. In our group 12 MFTs and 18 % FMTs refused the operation. Of all of them, 16.6 % of MFTs and 16.4 % FMTs were married.

6.5.3 Possible Unwanted Effects of Therapy

In the literature unwanted effects of hormone therapy have been described in cases in which dosages were higher or in which it was given to patients who had previously had other diseases for which hormone therapy was contraindicated, such as liver or renal insufficiency, thromboembolism, undiagnosed bleeding, carcinomas, porphyria, pregnancy, meningioma etc. Sometimes, wanting to obtain a typical characteristic of the opposite sex, patients multiply the doses themselves for a longer period. In the world of endocrinology the most important thing is to achieve the appropriate dosage of hormone therapy (Table 6.6).

Conclusion

Special expert gender teams have to be formed throughout the world in order to help transsexuals to have much better quality of life.

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Part II

Hormonal Contraception

How to Choose the Right Contraceptive Method for the Right Woman

7

Johannes Bitzer

7.1 Introduction

Contraceptive counseling and care are one of the mainstays of ambulatory women's health care. Prescribing the pill seems to be a very easy and simple procedure and not worth of further mentioning. Looking closer, it becomes however evident that there are some indicators that point to the fact that there is still room for amelioration:

- A persistent rather high prevalence of unwanted pregnancies [1–6]
- Some rare but severe complications in young healthy women [7–14]
- Frequent complaints about side effects with subsequent discontinuation and risk of unwanted pregnancy [15–18]

It seems therefore justified to look at the contraceptive decision-making process from a total quality management point of view, which includes a concept of quality-related outcome objectives [19–21]. Contraceptive counseling should thus [22, 23]:

- Maximize contraceptive efficiency
- Minimize health risk
- Optimize tolerability
- Realize additional health benefits
- Avoid unnecessary costs

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_7

7.2 The Contraceptive Triangle

To reach these objectives the medical professional needs to work with what we have called the contraceptive triangle. By this we mean the interaction of three entities: *method variables*, *patient variables*, and *situation variables* [22–25] (Fig. 7.1).

The science and art in contraceptive counseling and care consists in providing a perfect fit between these three interacting groups of variables.

7.2.1 Method Variables

- Objective characteristics derived from experimental data: pharmacodynamic properties, pharmacokinetics, way of application, interactions with other drugs, and metabolizing enzymes
- Probability characteristics derived from statistical data: Pearl index (Life Table Analysis), health risks, health benefits, and side effects

7.2.2 Patient Variables

- Subjective characteristics: individual preferences, values, and family planning objectives
- Biopsychosocial profile:
  - Biomedical characteristics: diseases and drugs (personal history), age, weight, blood pressure, and genetic outfit
  - Psychosocial characteristics: education and professional situation

7.2.3 Situation Variables

- Phase of life
- Relationship characteristics

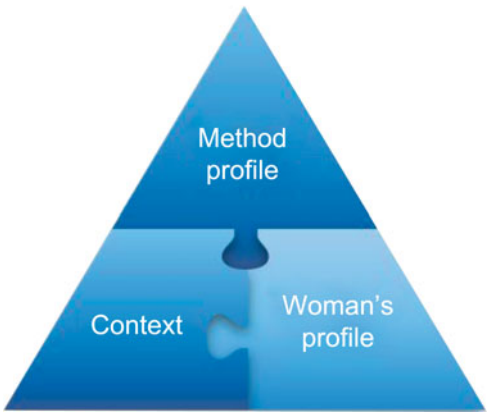

Fig. 7.1 The contraceptive triangle

7.3 Contraceptive Counseling and Care as an Interactive, Structured Process

A structured process is best suited to provide the optimal interaction of these variables. This process follows basic bioethical principles [26]:

- Respect of autonomy. This means in contraceptive counseling that the objectives and values of the patient (client) are respected.
- Nonmaleficence. Do not harm means that she or he is effectively protected against unwanted pregnancies and that health risks and negative side effects are minimized.
- Beneficence. This principle means that the health and well-being of the patient is promoted and cared for.
- Justice. All patients (clients) should have the same access to contraceptive information and care.

7.3.1 Step 1: Assess the Woman's Expectations and Preferences (*Respect of Autonomy*)

In the first step the professional should assess *the individual woman's expectations*, *objectives*, and *preferences*. This corresponds to the ethical principle of respect of autonomy.

Women may have very different objectives and values. The following are some examples:
Objectives

- *Absolute need to prevent pregnancy in the context of life situation*
- *Pregnancy not absolutely unwanted but not now*
- *Spacing pregnancies*
- *Family planning fulfilled, no more children*
- *Etc.*

Values and needs

- *Natural method*
- *Easy to use*
- *Independent of partner*
- *Involvement of partner*
- *Safety high priority*
- *Fear of health risks*
- *Etc.*

The information obtained in this part of the interview is important for step 4a in the decision-making process.

7.3.2 Step 2: Assess the Woman's Biopsychosocial Profile and Life Situation (Objective Patient and Situation Variables)

We differentiate between findings (objective facts), risks (probabilities), and conditions (elements of quality of life) [22–25].

7.3.2.1 Biomedical Dimension

- *Findings* (age, BMI, blood pressure)
- *Risks* (cardiovascular risks, neoplastic risks, metabolic risks, STI risks, bone risks)
- *Conditions* (hyperandrogenemic signs, dysmenorrhea, mastalgia, PMS, PMDD, etc.)

These data are assessed through a careful clinical history and examination. Findings and risks are important for step 4 (see below) in the structured process. Information about preexisting physical complaints and elements of quality of life are significant for step 5 (see below).

7.3.2.2 Psychological Dimension

- *Findings* (depression, anxiety, drug abuse)
- *Risks* (behavioral risks, STI risks)
- *Conditions* (somatoform disorder, sexual dysfunction)

The psychosocial history, the open interview, and the assessment of present complaints provide this information. Of special importance are the behavioral characteristics and preexisting emotional problems for step 4 and step 5 (see below).

7.3.2.3 Social Dimension

- *Findings* (socioeconomic status, education)
- *Risks* (cultural restrictions, dependence, migration)
- *Conditions* (stress, relationship issues)

Especially the sociocultural background and the present relationship characteristics are important elements of this part of the clinical interview, and they have an impact on step 4 (see below).

7.3.3 Step 3: Educate Women About Methods with Understandable Risk/Benefit Information Based on EBM Results (Method Variables) (Beneficence)

This step should empower women and help them to make informed choices. It is thus part of beneficence duty of the professional.

Women should be informed about the methods in a way that responds to two demands:

(a) The information should be based on the latest scientific evidence.
(b) The information should be given in didactic, understandable way and adapted to the individual needs of the patient.

The first request is quite easily feasible; the second is much more difficult. Some general guidelines of information giving are as follows:

Elicit preexisting knowledge and questions.
Provide clear and simple information:

- Give information in small units.
- Encourage questions.
- Summarize and repeat.

Elicit the understanding and the meaning given by the patient.

The issues and questions concerning the information exchange are as follows.

7.3.3.1 How Effective is Method x, y, and z to Prevent an Unwanted Pregnancy?

This question can be answered by a visual aid showing the efficiency of the methods if used by 100 women for 1 year.

The typical information to be given refers to the lowest expected percentage of women with a pregnancy during the first year of use [6, 15].

Highly effective methods:

Combination pill 0.1 %, progestin only 0.5 %, IUD copper T380A 0.6 %, levonorgestrel IUD 0.1 %, implant 0.1 %, injectable 0.3 %, female sterilization 0.2 %, and male sterilization 0.1 %

Medium effective methods:

Male condom 3 %, ovulation method 3 %, symptothermal 2 %, and post ovulation 1 %

Methods with low effectiveness:

Withdrawal 4 %, spermicides 6 %, diaphragm and spermicides 6 %, calendar 9 %, and cervical cap (parous women 20 %, nulliparous 9 %)

7.3.3.2 How Much is the Effectiveness Dependent on Proper Use?

The discussion of this issue points to the discrepancy between theoretical and typical Pearl index and allows a classification with respect to the necessary compliance and discipline [6, 15].

Methods with high demand on compliance:

Combination pill (lowest expected rate 0.1 % versus typical use rate 5–7.6 %)
Condom (lowest expected 3 % versus typical use rate 10–14 %)

Methods with low demand on compliance:

IUDs (lowest expected rate 0.1–0.6 % versus typical use rate 0.1–0.8 %)
Implants (lowest expected rate 0.2 % versus typical use rate 0.2 %)

7.3.3.3 What are the Health Risks of the Method?

This is a crucial part of the information exchange process. It is important to give a risk background and to describe risks in absolute numbers or give some points of reference [15, 23, 27].

High risk: between >1 and 1 in 100

For example: Gastrointestinal side effects of antibiotics 10 in 100; risk of pregnancy while using spermicides 6 in 100

Moderate risk: between 1 in 100 and 1 in 1,000

For example: Death due to smoking 10 cigarettes/day: 5 in 1,000
Having a baby with Down syndrome at age 35 years: 5 in 1,000

Low risk: between 1 in 1,000 and 1 in 10,000

For example: Venous thromboembolism attributable to COC: 3 to 6 in 10,000
Death due to car accident: 12 in 10,000
Diagnosis of breast cancer under 45 years possibly attributable to current OC use: 8 in 10,000

Very low risk: between 1:10,000 and 1:100,000

For example: Death due to soccer playing: 4 in 100,000
Risk of death from all causes in OC users: 1 in 100,000

After the general understanding of risk, the patient should be informed about the typical risks or the methods [15, 24, 27–34].

Combined OCs:

- Venous thromboembolic disease, myocardial infarction, and stroke – very low absolute risk (1 case in 10,000 users down to 3 in 100,000 users)
- Breast cancer and cervical neoplasia – very low absolute risk

Progestogen only:

- No or very low health risk

IUDs copper:

- Perforation, PID, and ectopic pregnancy – low to very low risk

Levonorgestrel IUS:

- Perforation, PID, and ectopic pregnancy – low to very low risk

7.3.3.4 What are the Factors that Influence the Health Risks (Increase or Decrease)?

This information helps the patient to understand her personal nonmodifiable and modifiable risks. She can learn about the impact of a healthy lifestyle on her individual risk during the use of different contraceptives [15, 27, 35, 36].

- Reduce cardiovascular risks by controlling weight, exercising, stopping smoking, and lowering cholesterol.
- Reduce risk of STI, PID, and CIN by using condom and avoiding sex with "risky" partners or under risk conditions (alcohol, drugs, etc.).

7.3.3.5 What are the Possible Noncontraceptive Health Benefits of the Method?

It is important to give not only information about risks but also about possible noncontraceptive health benefits of the methods.

For example, condoms diminish considerably the risk to acquire a sexually transmitted disease (for HIV with consistent use at about 97 %, against HSV highly effective, against HPV not very effective) [37].

For example, OC benefits are less endometrial cancer, less ovarian cancer, fewer ectopic pregnancies, more regular menses (less flow, less dysmenorrheal, less anemia), less salpingitis, increased bone density, probably less endometriosis, possibly less benign breast disease, possibly less rheumatoid arthritis, possibly protection against atherosclerosis, possibly fewer fibroids, and possibly fewer ovarian cysts [15, 38].

For example, levonorgestrel IUD reduces blood loss in hypermenorrhea, possibly diminishes fibroma size, and may protect against PID [34].

7.3.3.6 What are the Most Frequent Possible Negative and Positive Side Effects Having an Impact on the Quality of Life?

It is important to comment on possible negative and positive side effects at the same time. Many of the effects observed by the patient are very individual and cannot be predicted. Mentioning possible negative effects is important to avoid unnecessary anxiety, disappointment, and insecurity.

Hormonal Contraception

For example: combined OCs

The most important possible negative side effects which should be discussed including information about their frequency are changes in bleeding pattern (frequent), breast tension (sometimes), headache (rare), mood swings (rare), and skin changes (rare).
The most important possible positive side effects (health benefits) are diminution of dysmenorrhea (frequent), diminution of blood loss (frequent), and amelioration of acne (frequent) [15, 24, 27, 38].

For example: progestogen implant

The most important negative side effect is the occurrence of bleeding disorders. Positive side effects are in some women the establishment of a stable amenorrhea (if desired) and the decreased necessity of regular intake or compliance (see above).

For example: levonorgestrel intrauterine system

The most important possible side effect is irregular bleeding during the first months; much rarer are systemic side effects like depressed mood or acne. Even more seldom are functional ovarian cysts.
Positive possible side effects are induced hypomenorrhea and amenorrhea if desired by the woman [34].

Nonhormonal Contraception

For example: copper IUD

The most frequent side effects are hypermenorrhea and pain with a 15 % rate of removal due to bleeding and pain [15]. There are special positive side effects.
For example: condom and diaphragm
The most important side effect is the possible negative impact on sexual spontaneity and sexual interaction (condom) and an increased incidence of UTI (diaphragm).

7.3.3.7 When Do They Occur, for How Long Do They Typically Last, and What Medical Significance Do They Have?

Patients should be informed about the probable duration of side effects, whether these subside after the first months and whether or not patients must expect a recurrence. This time frame gives patients more control about the treatment and increases compliance.

For example: OCs and progestogen-only contraception

Intermenstrual bleeding and spotting occurs typically during the first months of treatment and disappears afterwards. These bleeding abnormalities do not have a pathologic significance.

7.3.4 Step 4: Shared Decision Making About Contraceptive Method

The medical professional can now enter into what is called shared decision making about the contraceptive method to be used by the individual patient. With respect to informed consent and shared decision making, we can distinguish four typical clinical situations:

1. Low risk with 1 therapeutic option = simple consent
2. Low risk with several therapeutic options = simple consent and shared decision making
3. High risk with 1 therapeutic option = informed consent
4. High risk with several therapeutic options = informed consent and shared decision making

Contraceptive counseling corresponds mainly to situation 2 and sometimes to situation 4. The shared decision-making process in contraception comprises two steps of exclusion of methods, one step of search for additional benefit and a final step of personal choice.

7.3.4.1 Step 4a: Exclusion of Methods Not Matching Patient's Expectations and Preferences (Respect of Autonomy)

In this step the patient has the lead. The values, past experiences, and health beliefs expressed during step 1 of the interview exclude some methods (Fig. 7.2).

For example, some patients do not want to take any hormonal contraceptive. It is of course important to discuss the background of this attitude or judgment, but it is important to show an a priori respect for this position and after information exchange in case of persisting wishes of the patient to accept her exclusions.

7.3.4.2 Step 4b: Exclusion of Methods with Respect to Major Somatic and Psychosocial Health Risks (Nonmaleficence)

By combining the results of the biopsychosocial profile of the patient (step 2) with the EBM-based characteristics of the methods (step 3), the medical professional can contribute his or her knowledge and experience [28, 29, 39–44] to exclude methods which should not be used because:

A. There is an unacceptable health risk.
B. The theoretical or proven risks usually outweigh the advantages (Fig. 7.3).

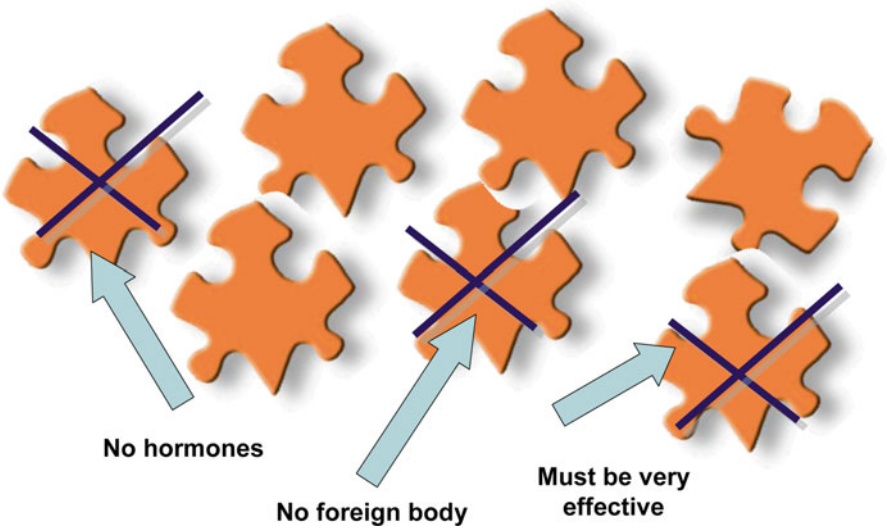

Fig. 7.2 Shared decision making about contraceptive method – women's expectations and preferences

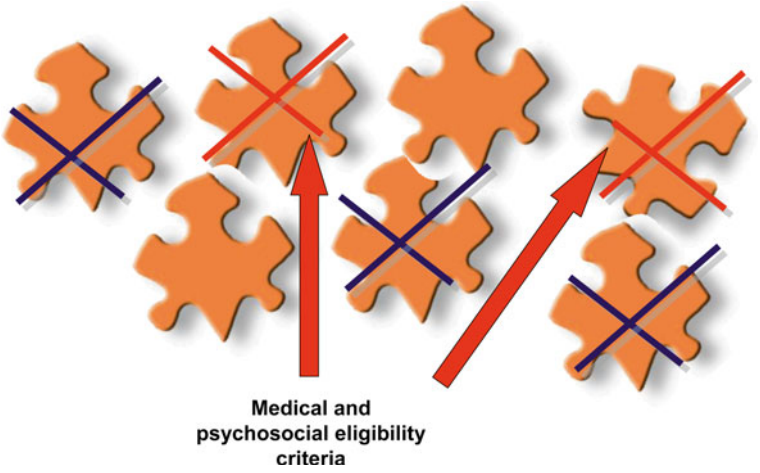

Fig. 7.3 Shared decision making – exclusion of methods with respect to major somatic and psychosocial health risks

Example A: Identified clotting abnormality of any kind; any past proven arterial or venous thrombosis excludes combined oral contraceptives.

Example B: Family history of parent or sibling <45 with thromboembolic disease with recognized precipitating factor would *under usual circumstances* exclude combined OCs, and personal history of high-risk sexual and addictive behavior would under usual circumstances exclude oral hormonal contraception.

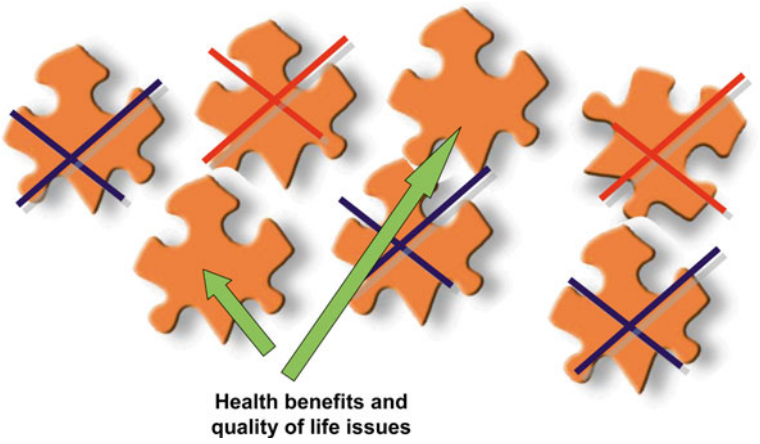

Fig. 7.4 Shared decision making – positive selection of methods with additional health benefits and QoL impact

Conditions which correspond to the description A are called absolute contraindications in older terminology and now are categorized by WHO as category 4 [28], meaning that the method should never be used in a patient with this diagnosis.

Condition B is much more directing towards the importance of the clinical judgment of the family planning professional. If, for example, the individual preference or value system of the patient would exclude medically safer methods (e.g., the IUD mentioned in the above example), then it is important for the clinician to negotiate with the patient and make the decision-making process transparent by visualizing the pros and cons and their respective weight [28].

7.3.4.3 Step 4c: Evaluation of Methods with Additional Health Benefits or in Case of Side Effects with the Actually Used Method Search for Alternatives (Beneficence)

After the two steps of exclusion, the information about relevant health conditions of the patient (step 2) is used to positively select methods that can contribute to an amelioration of clinical conditions and quality of life.

This is either in the case of, first, the active use of knowledge about *additional health benefits (a)* or, in the case of side effects with the present method, the use *of knowledge about side effect specific characteristics of methods (b)* [15, 34, 38, 45–49] (Fig. 7.4).

Example A: Skin problems respond positively to OCs, but especially to combined OCs with a progestogen having antiandrogenic properties.

PMS-like symptoms seem to correspond well to a drospirenone-containing preparation.

Preexisting cycle irregularities seem to respond well to vaginal hormonal contraception.

Example B: Nausea, headache, and breast tension under combined OC would request the change to a less estrogen dominant OC or progestogen-only contraception.

Bleeding irregularities under progestogen-only or low-dose combined OCs can be resolved by changing to higher dosage of EE or the vaginal contraceptive ring.

Lack of sexual desire while using OCs could be due to the SHBG increase and androgen decrease. Changing to an OC with less SHBG increase and possibly a progestogen with androgenic properties would then be helpful.

7.3.4.4 Step 4d: Personal Choice of the Contraceptive Method

Having gone together through these steps mentioned before, the medical professional and the patient will come to a shared decision about the contraceptive method to be used.

This structured process seems in our opinion to be the best precondition to reach the optimal outcomes described above.

7.3.5 Step 5: Evaluation of the Outcome and Ongoing Adaptation of Choices

Each follow-up consultation serves the purpose to evaluate whether the abovementioned objectives have been reached or whether there is room or necessity for amelioration and change.

7.4 Summary

The objectives of contraceptive counseling are to maximize contraceptive efficiency, minimize health risk, optimize tolerability, realize additional health benefits, and avoid unnecessary costs.

To reach these outcomes, contraceptive counseling and care has to be provided in an interactive, structured way following five steps which integrate patient-centered communication to assess patient's aims and values, biopsychosocial competence to determine the patient profile, professional patient education about methods, principles of shared decision making to choose the optimal method for the individual patient, and continuous evaluation to assess whether the objectives of contraceptive counseling and care for the individual patient have been reached.

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Hormonal Contraceptives: Progestogen and Thrombotic Risk

8

Adolf E. Schindler

8.1 Introduction

The various types of hormonal contraceptives have proven to be very effective modes of contraception [1]. However, the additional effects of hormonal contraceptives vary, and this is also true for thrombotic events that occur with the use of hormone replacement therapy (HRT).

As progestogens are to be considered with regard to thrombotic events, it has to be taken into account that the progestogenic steroids have the progestogenic effect in common, including the conversion of the endometrium into a secretory state, which prevents abnormal estrogen stimulation of the endometrium and in this way prevents abnormal endometrial hyperplastic changes, and last but not least, endometrial cancer [2]. Progestogenic action is also mandatory for proper secretory changes of the endometrium for implantation. If this occurs, further changes of the endometrium into decidualization take place and the blood flow to the uterus increases with trophoblastic invasion and proper development of the spinal arteries.

In addition, various progestogens have other different partial biological effects that are of clinical relevance. This is also true with regard to thrombosis incidence. Therefore, the partial biological effect pattern is different for the different progestogens and this is of utmost clinical relevance, if thrombotic events are taken into consideration [3].

Therefore, one can conclude that progestogens are not the same, based upon differences in structure, differences in the partial effect pattern (action profile) and differences in organ effects.

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*,
ISGE Series, DOI 10.1007/978-3-319-09662-9_8

Unfortunately, there is still a lot of confusion, even in well-known international journals such as *Climacteric*, where the title of an article talks about progesterone, but in the text only studies on medroxyprogesterone acetate (MPA) were reported. Indeed, MPA does have a vasoconstrictive effect on the arterial vessels – in this case the ophthalmic artery and retinal artery – while progesterone, in contrast, widens the arterial vessels and lowers the blood pressure, which was particularly well demonstrated in pregnant women with preeclampsia [4]. Nowadays, this can be clearly demonstrated and quantified by Doppler ultrasound measurements [5, 6]. Indeed, with the rise of the circulating progesterone in the corpus luteum phase, the blood flow to the uterus and the ovaries increases and if pregnancy occurs, the blood flow, which is common for all progestogens, increases. If no conception and implantation occur, the blood flow decreases.

The following partial effects – besides the progestogenic effect – are present for each progestogen in a particular way, which was alluded to more than 10 years ago [3]. Thus, each progestogen is associated with a particular partial effect pattern. The following partial effects should be considered: androgenic, antiandrogenic, estrogenic, antiestrogenic, glucocorticoid and antimineralocorticoid.

How do these partial effect patterns of the progestogens determine the different thrombotic risks of estrogen/progestogen combinations (COCs), oral, vaginal and transdermal, as well as in HRT? Answering this question will be the aim of this chapter.

8.2 Hemostasis and Thrombotic Events

The hemostatic system comprises coagulation and fibrinolysis

Normally, this system is in balance [7]. It consists of procoagulation, anticoagulation as well as profibrinolysis and antifibrinolysis. There can be venous and arterial thrombotic events. Afterwards, we focus on venous thrombosis. This is an essential risk factor for using a premenopause estrogen/progestogen combination, but also in postmenopausal HRT (oral, vaginal, transdermal). Risk factors for thrombosis are listed in Table 8.1.

8.3 The Risk of Venous Thrombosis, When Taking COCs

It has been known since the 1960s that oral estrogen/progestogen combinations are associated with an elevated risk of venous thrombosis. At first, the thrombotic risk was related to the type and dose of the estrogen component. In the 1990s the debate started that different progestogens are associated with different thrombotic risks. In general, the thrombotic risk is double compared with women of a similar age group who are not taking the pill. The number of events is highest in the first year and levels off over time. Therefore, the so-called pill pause is dangerous, as with each restart of the pill the thrombotic risk shoots up in the first year [8].

The frequency of venous thrombosis is as follows:

1. Non-user of COCs have a risk of 4–5/10,000 women years
2. COC users have a risk of 9–10/10,000 women years

Table 8.1 Risk factors for thrombosis

1. Increasing age
2. Increasing body weight
3. Pregnancy/post partum
4. Hormonal contraceptive pill as estrogen/progestogen combination (a) Type of estrogen (EE, E2, E2V) (b) Estrogen dose (c) Type of progestogen in combination with an estrogen (d) Dose of progestogen (e) Length of use (f) Type of application (oral, vaginal, transdermal)
5. Hormone replacement therapy (HRT) as estrogen/progestogen combination listed as above for a, b, c, d, e, f
6. Genetic predisposition
7. Family/personal history of thrombosis
8. Immobility (operation, accident)
9. Long distance air travel
10. Smoking

3. Pregnant women have a risk of 29/10,000 women years
4. Postpartum women have a risk of 300–400/10,000 women years [9]

Overall, the risk of venous thrombosis in users of a low estrogen dose (<50 μg ethinyl estradiol [EE]) COCs is two- to threefold higher than for non-users of COCs. Thrombotic risk is modified using COCs or HRT by the type and dose of the estrogen (EE, estradiol [E2], estradiol valerate [E2V]) and by the progestogen used, depending on the partial effect pattern of each progestogen. Extensive comparative studies with 35 versus 50 μg EE [7] or 20 versus 30 μg EE have been carried out, demonstrating the changes in the parameters of hemostasis depending on the EE dose [10].

Hormone replacement therapy can increase the thrombotic risk by up to three times depending on the estrogen/progestogen combination used and other risk factors such as changes in body composition (particularly an increase in visceral adipose tissue), pro-atherogenic changes in lipid metabolism, worsening of the imbalance in carbohydrate metabolism and the increasing risk of climacteric women of developing a metabolic syndrome [11].

8.4 Mode of Action of Progestogens in Combination with Estrogens (Pill, HRT)

The extent of the progestogens used on the hemostatic system is dependent on the extent of the modification of the total estrogen effect on the body – mainly the liver. There can be an increase or decrease in liver protein synthesis by the action of progestogen, which is reflected by the levels of sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG) and thyroxine-binding globulin (TBG).

Table 8.2 Comparison of indices of venous thrombosis in drospirenone (DRSP)- or levonorgestrel (LNG)-containing estrogen/progestogen combinations (COCs) per 100,000 years

	Australian study [17]	American study [18]
Drospirenone	23.0; 95 % CI 13.4–36.9	30.8; 95 % CI 26.6–26.8
Levonorgestrel	9.1; 95 % CI 6.6–12.2	12.5; 95 % CI 9.6–15.9
Incidence ratio	2.7; 95 % CI 1.5–4.7	2.8; 95 % CI 2.1–3.8

Table 8.3 Thrombotic risk with COCs with different progestogens compared with COCs containing LNG

Progestogen	Relative risk
Levonorgestrel	1.00
Norethisterone	0.98
Norgestimate	1.19
Desogestrel	1.82
Gestodene	1.86
Drospirenone	1.64
Cyproterone acetate	1.88

Indeed, SHBG levels using different EE/progestogen combinations vary when comparing the various COC preparations. In addition to the overall increase in SHBG there are differences in the extent of SHBG level elevation: ethinyl estradiol/cyproterone acetate (EE/CPA) is associated with a higher SHBG level than estradiol/drospirenone (EE/DRSP) and lower estradiol/desogestrel (EE/DSG) [12].

Progestogens induce through their different partial effect patterns (androgenic, antiandrogenic, estrogenic, antiestrogenic, glucocorticoid and antimineralocorticoid) the estrogen action of the estrogen used (EE, E2, E2V) regarding the production of proteins of the hemostatic system.

In addition, there are other risk factors such as genetically induced changes in the hemostasis inhibitors (antithrombin III, protein C and protein S) or a hereditary resistance of factor V Leiden against activated protein C (APC resistance).

Progestogens with a partial glucocorticoid effect (i.e. MPA, CPA) regulate the thrombin receptor and stimulate the procoagulatory activity at the vessel wall [13]. Stimulatory progestogens are MPA, CPA, gestodene, 3-ketodesogestrel and DRSP. This is not the case with levonorgestrel (LNG). These events only occur when these progestogens are used together with an estrogen (EE, E2, E2Val). COCs containing DSG or gestodene (third-generation progestogens) increase the risk of thrombosis by 70 % compared with COCs with LNG (second-generation progestogen) [14]. The elevated risk of gestodene- and DSG-containing COCs is associated with a higher SHBG concentration (increased liver protein synthesis) than LNG-containing COCs [15]. This was brought up again in 2009 with two articles published in the *BMJ* [8, 16]. These articles reported on the results of two retrospective epidemiological studies that assessed the risk of thrombosis using hormonal contraceptives. These studies suggested that COCs were associated with a differential risk of thrombosis caused by their progestogenic components. The risk of thrombosis was reportedly lower in women with LNG-containing COCs versus the so-called third-generation COCs and COCs containing DRSP [8, 16]. This was further

Table 8.4 Ratio between thrombosis and HRT used over 5 years according to Sweet et al. [26]

Type of treatment	Thrombotic risk
No medication	1:650
Oral estrogen alone	1:475
Estradiol/progestogen combination (norethisterone, norgestrel)	1:390
Estrogen/progestogen combination (MPA)	1:250

MPA medroxyprogesterone acetate

substantiated by the Australian study by Parkin et al. [17] and by the American study by Jick and Hernandez [18], as shown in Table 8.2.

The safest COCs with regard to thrombosis are those with LNG, norethisterone and norgestimate [19, 20]. Out of all this, it was recommended that women start COC use with pills containing 20 µg EE combined with norethisterone or LNG or norgestimate [21].

Data on the thrombotic risk of COCs using EE and various progestogens clearly indicate that progestogens with a more prominent androgenic partial effect pattern are more likely not to be burdened with an elevated thrombotic risk (Table 8.3).

Thrombotic risk is dependent upon the partial androgenic effect of the progestogen, which counteracts the protein synthesis in the liver by EE or E2/E2Val. This is reflected in a more subtle increase in SHBG that means decreased protein synthesis and therefore decreased activation of the hemostatic system. Indeed, treatment with tibolone, with the androgenic action of its metabolites, was found to induce a substantial risk reduction of venous thrombosis of 0.27 [22].

In addition to the reduction in protein synthesis (see SHBG) progestogens with an androgenic partial effect pattern are of importance for this favorable action on the hemostasis of COCs, but also of HRT by reduction of fibrinolytic inhibition by PAI-1 and Lp(a) [23].

Changing not only the dose of the estrogens but also the estrogen component in COCs or HRT reduces the risk of thrombosis. It could be demonstrated that when combining E2Val with dienogest (DNG) or DRSP the risk of thrombosis is similar or even lower than with LNG COCs such as Microgynon® [24]. A recent thorough evaluation concluded that the non-oral route of EE administration seems to be more thrombogenic than the oral route [25]. In contrast, low-dose oral progestogen-only contraceptives (POPs) as well as LNG IUS appear to be safe with regard to risk of thrombosis. Overall, newer progestogen formulations of estrogen/progestogen combination contraceptives in addition to non-oral COCs seem to be more thrombogenic than the second-generation COCs.

A similar risk pattern seems to prevail with HRT. There is a relationship with the progestogen used. The relative risk (RR) of HRT with MPA was 2.67; 95 % CI 2.25–3.17, while HRT with other progestogens had an RR of 1.91; 95 % CI 1.67–2.1. This difference is statistically highly significant ($p < 0.0007$; Table 8.4) [26].

In contrast, progesterone and dydrogesterone appear not to increase the RR in combination with estradiol (E2) in postmenopausal women [27]. As shown by Lideguard et al. [8] progestogen-only contraceptives do not increase the risk of thrombosis: LNG/NET RR 0.59, DSG RR 1.12, LNG-IUS RR 0.90 [25].

Conclusion

Estrogen/progestogen combinations carry a higher risk of venous thrombosis. This depends on the type of estrogen (EE, E2, E2V) and the daily dose. At present EE as low as 20 μg/day or replacement with E2 or E2V appear to be mandatory in significantly reducing the risk of venous thrombosis independently of other venous thrombosis risk factors. It also depends on the type of the progestogen used. COCs with progestogens with a partial androgenic effect carry a lower or no thrombotic risk. The second-generation progestogen LNG, in combination with estrogens, has a potentially lower risk of thrombosis than third-generation progestogens (DSG, gestodene, DRSP) or antiandrogenic progestogens such as CPA. Non-oral routes of COCs with EE seem to be more thrombogenic. Progestogen-only pills and LNG-IUS are not associated with risk of thrombosis. The common denominator appears to be the effect on liver protein synthesis as expression of the partial androgenic effect pattern, as expressed for instance by SHBG and profibrinolytic activity.

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Part III

Heavy Menstrual Bleeding, Fibroids, Adenomyosis and Endometriosis

Heavy Menstrual Bleeding: The Daily Challenge for Gynecologist

9

Johannes Bitzer

9.1 Introduction

Heavy menstrual bleeding (HMB) represents a common gynecological complaint among women of reproductive age.

The National Institute for Health and Care Excellence (NICE) in the UK defines HMB as "excessive menstrual blood loss that interferes with the woman's physical, emotional, social, and material quality of life, and that can occur alone or in combination with other symptoms."

The prevalence of HMB varies widely depending on its definition, and the methods used to ascertain magnitude of blood loss have ranged up to 52 % but the prevalence has been based on women's perception of heaviness.

MB >80 mL is objectively assessed; prevalence has been reported in up to 14 %. HMB is associated with psychological morbidity and negatively affects activities of daily living including social, professional, and family life.

A significant number of women diagnosed with HMB have iron deficiency anemia (hemoglobin less than 120 g/L) or a history of anemia.[7]

HMB is associated with increased use of health-care resources including high rates of surgical intervention.

9.2 How to Diagnose Heavy Menstrual Bleeding

There are several approaches to the diagnosis of heavy menstrual bleeding.

The objective measures which are used in studies are either the alkaline hematin method (measuring hematin in sanitary pads) or pictorial blood loss assessment scores.

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_9

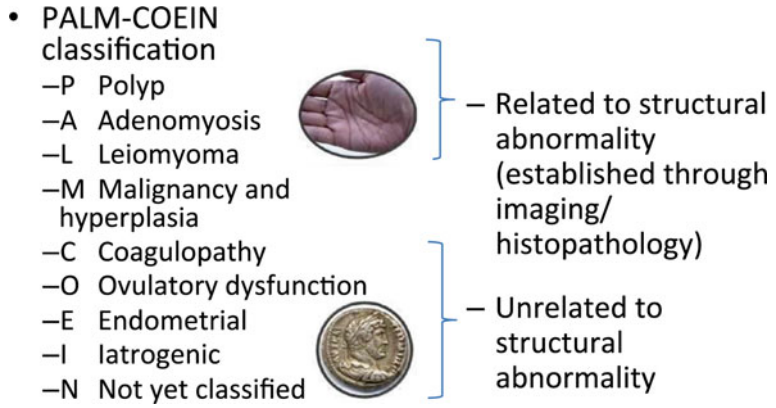
Questions to ask to help quantify blood loss during menses

Questions	Answer from women with normal MBL
How often do you change your sanitary pad/tampon during the peak flow days?	Change pads/tampons every 3 h
How many pads/tampons do you use over a single menstrual period?	Use fewer than 21 pads/tampons per cycle
Do you need to change the tampon/pad during the night?	Seldom need to change a pad/tampon during the night
How large are any clots that are passed?	Have clots less than 1 in. in diameter
Has a medical adviser told you that you are anemic?	Not be anemic

Matleson KA, Clark MA. *Women Health* 2010;50;195–211.
http://www.mayoclinic.com/health/menorrhagia/DSD0394/DSECTION=symptoms

9.3 Causes of Heavy Menstrual Bleeding and Diagnostic Classification

The FIGO Committee on Menstrual Disorders developed a descriptive terminology to characterize the frequency, regularity, duration, and heaviness of flow of a woman's menses[14] and the PALM-COEIN classification for causes of bleeding, based on discrete structural (PALM: *p*olyps, *a*denomyosis, *l*eiomyomas, and *m*alignancy/hyperplasia) and nonstructural causes (COEIN: *c*oagulopathy, *o*vulatory dysfunction, *e*ndometrial dysfunction, *i*atrogenic, and *n*ot yet classified).



Most women with a complaint of HMB do not have any structural or histologically identifiable abnormalities.

In the new PALM-COEIN classification, the classification will be abnormal uterine bleeding due to endometrial dysfunction (AUB-E).

9.4 Treatment Options

There are two basic therapeutic approaches.

The surgical approach comprises endometrial ablation/resection and hysterectomy. There is an approximative bleeding reduction of 87 and 100 %, respectively. The proportion of patients having less than 80 ml blood loss per cycle is 100 % in both procedures.

Properties of surgical methods in HMB treatment

	Ablation/resection	Hysterectomy
Patient satisfaction	83 %[a]	93 %[b]
Level of evidence for clinical efficacy	Several randomized and observational studies	Several randomized and observational studies
Validity and reliability of measured outcome	*High*: efficacy reliably assessed by amenorrhea rates and number of repeated interventions	*High*: definite procedure
Safety (potential ADRs as mentioned in the NICE guidelines)	Vaginal discharge, increased period pain or cramping (even if no further bleeding), perforation (but very rare with second-generation techniques)	Infection, damage to other abdominal organs, urinary dysfunction (frequent passing of urine and incontinence), thrombosis, death (rare)

[a]Busfield et al. *Br J Obstet Gynaeool*. 2006;113:257–253
[b]Aberdeen Endometrial Ablation Trials Group. *Br J Obstet Gynaeool*. 1999;106;360–356

Other clinical properties of these methods are summarized in the table.

The medical approach includes the following drugs:

- Combined oral contraceptives
- Oral/depot progestogen
- Tranexamic acid
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Progestogen-releasing intrauterine systems

9.4.1 Combined Hormonal Contraceptives

There are eight studies (involving 430 patients) available that assess the impact of combined hormonal contraceptives in the treatment of HMB, of which six were randomized controlled trials, five assessed combined oral contraceptives and one assessed the use of vaginal ring.

The medium bleeding reduction is about 43 %.

The advantage of this treatment is that it provides additional contraception if desired by the woman.

The treatment is under the control of the woman and in general well tolerated.

Commonly reported adverse effects of combined hormonal contraception include abdominal cramp/pain, acne, breast tenderness/discomfort, depression/mood changes, diarrhea, headache, nausea/vomiting, and weight gain.

As a class, estrogen-containing hormonal methods increase the risk of venous thromboembolism (VTE). The incidence of VTE with modern low-dose combined hormonal contraceptives is increased by about twofold compared with nonusers (from 4.7 per 10,000 woman years to 9.1 per 10,000 woman years), but remains less than that associated with pregnancy (20 per 10,000 pregnancies). The increased risk of venous thromboembolism is generally attributed to the estrogen component, but whether this increased risk is independent of the progestogen component continues to be a subject for debate. Of note, anemia has been shown to be associated with an increased risk of venous thromboembolism, which raises the possibility that HMB may predispose toward increased risk of this condition.

9.4.2 The Cochrane Review Summarized the Evidence

- COCs are frequently prescribed (off-label) to treat the symptoms of heavy and/or prolonged menstrual bleeding.
- However, no prospective, well-designed studies exist to validate and quantify this effect.
- Single case reports show high efficacy of two- to fourfold dosage in acute bleeding (e.g., in adolescents).
- Safety of such high dosages lacks systematic evidence.

9.4.3 Estradiol/Dienogest Combined Oral Contraceptive

Two placebo-controlled studies assessed the multiphasic E_2V/DNG combined oral contraceptive in over 260 women with HMB presumed due to endometrial dysfunction treated over seven cycles of treatment.[81, 82] A pooled analysis of the two studies identified reported an 88 % reduction in median MBL by treatment cycle 7 relative to baseline (vs. 24 % with placebo).

9.4.4 Oral Progestogens

The following progestogens are used to treat heavy menstrual bleeding:

- Lynestrenol
- Norethisterone acetate/norethisterone
- Medroxyprogesterone acetate (MPA)
- Dydrogesterone

- Chlormadinone acetate
- Progesterone

All twelve studies but one were randomized controlled trials.

The progestogens assessed were NETA and medroxyprogesterone acetate (MPA), administered as short-course (2 or less weeks OR ≤14 days per cycle) or long-course (3 or more weeks OR ≥21 days per cycle) treatment.

9.4.4.1 Short-Course Oral Progestogens

The available data with short-course oral progestogens (involving >150 patients) were generally inconsistent or, at best, suggest it had limited efficacy in reducing MBL.

Anovulatory patients (AUB-O), who are missing endogenous progesterone, may respond well to "short cycle" progestogen therapy.

One small study that included women with anovulatory HMB ($n=6$) reported mean MBL reductions of 39 and 51 % after 1 and 2 months of treatment, respectively, with NETA 5 mg or MPA 10 mg both three times daily from day 12 to 25 of the cycle.

9.4.4.2 Long-Course Oral Progestogens

In contrast, treatment with long-course progestogens (3 or more weeks per cycle) for AUB-E consistently reduced pictorial bleeding assessment scores (PBCAS) in studies involving >200 patients.

The average bleeding reduction is 0–22 % if used as labeled and 37–87 % in higher/longer doses than labeled.

In studies that reported adverse events during treatment with oral progestogens, these generally included headache, breast tenderness, nausea, and bleeding problems (any bleeding problem reported as an adverse event).

There are no major health risks reported.

9.4.5 Tranexamic Acid

There are 11 studies (>800 patients) reporting the impact of tranexamic acid on HMB; 9 are randomized and two are non-randomized trials all in women with HMB presumed due to endometrial dysfunction.

The average bleeding reduction is between 22 and 40 %.

The Cochrane Review states the following:

- AF therapy causes a greater reduction in objective measurements of HMB when compared to placebo or other medical therapies (NSAIDS, oral luteal phase progestogens, and ethamsylate).
- AF treatment is not associated with an increase in side effects compared to placebo, NSAIDS, oral luteal phase progestogens, or ethamsylate.
- There are no data available within randomized controlled trials which record the frequency of thromboembolic events.

No studies assessed the use of tranexamic acid for more than 6 months. The proportion of women subsequently receiving surgical treatment was only reported in one study which found that only 2/49 (4 %) underwent surgical treatment.

Adverse events were reported such as nausea/vomiting, headache, and allergies/allergic reactions.

In the placebo-controlled studies, there were no statistical significant differences in the frequency of any adverse events between treatment and placebo groups.

Although there is a theoretical risk that tranexamic acid could increase the risk of venous thromboembolism, the limited population-based studies do not support that conclusion. Nonetheless, it is regarded as wise to avoid its use in women with a history of or predisposition to thrombosis.

9.4.6 Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Of 19 studies of NSAIDs for HMB presumed due to endometrial dysfunction (involving >470 patients), 17 were randomized controlled trials.

The NSAIDs most frequently used are

- Mefenamic acid
- Ibuprofen
- Naproxen
- Meclofenamate
- Flurbiprofen, over 3–5 days of treatment during menstruation

Overall, use of NSAIDs appears to be associated with a consistent but limited reduction in MBL (range 10–40 % mean MBL reduction), which persists for up to 15 months of continued treatment.

These treatments provide no contraceptive effect.

There is evidence that an additional benefit is the reduction of dysmenorrhea.

The adverse events during treatment, which are reported in three or more studies, included nausea/vomiting, abdominal pain, and headache.

9.4.7 Progestogen-Releasing Intrauterine Systems

The evidence base for the use of the LNG-IUS in HMB is substantial. In women with HMB attributed to endometrial dysfunction (AUB-E), there are 17 randomized controlled trials (including altogether >700 patients [range 22–119 patients]) and 10 non-randomized trials (including 380 patients [range 10–66 patients]).

In 11 of the randomized controlled trials, the LNG-IUS was compared to surgical options.

The LNG-IUS had consistent reduction in MBL (or PBAC scores) over the first 3 months of treatment (70 %) (irrespective of whether mean or median reductions were reported, or type of study [randomized vs. non-randomized]), with further

reductions over the first year of treatment that are maintained through to at least 4 years of use.

In women with HMB attributed to uterine structural pathology or coagulopathy, the evidence was collected from 15 studies, including 2 randomized studies, and involved altogether >600 patients. Three studies were in women with coagulopathies, ten in women with leiomyomas, and two in women with adenomyosis.

These studies all reported MBL outcomes using PBAC scores, and one study also included data obtained with the alkaline hematin method.

The effectiveness of the LNG-IUS in reducing PBAC scores in women with coagulopathies appears mixed, with one study in women on anticoagulant therapy demonstrating rather modest mean reductions in PBAC scores of up to 35 % at 6 months of treatment and the other two studies in women with coagulopathies demonstrating similar reductions (median 61–84 % reduction in PBAC score over 3–12 months use) to those achieved in women with HMB presumed due to endometrial dysfunction.

Of note, women with HMB presumed due to intramural leiomyomas appear to experience similar benefits as in those with HMB presumed due to endometrial dysfunction which persisted for at least 3–4 years of treatment. The limited data in women with adenomyosis suggest that the LNG-IUS is equally effective in these women also.

The reported LNG-IUS expulsion (including partial expulsion) rates in women with HMB due to endometrial dysfunction in studies that specifically reported this outcome was 7 % (55/791) and 7 % (25/338) in women with HMB secondary to leiomyomas. Only one LNG-IUS expulsion was reported across the three studies in women with coagulopathies (1/60; 2 %) and three (3/102; 3 %) expulsions in women with adenomyosis. No uterine perforations were reported in any of these studies included in this review.

One-year continuation rates with LNG-IUS use in women with HMB due to endometrial dysfunction range between 80 and 95 % and 59 and 97 % in those with HMB secondary to leiomyomas. Women subsequently choosing to undertake or opt for surgical treatment varied between 0–24 % and 3–22 % in the two groups, respectively. The limited number of studies in women with coagulopathies or adenomyosis suggests similarly high 1-year continuations rates as in the other two groups of women with HMB. The need for subsequent surgical intervention was not discussed in the three studies in women with coagulopathies, and one (4 %) woman had a subsequent hysterectomy in one of the studies in subjects with adenomyosis.

In general, the need for subsequent surgical intervention was variably ascertained or was reported inconsistently across the studies.

Commonly reported adverse events with the LNG-IUS included bleeding problems (any bleeding problem reported as an adverse event), breast tenderness/pain, abdominal/pelvic pain, backache/pain, headache, ovarian “cysts” (persistent follicles), and acne.

As placebo-controlled trials are not possible in this context, it would difficult to definitively ascertain the proportion of adverse events that could be attributed to the nocebo phenomenon or background incidence.

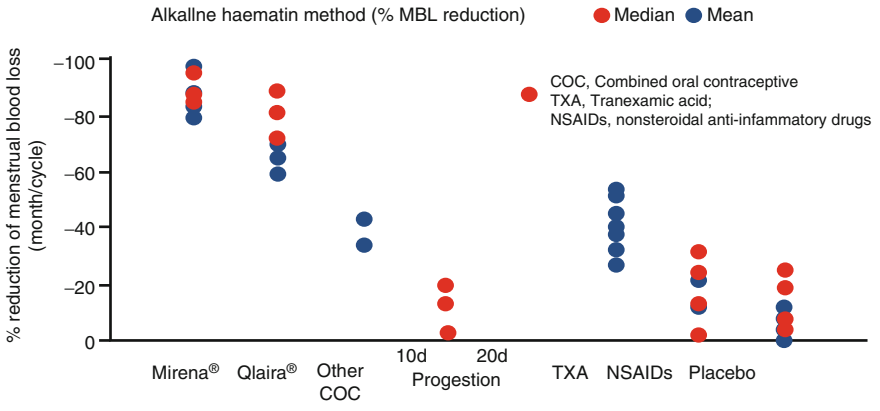
The efficacy of newer LNG-IUS (13.5 µg LNG/24-h initial release rate; Skyla™/Jaydess®) in treating HMB has not been assessed.

In summary, the LNG-IUS is the most widely studied medical therapy for HMB. The available data with the LNG-IUS suggest a consistent >60 % reduction in MBL (or PBAC scores) over the first 3 months of treatment, with further reductions over the first year of treatment that are maintained through to at least 4 years of use in women with HMB due to endometrial dysfunction. Moreover, the benefits of the LNG-IUS in reducing menstrual blood loss may also be extended to women with HMB secondary to leiomyomas or adenomyosis, as well as those with underlying coagulopathies. In general, the LNG-IUS appears well tolerated with high 1-year continuation rates. Other intrauterine systems have also been assessed in a limited number of studies, but whether these can be considered equivalent in terms of MBL reduction to the well-studied LNG-IUS has not been demonstrated.

9.4.8 Comparison of the Different Medical Interventions

Based on a large number of studies, it seems appropriate to classify and rate the different methods regarding their efficacy with respect to the treatment of heavy menstrual bleeding.

See the following table.



9.5 Summary

Heavy menstrual bleeding is a frequent problem in gynecologic practice. HMB has an important negative impact on the quality of life of women. HMB can be due to structural and nonstructural causes which are summarized in the PALM-COEIN classification. Surgical and medical treatment options are available and the decision regarding treatment should take into account the efficacy of the method, the side

effects, and the risks on one hand and the individual needs and preferences of the woman on the other hand (contraception, wish for a child, personal values and preferences, etc.).

References with the author

Challenges of Laparoscopic Resection of Uterine Fibroids in Infertility

10

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10.1 Introduction

Despite extensive research on the factors involved in the initiation and growth of uterine leiomyomas, the precise causes of these tumors still remain unknown. Chromosomal abnormalities have been found in 40–50 % of uterine leiomyomas [1]. Intrinsic abnormalities of the myometrium, congenitally elevated myometrial estrogen receptors (ER), hormonal changes, or a response to ischemic injury during menstruation may possibly be responsible for the initiation of genetic changes found in these neoplasms [2]. After these changes have developed, they are further influenced by ovarian steroids (promoters) and growth factors (effectors) [3].

The degree to which uterine fibroids contribute to infertility is controversial. It has been estimated that uterine myomas are associated with infertility in 5–10 % of cases by a number of mechanisms [4]. The role of fibroids in infertility was evaluated indirectly by fertility performance after myomectomy. The effect of submucosal, intramural, and subserosal uterine fibroids was also investigated on the reproductive outcome of assisted reproduction treatments (ART) [5]. It is well accepted that the anatomical location of the fibroid is an important factor, with submucosal, intramural, and subserosal fibroids, in decreasing order of importance, being a cause of infertility [6]. Submucosal myoma (SMM) or intramural myoma (IMM) may cause dysfunctional uterine contractility that may interfere with sperm migration, ovum transport, or nidation. Occluded tubes can be caused by intramural

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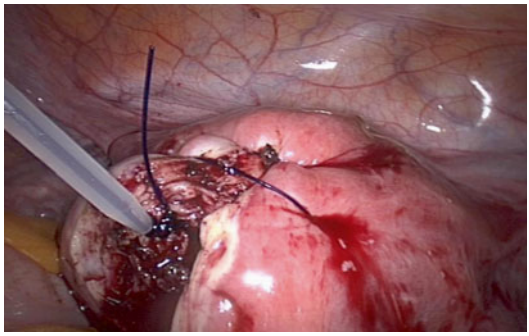

Fig. 10.1 Intraoperative closure after myomectomy with inverted absorbable monofilament suture

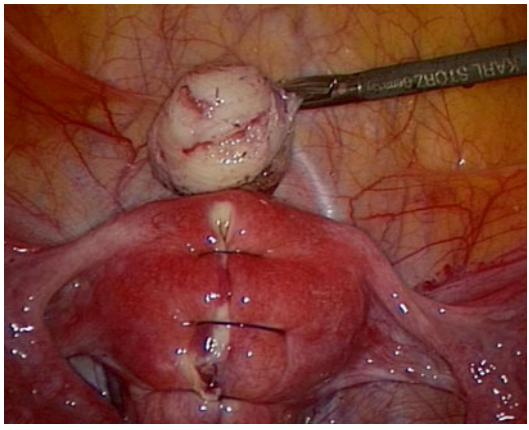

Fig. 10.2 Reconstructed uterine wall and enucleated myoma before morcellation and extraction

fibroids that can hinder the transport of gametes or the migration of spermatozoa. Submucous fibroids can hinder implantation and nidation of the embryo [7].

The benefits of the laparoscopic approach in gynecological surgery are well recognized [8]. Compared with conventional open surgery, it is associated with smaller incisions and better cosmetic results regarding wound healing, less tissue trauma, less blood loss, less postoperative pain, shorter duration of stay in hospital, faster recovery due to early ambulation with an earlier return to work, and subsequent resumption of full activity (Figs. 10.1 and 10.2). The major concern about laparoscopic myomectomy (LM) is suboptimal tissue apposition during repair of myometrial defects leading to uterine rupture in subsequent pregnancies. However, if the myometrial repair is performed with the same degree of care as it would be at open myomectomy, there appears to be no reason why the rate of uterine rupture should be higher after LM [9]. This gives more credit to the use of laparoscopically assisted myomectomy (LAM) in selected difficult cases but very little credit if any to the use of the conventional approach. Robotic technology for myomectomy gives even more precise adaption and suturing possibilities but certainly does not increase dampers or side effects. Aspects of LM and pregnancy outcome are discussed in this chapter, not, however, the impact of submucous fibroids or the hysteroscopic approach.

10.2 Material and Methods

Laparoscopic myomectomy was performed in patients with symptoms such as disturbed menstrual bleeding, pelvic pain, and infertility.

The laparoscopic enucleation of fibroids always followed the same pattern:

1. Injection of a 0.05 % vasopressin solution in 1–4 locations under the myoma capsule.
2. Longitudinal incision of the capsule with the aim of enucleating the fibroid under the capsule, leaving the capsule in situ (this can usually be easily peeled like an orange).
3. Grasping of the fibroid with a myoma screw, traction, and bipolar or ultrasound coagulation of spiral arteries. Coagulation of the myoma pedicle and the myoma is twisted out of its bed.
4. Rinsing of the myoma bed with Ringer's lactate and coagulation of larger bleedings.
5. Adaption of wound edges with several deep sutures to a depth of 5–20 mm without touching the endometrium. Only rarely is a double layer of sutures necessary. Whenever the uterine cavity is opened, it has to be closed with individual sutures.
6. Morcellation of the fibroid with one of the commercially available morcellators and fibroid extraction.

The hysteroscopic enucleation of a submucous fibroid is performed by filling the uterine cavity with Purisole® and then in a continuous movement slicing the fibroid into pieces (electroresection) and retracting the pieces through the cervix. Bleedings can be controlled by pressure release and coagulation with the roller ball or with the cutting loop.

10.2.1 Questionnaire for Patient Data

A questionnaire was sent to 392 patients with fertility problems who were treated by laparoscopy or hysteroscopy at the Department of Obstetrics and Gynaecology, University Hospitals Schleswig-Holstein, Campus Kiel. One hundred and fifty-four patients (40 %) returned the questionnaire that posed questions concerning myomectomies, endometriosis resection, ovarian cyst enucleation, and adhesiolysis.

Patients were evaluated as follows:

Group A = all patients ($n = 392$)
Group B = patients who answered the questionnaire ($n = 154$)
Group C = patients from group B who became pregnant ($n = 78$)

10.3 Results

Of the 392 patients who underwent laparoscopic surgery for fertility problems in our department in 2008/2009, in 129 cases (32 %) myomas (fibroids) were the indication for surgery. Of these 129 patients, in 56 cases (14.3 %) myomas were the

only indication for infertility. In 44 cases (11.2 %) myomas appeared together with another disease: in 20 cases (5.1 %) with other genital abnormalities, in 18 cases (4.6 %) with tubal pathology, in 3 cases (0.8 %) with endometriosis, and in 3 cases (0.8 %) with ovarian cysts. The combined appearance of myomas with more than one other genital disturbance was found in 29 patients (7.5 %).

10.3.1 Frequency of the Different Myoma Localizations

Figures 10.3, 10.4, and 10.5 show the frequency of myomas within the whole evaluation. Multiple sites often occurred and this resulted in a higher incidence ($n = 140$). The location of fibroids were evaluated as diffuse (within the uterine wall), submucous, intramural, subserous, and submucous as well as at multiple locations. Primarily a deep, diffuse myomatosis was found in 60 % of patients in group A, in 62 % of patients in group B, and in 59 % of patients in group C. Submucous fibroids occupied second position in group A (16 %) and subserous fibroids occupied second position in group B (19 %) and group C (21 %).

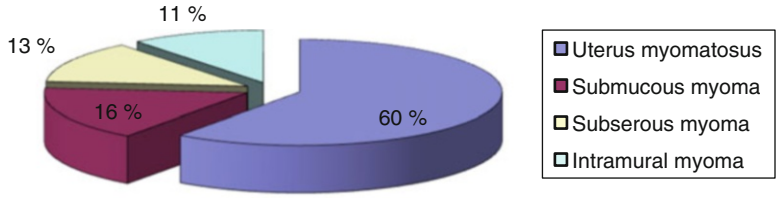

Fig. 10.3 Localization of myomas in the 392 patients (group A)

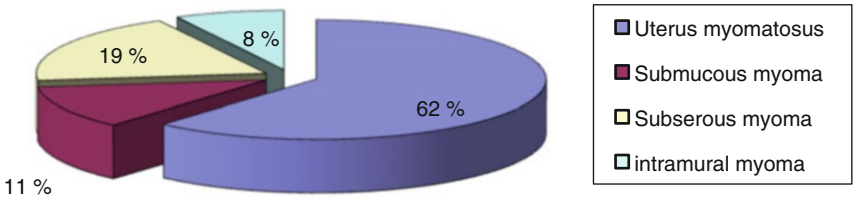

Fig. 10.4 Localization of myomas in the group which answered the questionnaire (group B)

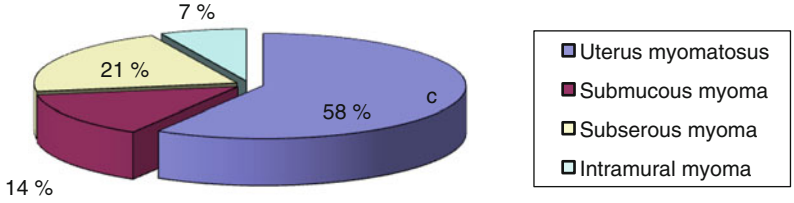

Fig. 10.5 Localization of myomas in the group which became pregnant (group C)

Table 10.1 Frequency of myoma locations in the individual groups, A, B, and C

Location	Group A (all patients)	Group B (patients who answered the questionnaire)	Group C (patients who became pregnant)
Combined subserous-intramural	84	32	17
Submucous	23	6	4
Subserous	18	10	6
Intramural	15	4	2
Total	140	52	29

Third position was occupied by subserous fibroids in group A (13 %) and by submucous fibroids in group B (12 %) and group C (14 %). In all three groups, intramural fibroids were the most rarely found: group A (11 %), group B (8 %), and group C (7 %) (Table 10.1).

10.3.2 Side Effects and Symptoms

The following side effects were observed in descending frequency: bleeding abnormalities (33.3 %), tubal patency, degree 1–2 (23 %), adhesions (22 %), and intramural tubal occlusions (15 %).

In 122 patients a laparoscopic myoma enucleation was performed. In 61 % of patients the myomas were situated subserous-intramural, in 18 % submucous, in 13 % subserous, and in 8 % intramural. In 33 patients adhesiolysis was necessary prior to the myomectomy.

Figure 10.6 shows the procedures performed on the 392 patients who underwent laparoscopic surgery for infertility in 2008/2009.

10.3.3 Additional Previous Therapy for Fibroids

Figure 10.7 shows clearly that pregnancy rates increased after pretreatment and surgery.

10.3.4 Pregnancies and Deliveries

The average age of the evaluated patients was 34.6 years. Different pregnancy rates resulted depending on the localization of the fibroids. The lowest pregnancy rate was achieved after intramural fibroid resection. The resection of intramural-subserous fibroids resulted in a good pregnancy and delivery rate, and the highest pregnancy rate was achieved after submucous fibroid resection (Figs. 10.8 and 10.9).

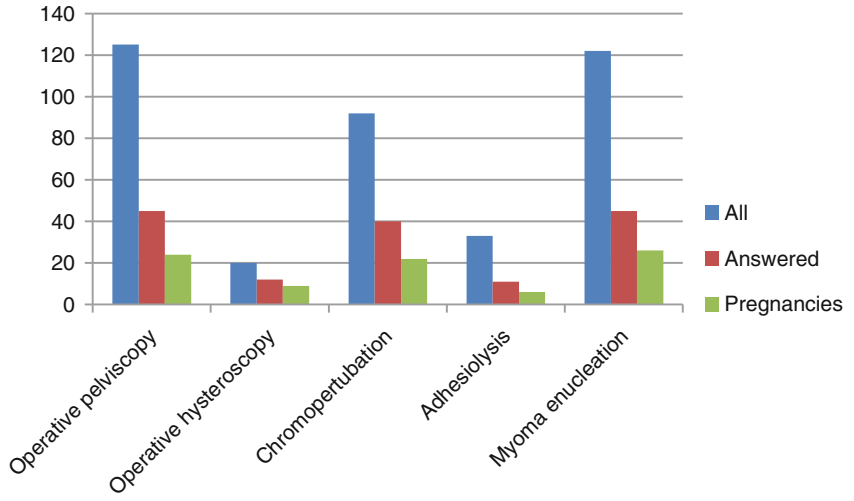

Fig. 10.6 Laparoscopic surgical procedures performed for infertility according to groups A, B, and C

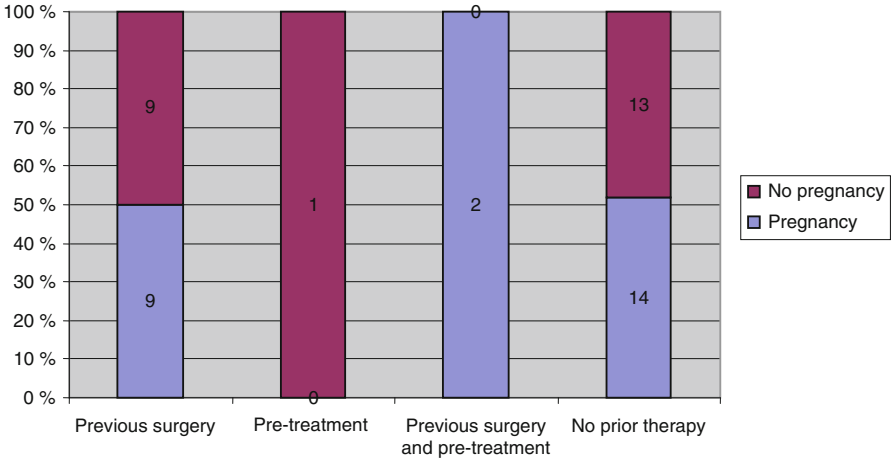

Fig. 10.7 Influence of surgery and pretreatment on pregnancy rates of patients with myomas

10.3.5 Mode of Delivery

Eleven of the 129 myomectomy patients underwent a cesarean section. Of these 129 patients, only 25 suffered from myomas alone; all others had multiple morbidities. The 14 pregnancies (56 %) which resulted in this group of 25 led to 12 deliveries (48 %), 5 (42 %) of which were spontaneous and 7 (58 %) cesarean sections. In the group of patients who underwent myomectomy for fertility problems, we had a pregnancy rate of 53 % ($n = 17$) and a delivery rate of 47 % ($n = 15$).

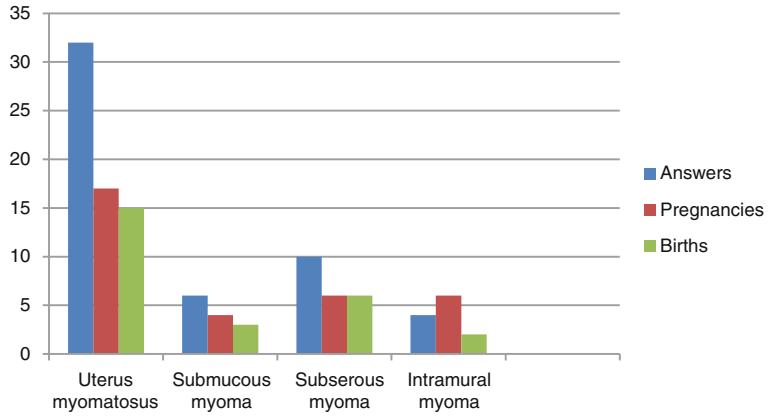

Fig. 10.8 Number of pregnancies and deliveries according to localization of myoma with display of answers

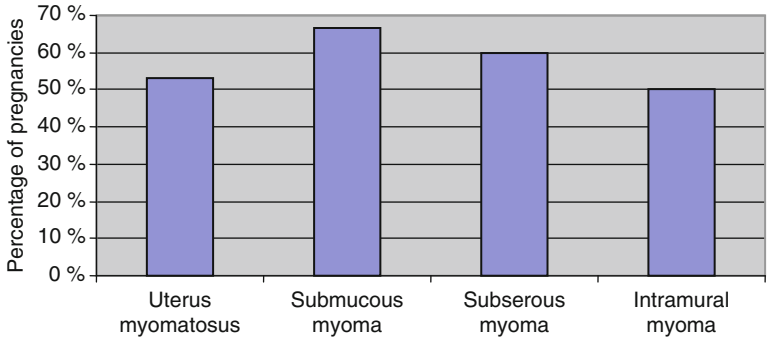

Fig. 10.9 Number of pregnancies according to myoma localization

10.3.6 Complications

Four complications occurred in the group of myomectomy patients at or after delivery: bladder descensus after delivery, placenta accrete, one uterine rupture, and one emergency cesarean section due to imminent asphyxia of the baby.

10.4 Discussion

Recent advances in endoscopic surgical techniques and the increased sophistication of surgical instruments have offered new operative methods and techniques for the gynecologic surgeon [10]. Recent years have witnessed a marked increase in the number of gynecological endoscopic procedures performed, mainly as a result of technological improvements in instrumentation. Laparoscopy has become an

integral part of gynecologic surgery for the diagnosis and treatment of abdominal and pelvic disorders of the female reproductive organs. Endoscopic reproductive surgery intended to improve fertility may include surgery on the uterus, ovaries, pelvic peritoneum, and fallopian tubes.

10.4.1 Laparoscopic Myomectomy and Pregnancy Outcome

Uterine leiomyomas are the most common benign tumors of the female reproductive tract and affect 30–40 % of reproductive-age women. Although they are seldom the sole cause of infertility, myomas have been linked to fetal wastage and premature delivery. Several elements indicate that myomas are responsible for infertility. For example, the pregnancy rate is lower in patients with myomas, and in cases of medically assisted procreation, the implantation rate is lower in patients presenting with interstitial myomas. There is other indirect evidence supporting a negative impact, including lengthy infertility before surgery (unexplained by other factors) and rapid conception after myomectomy [11]. Approximately 50 % of women who have not previously conceived become pregnant after myomectomy [12]. Because medically treated fibroids tend to grow back or recur, most fibroids that cause symptoms are managed surgically (Table 10.2).

Depending on their number and their location, myomas with mostly intracavitary development should be dealt with by hysteroscopy. Interstitial and subserosal myomas can be operated either by laparotomy or by laparoscopy. Technological advancements in endoscopic instrumentation, equipment, and the surgeon's

Table 10.2 Treatment modalities for uterine leiomyomas

Surgical treatment	Nonsurgical treatment	Hormonal treatment
Hysterectomy (laparoscopy or laparotomy)	Myoma embolization	Gonadotropin-releasing hormone agonists
Abdominal myomectomy	Magnetic resonance-guided focused ultrasound surgery	Others (mifepristone, danazol, gestrinone, raloxifene, levonorgestrel-releasing intrauterine system)
Laparoscopic myomectomy (LM)		
Laparoscopic-assisted myomectomy (LAM)		
Vaginal myomectomy (VM)		
Laparoscopic-assisted vaginal myomectomy (LAVM)		
Hysteroscopic myomectomy		
Interstitial laser photocoagulation		
Laparoscopic cryomyolysis		
Interstitial magnetic resonance imaging-guided thermo-ablation		
Interstitial magnetic resonance imaging-guided cryotherapy		
Laparoscopic uterine artery occlusion		

expertise have led to an ever-increasing number of informed women choosing the advantages of the new and innovative techniques utilizing hysteroscopy and laparoscopy. Laparoscopy is most often employed in women that are diagnosed early when their fibroids are small and more suited to laparoscopic removal. However, new surgical devices called oscillators allow the safe and efficient removal of fibroid tumors much larger than could have been accomplished in the past. It is imperative to know the size, location, and number of uterine myomas. This is especially important in a laparoscopic approach to myomectomy as tactile feedback is diminished [13].

As fertility preservation is one of the primary goals of myomectomy, the marked reduction of adhesion formation by laparoscopic myomectomy (LM) gives it a distinct advantage over laparotomy. The incidence of adhesions following laparotomic myomectomy and laparoscopic myomectomy is nearly 100 and 36–67 %, respectively [14]. These adhesions can adversely affect fertility, cause pain and small bowel obstructions, and increase the risk of ectopic pregnancy.

Dubuisson et al. studied the risk of adhesions after LM [15]. A second-look procedure was performed in 45 of 271 LM patients. Additional laparoscopic procedures were performed at the time of LM in 19 patients (42.2 %). The overall postoperative adhesion rate was 35.6 %, with 16.7 % of myomectomy sites affected. Most importantly, the adnexal adhesion rate was 24.4 % with 11.1 % bilaterally. In patients without associated laparoscopic procedures, the adhesion rates were even lower, with an overall adhesion rate of 26.9 % and an adnexal adhesion rate of only 11.5 %, none of which was bilateral. Other factors that are related with the increase in the risk of adhesions are depth (intramural and submucosal), posterior location, and suturing.

The factors responsible for prolonged surgical times in LM are the need to morcellate large or multiple fibroids for removal through the trocar and suture repair of the myometrium. Laparoscopically assisted myomectomy (LAM) where myoma enucleation is done laparoscopically or through a 5 cm Pfannenstiel minilaparotomy, following which the uterus could be exteriorized for palpation and multilayered open suturing done, has also been described [16]. This technique combines the advantages of increased exposure, visibility, and magnification provided by the laparoscope (especially for evaluation of the posterior cul-de-sac and under the ovaries) with the ease of adequate uterine repair and removal of specimen that is associated with minilaparotomy.

LAM is a safe alternative to LM and is less difficult and less time consuming. This technique can be used for large (greater than 8 cm), multiple, or deep intramural myomas. Using a combination of laparoscopy and a 2–4 cm abdominal incision, the uterine defect can be closed in three layers to reduce the risk of uterine dehiscence, fistula, and adhesion formation. Women who desire future fertility and require myomectomy for an intramural myoma may benefit from LAM to ensure proper closure of the myometrial incision. Cesarean delivery is recommended in patients who have deep intramural or multiple myomas even if the endometrial cavity is not entered. One of the concerns regarding LM has been adequate reconstruction and healing of the uterine defect with subsequent ability for the uterus to withstand the elements associated with pregnancy and labor.

Concerns have been raised regarding complications of pregnancy after LM, such as uterine dehiscence or rupture. This latter complication is rare and has been reported in women who conceive after both laparotomic myomectomy and laparoscopic myomectomy. Its real incidence remains unknown, as several reports investigating the follow-up of myomectomy failed to document any case of uterine dehiscence. Events leading to uterine scar dehiscence in subsequent pregnancies are thought to include suboptimal suturing of the uterine incision and/or impaired wound healing from extensive use of coagulation or any tissue-destroying modality. This may contribute to adjacent myometrial necrosis, thereby impairing surgical wound healing. At laparotomy, closure of the excision site is usually accomplished by a multilayered suture. With operative laparoscopy, suturing can be cumbersome and tedious, and restoration of the uterine wall integrity to an equivalent manner may be difficult.

There are no data suggesting that any one suturing technique is superior in minimizing this risk – whether continuous or interrupted sutures are placed, whether the knots are tied intracorporally or extracorporally, or whether the suturing is done by hand or a suturing device. Sutures with shorter half-lives or ones that may lose strength in the presence of infection (e.g., chronic) should most likely not be used. All in all, careful closure of the uterine incision with minimal coagulation is most critical [17]. Few cases of dehiscence following LM have been reported to have occurred during the third trimester of pregnancy [18].

Fibroids may also increase the rate of pregnancy complications during the second and third trimesters [19]. Adhesions form in >90 % of abdominal myomectomy cases. The incidence is highest with posterior uterine incisions and lower with fundal or anterior incisions. The laparoscopic approach may reduce this complication but definitive evidence is still lacking [20].

In any case, LM should be performed cautiously. Excess thermal damage should be avoided and adequate uterine repair must be assured using multiple-layer suturing.

Aside from the dehiscence case reports, few studies have evaluated the pregnancy rate after LM [14, 21–26]. Their results are summarized in Table 10.3.

Additionally, few studies [27, 28] have evaluated the effect of uterine fibroids on the pregnancy rate after assisted reproductive treatment (ART). Eldar-Geva et al.

Table 10.3 Pregnancy outcome after laparoscopic myomectomy

Author	No. of patients	Average number of myomas removed	Average size of myomas (cm)	No. of pregnancies achieved
Hasson et al. [14]	56	144 total	range 3–16	15
Dubuisson et al. [22]	21	2	6.2	7
Stringer et al. (1996)	5	2	3.6	5
Seinera et al. [24]	54	1	4.2	5
Darai et al. [25]	143	1.5	5.4	19
Nezhat et al. [21]	115	3	5.9	42
Dessolle et al. [26]	88	1.7 (range 1–4)	6.2 (range 3–11)	42

compared 106 ART cycles in patients with uterine fibroids with 318 ART cycles in age-matched patients without fibroids and concluded that implantation and pregnancy rates were significantly lower in patients with intramural or submucosal fibroids, even those with no deformation of the uterine cavity [27]. Stovall et al. showed that even after patients with submucosal fibroids are excluded, the presence of fibroids reduces the efficacy of ART [28]. Therefore, if women with unexplained infertility have a better chance of conception after myomectomy and if the main factors in treatment success are patient age and duration of infertility, this conservative operation should not be postponed for too long.

Although the indications for laparotomy and for laparoscopic surgery for myomectomy are completely different, the fertility results observed after each of these techniques are comparable. Excellent pregnancy rates are obtained for those infertile patients with no other associated factor to explain their infertility. After IVF, implantation rates are better in patients without interstitial myoma. Consequently, the goal of the myomectomy will essentially be to optimize the results of ART, rather than to hope for a spontaneous pregnancy.

10.4.2 Complications

Basically, lacerations at laparoscopic entry by Veress needle and trocar insertion as well as secondary lesions caused by different instruments may occur as vascular, bowel, bladder, ureter, or other organ lesions. They are, unfortunately, more frequent than injuries caused by the procedure itself.

At our department in Kiel in the years 1987–1991, Mecke et al. evaluated 5,035 laparoscopies and found a complication rate of 2 % [29]. In another retrospective study, Kolmorgen investigated laparoscopic complications in preoperated patients compared to patients without previous surgeries and observed a complication rate of 2.15 % among the preoperated patients compared to 1 % in patients without previous surgeries [30]. Myoma enucleations per se do not carry any higher surgical risk whether performed by laparoscopy or laparotomy [31].

Conclusions

Advances in endoscopic surgery have revolutionized our approach to gynecological surgery. Most fertility operations can be easily and effectively performed laparoscopically. The variety of conditions indicative of surgery demonstrates the importance of maintaining good surgical skills in the practice of reproductive medicine so that patients can be offered the most appropriate treatment. It appears that endoscopic surgery for infertility patients, when performed by an experienced endoscopist, is efficacious and can produce as good as or even better results than conventional procedures. Correct case selection and optimal tissue apposition with good and meticulous laparoscopic suturing are vital and the key to the success of LM. Results so far are encouraging in terms of fertility outcome after laparoscopic myomectomy (LM) in patients in whom myomata are associated with the presence of unexplained infertility.

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Effects on Sexual Function of Medical and Surgical Therapy for Endometriosis

11

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11.1 Background

Endometriosis is a chronic and progressive disease affecting 1 out of 10 women during reproductive years. Unfortunately the majority of these women has not been diagnosed and treated early. The most common complaints of women with endometriosis are pelvic pain and infertility. Pain may take the form of dysmenorrhea, deep dyspareunia (DD), chronic pelvic pain, menstrual dyschezia, or cycle-dependent dysuria. More than half of women with endometriosis experience dyspareunia during their entire life. However, DD is a heterogeneous disorder, and other conditions may overlap to endometriosis contributing to the pathogenesis of the pain during intercourse. Pelvic adhesions, pelvic congestion, pelvic inflammatory disease, and interstitial cystitis may cause DD. The relation between pain and endometriosis is not yet clearly understood.

11.2 Sexual Function

Sexual function is an important aspect of health and quality of life, likely to be influenced by medical conditions and health-care interventions, especially when gynecologic disorders are involved. Pain at intercourse is among the factors that affect sexual functioning. However, sexuality is a complex phenomenon influenced by psychosocial (personality, former experience, personal attitudes toward sexuality) as well as physiological factors affecting not only physical health but

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_11

also psychological well-being and therefore conducting to reduced sexual function. In addition, personality traits, coping capacity, degree of couple intimacy, partner emotional support, participation, solicitousness or hostility, marital adjustment, and even quality of medical information and care may greatly influence the level of perception, interpretation, and acceptance of such a multifaceted symptom [1–3]. Sexual dysfunction can be evaluated using multidimensional questionnaires including, among others, the Female Sexual Function Index (FSFI), the McCoy Female Sexuality Questionnaire, and the Sabbatsberg Sexual Self-Rating Scale.

11.3 Sexual Function and Endometriosis

Endometriosis constitutes the most frequent organic origin of DD, and women with the disease have a ninefold increase in risk of experiencing this symptom compared with the general female population of corresponding age [4]. DD is particularly upsetting because it usually occurs when intercourse is attempted, whereas dysmenorrhea and dyschezia typically afflict women for a limited number of days each month. The experience of pain and the loss of pleasure are recurrently recognized and become reinforced by repeated experiences. Pain during coital activity may be caused by traction of scarred and inelastic parametria, by pressure on endometriotic nodules, by infiltration of subperitoneal or visceral nerves, and by immobilization of posterouterine pelvic structures. In addition to these reasons for painful intercourse, women with endometriosis generally experience major exacerbation of pain when minor pressure is exerted on nodules or indurated lesions. Moreover there is evidence that the presence of endometriosis is associated with increased pain perception. This type of neuropathic pain is usually related to nerve injury or inflammatory stimuli, conditions found in deep infiltrating endometriosis (DIE) [5]. DIE is defined a form of endometriosis that penetrates for more than 5 mm under the peritoneal surface [6]. It is estimated that its incidence is around 20 % of women with endometriosis. DD is present in two-thirds of patients with DIE compared with one-half of those with peritoneal or ovarian lesions [4]. Anatomic locations of DIE seem to be associated with the prevalence of DD [7]. In particular, DD was found to be 90 % in case of uterosacral ligaments' infiltration, 42 % in case of bladder involvement, 40 % in case of adnexal adhesions, 27 % in case of bowel involvement, and 25 % in the presence of endometrioma. Among subjects with DD, those with DIE of the uterosacral ligaments or the vagina have the most severe impairment of sexual function, as assessed by both quantity and quality of sexual experience [8, 9]. This correlation can be explained by the fact that the uterosacral ligaments contain a considerable amount of nerve tissue and that neural invasion by endometriotic lesions is correlated with the severity of pain. In addition, the presence of a vaginal nodule may affect sexual function through its direct stimulation during intercourse.

Sexual problems are distressing for women as feelings of guilt, sacrifice, and resignation encourage these women having sexual intercourse even if they suffer from dyspareunia. These facts show that partner's pleasure is more important for many women than their own pleasure. On the other hand, women with dyspareunia

have lower frequency of intercourse and lower levels of desire and experience fewer orgasms. However, only limited information is available about the consequences of symptomatic endometriosis on female sexual function, especially in case of DIE. In this group of patients, sexual dysfunction seems to arise and increase during time, most probably as a result of the development of deep lesions. Fritzer et al. [10] evaluated 125 patients with dyspareunia lasting for at least 6 months. They reported a prevalence of 78 % of sexual dysfunction in women with endometriosis and almost half of them had sexual dysfunction and sexual distress simultaneously. The results of coital pain were a reduced number of episodes of sexual intercourse, interruption, and avoidance. Not surprisingly, more than half of women were afraid of pain before/during sexual intercourse. These results were confirmed by another cross-sectional study made by Jia et al. [11] which also reported a prevalence of 73 % of sexual dysfunction among 111 women with endometriosis. Authors found that pain intensity (OR 0.3) and III-IV AFS (OR 4.4) are negatively associated with sexual function. Advanced stages are often associated with development of considerable adhesions in the pelvic cavity, resulting in the immobilization of pelvic organs during coital activity. However, a case control study by Varcellini et al. [4] found little differences regarding sexual dysfunction, between the different locations of DIE. Endometriosis seems to impair all aspects of sexual life including orgasm, satisfaction, and desire, but the relationship between endometriosis and sexual dysfunction is much more complex than can be explained by anatomic distribution of lesions. No significant correlation could be demonstrated between severity of dyspareunia and sexual functioning, suggesting that that DD should be viewed in a broader clinical perspective, considering also the potential psychological and interpersonal consequences.

11.4 Endometriosis Comorbidities and Sexual Function

Depression is related with chronic pelvic pain, and there is no consensus as to which the cause is and which is the consequence. Women suffering from endometriosis present greater susceptibility to mental disorders. On the other hand, depression and anxiety also play a role in the development and chronicity of pelvic endometriosis. Although depression in women with chronic pelvic pain has been the target of many studies, it continues to be underdiagnosed. Certain factors can contribute to the development of mental disorders in women with chronic pelvic pain. Factors related to emotional suffering (socioeconomic condition, history of physical or sexual abuse, and domestic violence) and low socioeconomic level are some of them. The infertility caused by pelvic endometriosis can also contribute to the development of mental disorders. A recent study by Sepulcri and do Amaral [12] evaluated 104 patients with endometriosis and found a prevalence of 86.5 % for depressive symptoms (mild in 22.1 %, moderate in 31.7 %, and severe in 32.7 %) and 87.5 % for anxiety (minor in 24 % and major in 63.5 %). The high prevalence may be explained by the fact that women with pain and anxiety show less tolerance to pain. The intensity of pain was significantly correlated with depression and anxiety.

11.5 Effect of Surgical Endometriosis Treatment on Sexual Function

As endometriosis is a benign disorder, the main goal of treatment should be to alleviate pain and improve quality of life. In other words, the treatment should be safe and should not cause adverse events. Conservative measures, including hormonal medication, can be considered safe and harmless but unfortunately medical therapy is often ineffective, especially in DIE. Although the optimal treatment of DIE remains a matter of controversy, it is commonly accepted that surgery should aim at complete excision of all visible endometriotic lesions and adhesions. This has been shown to result in a significant reduction of pain and an improvement in the quality of life and sexual function, although data is limited [13–15]. Setälä et al. [16] evaluated the sexual function and the quality of life 12 months after radical endometriosis surgery including vaginal resection in patients with DIE. Their findings showed significant improvement in sexual functioning, which was due mainly to cessation of pain, especially dyspareunia. In addition, a recent study [17] also demonstrated a better sexual satisfaction 1 year after laparoscopic rectosigmoid resection for deep colorectal endometriosis. However surgery of DIE is difficult and challenging with a documented risk of bowel and urinary complications. Although the rate of major complications is low, these operations should be performed only after thorough consultation with the patient and consideration of the benefits and possible adverse effects. They should preferably be performed in centers specialized in advanced endometriosis surgery. In addition, further investigations are required in order to determine whether these improvements persist at long-term follow-up.

11.6 Effect of Medical Endometriosis Treatment on Sexual Function

Hormonal drugs do not cure endometriosis but only induce temporary quiescence of active foci, and as mentioned above, in many cases, surgery is the definitive solution. Hormonal treatments fail in approximately 1 woman out of 3 and are associated with a high recurrence after discontinuation. In addition they cannot be used in women seeking conception as they inhibit ovulation and may interfere with sexual desire and arousal [5]. However, some women who have already undergone non-radical interventions might prefer to avoid further surgery, and others may want to postpone reoperation or do not accept the risk of additional morbidity. Many medical therapies (vaginal danazol, intramuscular depot GnRH analogues, intrauterine/oral progestogens, estrogen-progestogen combinations, oral aromatase inhibitors) have been demonstrated to benefit women with endometriosis-associated deep dyspareunia, and different therapeutic regimens usually achieve similar pain relief as long as ovulation and menstruation are suppressed [18]. Accordingly, it seems that comparisons of safety, tolerability, and cost are more relevant than comparison of efficacy per se. In this regard, it is obvious that drugs such as GnRH analogues could relieve pain faster and to a greater extent compared with progestogens or birth

control pills [19]. However, the former drugs do not seem suitable for prolonged use, and this constitutes a major therapeutic limit in patients with long-standing chronic pain symptoms. Dienogest, a selective progestin that combines the pharmacological properties of 19-norprogestins and progesterone derivatives, seems to have equivalent efficacy to depot leuprolide acetate in relieving pain associated with endometriosis [20].

An interesting recent study by Vercellini et al. [21] showed that surgery and low-dose oral norethisterone acetate demonstrated a similar final beneficial outcome in women with endometriosis-associated deep dyspareunia in terms of improvement of sexual functioning, psychological well-being, and health-related quality of life at 1-year follow-up. However, these findings should be considered with caution owing to lack of randomization, potential between-group heterogeneity, and difference in dropout rates. Ferrero et al. [22] suggested that the best results can be obtained with surgery, followed by postoperative medical treatment. The combination of surgical and long-term adjuvant pharmacological therapy deserves further research but seems to be a promising option.

Conclusion

The interaction between endometriosis and endometriosis-associated pain is complex and DD is only a part of global sexual dysfunction. Although endometriosis is a frequent disease of reproductive age, sexual dysfunction has not yet fully investigated in this group of patients, especially in case of DIE. The high incidence of sexual dysfunction in endometriosis patients is underestimated and the long-time social consequences for her and her relationship are largely unknown. In addition psychopathology may increase endometriosis-associated pain and sexual dysfunction. Hence, it is very important that gynecologists involved in the management of endometriosis offer patients a profound conversation about their sexuality. Psychological and psychosexual counselling should be offered when dealing with these patients. Finally, surgical and medical treatments may improve sexual dysfunction, although further studies are needed.

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Part IV

Assisted Reproduction: the Endocrine Impact

In Patients with Only One or Two Oocytes, Is IVF-ET or ICSI Better?

12

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12.1 Introduction

One of the aims of assisted reproduction technologies (ART) is the recruitment of multiple follicles ensuring the recovery of good-quality oocytes upon controlled ovarian hyperstimulation (COH). In recent years, the number of patients in whom few oocytes are obtained in response to COH is increasing. This phenomenon mainly is probably related to the postponement of childbearing to the fourth decade of life. In this group of patients, multifollicular response to COH remains a challenge, but the optimisation of laboratory strategies may help to maximise their chances of pregnancy. Ovarian response to COH varies widely among patients and is strictly dependent on the size of the ovarian pool of resting follicles, the so-called ovarian reserve [1]. In women with a reduced ovarian reserve, a poor ovarian response results in a low number of retrieved oocytes despite the high dose of gonadotropins administered. Hence, although tests for predicting ovarian reserve are available [2], the parameter that best categorises a woman as a 'poor responder' remains the ovarian response itself. The incidence of poor ovarian response (POR) is estimated between 9 and 24 % [3–5]. This value increases with age [3, 5] reaching about 50 % in women over 40 years [6]. Women who respond poorly to COH have pregnancy rates that vary from 7.6 to 17.5 %, while in normal responders, they vary from 25.9 to 36.7 %. Female age plays a distinct role in predicting poor response to COH; in fact, older poor responders have lower pregnancy rates (ranging between

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*,
ISGE Series, DOI 10.1007/978-3-319-09662-9_12

1.5 and 12.7 %) compared with younger poor responders (ranging between 13.0 and 35 %) [2]. A second predicting factor of pregnancy outcome in poor responders is the degree of poor response. A lower number of retrieved oocytes results in fewer embryos to transfer and a lower chance of pregnancy, in addition to the expected negative effect of poor ovarian function on oocyte quality.

The choice of the technique of fertilisation to use in poor responder patients in the absence of male factor infertility is still the object of controversy.

It is well known that ICSI is usually preferred when a male factor exists, but often this technique is chosen even in case of non-male factor indication with the aim to avoid fertilisation failure [7, 8]. However, some recent studies suggest that the use of ICSI is not strictly necessary, and its use in the absence of indication is questionable [9–11].

Following the study by Moreno et al. [9] that demonstrated that the technique of fertilisation is not related to the reproductive outcome in poor responders, other authors have reported no differences in terms of fertilisation and good-quality embryo rates even in patients with one [10] or few oocytes inseminated [11]. In Italy, ART have been regulated since 2004 by Law n. 40/2004, until the decision n. 151/2009 of the Italian Constitutional Court that addressed the constitutional legitimacy of several provisions of Law n. 40. One of the crucial points of Law n. 40 was that no more than three oocytes could be inseminated, in order to prevent the formation of unnecessary embryos. All the developed embryos must be transferred into the uterus, and embryo cryopreservation was not allowed. As a result, many Italian clinics began to perform ICSI even when sperm quality was suitable for conventional IVF [11].

Natural selection of the fertilising sperm resulting from conventional IVF may improve reproductive success in poor responder patients with favourable semen quality. As a consequence, we recently compared reproductive outcomes following conventional IVF or ICSI in patients in whom only one or two oocytes were retrieved at ovarian pickup by taking into account the impact of reproductive ageing [12].

12.2 Our Study

In our recent study, we retrospectively analysed a total of 425 cycles (386 patients) attending ART at the Centre of Infertility and Assisted Reproduction of the Department of Clinical and Experimental Medicine of Pisa University between January 2007 and July 2012. Patients were all poor responders [6] and were included in the study when only one or two oocytes were retrieved during ovarian pickup and male factor infertility was absent. Patients were all aged between 27 and 47 years (mean age 38.23 years ±3.82 SD).

We divided the cycles into two groups on the basis of the technique used. IVF and ICSI groups were furthermore divided in three subgroups based on the age of women (<35 years, 35–38 years, >38 years), whose results were also compared. Patients underwent a standard controlled ovarian hyperstimulation (COH) with 150–450 UI/day of recombinant FSH and a GnRH antagonist according to basal

FSH and AMH levels and age. The fertilisation technique was chosen on the basis of the clinical history of patients and reproductive outcomes in previous ART cycles. As a result, we observed that fertilisation rate, cleavage rate and good-quality embryo rate did not differ between IVF and ICSI group when these were not divided by age, while for what concerns implantation rate (13.05 vs. 5.26 %) and pregnancy rates (PRs) (16.12 vs. 6.73 %), IVF was found to be more advantageous with a level of significance of $p=0.003$ and $p=0.003$, respectively.

In patients under 35 years old, we did not observe any differences in fertilisation rate, cleavage rate and good-quality embryo rate between IVF and ICSI group, while we found that IVF was more advantageous for what concerns implantation rate (25.92 vs. 3.70 %; $p=0.002$) and PRs (32.55 vs. 4.76 %; $p=0.001$). Although miscarriage rate was higher in the IVF group, this difference was not significant.

Even in patients aged between 35 and 38 years old, we did not find any significant difference in fertilisation rate, cleavage rate and good-quality embryo rate, while implantation rate and PRs were 20 % vs. 6.34 % ($p=0.025$) and 26.31 % vs. 7.01 % ($p=0.010$), respectively. Even in this subgroup, despite a greater percentage of miscarriage in the IVF group, this difference was not significant.

In patients over 38 years old, there were no significant differences in fertilisation rate, cleavage rate and good-quality embryo rate, but in the ICSI group, the percentage of cycle cancelled, due to fertilisation failure or cleavage failure, was significantly higher compared to the IVF group (21.1 % vs. 10.2 %; $p=0.27$). In this subgroup of patients, we did not find any differences for what concerns implantation, pregnancy and miscarriage rate.

12.3 Discussion

The question whether the choice of fertilisation procedure may be relevant to reproductive success in poor responder patients is still debated, and clear knowledge of both short- and long-term differences between IVF and ICSI fertilisation is still lacking. Although ICSI was originally indicated for treating couples with severe male factor infertility [13], in recent years some studies suggested that it could provide similar or higher fertilisation rates [14–16] and better embryo quality even in non-male factor couples [17]. Results from our recent study strongly question the superiority of ICSI over conventional IVF in patients with non-male factor infertility and lead us to hypothesise that under specific conditions, ICSI could negatively affect reproductive potential. In 1998, Moreno et al. [9] analyse 96 couples with six or fewer retrieved oocytes and observed that IVF and ICSI in the absence of male infertility factor produce the same results. The same hypothesis was proposed again by other authors [18, 10, 19]. On the other hand, our results are in contrast with Khamsi et al. [17] who observed that ICSI procedure increased fertilisation rate and good-quality embryo rate even in the absence of male factor infertility. In our study we show that on cohorts of poor responder patients with different reproductive age, the use of ICSI decreases reproductive potential in women below 35 years or aged between 35 and 38 years. Although we found no significant differences

in fertilisation and cleavage rates in these subgroups of patients, IVF was significantly more advantageous than ICSI for what concerns implantation and PRs. Our results partially agree with those by Fang et al. [20] who retrospectively compared 196 couples undergoing IVF/ICSI cycles with one or two retrieved oocytes with good-prognosis sperm. They found that ICSI patients had higher fertilisation rates although no difference in good-quality embryo rate or PR was noted. The discrepancy between this study and our findings in relation to fertilisation outcome may be ascribed to differences in the size of the cohorts enrolled in the two studies. In fact, our results are consistent with those by Xi et al. (2012) who retrospectively analysed 406 cycles with three or fewer oocytes retrieved from women with similar age undergoing IVF (34.5 ± 4.6 years) or ICSI (36.1 ± 5.5 years) and noted that the PRs and implantation rate were lower in the ICSI group compared with the IVF group [21]. Xi explained the higher PRs and implantation rate after IVF with the lack of 'natural sperm selection' when most steps of the fertilisation process are bypassed by sperm injection. In conventional IVF, upon laboratory selection of motile sperm, the sperm which fertilises is further selected through the biological process of sperm–oocyte interaction beginning at the zona pellucida level (ZP) or during sperm penetration through the cumulus matrix [22]. Indeed, the finding that the majority of sperm (average >92 %) bound to the ZP have normal nuclear chromatin DNA strongly suggests that scientist-selected sperm may have a lower quality compared to ZP-bound sperm [23]. Moreover, increased knowledge in the biology of fertilisation process has revealed that sperm–oocyte interaction at the membrane level involves numerous molecular actors with a possible role in sperm fusion and gamete selection [22]. These mechanisms may also act against sperm carrying chromosomal anomaly from paternal origin as well as against chromosomally abnormal oocytes, avoiding the generation of developmentally defective embryos that could lead to pregnancy failure or miscarriage [21, 24]. In addition, decreased chances for successful fertilisation and pregnancy could result from the possible mechanical damage to the oocyte after ICSI [25] as well as the introduction of foreign material such as culture medium or exogenous DNA and infectious material [26]. Finally, our results in reproductively young women can be well explained by considering the relevance of early events of oocyte activation in promoting successful implantation. These include the sperm-induced calcium signal that drives meiosis resumption and embryo development, as well as implantation and postimplantation events, through a specific spatiotemporal pattern of Ca2+ oscillation [27]. Beyond the delivery of sperm DNA, the main reason for ICSI to succeed is that it allows the delivery of PLCz, the sperm component that is capable of generating the fertilisation calcium signal upon sperm fusion [28]. Nevertheless, the finding that abnormal calcium signals were observed in oocytes following ICSI [29, 30] suggests that missing gamete interaction at the surface level in ICSI fertilisation would result in missing or abnormal signalling pathways with a role in subsequent embryonic development. An additional factor with a negative influence on reproductive outcome is ICSI-related risk of parthenogenetic activation caused by oocyte manipulation [31–33]. This may cause asynchrony between the timing of oocyte activation and

sperm injection leading to cleavage abnormalities and early embryonic arrest [25]. Our finding that reproductive outcome in patients aged over 38 years undergoing IVF or ICSI was comparable for all parameters analysed strongly indicates that the advantage of IVF over ICSI tends to disappear with the increasing of age. This result can be ascribed to the phenomenon of ovarian ageing responsible for the production of oocytes with a reduced developmental competence related to defective molecular storage, mitochondrial dysfunctions and poor control of chromosome segregation during meiosis [34, 35]. These defects represent a reliable reason why aged oocytes do not benefit from fertilisation mechanisms preserved in IVF and lost in ICSI. Nevertheless, a further reason could be found in the low activation competence of aged oocytes suggested by the observation of abnormal signalling upon exposure to parthenogenetic agents [36].

Conclusions

The main goal of reproductive medicine is to apply the simplest, cheapest, and least invasive method to ensure a positive outcome. We suggest that obtaining one or two oocytes in one cycle is not an indication for ICSI when the sperm sample is apparently normal. However, a relevant factor to the choice of IVF technique under these conditions is represented by female age. Despite the effects of a low ovarian reserve, oocytes from young poor responder patients can still benefit from the advantage of IVF probably counting on biological resources definitively lost with ageing. We suggest that IVF could be used as a technique of choice in young poor responder patients in the absence of male factor infertility. Surely, a limit of our study is to be a retrospective study, and only further randomised trials will be able to confirm our results. We conclude that in addition to the optimisation of stimulation regimens, further biological knowledge of IVF techniques will be helpful in tailoring the best ART to individual patients in order to give infertile couples the best chance of conceiving a healthy baby.

Declaration of Interest The authors report no declaration of interest.

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Supplementation with DHEA in Poor Responder Patients

13

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13.1 Introduction

Poor response to ovarian stimulation (POR) usually indicates a reduction in follicular response to ovarian stimulation during in vitro fertilization (IVF) cycles resulting in a reduced number of retrieved oocytes. In recent years, mainly due to the postponement of childbearing and the consequent decrease of ovarian reserve, often a POR occurs during IVF despite the high dose of gonadotropins administered. Incidence of POR has been reported from 9 to 24 % [1, 2], and even if this condition may occur unexpectedly, its prevalence increases with age, and it is >50 % in patients over 40 years [3]. Patients with POR are defined as *poor responders*.

In March 2010, the European Society of Human Reproduction and Embryology (ESHRE) established the criteria for POR diagnosis. Until that, in fact, there was not a uniform definition and the term POR indicated heterogeneous groups of patients. The ESHRE established that at least two of the following three features must be present, in order to diagnose POR:

1. Advanced maternal age (≥40 years) or any other risk factor for POR
2. Previous POR (<3 oocytes) with a conventional stimulation protocol
3. Abnormal ovarian reserve test (ORT) (i.e., AFC <5–7 follicles or AMH <0.5–1.1 ng/ml)

Two episodes of POR after maximal stimulation are sufficient to define a patient as a "poor responder" without advanced maternal age or abnormal ORT. In the case

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_13

of women over 40 years with an abnormal ORT, we are allowed to talk about "expected POR" [3].

Poor responders remain a challenging group of patients to manage in an IVF program. Despite that in literature there are several publications about poor ovarian response, there is not enough evidence to support the use of any particular protocol in poor responder patients.

13.2 Ovarian Reserve Assessment for Fertility Management

Age and day 3 levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) have been used as indicators of ovarian response to ART for several years. The basal FSH concentration is the most common test used for ovarian screening [4]. However, it has been reported that the increase in FSH levels occurs late in the sequence of events associated with ovarian aging [5]; hence, this increase may be of limited clinical use as a marker [6].

Several studies reported the efficiency of antral follicle count (AFC) and ovarian volume in predicting ovarian response to ovarian stimulation [7]. Ovarian antral follicles larger than 2 mm are extremely sensitive and responsive to FSH and are defined as "recruitable." They can be visualized and measured with transvaginal ultrasound, and the total number of 2–10 mm follicles in both the ovaries represents the AFC [8, 9].

A new endocrine marker, anti-Müllerian hormone (AMH), was evaluated by several study groups as a marker of ovarian response. In women, AMH is produced in the ovary by the granulosa cells surrounding preantral and small antral follicles [10, 11]. AMH expression in ovaries has been observed as early as 36 weeks of gestation in humans [12], is barely detectable in the serum at birth, and increases after puberty [12, 13]. AMH expression declines with advancing female age, to become undetectable again at the time of the menopause [14]. The correlation between AMH levels and the number of antral follicles measured by ultrasound is well established [15–17]. Therefore, AMH levels are believed to be the best representation of the gradual decline in reproductive capacity in women [18, 19], and AMH has been shown to be an accurate marker for the occurrence of poor response to ovarian hyperstimulation with gonadotropins in IVF [16, 20–22]. AMH and AFC are nowadays considered two markers with similar diagnostic performance [23, 24].

13.3 Management of Infertility

Management of poor responder patients is challenging for fertility experts. Women with POR retrieve less oocytes and have less embryos for transfer, and their chances of pregnancy are obviously lower. Frequently, their cycles have to be cancelled because of the absence of follicular development, the lack of oocytes retrieved, or the failure to develop embryos [1, 3, 25, 26]. Poor responder patients can be treated in various ways, either by trying stimulation protocols using high doses of

gonadotropins associated with different dosages and timing of GnRH analogs or antagonists or by trying IVF in a natural cycle or with minimal stimulation. Several studies finally suggested the supplementation with hormones like growth hormone, estradiol, androgens, and dehydroepiandrosterone.

13.4 Physiology of DHEA

Dehydroepiandrosterone (DHEA) is a weak androgen produced by the conversion of cholesterol by the adrenal cortex, the central nervous system, and the ovarian theca cells and is converted mainly in peripheral tissue to more active forms of androgen or estrogen [27]. DHEA is abundant during female reproductive life and progressively declines by approximately 2 % per year [28]. This has led some authors to hypothesize that DHEA supplementation may slow down the aging process [29]. Even after 70 years of research, the physiology of DHEA is not fully understood.

DHEA beneficial effects increase over time, and best results are obtained after 4–5 months of supplementation with 75 mg of micronized DHEA daily, a time period similar to the complete follicular recruitment cycle [30]. Numerous hypotheses have been made on how DHEA promotes fertility. Besides serving as an essential prohormone in ovarian follicular steroidogenesis, facilitating follicular function and growth [31, 32], DHEA seems to increase follicular insulin-like growth factor-I (IGF-I) concentrations by ≅150 %, probably independent of changes in GH secretion [33, 34]. This may indicate that DHEA stimulates hepatic and end-organ IGF-1 response to GH, which can promote the gonadotropin effect. In animal models, DHEA has also shown to promote a polycystic environment in the ovaries, with promotion of antral follicle growth, increased levels of active oocytes, and decreased atretic effects [33, 35–37]. Androgens, long considered antagonist of normal follicle recruitment and development, thus assume a crucial role in female fertility: some reports demonstrated that androgens act on folliculogenesis by increasing the number of FSH receptors expressed in the granulosa cells [38]. On the other hand, the addition of androgens in COH is thought to have a positive role in follicular recruitment and granulosa cell proliferation [39]. Moreover, studies have shown the beneficial effect of DHEA administration on vascular function. In fact, DHEA increases vascular endothelial proliferation, migration, and vascular tube formation. DHEA also promotes nitric oxide synthesis, at physiological levels, in intact vascular endothelial cells, inducing vasodilatation [40]. This effect can be very important for vascular function also in the female reproductive system, considering that ovarian folliculogenesis is accompanied by a very finely regulated angiogenesis.

VEGF *(vascular endothelial growth factor)* is a molecule produced by follicular granulose and ovarian thecal cells in response to gonadotropin stimulation [41]. Indeed, VEGF is implied in endothelial sprouting, enhanced vascular permeability, expression of tissue matrix metalloproteinases and finally in the digestion of matrix, required for the endothelial cells to move [42]. Among its function, VEGF has the role of primary mediator for the formation of a vascular network in the thecal cell layer of the follicle [42, 43].

Van Blerkom et al. [44] observed higher VEGF levels in follicles with higher dissolved oxygen contents and with increased blood flow observed at Doppler, but they failed to find a specific association between follicular VEGF levels and the presumed extent of perifollicular vascularization. A similar conclusion was obtained by Barroso et al. and Battaglia et al., even if FF (*follicular fluids*) levels of VEGF in poor responder patients were found higher than in normo-responders [45, 46]. Besides, Kan and associates more recently did not show any difference in FF VEGF concentrations among poor responders with and without high-grade perifollicular vascularity [47].

As a consequence, other angiogenic factors might be involved in the process of cellular reaction to hypoxia, acting synergistically or additionally with VEGF, and actually follicular oxygen content seems not to be predictable only by US. Transcriptional upregulation of VEGF is stimulated by HIF1 (*hypoxic-inducible factor 1*), during cellular adaptation to hypoxia. HIF1 is a transcription factor sensible to low oxygen tension, which prevents fatal depletion of oxygen and subsequent cell death. As a consequence, FF concentrations of this factor are linked by an inverse correlation with the available oxygen, being involved in a certain way in the determination of oocyte developmental competence.

13.5 Therapy with DHEA

Casson and associates, in 2000, firstly suggested an improvement of ovarian function in patients with reduced ovarian reserve from supplementation with DHEA [48]. In their study, they presented young women with unexplained infertility and FSH levels <20 mIU/ml treated with a dose of 80 mg of DHEA daily for 2 months. They did not observe any significant improvements of pregnancy rates, but E2 levels were tripled in all women, and the number of follicles retrieved was doubled. Few years later, Barad and Gleicher published a case-control study in which 25 women were evaluated in their respective IVF cycle outcomes pre- and posttreatment with DHEA, with the same ovarian protocol stimulation [30]. The supplementation was well tolerated by all patients, demonstrating higher number of fertilized oocytes, transferred embryos, and embryo score per oocyte, besides improved oocytes and embryo quality.

In 2007, Barad and Gleicher published a case-control study on 190 women aged more than 30 with poor ovarian response, treated with the same stimulation protocol [37]. Study group used supplementation with 25 mg DHEA three times daily for up to 4 months, while the control group underwent infertility treatment but without DHEA. In the DHEA group, they observed a lower cancellation rate, even if not statistically significant, and a better clinical pregnancy rate (PR), in respect to the control group, despite prognostically more favorable controls and higher mean age in the DHEA group. The miscarriage rate per clinical pregnancy was also found lower in the study group, but these data were not statistically significant.

In 2007 in a small pilot study, the same authors presented 8 patients with premature ovarian aging (POA), who received DHEA for at least 1 month (study group),

and 19 women with POA who were not treated with DHEA (control group). The study group demonstrated that DHEA may reduce aneuploidy, but unfortunately, the small number of patients in the study awarded to it an insufficient statistical power [49].

This result was confirmed by the study of the same authors published in 2010, where they concluded that the beneficial effects of DHEA supplementation on miscarriage rates were, at least partially, the likely consequence of lower embryo aneuploidy [50].

An interesting study conducted by Gleicher and collaborators in 2009 reported a significantly decreased miscarriage rate after DHEA supplementation, as opposed to total miscarriage rate in the national US registry, that was attributed by the authors to diminished aneuploid embryo rates, as aneuploidy is a consequence of ovarian aging [51].

A study by Mamas and Mamas, in 2009 [31], presented really interesting results: five premature ovarian failure (POF) patients conceived after at least 2 months of DHEA supplementation, which led to regular periods and decreased serum FSH concentrations and increased serum estradiol concentrations.

In the same year, Sonmezer and associates compared the result of a second cycle of 19 patients treated with DHEA 25 mg t.i.d. with the parameters of the previous, failed, cycle of stimulation. They noted a statistically significant improvement in the number of follicles >17 mm recruited, oocytes retrieved, and MII oocytes and a better quality of embryos. Furthermore, there was a statistically significant improvement in pregnancy rate per patient and per transferred embryo, clinical pregnancies, and implantation rate.

Wiser and associates most recently published the first randomized, prospective, controlled study of supplementation with 75 mg of DHEA orally once a day, at least 6 weeks before starting the first IVF cycle. DHEA patients showed significantly higher live birth rates [52].

In our study [53], published in 2012, we analyzed the effect of DHEA supplementation on follicular microenvironment and on in vitro fertilization (IVF) outcomes among 24 poor responder patients. One group received 25 mg/die of DHEA three times daily for 3 months previous to IVF cycle, while the other group did not receive any treatment. In both groups, we evaluated perifollicular vascularization of recruited follicles through power Doppler blood flow analysis, and follicles were graded as described by Chui et al., according to the percentage of follicular circumference in which most flow was identified from a single cross-sectional slice [54]. The grading system was as follows: <25 % follicular circumference in which blood flow was identified (F1), 26–50 % (F2), 51–75 % (F3), and 76–100 % (F4). Follicular fluids (FF) from F3 to F4 follicles were collected, and FF levels of vascular endothelial growth factor (VEGF) and hypoxic-inducible factor 1 (HIF1) were measured. Results showed that FF levels of HIF1 were statistically significantly lower in women treated with DHEA (14.76 ± 51.13 vs. 270.03 ± 262.18 pg/ml; $p = 0.002$). On the contrary, VEGF levels did not differ between the two groups. Concerning COH, in the DHEA group, the mean duration of treatment was significantly shorter (9.83 ± 1.85 vs. 12.09 ± 2.81; $p = 0.023$).

Total numbers of oocytes retrieved, fertilized oocytes, good-quality embryos, transferred embryos, and clinical pregnancies tended to be higher in study group, but the results were not significant. On the other hand, considering the oocytes retrieved in selected F3–F4 follicles, there was a relation between HIF1 levels and oocyte quality. In fact, mature oocytes retrieved in selected follicles were significantly more numerous in the DHEA group (0.50 ± 0.52 vs. 0.08 ± 0.29; $p = 0.018$). Therefore, our data show that DHEA supplementation in poor responder patients can improve the perifollicular vascularization, enhancing oxygen levels in follicular fluid, which is important in order to develop oocytes and embryo of good quality. Thus, the improvement of reproductive parameters after DHEA supplementation in poor responder patients could be explained through the effect that this prohormone has on follicular microenvironment.

Recently, Fusi and associates described unexpected spontaneous pregnancies in poor responder patients with long-term infertility, treated with DHEA supplementation prior to IVF. They analyzed two groups of women. The first group included 39 young women with <40 years all treated with DHEA because of a previous poor response. The second group included 38 women over 40 years who received DHEA supplementation. Controls for the latter group were 24 comparable women who had not been treated with DHEA before the first IVF cycle to evaluate the spontaneous pregnancy rate during preparation to IVF. Three tablets daily of 25 mg micronized DHEA were administered for at least 12 weeks before starting a long stimulation protocol for IVF. Surprisingly, they observed 10 spontaneous pregnancies and 9 spontaneous ongoing pregnancies among young poor responders. Pregnancy rate and ongoing pregnancy rate obtained before starting the IVF cycle were also significantly higher in older women treated with DHEA than in the control group: 21.05 and 13.15 and 4.1 % and 0, respectively [55].

Conclusions

In conclusion, despite the need of more strong data from good-quality randomized controlled trials (RCTs) with relevant outcomes and follow-up [26], it seems clear that DHEA represents a promising option for the treatment of a large number of women who are really challenging for IVF specialists. In addition to the possible benefits in terms of increase of reproductive parameters, DHEA offers the possibility to choose a milder and more cost-effective hormonal protocol. Without supplementation with DHEA, specialists would be forced to use heavy hormonal doses, with minimal response or, as the last resort, egg donation [56].

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Premature Ovarian Failure: Fertility Challenge

14

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Premature ovarian insufficiency (POI) (also known as premature menopause) is a heterogeneous disorder of multifactorial origin defined as the occurrence of secondary amenorrhoea, hypergonadotropism (follicle-stimulating hormone above 40 IU/L) and hypoestrogenism (oestradiol below 50 pmol/L) in women under the age of 40 years.

Number of total follicle count during gestation decreases from seven million during the 20th week to 300,000 during puberty. In the climacterium the expected number of follicles is 1,000. A possible mechanism of the origin of premature ovarian failure can be decreased number of primordial follicles due to atresia or altered follicle maturation. The decline in the ability to repair DNA double-strand damages by homologous recombinant repair during meiosis, due to decline in repair genes BRCA1, MRE11, Rad51 and ATM, leads to the accumulation of these damages that contribute to the depletion of the ovarian reserve.

Women with POI have 5–15 % chance of spontaneous conceiving at sometime after confirming diagnosis. Therefore it is essential to find if women wish to become pregnant or not. After initiating oestroprogestagen therapy follicle growth is possible and pregnancy can happen [1].

14.1 Ovarian Reserve Test

A number of ovarian reserve tests have been designed to determine ovarian reserve and quality [2].

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_14

These include early follicular phase (day 2 or 3) blood levels of FSH, luteinizing hormone (LH), oestradiol, antimullerian hormone (AMH) and inhibin B. Total ovarian volume and follicle count can be measured by ultrasound. There are four grades of ovarian insufficiency depending on FSH levels. Levels of FSH between 10 and 15 IU/L represent and FSH over 40 IU/L represents 4th grade of the ovarian insufficiency.

14.2 Oestradiol

The first-line therapy is a trial with oestradiol replacement with close monitoring of the ovulation.

Exogenous oestrogens could act by sensitizing and differentiating granulosa cells. They downregulate FSH and LH receptors and increase response of FSH and number of LH receptors previously induced by FSH. They lower LH and prevent premature luteinizing of the follicle. The study of Taylor et al. [3] has shown that 46 % of patients ovulate at least once during the first 12 months of oestradiol therapy. Oestradiol stimulates endometrial proliferation and production of cervical mucus.

Suggested doses are twice as high as recommended doses in the menopause. Transdermal dose of oestradiol is 100–150 ug, conjugated equine oestrones 1.25 mg and oestradiol 2–4 mg orally. Micronized progesterone in a dose of 200 mg per day or medroxyprogesterone 10 mg is advised 10 days in the luteal phase.

14.3 Oestradiol and Autoimmune POI

Oestradiol decreases activated T lymphocytes and enhances autoimmune activation of effector helper T lymphocytes and macrophages. It facilitates the maturation of pathogenic autoreactive B lymphocyte cells and diminishes the production of potentially protective B cells [4].

Blumenfeld et al. [5] performed induction of ovulation with GnRH agonist, relatively high doses of gonadotrophins and small doses of glucocorticoids. The goal of this treatment is lowering the high endogenous FSH, which is ineffective in stimulating folliculogenesis and possibly ameliorating the downregulation or desensitization of diminished FSH receptors. Release of the few FSH receptors may diminish the autoimmune process and possibly lowers the levels of the activity of these antibodies. Correnblum et al. [6] suggested prednisone 4 × 25 mg 4 weeks for ovulation induction in cases with the autoimmune cause of premature ovarian insufficiency. But corticosteroid therapy is not indicated generally in clinical practice due to a risk for osteonecrosis. No prospective randomized studies have unequivocally validated the efficiency of this combination.

14.4 Ovulation Induction Protocols

The pregnancy rate depends not only on the ovarian reserve but also on the type of infertility, the cycle number and uterus characteristics [7].

Table 14.1 Protocols for ovulation induction in premature ovarian insufficiency

Oestroprogestogens	Aspirin
Gonadotrophins	Nitric oxide
Clomiphene citrate	Prednisone
Aromatase inhibitors	Plasmapheresis
GnRH agonists	Pentoxifylline-tocopherol
GnRH antagonists	Apoptotic inhibitor
Recombinant LH	Sphyngosine-1-phosphate
Recombinant growth hormone	DHEA

Table 14.2 Other approaches to pregnancy in POI

Donor oocyte
Embryo freezing
Freezing of mature eggs
Cryopreservation and tissue transplantation
Vitrification
In vitro activation

Natural cycle or cycle modified with oestroprogestagens represents the method of choice nowadays with 5–15 % of success resulting in pregnancy.

Loutradis et al. [8] found that low-dose human chorionic gonadotrophin in the first days of the ovarian stimulation had promising results in grade I POI.

Oocytes of women with diminished ovarian reserve are prone to a high rate of meiosis errors leading to a high rate of aneuploidy [9].

It was found that GnRH does not improve the successful ovulation induction with exogenous gonadotrophins. van Kesteren et al. [10] gave 4 weeks intranasal buserelin 1,000 ug daily or placebo, the 3-week human menopausal gonadotrophin in weekly augmented dose, but no difference in pregnancy rate was found. Gonadotrophin therapy carries a theoretical risk for exacerbating autoimmune POI.

Dehydroepiandrosterone (DHEA) is converted to oestradiol which suppresses FSH. Increasing of the testosterone production by the very early follicles stimulates androgen receptors allowing more preantral follicles to progress to more mature antral follicles [11].

In a case of failure of all mentioned protocols, some new therapeutical options can be performed.

14.5 Modern Technique for Ovulation Induction in POI

Donor oocytes can be advised to a woman with POI failing to conceive under oestroprogestogens previously and with well-prepared endometrium (Table 14.2).

Cryopreservation is freezing of tissue or cells in order to preserve for the future [12]. Methods can be slow freezing or vitrification (ultrarapid freezing).

Vitrification is a process of converting something into a glasslike solid that is free of crystal form. By adding a cryoprotectant, water can be cooled until it hardens like

glass without crystal formatting. It is important because ice crystal formate can damage frozen embryo.

Ovarian tissue cryopreservation can be performed in prepubertal girls at risk for POI, and this procedure is as feasible and safe as comparable operative procedures in children [13].

Ovary transplantation can be done with fresh cortical ovarian tissue transplantation, frozen cortical ovarian transplantation or whole ovary transplantation.

In vitro activation (IVA) requires ovaries to be removed from a woman, treated outside the body, then reimplanted near the fallopian tubes. The woman is then treated with hormones to stimulate the growth of specialized structures in ovaries called follin. These women still have very tiny primordial, primary and secondary follicles and may be treatable.

PTEN is a gene that encodes for a protein involved in several critical signalling pathways inside cells including metabolism, growth and survival. It controls follicular growth. Blocking the activity of PTEN in mouse and human ovary was enough to stir dominant follicles into growth and production of mature eggs. Ovaries can be treated with substances modulating the PTEN pathway.

Hippo pathway is another pathway for ovulation induction. Cutting ovaries into pieces disrupts a growth arrest pathway called Hippo. Hippo signalling modulates the growth of many organs. In the ovary the hippo pathway appears to ensure that only a few follicles at a time are growing.

Kawamura et al. [14] removed ovaries and ovaries from their patients and fragmented them to disrupt the Hippo pathway. Drug treatment was given to stimulate the Akt signalling pathway. After grafting the ovary tissue back to the patient, they found rapid follicular growth leading to increased expression of downstream growth factors.

Adult ovaries possess rare numbers of oogonial stem cells that can stably proliferate for months and produce mature oocytes in vitro. Injection of labelled ovarian stem cells into mouse ovaries leads to differentiation of these cells into mature oocytes that are ovulated, fertilize and generate viable neonates [15].

Intraovarian environment is important for differentiation to mature normal oocytes. However, the clinical utility of these cells for treatment requires more evidence to confirm their safety, especially the effects from epigenetic changes during in vitro culture.

It is necessary to provide the optimal therapeutic regimen, individually determined for women wanting pregnancy with premature ovarian insufficiency before oocyte donor programme. Decreasing gonadotrophin levels to the physiological range before embarking on any treatment is the most important.

Multicultural, randomized placebo-controlled trials should be carried out in the future. This may standardize the treatment of women with premature ovarian insufficiency who wish to conceive and ultimately have their biological child.

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Part V

Metabolic Syndrome

Endocrine and Metabolic Disorders in Aging Women

15

Diana Jędrzejuk, Andrzej Milewicz, Anna Arkowska, Urszula Mieszczanowicz, Jerzy Chudek, and Tomasz Zdrojewski

15.1 Introduction

Aging in women is associated with several hormonal and metabolic disorders. Sex hormone transformation in aging women is associated with fat distribution changes caused by insulin resistance and atherogenic lipids profile. Cardiovascular diseases (CVD) are the most common reason for mortality in women over 50 years of age. Several predictors can be recommended to recognize the risk of CVD such as body mass index (BMI) >30.0 kg/m^2, waist circumference over 80 cm for women and 94 cm for men, serum fasting glucose >100.0 mg% (5.6 mmol/l), serum triglycerides >150.0 mg% (1.7 mmol/l), serum high-density lipoprotein (HDL) cholesterol <50.0 mg% (1.1 mmol/l) for women and <40.0 mg% (0.9 mmol/l) for men, and hypertension >130/85 mmHg [1].

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*,
ISGE Series, DOI 10.1007/978-3-319-09662-9_15

15.2 Materials and Methods

The assumptions of the PolSenior study was described in detail elsewhere [2]. This study included subjects randomly selected out of 15.574 from the whole of Poland. A total of 1.971 women and 2.087 men aged 50–100 years old were studied. Anthropometric parameters (BMI, waist circumference), fasting glucose and homeostatic model assessment (HOMA), fasting triglycerides and HDL cholesterol were estimated using standard methods. Serum insulin, estradiol, testosterone, sex hormone-binding globulin (SHGB) were evaluated using radioimmunoassay (RIA) methods and the free androgen index (FAI) and the free estradiol index (FEI) were calculated.

15.3 Aim

The aim of the study was to answer questions:

1. What is the frequency of CVD predictors in aging Polish women?
2. How do the sex hormones levels correlate with CVD predictors in aging women?
3. How is endogenous vitamin D concentration related to CVD predictors in women?
4. What is the thyroid function in aging women?

15.4 Frequency of CVD Predictors in Aging Polish Women

Among the women participating in the PolSenior study the frequency of obesity was 39 % (overweight – 36 %). It is very difficult to compare this result with those of the rest of Europe because of the various methods of measurements and geographical and race differentiation (≥30 % according to a WHO report [3]). In our study obesity was most common among women between 65 and 74 years old (41 %). We also diagnosed malnutrition; the highest frequency (4.8 %) was detected among women over 90 years of age. There was a very large group of women with abdominal obesity – metabolic obesity with a waist circumference above 80 cm (86 %). On the other hand, serum fasting glucose above 100 mg% was detected only in 36 % of women. A more accurate measurement indicating glucose intolerance (HOMA) was calculated and 43 % of participating women had abnormal results. Lipid disturbances were also frequent; serum HDL cholesterol below 50 mg% was measured in 44 %, and serum triglycerides above 150 mg% in 30 % of aging women. The frequency of ideal metabolic women (the women met all the IDF Consensus Berlin criteria) was 8.8 %. These criteria are strongly connected with CVD morbidity. However, the correlation ($p = 0.002$) between age and BMI is negative (which can be concluded from the results described above). The correlation between age and serum HDL cholesterol is also negative and statistically significant ($p = 0.012$), which indicated the great influence of aging on increasing CVD risk factors.

We conclude that the frequency of obesity in Polish aging women (39 %) is higher in comparison to Europe (30 %) and the USA (33 %). Aging has a significantly negative influence on BMI and serum HDL cholesterol levels in women.

15.5 Sex Hormone Levels Correlate with CVD Predictors in Aging Women

Serum estradiol in aging, postmenopausal women is very low (most commonly less than 20–30 pg/ml). The increase in CVD risk factors after the menopause is often connected to lowering estradiol concentrations. In our results estradiol and FEI play an important negative role in aging women. The statistically significant positive correlations between estradiol and FEI were found with BMI, waist circumference, serum triglycerides, glucose, and HOMA, and the negative with HDL cholesterol. The relationship between serum estradiol and CVD risk factors is probably not linear.

Testosterone levels correlated positively only with BMI and HOMA, but FAI correlated positively with BMI, waist circumference, triglycerides, glucose concentration and HOMA with $p=0.0001$, and negatively with HDL cholesterol ($p=0.0001$). Serum SHBG is also expected to correlate with the same factors, but negatively (only HDL cholesterol correlates positively); $p=0.0001$.

Many publications show the important role that endogenous dehydroepiandrosterone (DHEAS; weak androgen) concentrations play in CVD prevention [4, 5]. In our study serum DHEAS correlates with BMI and triglycerides positively ($p=0.035$ and 0.005 respectively), which indicates the abnormal influence of endogenous DHEAS in elderly women.

Physiologically, the serum levels of sex hormones should be expected to lower with age. In the PolSenior study only serum testosterone did not correlate with age; serum estradiol, DHEAS, FAI, FEI and SHBG correlated significantly negatively with age in aging women.

We conclude that serum estradiol, the free estradiol index and free androgen index significantly correlated with CVD predictors in women. SHGB has a significant influence on CVD predictors in women but the influence of aging must be also included.

15.6 Endogenous Vitamin D Concentration Is Related to CVD Predictors in Women

The 3rd National Health and Nutrition Examination Survey (NHANES III) study assessed the mortality in 13,331 persons over 20 years of age in 1994–2000 and showed that the highest mortality rate was revealed in persons with vitamin D (25 OHD) deficiency; serum vitamin D level below 17.8 ng/ml is an independent mortality risk factor [6]. For bone health a vitamin D level of 30 ng/ml is optimal. Another observation of 182,152 persons shows a significant correlation between

mortality and vitamin D deficiency [7]. In the PolSenior study we observed the negative correlation between serum vitamin D concentration and age ($r = (-)\ 0.286$; $p = 0.001$). After dividing the whole group of women into those below and those above a vitamin D level of 20 ng/ml we realized that there is no difference in the BMI, percentage of body fat, waist circumference and carbohydrate metabolism. Only total cholesterol and LDL cholesterol were statistically significantly higher in the group with a lower vitamin D concentration.

We conclude that endogenous serum vitamin D concentration decreases with biological age. In aging women with a level of vitamin D lower than 20.0 ng/ml, significantly higher serum total cholesterol and LDL cholesterol levels were observed. The serum vitamin D levels were not associated with obesity and carbohydrate metabolism disturbances in aging Polish women.

15.7 Thyroid Function in Aging Women

Serum TSH levels changes did not correlate with biological age in women participating in the PolSenior study. 47.9 % of women and 28.04 % of the men had elevated titers of anti-TPO. The thyroid disturbances were more often recognized in women than in men; the frequency of hypothyroidism was 10.35 and 5.3 % respectively, hyperthyroidism 3.52 and 2.38 %. What is most important is that up to 57.8 % of subjects with abnormal thyroid hormone concentrations were not treated. Another question is whether or not they should be treated, because subclinical hypothyroidism is not an absolute indication for the treatment.

15.8 Summary

1. Aging has an important influence on BMI and serum HDL cholesterol levels in women.
2. Serum estradiol, the free estradiol index, and the free androgen index correlated significantly with CVD predictors in women.
3. Sex hormone-binding globulin has a significant influence on CVD predictors in women, but the influence of aging must be also included.
4. The endogenous serum vitamin D concentration decreases with biological age; in patients with levels lower than 20.0 ng/ml we can expect an atherogenic lipids profile.
5. Thyroid diseases (especially hypothyroidism) are common disorders in aging women.

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Obesity and Metabolic Syndrome: Impact and Relationship with Menopausal Transition

16

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16.1 Introduction

The World Health Organization defines obesity as a chronic condition, characterized by excessive weight gain due to extreme fat mass deposition that negatively affects health and quality of life. Obesity has a multifactorial etiology, with an increased incidence in the overall population, in particular during childhood and adolescence, and its prevalence will further increase over the next few decades.

In the Italian population, one third of women are overweight or obese [1]. It is well known that there are two different kinds of obesity: visceral or central obesity (android) and peripheral obesity (gynoid). Central obesity, typical of men and postmenopausal women, is characterized by an increase in waist circumference, as measured using a waist/hip ratio (WHR) of more than 0.80. In gynoid obesity, which is typical in fertile women, fat is mainly localized in the thighs and buttocks. This different fat distribution reflects the different body structure of males and females, because of the ancestral role of the two genders: the man's abdominal obesity permits hunting and escaping, while gynoid fat distribution protects pregnancy in both mechanical and metabolic ways [2]. Moreover, around menopausal transition, many women experience weight gain and an increase in central adiposity. Central/visceral obesity is associated with important changes in lipid and glucose profiles, insulin resistance and/or diabetes mellitus, with an increase in metabolic and cardiovascular risk. The central and the peripheral fat mass also present structural differences in the fat cell: the adipocytes of gynoid obesity have few sides, a higher insulin sensibility, and greater density of estrogenic receptors, thus promoting higher fat mass deposition than in the android fat cells. On the contrary, the latter are more

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_16

responsive to androgenic stimulation and produce and release a greater amount of pro-inflammatory adipocytokines in the portal circulation. The different estrogenic or androgenic responsiveness of the fat mass cells, depending on the site of fat deposition, may explain the reason for the different obesity localization in the two genders and during a woman's life [3].

A positive relationship exists between the waist girth increase and the worsening of the cardiovascular profile, even in people of normal weight, especially women [4]. In fact, more than body mass index (BMI), the main positive predictive factor of the negative impact of obesity on health is abdominal fat. According to the International Diabetes Federation (IDF) criteria, the waist circumference is the main diagnostic element of metabolic syndrome, which inextricably links the visceral adiposity with the worsening of the metabolic profile (Table 16.1).

The metabolic syndrome represents a whole heterogeneous disorder that correlates with high mortality and morbidity rates and high economic and social costs. The syndrome affects 20–25 % of the general population with an increased prevalence with aging, in particular among older people 50–60 years of age. The characteristics of the syndrome are visceral obesity, abnormal lipid and glucose metabolisms and high blood pressure: the specific pathophysiological feature is represented by insulin resistance, which may explain each of the metabolic impairments: the insulin resistance promotes the storage of fat tissue at a visceral level, less sensitive to insulin action, and as a consequence a higher lipolytic function may increase the release of non-esterified fatty acids (NEFAs) into the liver circulation. These NEFAs cause abnormal synthesis of glucose and triglycerides that in turn compromises hepatic insulin clearance. Furthermore, the fat mass is not considered to be simply an energetic store but an active endocrine tissue that releases a large number of adipocytokines, some of which have pro-inflammatory and pro-atherogenic functions (TNF α, IL-6, leptin, adiponectin, etc.) with an active role in modulating insulin sensitivity: for example, the reduced secretion of adiponectin plays a crucial role in inducing insulin resistance, but also in determining the clustering of elevated triglycerides and small, dense LDL particles. Increased leptin secretion may be responsible for sympathetic nervous system overactivity and hypertension, while reduced omentin may play an important role in the development of atherogenic processes [5].

Insulin resistance promotes sodium retention at the kidney level, with a consequently negative impact on blood pressure homeostasis. Finally, when the pancreatic compensatory mechanisms for insulin resistance become inadequate, the fasting glucose increases and, because of the reduced glucose cell intake, diabetes progresses: the metabolic syndrome is taking place (Fig. 16.1).

Insulin resistance, in turn, may be dependent on different problems: an intrinsic/structural cell disorder, owing to receptoral or post-receptoral function defects, or an acquired disorder, such as excessive weight (overweight or obesity), which increases the amount of fat and induces a change in the receptor binding ability of hormones. Insulin resistance is also dependent on familial predisposition, especially when there are diabetic relatives and often with the combination of many of the elements described above.

Table 16.1 The differences in the diagnostic criteria for metabolic syndrome

	WHO (1999)	ATP-III (2001)	IDF (2005)
Fasting glucose	Diabetes mellitus, impaired glucose tolerance	>110 mg/dl	>100 mg/dl or previously type-II diabetes
Blood pressure	≥140/90 mmHg or use of medication	>130/85 mmHg or use of medication	>130/85 mmHg or use of medication
Dyslipidemia (TG)	≥150 mg/dl	≥150 mg/dl	≥150 mg/dl
Dyslipidemia (HDL-CH)	<35 mg/dl for males	<40 mg/dl for males	<40 mg/dl for males
	<39 mg/dl for females	<50 mg/dl for females	<50 mg/dl for females
Central obesity	WHR >0.9 in males	Waist circumference	Waist circumference
	>0.85 for females and/or BMI >30	≥102 cm for males	>94 cm for males
		≥88 cm for females	>80 cm for females of Caucasian race
Microalbuminuria	Urinary albumin excretion ratio ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g		
Diagnostic criteria	MD type II or IGT and two criteria	Three or more criteria	Central obesity and two criteria

WHO World Health Organization, ATP-III National Cholesterol Education Program-Adult Treatment Panel III, IDF International Diabetes Federation, TG triglycerides, HDL-CH high-density lipoprotein cholesterol, WHR waist/hip ratio, BMI body mass index

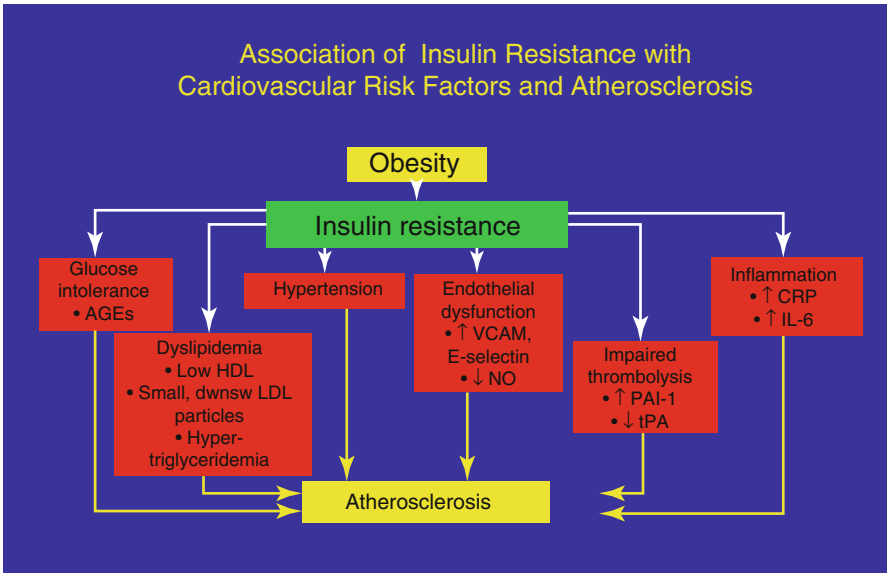

Fig. 16.1 The metabolic impact of the combination of obesity and insulin resistance and cardiovascular risks

16.2 Relationship Among Obesity, MS and Menopausal Transition

As we know, menopausal transition is characterized by an early (approximately 10 years before the start of the menopause) and a progressive increase in FSH levels, linked to a decrease in inhibin production by the ovaries; at the same time, the higher frequency of anovulatory cycles induces a decrease in progesterone during the luteal phase, resulting in relative hyperestrogenism, followed by a long period of hypoestrogenism when the menopause has actually taken place.

At present, although a large number of publications have been produced, the change in body weight during menopausal transition represents a important topic of discussion.

Usually, the modifications of weight are dependent on an increase in energetic impute and/or a decrease in energy consumption, mostly because of physical activity and resting energy expenditure. It is well known that women after the age of 45–50 years, in the absence of changes in their lifestyle (feeding and physical activity), show a progressive increase in bodyweight. What is the cause of this?

Whereas weight gain per se cannot be attributed to the menopause transition, the change in the hormonal milieu at menopause is associated with an increase in total body fat, and in particular there is an increase in abdominal fat [6]. Lovejoy et al. [7] showed that progressively, during perimenopause, there is an increase in abdominal fat mass, concomitant with climacteric hypoestrogenism, with a slow increase in weight despite the reduced trend in total calorie intake (Fig. 16.2).

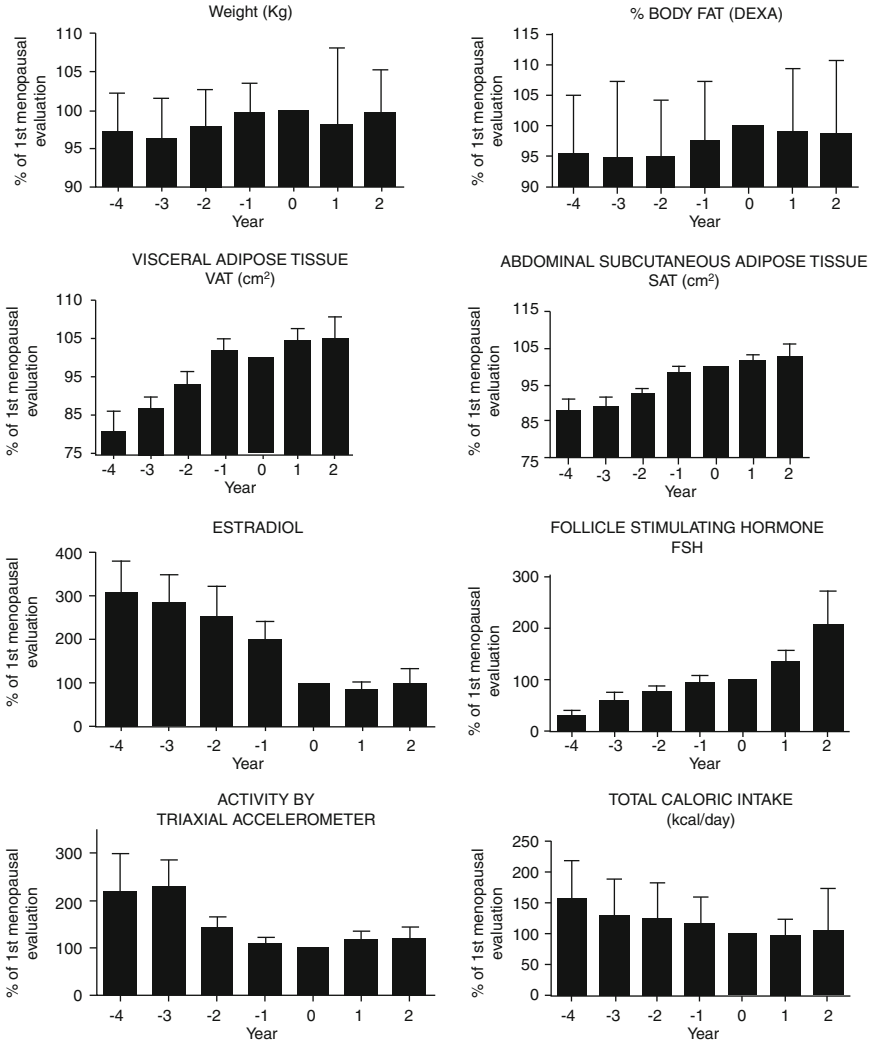

Fig. 16.2 Despite weight that remains the same, there is an increase in body fat mass and in visceral adipose tissue (Modified from Lovejoy et al. [7])

From the clinical point of view, it is important to know the metabolic condition of our patients: during reproductive life, they may have suffered from some metabolic disorders, including thyroid dysfunction or mellitus diabetes and/or insulin resistance, as in the case of polycystic ovary syndrome (PCOS) or a history of being overweight/having obesity. The exposure to environmental factors, until the beginning of childhood, can affect the normal weight and worsens it: in general, personal health history affects the metabolic change that occurs during menopausal transition.

The gonadal steroid hormones have specific metabolic effects during perimenopausal transition. As mentioned before, menopausal transition is characterized by

alternating hypoestrogenic and/or hyperestrogenic periods with low progesterone levels. Indeed, during the luteal phase of the menstrual cycle, the typical increase in P/E2 ratio induces an increase in body temperature of about 0.4 °C [8]: this temperature rise causes an elevation of basal metabolism of about 200 kJ (50 kcal) per day [9]. On the contrary, the absence of a progesterone increase during menopausal transition determines the lack of energy consumption under resting conditions typical of the luteal phase (about 50 kcal a day, for 12–14 days: approximately 600–700 kcal every month). This event is at the basis of the increase in fat mass deposition during the perimenopause [10] and does not induce the physiological burning of calories during the luteal phase.

This decline in energy consumption seems to be not exclusively dependent on progesterone deficiency but also on other factors, such as the amount of lean mass, the activity of the sympathetic nervous system (SNS), the endocrine status and the ageing-mediated physiological changes. In fact, the decline in basal metabolism observed in post-menopausal women may also depend on aging [11]. However, the basal metabolism decreases more during menopausal transition than could be attributed to the aging process [12]. Oestrogen depletion probably contributes to the acceleration of this decline. As the perimenopause becomes the menopause, the progressive reduction of oestrogen levels induces a progressive worsening of the insulin resistance, which is also increased owing to the concomitant cortisol increase (typical of aging and the menopause). This latter event induces gluconeogenesis and further promotes insulin resistance. The hypoestrogenism also partly induces a fall in GH levels, which produces an increase in the storage of abdominal fat mass with a decrease in lipid metabolism [13, 14].

Further confirmation of the role of oestrogen in fat mass control comes from experimental studies on animal models where in ovariectomized mice, the oestrogen treatment reduces the fat mass and the adipocyte cell size, independently of the energy intake. In particular, oestradiol seems to accelerate the fat oxidation pathways in the muscles and adipocyte lipolysis [15].

In summary, the decrease in basal metabolism induces the gain in fat mass which, in turn, may contribute to improving the incidence of obesity-related diseases, such as worsening of the cardiovascular profile and type II diabetes. The increase in visceral adiposity further worsens insulin sensitivity, in particular at the liver level, so that higher amounts of insulin are needed to control glucose intake at tissue levels. All these changes determine the increase in the rate of incidence of the metabolic syndrome in overweight/obese women during the menopausal transition.

Recently, it has been suggested that another possible link between menopausal hypoestrogenism and appetite control/weight gain is the increase in levels of orexin-A plasma [16]. This recently discovered hypothalamic neuropeptide is involved in the regulation of feeding behavior, of the sleep–wake rhythm and of neuroendocrine homeostasis [17, 18]. In post-menopausal women, while estrogens are at low levels, plasma orexin-A levels are significantly higher, being part of the induction for some cardiovascular risk factors, such as blood glucose, lipid profile, blood pressure and body mass index [19].

16.3 The Approach to Obesity and Metabolic Syndrome During Perimenopause

The approach to overweight/obese pre-menopausal women has to consider and evaluate a careful anamnesis and medical investigation, especially with regard to the age at obesity onset, any recent relevant weight change and if there are any members of the family with diabetes or other endocrinological diseases and/or obesity The purpose of this check is to exclude any clinical cause that might require specific therapeutic approaches, such as any uncommon secondary obesities, due to genetics, neurological or psychiatric conditions.

It is important to know if the patient has suffered in the past with PCOS and/or premenstrual syndrome and premenstrual dysphoric disease (PMS-PMDD). It is well recognized that insulin resistance is a frequent feature of the PCOS, especially for 50–60 % of the patients who are overweight/obese [20]. Moreover, we recently demonstrated [21] that people with PCOS and insulin resistance have a double chance of suffering from PMS-PMDD and mood disorders up to depression, during their reproductive life, mostly during menopausal transition. This condition seems to be due to reduced production of neurosteroids, in particular allopregnanolone, which is the most powerful endogenous anxiolytic and anti-depressant substance derived from progesterone catabolism [22]. These PCOS and hyperinsulinemic patients, during menopausal transition, are at a higher risk of suffering from more intense climacteric symptoms, in particular those due to neurosteroid deficiency (allopregnanolone), such as mood disorders, depression and anxiety, if they did not undergo a specific treatment to reduce insulin resistance and weight gain [23].

In addition to the clinical investigation, it is therefore necessary to assess the presence of insulin resistance, even in non-obese women; in fact, these patients may have a normal weight thanks to their lifestyle even though they have a predisposition to insulin resistance that is only disclosed by undergoing an oral glucose tolerance test (OGTT). This test is usually carried out over 4 h, but a positive response to this test can equally be achieved with just two blood samples, at time 0 (i.e. before drinking the glucose) and 60 or 90 min after a glucose load of 75 g of sugar: an insulinemic state is diagnosed when the insulin response is higher than 60 μU/ml [24, 25]. In women with a history of PCOS, insulin resistance has been demonstrated frequently during both pre- and post-menopause (Fig. 16.3) [26].

The therapeutical approaches for women during menopausal transition have to consider the body weight at the moment of the perimenopausal transition: women of normal weight and overweight/obese women should be treated differently. In the first case, the approach targets the prevention of weight gain, while in the latter group it is important to avoid a further weight increase, and/or to treat the metabolic abnormalities. In both cases, the first recommendation is a modification of lifestyle through the combination of a hypocaloric diet with physical activity.

Endurance training (aerobic exercise for 45 min a day, three sessions per week) has been shown to promote body weight and fat mass losses and to reduce waist girth and blood pressure in overweight/obese women. Moreover, these interventions

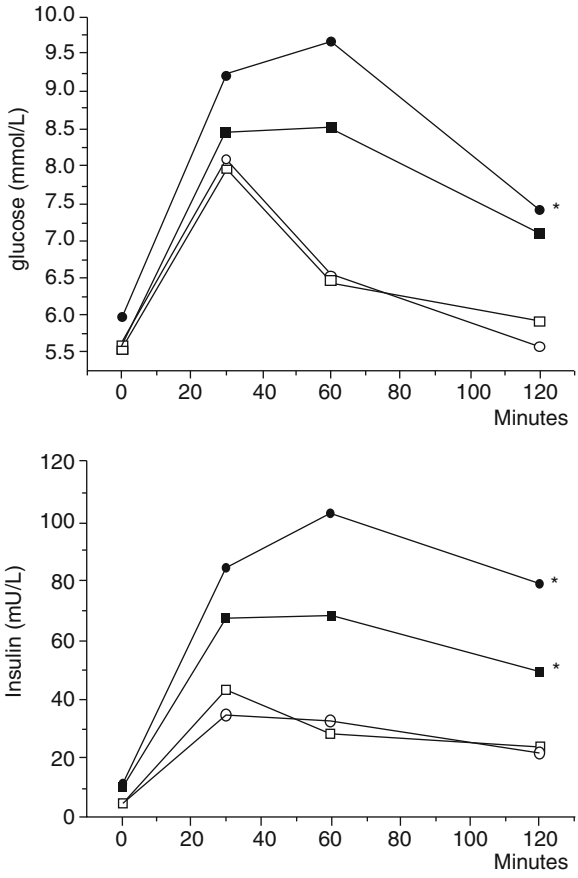

Fig. 16.3 The area under curve (AUC) is significantly higher in pre-/postmenopause groups of women with polycystic ovary syndrome (PCOS) than in control groups (Modified from Puurunen et al. [26]). □ pre-menopause control, ○ post-menopause control, ■ pre-menopause PCOS, ● post-menopause PCOS

decrease plasma triglyceride, cholesterol and low-density lipoprotein cholesterol levels and increase high-density lipoprotein cholesterol concentrations; the greatest improvement in metabolic risk profile has been observed in women with two or more determinants of the metabolic syndrome, but still with no coronary heart disease [27]. In addition, physical exercise amplifies triggers of an anorectic response, limiting the consumption of food [28]. Unfortunately, the association of diet and physical activity is effective in the short period, but is less valid for maintaining the weight loss in the long term.

In women of normal weight with climacteric symptoms, hormonal replacement therapy (HRT) has been successfully demonstrated to protect against perimenopausal changes in body composition [29, 30]. In these patients, no significant variations in weight, fat mass content and distribution have been observed, probably also thanks to the route of administration of HRT. In particular, transdermal estrogens seem to be more protective against fat mass increase and android fat distribution [31, 32]. Similar effects on body composition and on fat tissue have been observed when administering tibolone and raloxifene.

In obese women during menopausal transition, behavioral therapy is essential to achieve the weight control in the long term, but there are some medications such as metformin, inositol, orlistat, etc. that may help and facilitate weight loss. Metformin, a well-known anti-diabetes drug, reduces insulin levels, improving insulin sensitivity through an increase in glucose cell uptake, a treatment often administered to PCOS women during their fertile years. Also, myo-inositol in combination with chiro-inositol integrative administration may enhance insulin sensibility through an improvement in post-receptoral efficiency. Outside of the gynecologist's field of expertise, orlistat is a specific obesity treatment that reduces the absorption of dietary fats, promoting their fecal elimination.

In conclusion, overweight, obesity and metabolic syndrome are tightly linked with the changing of the hormonal pattern during menopausal transition. In fact, the progressively declining levels of estrogens and progesterone induce specific metabolic impairments, as the worsening of insulin resistance or the increasing of central fat mass storage. At the same time, obesity is an important factor that modulates hormone changes during menopausal transition, as women with higher BMI were more likely to enter the earliest transition stage, although they were slower to reach the post-menopausal stage than those with lower BMI [33]. Further, if during the fertile age the women had PCOS associated with overweight/obesity, it is more likely that insulin resistance led to a metabolic syndrome predisposition and to mood disorders, exacerbated by the arrival of the climacteric transition, which clinically happens in 45- to 50-year-old women.

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Part VI

Menopause

Cardiovascular Prevention at the Menopausal Transition: Role of Hormonal Therapies

17

Stefania Spina, Guja Bernacchi, Elena Cecchi, Andrea R. Genazzani, and Tommaso Simoncini

17.1 The Menopausal Transition: Definitions

As defined by the Stages of Reproductive Aging Workshop (STRAW) held in July 2001 and updated in 2011, the menopausal transition (MT) begins with variations in menstrual cycle length associated with a decrease in inhibin B and anti-Müllerian hormone (AMH) concentration and a rise in follicle-stimulating hormone (FSH); it ends with the final menstrual period (FMP), classically confirmed only when followed by 12 months of amenorrhea [1]. Typically, the MT starts in the late 40s or early 50s and continues for about 4–7 years.

The original STRAW staging system is widely considered to be the gold standard for characterizing reproductive aging throughout menopause using menstrual patterns, endocrinological markers, and ovarian imaging. Moreover, the STRAW + 10 criteria update the 2001 STRAW criteria by providing greater clarity for menstrual patterns, including duration of phases and stages. This system classifies reproductive and postreproductive life into seven stages, with the MT accounting for two of those stages. The main event is the FMP; five stages come before FMP and two stages follow it (Fig. 17.1).

17.2 Impact of the Menopause Transition on a Woman's Life

Menopausal transition is a physiological event in every woman's life; nevertheless, it can profoundly affect quality of life. In fact during this period, women complain about new and unexpected annoying symptoms and their bodies are at the mercy

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*,
ISGE Series, DOI 10.1007/978-3-319-09662-9_17

Menarche						FMP (0)				
Stage	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*Variable*				*Variable*	1-3 years	2 years (1+1)	3-6 years		*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtie changes in flow length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low	Stabilizes Very Low Very Low		
Antral Follicle Count			Low	Low	Low	Low	Very Low	Very Low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ – elevated

** Approximate expected level based on assays using current international pituitary standard

Fig. 17.1 The Stages of Reproductive Aging Workshop (STRAW) +10 staging system (Adapted from Harlow et al. [1])

of intense hormonal and physical changes. The clinical signs associated with this period are vasomotor symptoms, sleep disruption, mood alteration, urogenital complaints, and sexual dysfunction. Among these, the most frequent are vasomotor symptoms, which afflict 75 % of women and usually disappear within 1–5 years.

Moreover, the years around the menopause are associated with weight gain, increased central adiposity and waist circumference. The annual rate of weight gain, estimated to be about 0.5 kg, is independent of menopausal status, while it is consistently related to chronological aging [2]. In contrast, adverse changes in either body fat distribution, from a more gynoid pattern to a more android pattern, or body composition with increased fat mass and decreased lean mass may be due to hormonal changes occurring during the menopausal transition [3]. The deleterious change in body fat distribution consists of an increase in abdominal adiposity owing to the selective accumulation of fat in the intra-abdominal compartment [4], independent of age and total body fat mass [5]. Specifically, increased abdominal adiposity is known to increase the risk of developing CVD.

Data from the Women's Healthy Lifestyle Project provide clear evidence that weight gain and increased waist circumference, along with elevations in lipid levels and other risk factors for coronary heart disease (CHD), are preventable through use of lifestyle intervention in healthy menopausal women. In fact, although these changes are inevitable with age and menopause, physical activity may attenuate the impact of both events. Thus, weight gain prevention should be recognized as an

important health goal for women before they approach menopause and women should do regular physical activity [6].

As hormonal changes during the MT directly or indirectly adversely affect quality of life, body composition, and risk of cardiovascular disease (CVD), the maintenance of health parameters in the premenopausal years is crucial for a healthy postmenopausal life.

17.3 Estrogens and Cardiovascular Risk

Estrogens and the other sex hormones regulate some of the fundamental cardiovascular functions including blood pressure, blood flow, vasodilatation and vasoconstriction, vascular inflammation and remodeling, and atherosclerosis [7]. The actions of endogenous estrogens on the cardiovascular system can be mediated directly on the vessels or indirectly through the modulation of cardiovascular risk factors.

Estrogen exerts pleiotropic functions on the cardiovascular system through both genomic and nongenomic effects [8, 9]. Traditionally, estrogen receptors (ERs) act as transcription factors regulating the expression of target genes by directly binding to specific DNA sequences, the estrogen response element (ERE). Nongenomic effects are rapid responses that occur too quickly to be mediated by gene transcription, instead involving modulation of membrane and cytoplasmic proteins.

At this level, estrogen triggers rapid vasodilatation, exerts anti-inflammatory effects, regulates vascular cell growth and migration, leading to a protective action on vessels [10]. These rapid and nongenomic effects are reached by complex interactions with membrane-associated signaling ERs, leading to the activation of downstream cascades such as mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-OH kinase (PI3K). These cascades are responsible for the important cardiovascular actions of estrogen, for instance, the activation of nitric oxide (NO) synthesis or the remodeling of the endothelial actin cytoskeleton. Moreover, these cascades play crucial roles in regulating the expression of target proteins implicated in cell proliferation, apoptosis, differentiation, movement, and homeostasis [11].

Furthermore, estrogens also have systemic effects that may have an influence on cardiovascular risk, altering the serum lipid concentrations, the coagulation and fibrinolytic systems, and the antioxidant system [7]. In fact, through ER estrogens regulate hepatic expression of apoprotein genes and several coagulation and fibrinolytic proteins. The net effect of these changes is to improve the lipid profile and to promote vasodilatation and antioxidant activities. By contrast, the menopause leads to an overturning of all these effects, increasing the cardiovascular risk.

Recent advancements in the characterization of the molecular basis of the actions of estrogen help us to understand its biological functions and would be beneficial in elucidating current controversies on its clinical efficacy in the cardiovascular system.

17.4 The Menopausal Transition and Cardiovascular Risk

Cardiovascular diseases are the number one cause of death globally, both for men and women. It is well documented that morbidity and mortality rates from CVD are higher in men than in women; however, this gender gap narrows after the menopause, suggesting that female sex hormones and aging might play a role [12]. In fact, the incidence of CVD in women increases substantially with aging, probably because the menopause diminishes the gender protection contributing to an adverse impact on cardiovascular risk variables [7]. Nevertheless, whether this higher cardiovascular risk is a function of aging or a consequence of the loss of endogenous estrogen due to the menopause, or both, has been debated in the literature for many years [13, 14].

In this respect, it is worth mentioning the results of the Study of Women's Health Across the Nation (SWAN). SWAN is a multicenter, multi-ethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition and to observe their effects on subsequent health and risk factors for age-related diseases. A total of 3,302 women were enrolled at seven clinical sites between 1996 and 1997. At the time of enrollment, women were premenopausal, not taking hormones and between 42 and 52 years of age. Participants self-identified as African–American (28 %), Caucasian (47 %), Chinese (8 %), Hispanic (8 %), or Japanese (9 %). SWAN has a multidisciplinary focus and thus has repeated measures of bone health, cardiovascular risk factors, psychosocial factors, and ovarian hormones [15].

In this setting, Matthews et al. [16] evaluated the change in CHD risk factors in relation to a very particular and critical period of a woman's life, the FMP. Women who experienced a natural menopause (1,054 out of the total) were analyzed independent of age and other confounders. The results showed significant increases in total cholesterol, LDL-C, and Apo B within a year of the FMP; importantly, the rate of change relative to the FMP did not vary by ethnicity, suggesting that the menopause might have a uniform influence on lipids. The other risk factors changed in a linear pattern consistent with chronological aging: triglycerides, lipoprotein (a), insulin, factor VIIc, and systolic blood pressure increased; diastolic blood pressure, tissue plasminogen activator antigen, fibrinogen, and high-sensitivity C-reactive protein did not change.

In conclusion, the year immediately around the FMP has been identified as the critical time period of changes in the lipid profile leading to an increased risk of CVD in the post-menopausal years. Although a significant portion of this increased risk is likely due to changes in plasma lipid–lipoprotein levels secondary to estrogen deficiency, a number of other hormonal and physiological changes that occur during the menopause transition may also contribute. Therefore, during the menopausal transition several adverse changes take place and modify cardiovascular risk factors. It may thus be necessary to encourage lifestyle measures and therapeutic interventions such as hormone replacement therapy throughout the menopausal transition to counteract or prevent these events.

17.5 Hormone Therapy: A Debate Still Open

Hormone replacement therapy (HRT) for postmenopausal women has been available for more than 60 years. Since that moment, HRT has been the subject of discussion and debate. In the early 1990s, the effects of HRT were thought to be beneficial because of a reduction of 30–50 % in the risk of CVD and osteoporosis. These effects were confirmed by a large number of observational studies [17, 18]; thus, in 1992 the American College of Physicians published guidelines strongly advising a preventative use of HRT [19]. In those years an escalation in the use of HRT was registered across the world [20].

However, in the late 1990s, a number of studies started questioning the protective role and the safety of HRT. Randomized clinical trials (RCTs) overturned the previous hypothesis about the advantage of HRT, showing no evidence of cardiovascular benefit, but instead a negative effect on women's health. Among these, the Women's Health Initiative (WHI) trial had a great impact. Over 16,000 menopausal women between the ages of 50and 79 (mean age 63 years) were enrolled across 40 clinical centers in the USA. After a mean of 5.2 years of follow-up the study was stopped because of an increased risk for cancer and adverse effects on the cardiovascular system [21, 22]. The consequent release in 2002 of the principal findings from the WHI was associated with a substantial decline in use by postmenopausal women [23].

Nevertheless, more recent subgroup analyses suggested that the lack of benefit or increase in CVR observed in the WHI might result from the harmful effect of HRT in older women well after the menopause. It is clear that the characteristics of women selected for RCTs were markedly different than those of women studied from the general population in observational studies from which the estrogen cardioprotective hypothesis was generated. Therefore, these secondary analyses pointed out that the benefit of HRT may be dependent upon both the age of the women at the time of HRT initiation and the timing of the initiation of hormone exposure. Not only the role of timing, but also the role of the type, dose, and route of HRT should be analyzed. These hypotheses have encouraged two new RCTs: the Kronos Early Estrogen Prevention Study (KEEPS) and the Early vs Late Intervention Trial with Estradiol (ELITE). KEEPS is a randomized clinical and controlled study with the objective of clarifying the controversy about the effects of HRT on the progression of the atherosclerosis risk–benefit factor with the use of estrogens in postmenopausal women. Healthy women aged 42–58 years who are within 36 months of their last menstrual period have been recruited to receive either oral estrogens or estradiol patches; in addition, both groups are given oral micronized progesterone for 11 days of each month. Outcomes will be carotid–intima media thickness and the accrual of coronary calcium. Preliminary reports on this study have been distributed, but a full publication is still awaited. On the other hand, ELITE randomized women based on the number of years since menopause (less than 6 years or more) to receive either estradiol or placebo. As in KEEPS, the primary endpoint is the change in carotid intima-media thickness. The results from these studies will help us to clarify some of the aspects that are still unsolved.

The most recent Position Statement of the North American Menopause Society on hormone therapy published in early 2012 clarifies the existing data and provides easy-to-follow recommendations for menopause management [24]. HRT should be given to healthy and chronologically young perimenopausal women within 10 years of the onset of menopause in the lower dose regimens [25]. Based on the available evidence, those women with these characteristics who carry on the use of HRT for several years experience a significant decrease in their risk of developing a heart attack.

17.6 The Window of Opportunity

Over the last decade, a large quantity of data have strongly supported the notion that the presence of a window of therapeutic opportunity for the use of estrogens in healthy women with recent menopause appears to be the key to successful prevention and amelioration of any further damage [26]. Timing of the initiation is important because hormone replacement is effective before tissue damage due to aging becomes too extensive [27]. The major clinical implication is that whereas HRT is not recommended for reduction of CVD risk by the WHI and other RCTs, its use for other indications should not be hampered by the fear of increasing CVD in younger, newly menopausal women [28].

These hypotheses could have a biological basis. In fact, around the time of menopause, women still have healthy arteries, allowing a "window" for HRT to produce cardiovascular benefit. However, aging arteries become less responsive to the beneficial effects of estrogens. Indeed, the menopause is associated with endothelial dysfunction, decreased NO-dependent relaxation and intimal thickening; moreover, age-related changes in ER amount, distribution or affinity may also contribute to cardiovascular risk [29].

It is well established that estrogen may have a different and controversial effect on the atherosclerotic process, depending on its stage. Estrogen inhibits early development of atherosclerosis by preventing the accumulation of foam cells in the endothelium, whereas it may increase the cardiovascular risk once atherosclerosis has been established, causing disruption of the fibrous cap and rupture of the plaque by increasing expression of matrix metalloproteinases (MMPs) [30]. Thus, the preexisting cardiovascular condition could affect the outcome of HRT.

17.7 Rethinking Menopausal Hormone Therapy

A new study, published by the *British Medical Journal*, is now adding interesting evidence to the debate. The paper, authored by Schierbeck et al. [31], reports the long-term follow-up of a cohort of postmenopausal women originally enrolled in the Danish Osteoporosis Prevention Study (DOPS), a randomized, open-label trial investigating the effect of hormone intervention with estradiol or a combination of estradiol and a synthetic progestin on osteoporotic fractures. The study enrolled

1,006 patients aged 45–58 who were recently menopausal or had perimenopausal symptoms between 1990 and 1993, with a planned duration of 20 years; both the 502 women who received HRT and the 504 who received no treatment were followed for nearly 16 years (10 years of treatment and 6 years of follow-up). The intention-to-treat analysis on the cohort of more than 1,000 provides an interesting set of results, which were awaited by many in the field.

The key result is that women receiving hormone replacement had a significantly lower incidence of CHD. The magnitude of this reduction was around50 % and applied both to the period of active treatment and to the later observational phase. In addition, no differences in stroke, venous thromboembolism or breast cancer were recorded throughout the study. There are at least two key differences between this study and the ones that have been available so far: the age of the women enrolled and the characteristics of the medication. In fact, this trial looks at women who started hormone replacement very close to the menopausal transition. By contrast, the WHI [32], enrolled nearly 75 % of patients over 60 years, and less than 5 % of the entire population were close to the menopause. Moreover, women were treated with 17β-estradiol and norethisterone acetate instead of conjugated equine estrogens and medroxyprogesterone acetate, emphasizing that the use of a progestin during hormone replacement, particularly medroxyprogesterone acetate, is associated with a higher risk of CVD [22] compared with estrogen-only therapies. It was also found in this study, that women who did not receive the progestin had a trend toward having a lower incidence of cardiovascular events [31].

Nevertheless, after nearly 20 years of debate, the never-ending contradiction between studies showing the benefit of HRT and guidelines stating that HRT should not be used to prevent chronic disorders still exists. The last and most recent one published by the US Preventive Services Task Force [33] in 2012 explicitly advises against the use of either estrogens or of combinations of estrogens and progestins for the prevention of chronic conditions.

It is established that HRT is generally initiated in the real clinical world because women suffer from hot flashes or vulvo-vaginal atrophy, with the only aim of counteracting these symptoms. However, this study should raise awareness in the media, the regulatory authorities, and the general population that menopausal hormone therapy saves lives and reduces disability. This is not trivial and a shift in communication and clinical attitude could lead to enormous benefits for women and health systems throughout the world.

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Menopause and HRT: Doubts and Certainties

18

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18.1 Menopause, Aging, and the Role of HRT

A woman's life is characterized by physiological changes of sex steroid hormone concentrations, especially during menstrual cycle, pregnancy, and menopause.

Menopause is a consequence of loss of ovarian function. Deprivation of estrogen and progesterone levels causes menopausal symptoms. This hormonal change affects a large series of bodily targets, causing atrophy of tissues and metabolic modifications along with psychological and sexual changes that are variably experienced by women. Short-term consequences of estrogen deficiency include CNS-related symptoms and urogenital symptoms. Long-term consequences of estrogen deficiency include osteoporosis, cardiovascular disease, cognitive impairment, and dementia.

Good quality of life is an aspiration for all women. Menopause and aging both contribute to the decrease in quality of life experienced by most women at this stage in their life. In addition, according to the current literature, those women who particularly suffer from a reduced quality of life also tend to develop osteoporosis, diabetes, colorectal cancer, and cardiovascular diseases, thus suggesting that symptomatic individuals may be particularly vulnerable to menopausal changes.

There are two major categories of measures of quality of life: generic and specific tools. Among the most commonly used generic measures is the Short Form (SF)-36 Health Survey, which evaluates domains under the headings of physical functioning, role-physical, bodily pain, and general health with vitality, social functioning, role-emotional, and mental health under the mental health section. The Women's

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*,
ISGE Series, DOI 10.1007/978-3-319-09662-9_18

Health Questionnaire (WHQ) [1] provides instead a good example of a questionnaire investigating specific measures. Use of such tools can be useful in clinical trials as well as in busy practices to screen for those women who may specifically benefit from menopause-targeted interventions.

Use of hormone replacement therapy (HRT) in postmenopausal women has been popular for a long period but has now lost momentum due to emerging evidence that has highlighted the risks and advantages of this strategy. However, misperceptions on the real impact of hormone replacement have heavily impacted the dissemination of the use of these hormones, sometimes limiting the potential advantages for women who would have benefited from hormone use. This paper reviews the areas of certainty and those of doubt in this hot scientific field, with the aim to highlight the settings where use of HRT is beneficial and those where it may carry risks.

18.2 HRT: Types and Goals

HRT represents the most effective therapy for climacteric symptoms. It helps manage the short-term consequences of the fall of estrogens such as hot flushes, nocturnal sweats, anxiety, and mood swings. It also prevents long-term diseases such as bone mass loss, cardiovascular disease, and possibly degenerative neurological disorders. Efficacy on these targets of HRT depends on the administration of exogenous estrogens [2]. All women with an intact uterus who use systemic estrogen therapy (ET) should also be prescribed adequate progesterone support. Understanding the benefits and the risks of HRT is critical. 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 [3].

18.3 Short-Term Consequences

18.3.1 Vasomotor Symptoms

Sex steroids have a neuroprotective function and play region-specific roles in the central nervous system because of the presence of estrogen receptors throughout the brain, particularly in the basal forebrain and cortex. Consequently, gonadal steroid withdrawal during menopause heavily impacts brain function, negatively affecting mood, anxiety, and cognitive function. The most evident effect linked to estrogen deficiency in the brain is the development of hot flushes. Hot flushes represent thermoregulatory dysfunction due to inappropriate peripheral vasodilatation with increased cutaneous blood flow and perspiration, resulting in a rapid heat loss and a decrease in core body temperature below normal.

HRT is the most effective treatment for vasomotor symptoms and their potential consequences such as diminished sleep quality, difficulty in concentrating, irritability, and in general reduced quality of life [4, 5]. Low doses are efficient in resolving vasomotor symptoms in almost all symptomatic women; it is therefore appropriate

to begin hormonal therapy at low dosages and to increase them after some weeks if symptoms persist. Progesterone alone also reduces vasomotor symptoms but is not as effective as estrogen [6].

18.3.2 Urogenital Symptoms

The epithelial linings of the vagina and urethra are very sensitive to estrogens. Atrophy of vaginal mucosal surfaces takes place quite consistently after the menopause. Vaginal atrophy causes vaginal dryness and itching. Vaginal pH, which is usually <4.5 in the reproductive years, increases to 6.0–7.5 in postmenopausal women. The increase in pH and the vaginal atrophy both decrease the protection against infections. HRT and vaginal estrogen therapy (ET) reduce symptoms related to urogenital atrophy such as vaginal dryness, vaginitis, and dyspareunia [7]. Local Et also benefits women with overactive bladder [8]. In contrast, systemic HT may worsen or provoke stress incontinence [9–11], although this is controversial. Some studies reported a decreased risk of recurrent urinary tract infections with vaginal estrogens [12, 13]. Low doses of vaginal estrogens improve sexual satisfaction by improving blood flow and lubrication.

18.4 Long-Term Consequences

18.4.1 Osteoporosis

Osteoporosis is characterized by low bone mass with microarchitectural disruption and skeletal fragility, resulting in an increased risk of fractures. Estrogen deficiency has been well established as a cause of bone loss. From 1.5 years before to 1.5 years after the menopause, spine bone mineral density has been shown to decrease by 2.5 % per year, compared with a premenopausal loss rate of 0.13 % per year. Sex hormones have a protective effect on the bones, reducing skeletal remodeling through many mechanisms: reduction in activation of bone metabolic units, enhanced survival of osteoclasts, improved efficiency of gastrointestinal calcium absorption, and renal calcium conservation [14]. HRT is effective to maintain or improve bone mineral density. It reduces postmenopausal osteoporotic fractures, even in women without osteoporosis [15, 16].

The results of the double-blind Postmenopausal Estrogen/Progestin Intervention (PEPI) trial and the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial suggested that women treated with estrogen or estrogen/progesterone therapy have a significant increase in the body mass density (BMD) versus the placebo group, in which a loss of bone mass was observed [17]. In the Women's Health Initiative study (WHI), there was an evident reduction of all fractures among women receiving continuous combined conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) versus the placebo group. Total femoral bone mineral density increased by 3.7 % after 3 years of estro-progestin therapy versus 0.14 % recorded in the placebo group [18].

The WHI trial also confirmed the importance of an adequate concomitant calcium supplementation to prevent fractures.

The main role of HRT stays in the prevention of osteoporosis rather than in its treatment. However, HRT is an option to treat women with osteoporosis and a high risk of fractures when osteoporosis therapies are not appropriate or cause adverse effects or are incompletely effective. There is no evidence that HRT stops working with long-term treatments. The benefits of HRT decrease quickly after the discontinuation of treatment; in these cases, when needed to preserve bone mass, it is important to introduce a different treatment for osteoporosis [19, 20].

18.4.2 Cognitive Impairment and Dementia

Estrogens exert a number of protective effects on the brain, including inhibition of beta-amyloid formation, stimulation of cholinergic activity, reduction of oxidative stress, and protection against vascular risks [21].

Estradiol, in vitro, promotes breakdown of the β-amyloid precursor protein preventing the accumulation of β-amyloid. There is a clinical hypothesis that estrogens help to maintain cognition in women and prevent or delay the development of neurodegenerative disorders. In the long term, estrogen deficiency facilitates cognitive impairment and dementia.

Observational studies have reported association between HRT and reduced risk of developing Alzheimer disease [22]. Opposed to this rationale, the Nurses' Health Study (NHS) found no improvement on cognitive function from long-term use of HRT; in addition, there was evidence of a more rapid cognitive decline among those HRT users who started HRT long after their final menstrual period [23]. These results are probably associated with the detrimental effects on vascular events, even at the subclinical level, in this population of advanced age, that are nowadays established as a side effect of starting estrogen administration in elder women far from their menopause. The Women's Health Initiative Memory Study (WHIMS) has provided similar evidence, showing a worsening of verbal memory along with a positive effect on figural memory among elder women starting HRT [24]. However, in the Study of Women's Health Across the Nation (SWAN), a trial that looked at women at the time of their menopausal transition, women who initiated HRT before their final menstrual period had a beneficial cognitive effect. In line with the other studies, also in SWAN women who initiated HRT long after the final menstrual period had a worse effect on cognitive performance [25]. To date, it is not clear if HRT used soon after the menopause increases or decreases the rate of cognitive decline or later dementia risk.

18.4.3 Cardiovascular Disease

Cardiovascular risk increases in postmenopausal women and the possible reasons are the accelerated rise in total cholesterol, changes of weight, blood glucose, and blood pressure with aging and menopausal status. Estrogen withdrawal also heavily

affects endothelial function. Decreasing of estrogens levels might independently contribute to all this conditions. Premature menopause and bilateral oophorectomy in young women are associated with an increased risk of cardiovascular disease, myocardial infarction and overall mortality. Observational studies suggest an interval of 5–10 years between loss of ovarian function and increased risk of cardiovascular disease.

Observational studies suggest that HRT prevents cardiovascular disease in postmenopausal women: HRT reduces the risk of coronary heart disease (CHD) of about 40 %. This has been largely confirmed by the Women's Health Initiative (WHI) trial, showing that women in whom HRT is initiated early around the time of menopausal transition have a significantly lower risk of cardiovascular disease such as myocardial infarction and heart failure. 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 [18].

It is important to evaluate the levels of preexisting cardiovascular disease (CVD) at the time of therapy initiation because it influences the potential cardioprotective effects (and mostly the side effects) of HRT [26]. Consistent with the WHI findings, the Estrogen Replacement and Atherosclerosis (ERA) clinical trial reported that women with preexisting atherosclerosis receive no benefit on the progression of carotid atherosclerosis by HRT [27]. While estrogen levels may protect against the development of atherosclerosis, it does not appear to be protective against existing atherosclerosis. Trials are currently ongoing to assess whether use of HRT in younger postmenopausal women may slow down the progression of atherosclerosis.

18.4.4 Breast Cancer

Breast cancer is the most common cancer in women in Western countries. The pathogenesis is linked to estrogens that play an important role in the proliferation of breast cancer cells in vivo and in vitro [28].

Menopause is associated with important modifications in the breast. The fall of the cyclical exposure to estrogen and progesterone causes progressive atrophic changes in the glandular component and the breast becomes mostly constituted by adipose tissue. The climacteric is the time in a woman's life when breast diseases often became clinical evident and the risk in developing a breast carcinoma is stronger linked to aging rather than the fall of estrogens and progestins. Less is known on what particular hormone plays the major role in this phenomenon. Traditionally estrogen has been indicated as the main player, but recent evidence points out that progesterone and ovarian androgens might be more relevant.

Most 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. This concept has been recently overturned by studies showing that HRT containing some specific types of progestin seem to be associated with higher risk of breast cancer.

Association between breast cancer risk and HRT 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 it is associated with the duration of use. This excess risk is reduced after HRT cessation and disappears within 5 years [29]. The WHI study reported a 26 % increase in the relative risk of breast cancer for combined estrogen–progestogen when compared with placebo. 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 [18]. This study, along with the long-term analysis of the Nurse's Health Study, in general suggests that the impact on the incidence of breast cancer of hormone replacement therapy is limited and associated only with very long administrations, after 15–20 years of treatment [30]. The risk of breast cancer due to HRT is similar to that conferred by obesity and is not additive [31].

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 [32].

It is not clear the role of HRT in survivors of breast cancer. Observational studies show that HRT may not increase the risk of recurrent breast cancer; these results have been questioned because of possible bias from the enrolment of women at lower risk [33–39]. The LIBERATE trial looked at the use of HRT with tibolone in women with a history of breast cancer and was terminated early, after 2 years of follow-up, when a significant number of new breast cancers were diagnosed. To date, HRT use in breast cancer survivors is considered by all guidelines contraindicated [40].

18.4.5 Endometrial Cancer

The risk of all endometrial malignancies occurs mostly in perimenopausal and early postmenopausal women. The possible biological explanation 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. HRT with estrogen alone increases endometrial cancer risk, whatever the type and the dose of estrogen and the route of administration [41]. The addition of a progestin to ET is important to outset endometrial cancer risk, contrasting the stimulation of the endometrium by estrogens. With progestin the endometrial cancer risk is decreased either with cyclic or continuous HRT. Cyclic regimens including more

than 10 days of progesterone exposure per month appear to provide sufficient protection [42]. In general HRT is contraindicated in women with a history of endometrial cancer.

18.4.6 Colorectal Cancer

Colorectal carcinoma is the second most common cancer in women after breast cancer. Sex steroids play an important role on bile acid metabolism and directly affect the colonic epithelium [43]. Growing evidence shows that the incidence of colorectal carcinoma can be significantly reduced by HRT. A meta-analysis of 18 epidemiological studies of colorectal cancer and HRT showed a 20 % reduction of colorectal cancer risk in women who had ever taken HRT compared with those who had never used HRT [44]. The same results were showed by the WHI trial.

Conclusions

The clinical effect of HRT in postmenopausal women has been widely investigated. Although areas of uncertainty remain, there is also a lot of solid ground to provide counseling (Fig. 18.1). HRT is the best option to treat menopausal symptoms and should not be denied to women that have no contraindications. Use of HRT for longer periods of time has beneficial effects of the bones and on cardiovascular risk, particularly if initiated in early postmenopausal women. Thus, reassurance should be provided to these individuals. Breast cancer risk is mostly related to aging, and the possible additional risk imposed by HRT does not make a big difference and may largely depend on the formulation used. This is an area of current investigation and should not preclude use of HRT in women. Rather, women should be given correct information on the entity of the benefits and risks and followed up as clinically indicated. In this setting HRT is and will remain a precious clinical tool to manage menopausal women.

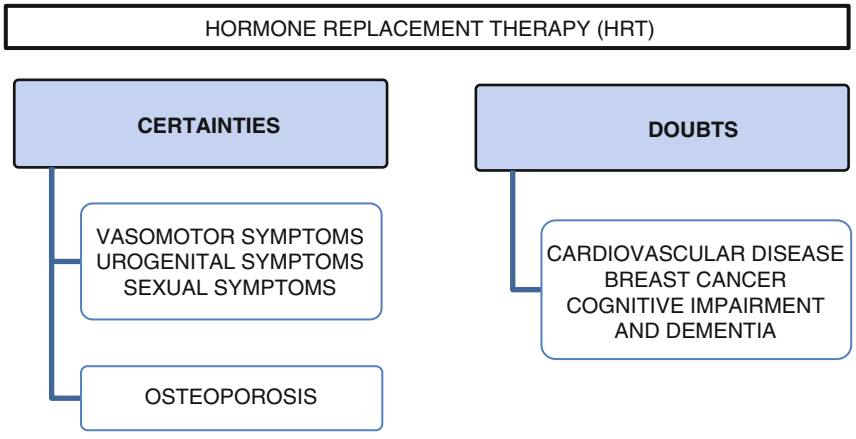

Fig. 18.1 Effects of *HRT* on menopausal disfunctions: doubts and certainties

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Part VII

Breast Cancer

Androgen Receptor and Breast Cancer

19

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Androgen receptor (AR) is a member of the family of steroid nuclear receptors which also include the estrogen and progesterone receptors. It has a number of ligands including the endogenous testosterone (T) and 5-dihydrotestosterone (DHT) as well as a variety of synthetic agonists and antagonists, and it is involved in a complex network of signaling pathways that collectively regulate cell proliferation. Androgen receptors (ARs) are frequently expressed in breast cancer (BC) cells, but molecular mechanisms underlying BC progression and their implication as a prognostic and/or predictive marker in BC patients are still controversial. Long-debated issue are: the androgen effect on BC cell lines, the prognostic significance of the presence of ARs in the different BC subtypes, and the resulting clinical implications of ARs' expression in breast cancer patients.

Androgens are the major circulating sex hormones in females. In *premenopausal women* testosterone is mainly synthesized and secreted by the ovaries and adrenal glands, with additional biosynthesis occurring within peripheral tissues via metabolic conversion of circulating adrenal proandrogens. In *postmenopausal women*, large amounts of active androgens and the totality of estrogens are synthesized in peripheral tissues from the adrenal precursor dehydroepiandrosterone (DHEA). A part of testosterone is metabolized to estradiol as a result of activity of aromatase. In *normal breast tissue,* androgen and AR signaling exerts an antiestrogenic, growth-inhibitory influence, and the relative levels of circulating sex hormones influence the proliferative capacity of breast epithelial cells. In the absence of estrogenic hormone stimulation, postmenopausal breast tissue undergoes a progressive

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*,
ISGE Series, DOI 10.1007/978-3-319-09662-9_19

involution characterized by increasing atrophy of glandular tissue and fibrosis of the stroma. These morphological changes may be due to unopposed androgen action.

The clinical-pathological implication of the androgen/AR pathway *on breast cancer growth* is not yet well known. Preclinical studies suggest that the action of androgens is *bidirectional:* mainly proliferative, because circulating androgens are the precursors of estrogens, but also antiproliferative, because AR activation restrains ER activity, inhibiting normal breast tissue growth.

The *proliferative action* is indirect: testosterone is metabolized by aromatase within breast tissue to 17-estradiol (E2), that is the most potent natural ER-ligand. Therefore the influence of circulating testosterone on the proliferative capacity of breast epithelial cells is in part dependent upon the relative expression and activity of aromatase. In studies of transgenic mice that overexpress the aromatase gene (AROM), males undergo abnormal breast development due to excess exposure to estradiol. Administration of an aromatase inhibitor (AI) to AROM transgenic male mice causes involution of the breast tissue, regression that is associated with increased exposure to testosterone, and induction of AR expression in the breast epithelium [1].

The antagonistic cross talk between AR and ER explains the *antiproliferative action* of androgens on ER-positive BC cells. In molecular study, AR did not bind to ERß, suggesting that this oppositional mechanism is specific for the ERα-isoform [2]. Peters et al. [3] demonstrated that *loss of AR expression* is significantly associated with poor 10-year survival outcome in grade III invasive breast ductal adenocarcinomas. They also evaluated potential regulatory mechanisms that may account for the loss of AR expression. Showing that DNA hypermethylation in the AR promoter is associated with loss of AR expression in breast cancer cells.

Recently, the androgen receptor is intensively discussed as a *prognostic and/or predictive* marker in BC patients. The AR is the most prevalent sex steroid receptor in in situ*, invasive, and metastatic* breast cancers, occurring in up to 90 % of primary tumors and 75 % of metastases [4]. AR-positive phenotype was found associated with favorable tumor characteristics, such as small tumor size, low histological grade, ER- and progesterone receptor (PR)-positive status, and with better outcomes than in patients with AR-negative tumors [5]. However, ARs play different roles at different stages of disease or in different subtypes of BC, and their significance is still under investigation.

ARs are expressed in up to 70 % of *ER-positive BC*. High levels of ARs confer a survival advantage, which suggests that ARs action may have a tumor-suppressive effect in malignant ER-positive BC cells. In this subtype of BC patients, AR expression is also associated with chemotherapy responsiveness [6].

Hickey et al. [2] observed that AR positivity was over 75 % in the large majority of prospectively collected cases of ER-positive breast cancers. This degree of AR positivity was higher than that observed in normal breast tissues. They hypothesized that AR levels increase with the progression of ER-positive tumor in a homeostatic attempt to restore the balance of sex hormone activity that normally regulates mammary epithelial cell proliferation. Failure to upregulate AR signaling may result in insufficient androgenic antagonism.

As mentioned above, multiple studies show that AR levels predict positive outcomes for women with luminal breast cancers; Castellano et al. [7] showed that AR is an independent prognostic factor in the luminal B subtype, which is a more aggressive form of luminal disease. They developed a new prognostic index (PI) specific for ER-positive breast cancers (ERPI), in contrast with other PIs that have been created for breast cancer in general. This new ERPI takes into account the expression of AR and demonstrates the prognostic relevance of its expression in breast cancers.

Up to 50 % of *ER-negative BC* are reported to be positive for ARs. Currently, epidemiological, clinical, and preclinical data on the role of androgens and ARs on this BC subtype are still controversial. The prognostic value of AR as an independent predictor of relapse-free or overall survival in ER-negative disease is less clear [2].

In *HER2-expressing cell lines*, preclinical studies suggest that ARs have a proliferative effect, probably due to the cross talk between ARs and HER2 pathways [8]. Micello et al. [9] studied a specific group of patients with breast cancer who were ER- and PR-negative and c-erbB-2-positive for their AR status and found that the group having positive AR had more frequent nodal involvement but similar survival rates. Arslan et al. [10] analyzed the same subtype of BC patients, but AR was not shown to be a prognostic factor. However, they concluded saying that they still do not exactly know the function of AR and its prognostic effect in this specific group of patients.

Finally, the biological significance of AR in *triple-negative breast cancer* (TNBC) has remained relatively unknown. The rate of AR positivity among TNBC cases varies depending on the study population (0–53 % of all TNBC patients) [11]. There are conflicting data on the issue; in the Tike et al. study [12], disease-free survival was significantly better in androgen receptor-positive, triple-negative breast cancer with a trend observed for improved overall survival. Androgen receptor positivity was associated with a favorable clinical outcome and a lower rate of recurrence within 5 years of diagnosis. The loss of AR expression was significantly associated with worse pathological parameters. However, there are data in the opposite direction that show AR as a negative prognostic factor for patients with TN breast cancer [13].

Many theoretical and experimental models indicate that androgen receptors can play an important role as prognostic factors in BC patients. But AR can be also considered as a *new therapeutic target*. Historically, systemic *androgen treatment* was used in the clinical management of breast cancer and was associated with a 15–30 % incidence of disease regression, particularly when the tumor expressed ER [14]. Additionally, treatment with the androgen resistant to metabolism fluoxymesterone was associated with a tumor-suppressive effect similar to the selective estrogen receptor modulator tamoxifen, with some evidence for beneficial combinatorial treatment effects [15]. Fluoxymesterone was also reported to improve the therapeutic efficacy of chemotherapy. Possibly, the efficacy of androgen treatment was in part due to its antiproliferative, antiestrogenic actions in the breast tumor cells, particularly those of a luminal phenotype. Recent literature has shown that dehydroepiandrosterone and its sulfate have growth-inhibitory effects on ER- and PR-negative breast cancer cell lines that show androgen receptor expression [16]. These may

potentially be applied as adjunctive therapy to ER-negative/androgen receptor-positive BC, considering the few treatment options for this BC subtype.

Another debated issue is the relationship between androgens and *aromatase inhibitors (AIs).* In contrast to tamoxifen, aromatase inhibition blocks conversion of androgens to estrogens increasing levels of available testosterone and/or DHT. Studies have implicated activation of AR as a partial mediator of aromatase inhibitor therapeutic efficacy in ER-positive BC [17]. Androgen treatment for hormone therapy may be considered in ER-positive disease that either do not respond to hormone therapy or become resistant [18].

In conclusion AR is an emerging target in breast cancer, with potential significance as a prognostic and/or predictive marker and for therapeutic management of both primary and advanced disease. Further prospective larger studies are needed for a more comprehensive investigation of the role of androgens and ARs in breast carcinogenesis. The simultaneous evaluation of ER status, AR expression, and circulating testosterone levels may identify different subsets of breast cancers whose management may be influenced by personalized treatment.

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Fertility Preservation and Pregnancy After Breast Cancer: When and How?

20

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20.1 Paper

Breast cancer is the most common malignant tumor in women. Survival has been steadily increasing in the last 15 years, with an actual 5-year survival of 87 %. Around 6 % of breast cancer cases occur in women younger than 40 years. These patients face specific issues compared to older women, including an increased risk of recurrence, inferior survival, and the need of a broader psychosocial support. Issues related to the effects of local and systemic treatments such as the alteration of body image, sexuality complaints, and fertility impairment have a higher priority in this young women population. A recently published EUSOMA recommendation states that fertility issues must be discussed before the start of any type of anticancer treatment and that the optimal type of fertility preservation, endocrine treatment duration, and the effect of subsequent pregnancies on breast cancer prognosis remain research priorities [1].

Currently *fertility preservation techniques* rely on cryopreservation of embryos, of mature oocytes, and of ovarian tissue and on the administration of GnRHa concomitant to chemotherapy [2]. The first three techniques are a part of a medically assisted reproduction program and require the patient's referral to a specialized center. Each of these techniques has advantages and disadvantages that must be evaluated considering each single case, but all of them must be carried on before starting oncologic treatments. *Embryo cryopreservation* is a well-established technique, but the need of a male partner or sperm donor for embryo cryopreservation is a requirement that cannot always be fulfilled. The ethical implications of the increasing number of embryos stored in IVF clinics and law restrictions make other techniques the

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_20

preferred option for fertility preservation [3]. *Oocyte cryopreservation* requires ovarian stimulation, mature oocyte retrieval, and subsequent slow freezing or vitrification. Thawing and subsequent intracytoplasmic sperm injection (ICSI) with embryo transfer can be performed years after the procedure. Controversial issues include the delay that this procedure might determine in the beginning of adjuvant therapy and the high estrogen levels reached during the stimulation. The delay is not such a relevant issue considering that ovarian stimulation requires approximately 2 weeks from the beginning of menstrual cycle and several studies of adjuvant chemotherapy suggest no detrimental effects, on survival or recurrence, if chemotherapy is started within 12 weeks after surgery [4]. Concerning the use of gonadotropins in ER+ and in ER− patients, the levels of serum estradiol (E2) during ovarian stimulation could be 30 times higher than those detected in a natural menstrual cycle. The potential detrimental effect of this estrogenic peak generated a vigorous debate on the risk of recurrence not only in ER+ but also in ER− patients. Some authors believe that there is no real risk in having a short-term increase in hormonal levels [5], if this is followed by chemotherapy. Recently, ovarian stimulation protocols with aromatase inhibitors have been proposed in order to avoid high estradiol levels and the recurrence rate of breast cancer does not seem to be increased [6, 7]. Due to the relatively short-term follow-up and the small number of patients, a final statement on the safety of this approach cannot yet be rendered. Azim et al. suggest that the use of letrozole and gonadotropins for controlled ovarian stimulation was unlikely to result in a significant increase in recurrence of breast cancer. Further research, including longer-term follow-up are needed to confirm these findings; in the meantime, the use of letrozole-FSH protocol in women with breast cancer who wish to preserve their fertility by oocyte or embryo cryopreservation is certainly a viable option [8]. *Ovarian tissue cryopreservation* is still considered an experimental technique but in recent years is achieving interesting results. The pickup of ovarian tissue can be done at any time of menstrual cycle, without delay in starting therapies, and it may be performed laparoscopically. At the appropriate time, when the patient decides to search pregnancy, the orthotropic transplantation has the greatest chances of success [9]. This technique does not require hormonal stimulation and allows the storage of a very large number of follicles. To date, approximately 20 children have been born worldwide after ovarian tissue cryopreservation [3], and the first live birth in Italy took place in February 2012. Some studies showed the effectiveness of *associating GnRHa to chemotherapy* in preserving ovarian function, probably for the temporary ovarian suppression during the treatment [10], but an international consensus on the gonadoprotective role of GnRHa has not been reached, and ovarian suppression with GnRHa during chemotherapy as a method to preserve fertility remains a highly controversial topic. The very recently updated clinical practice guidelines for fertility preservation in cancer patients released by ASCO in 2013 conclude that, given the current status of knowledge on this issue, GnRHa is not an effective method of fertility preservation, and encourage to include the patients in clinical studies [11]. To the same conclusions, get the ESMO recommendations on cancer, pregnancy, and fertility [12]. The large differences among studies in the definition of amenorrhea and the lack of more standardized and reliable

markers of residual ovarian reserve contribute to maintain this debate open. In the largest published randomized study (PROMISE) which included about 300 patients, about 9 % of patients in the GnRHa arm did not resume menses or showed FSH levels in the postmenopausal range after 1 year versus 26 % in the arm with chemotherapy alone [13]. On the other hand, the ZORO study failed to show any protective effect of the concurrent administration of goserelin on the rate of amenorrhea at 6 months, albeit the sample included was much smaller [14].

Concerning the safety and feasibility of pregnancy after breast cancer, many literature data have shown that *pregnancy* does not affect the *prognosis*, both in ER+ and ER− patients, even supposing a protective effect of pregnancy. In 2010, a large meta-analysis was published by Azim et al., with data from 14 studies for a total number of 1,244 cases and 18,145 controls. Authors showed a better overall survival (OS) for women who got pregnant following breast cancer diagnosis compared to those who did not get pregnant [HR: 0.59; 95 % CI 0.50–0.70]. Authors hypothesized that these results could present a selection bias, earlier described as the "healthy mother effect" phenomenon, but also the sensitivity analysis, performed including only those studies that had breast cancer controls known to be free of relapse, showed a trend toward improved survival for women who got pregnant, although not statistically significant [HR: 0.85; 95 % CI 0.53–1.35] [15]. Similar results were described by Kranick et al. in the same period, confirming no difference in prognosis, in terms of OS and disease-free survival (DFS) between cases and controls, respectively, for breast cancer patients who get pregnant or not [16]. Recently, these evidences have been confirmed by Azim et al. in another large multicenter study, evaluating the prognostic impact of pregnancy in the subgroup of women with a previous ER+ breast cancer. A total of 1,207 patients were included in the study, 333 women who became pregnant after breast cancer and 874 controls who did not became pregnant. No difference in overall event rate was observed between cases and controls [HR: 0.84; 95 % CI 0.66–1.06; $p=0.14$]. Of note, no difference was observed for either ER+ or ER− cohorts. Better overall survival was reported in the group of pregnant patients ($p=0.03$), independently from ER status ($p=0.11$). Moreover, in this study, breastfeeding and *time to pregnancy* seemed to have no effect on risk of relapse in women who achieved a term pregnancy [17]. The *timing of pregnancy* following breast cancer diagnosis is a crucial point. Biological evidence suggests that pregnancy might serve as a fertile soil for incipient lesions in the breast in the short term [18]. A recent population-based study [19] has shown that the risk of death decreases significantly with increasing interval between diagnosis and subsequent childbirth. In an interesting review, Azim Jr. and colleagues [20] found that pregnancy 2 years following breast cancer diagnosis conferred a significant reduction in overall mortality (pooled relative risk: 0.55; 95 % CI: 0.36–0.84; p-value for heterogeneity = 0.16). Therefore, it is common practice that a minimum period of 2 years following diagnosis should be allowed before attempting to get pregnant. For patients with a history of ER-positive breast cancer, *5 years of adjuvant hormonal therapy* remains the current standard of care [21], and pregnancy should be postponed to allow the complete endocrine treatment. This allows a reduction in the relative breast cancer recurrence risk and the relative risk of death.

A conflict will always remain for those women with ER-positive disease who wants to *prematurely stop their hormonal therapy* to become pregnant. The best option is to wait until the end of the treatment, with a tamoxifen-free interval of at least 3 months. Nonadherence to tamoxifen therapy, in particular early discontinuation of treatment, is likely to result in worse outcomes, notably in high-risk patients. Comparison of treatment durations indicates that women receiving less than 5 years therapy have higher breast cancer recurrence rates and mortality. Discontinuing tamoxifen after 2–3 years reduces the clinical benefit but allows to satisfy the desire for motherhood in young women; moreover, tamoxifen treatment could be completed after childbirth. If in case of spontaneous pregnancy during tamoxifen use, it should be stopped as soon as possible to avoid its possible teratogenic effects. Finally, before a planned pregnancy is initiated, a complete checkup including clinical breast examination, mammography, ultrasound scan, and, if necessary, MRI should be performed, as well as a complete metastatic workup.

The large number of publications on the issue of fertility preservation and pregnancy in breast cancer patients underscores the extreme relevance of this topic and supports the guideline recommendation to offer to all young patients a fertility counseling before starting any antineoplastic treatment. Fertility preservation is a multidisciplinary field that requires the collaboration and coordination of professionals from different specialties. Physicians should share with patients the available options for fertility preservation and the evidence about safety of pregnancy after cancer to make a customized and informed decision.

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Low Malignant Potential Tumors

21

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21.1 Etiology and Associated Factors

The *etiology* of LMP tumors remains unclear because of the small number of cases. Risks factors are similar to those involved in malignant epithelial ovarian cancers: increasing parity, breastfeeding, and use of oral contraceptives reduce the risk, and the effect is most pronounced for serous tumors; high body mass index (BMI) is associated with elevated risk of serous borderline tumor; current smoking is a strong risk factor only for mucinous tumors; finally, increasing consumption of milk increases the risk of borderline tumors in general [1]. *BRCA* mutations and other hereditary breast-ovarian cancer syndromes do not seem to play a significant role in the development of borderline ovarian tumors [2].

21.2 Pathology

On the basis of recent morphologic and molecular genetic studies, a dualistic pathogenesis of ovarian cancer has been shown, and two broad categories of epithelial ovarian tumors have been proposed [3]. *Type I* tumors comprise low-grade serous, low-grade endometrioid, mucinous, and clear cell carcinomas. *Type II* tumors include high-grade serous, high-grade endometrioid, undifferentiated carcinomas

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9_21

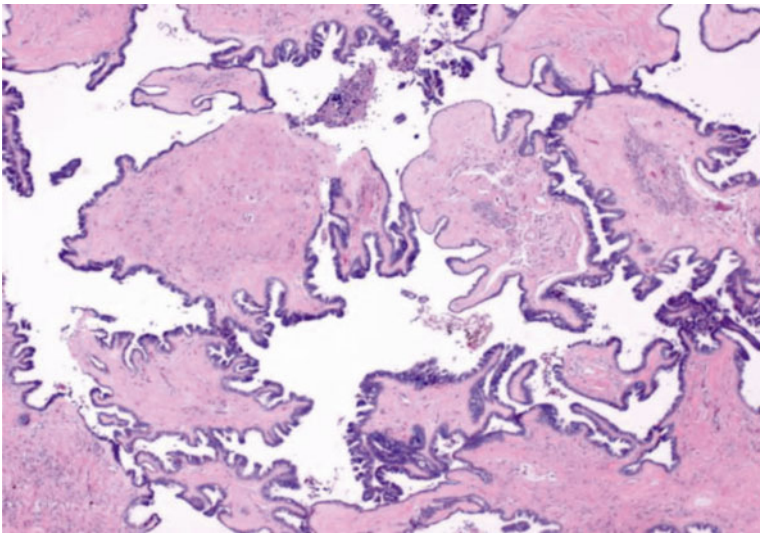

Fig. 21.1 Serous borderline tumor

and malignant-mixed mesodermal tumors. In such a classification, borderline tumors should be part of a stepwise progression from benign through varying degrees of atypia to noninvasive and then invasive low-grade carcinoma (type I) [4]. Type I tumors have a relatively indolent course and are associated with mutations in KRAS, BRAF, PTEN, PIK3CA, CTNNB1, ARID1A, and PPP2R1A [5], instead of type II tumors, which are aggressive and typically present at an advanced stage, which contributes to their high fatality.

Grossly, borderline tumors are cystic masses, whose size can range from 2 to 25 cm, and they may not be distinguishable from cystoadenocarcinomas. Histologically, borderline tumors must have at least two of the following features: nuclear atypia, stratification of the epithelium, formation of microscopic papillary projections, cellular pleomorphism, and mitotic activity. They are distinguished from invasive carcinomas because borderline tumors do not have stromal invasion. However, around 10 % of LMP tumors may present focal microinvasion areas smaller than 3 mm of diameter and involving less than 5 % of the surface of the neoplasm [6]. For these reasons, it could be pretentious to diagnose an LMP tumor during the frozen section [7].

Serous and mucinous borderline tumors are the most common subtypes, but other rare entities (Figs. 21.1 and 21.2), such as endometrioid, clear cells, and Brenner tumors, have been reported in literature with a very low incidence (<5 %).

A minority of serous borderline tumors (6–18 %) have an unusual micropapillary histological pattern (Fig. 21.3). A continuous 5 mm micropapillary growth pattern in a single slide is generally required for the diagnosis. They are more often bilateral, have a higher frequency of advanced stage, and, according to some authors, have a more aggressive course.

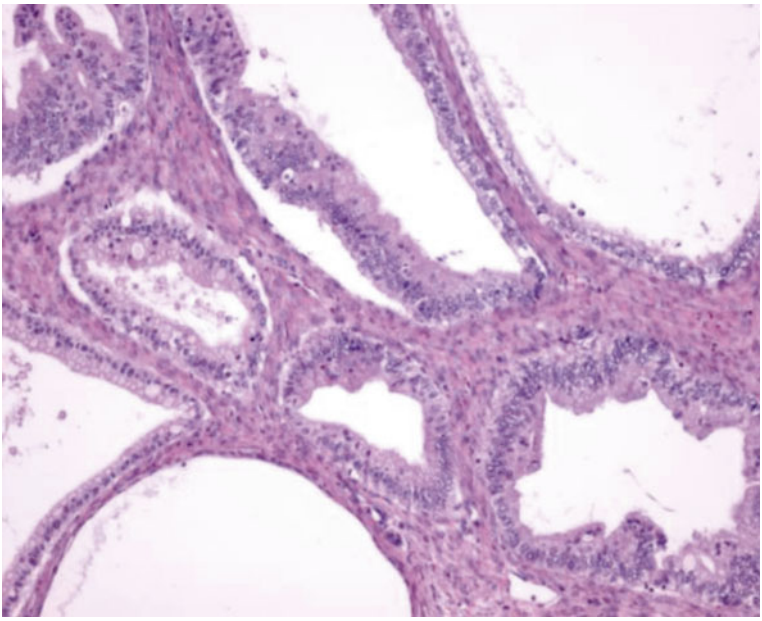

Fig. 21.2 Mucinous borderline tumor

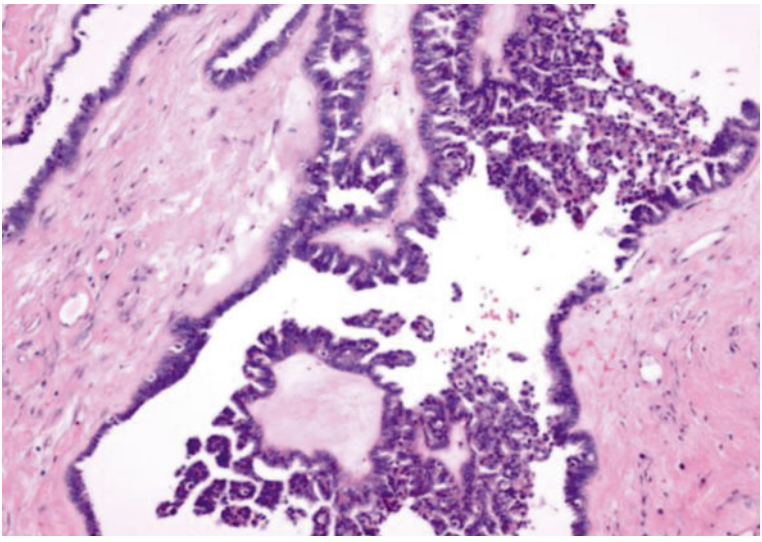

Fig. 21.3 Serous borderline tumor with micropapillary pattern

LMP tumors are staged as invasive ovarian cancer [8]. The documentation of a surface component or intraoperative rupture is important for an appropriate staging.

Peritoneal disease from borderline ovarian tumors is considered implants and not metastases, and they are distinguished as noninvasive (nearly 85 %) or invasive, according to the presence of stromal invasion. An important review reports a mortality rate for patients with noninvasive and invasive implants of 4.7 and 34 %, respectively [9], and for others the prognosis is similar.

Lymph node involvement at the time of surgery is rare, and few patients develop postoperative lymph nodal disease.

The risk of progression to invasive carcinoma is very low and estimated around 2–3 %.

21.3 Clinical Features and Diagnosis

Ovarian borderline tumors have the same clinical features of other *pelvic masses*. Woman can complain pain or distension of the abdominal circumference. More frequently, the mass can be completely asymptomatic and found during routine pelvic examination or abdominal ultrasound scan.

The relevance of serum tumor markers in patients with LMP tumors is controversial. Elevated serum concentrations of CA125 are reported in about 40 % of patients with stage I borderline ovarian tumors and in 83 % of women with advanced-stage disease. No data are available about other serum tumor markers (CA15.3, CA19.9, carcinoembryonic antigen).

Pelvic ultrasound is the gold standard for the definition of the pelvic masses, and many classifications have been proposed in literature [10].

Findings of radiological studies underline the contribution of perfusion-weighted and diffusion-weighted MRI sequences for differentiation between benign lesions, borderline ovarian tumors, and ovarian cancer [11].

Finally, the large majority of LMP tumors have been diagnosed incidentally intra- or postoperatively, and this issue represents a further complication in the management of this disease.

21.4 Treatment

Standard surgical treatment for LMP ovarian tumors includes *bilateral salpingo-oophorectomy* with or without hysterectomy.

In those patients with intraoperative diagnosis, staging surgery must be provided, and it consists in peritoneal washing, infracolic omentectomy, random peritoneal biopsies in at least six different areas of the abdomen, contralateral ovarian biopsy (if conservative surgery), and appendectomy in mucinous tumors [12]. The value of complete staging has not been demonstrated for early-stage cases, but the opposite ovary should be carefully evaluated for evidence of bilateral disease [13].

Patients with advanced disease should undergo a total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, node sampling, and aggressive cytoreductive

surgery. Patients with stage III or IV disease with no gross residual tumor have had a 100 % survival rate in some series regardless of the follow-up duration [14].

In the last decade, because of the young age of most patients with LMP tumors and the highly favorable prognosis, *conservative surgery* that contemplates the preservation of the uterus and at least a part of one ovary is strongly increasing.

Several studies have been reported about conservative treatment in early-stage LMP ovarian tumors. *Fertility-sparing* surgery is associated with a higher rate of recurrences than radical surgery, but it does not affect on survival, because most recurrences are borderline lesions again and can be treated with secondary surgery, possibly conservative [15–17].

Conservative surgery can be either unilateral salpingo-oophorectomy or cystectomy. In case of cystectomy, the cyst is stripped off from the remaining ovarian parenchyma, and rupture or spillage inside the abdomen must be avoided. In case of laparoscopy, the specimen must be removed through an endo-bag.

In the literature, recurrence rates are between 0 and 20 % after unilateral salpingo-oophorectomy, between 12 and 58 % after *cystectomy*, and between 3 and 6 % after radical surgery [18]. The safety of conservative surgery for patients with stage I LMPT has been largely confirmed by many studies, and unilateral salpingo-oophorectomy must be considered as the first choice of conservative treatment; cystectomy should be counted for patients with a history of contralateral oophorectomy or in case of very young patients with bilateral tumor [16].

In case of fertility-sparing surgery, *endometrial biopsy* is recommended, because synchronous endometrial disorders (low-grade tumor or hyperplasia) may occur more frequently in young women.

After completion of childbearing, in patients with borderline tumors and in postmenopausal women, prophylactic contralateral salpingo-oophorectomy and hysterectomy are recommended.

The role of *laparoscopy* has been long discussed, because of the higher risk of cyst rupture and the potential risk of tumor metastasis in the port site [19]. Indeed, the frequency of cyst rupture during laparoscopy was the same as during laparotomy [20], and the rate of recurrence after laparoscopy is similar to conservative treatment. Few cases of port-site metastasis have been reported in literature after laparoscopy for borderline ovarian tumors, and none of them died of the disease.

In case of laparotomy, a vertical median incision is preferred to guarantee the access to the upper abdomen.

A very low rate (38 %) of adequate *staging* (peritoneal washing, peritoneal biopsy, and omentectomy) is reported in the literature during initial surgery, even when the borderline is intraoperatively diagnosed. In case of diagnosis with the final histology, every case should be discussed with a gynecologic oncologist. A surgical restaging does not seem to be necessary if the disease appears confined to a single ovary, because data suggest that complete staging does not improve the outcomes. However, the rate of recurrence is lower in those patients who received a complete staging than in those with incomplete staging [21]. According to available literature, surgical restaging could probably be omitted provided that the peritoneum is clearly

reported as "normal," there is no micropapillary pattern, and the patient accepts a stringent follow-up. On the opposite mucinous borderline ovarian tumors treated by cystectomy, those with micropapillary pattern and microinvasion possibly should undergo secondary restaging.

In advanced LMP tumors, surgery should include resection of all macroscopic peritoneal implants. Surgical procedures to achieve complete removal of peritoneal disease are the same as in advanced ovarian cancer, and *postoperative residual disease* is one of the most important prognostic factors [22]. In addition to the therapeutic effect, complete removal of peritoneal implants allows an accurate histological diagnosis.

Lymph nodes are involved in about 25 % of advanced [23], but several authors did not report any beneficial effect of the nodal dissection on survival in patients with borderline ovarian tumors [24]. In the absence of enlarged nodes or a frozen section suggestive of invasive implants, pelvic and para-aortic lymphadenectomy is not necessary.

The value of the second-look surgery in patients treated with conservative surgery has not been assessed in any study.

Adjuvant *chemotherapy* in women with early-stage serous borderline ovarian tumors does not have any beneficial effects on overall survival. In the same way, no advantages of adjuvant chemotherapy are recorded in patients with FIGO stage II–IV borderline ovarian tumors [25]. Debate persists for patients with invasive implants. Without any proven effectiveness, chemotherapy (platinum-based regimen with paclitaxel) is often proposed in patients with advanced LMP ovarian tumor with invasive implants. Some authors suggest the inhibition of PARP1 or MAPK pathway in specific settings.

21.5 Prognosis, Surveillance, and Recurrent Disease

The *prognosis* of patients with LMP tumors is excellent. Five-year and ten-year survival rates for stage I, II, and III disease are 99 and 97 %, 98 and 90 %, and 96 and 88 %, respectively [26].

Multiple prognostic factors are reported in literature: invasive implants and residual peritoneal disease are the most accepted. Micropapillary pattern, conservative treatment with cystectomy, and surgical staging and restaging are still debated. Laparoscopic approach and conservative treatment with unilateral salpingo-oophorectomy are not considered as prognostic factors anymore.

Few series have been published specifically on the *follow-up* of LMP tumors. A raised serum level of CA125 usually represents the initial step for the recurrence diagnosis. Transvaginal ultrasonography is the most effective procedure after conservative management of early-stage disease. A combination of follow-up procedures (pelvic exploration, abdominal ultrasound, and CA125) seems to be an adequate option, particularly in patients treated with conservative surgery. CT or MRI should be proposed only for women with abnormal or inconclusive findings on ultrasound.

Many series about *fertility* in patients conservatively treated for LMP tumors are reported. Patients with borderline tumors frequently (10–35 %) present with a history of infertility [27] and a somewhat increased risk after fertility treatment is described. The use of cystectomy improves fertility results; this treatment should be preferred in patients with bilateral tumor or previous contralateral oophorectomy [28]. The age of the patient should be taken into account when deciding for fertility-sparing surgery: many studies clearly demonstrate that spontaneous fertility is lower in patients older than 40 years [29]. The histologic subtype of the tumor seems to be associated to fertility: non-serous tumors (mainly mucinous) have better fertility outcomes when compared with serous LMP tumors [24]. Little is known of the impact of fertility drugs after conservative treatment for LMP. Cryopreservation of ovarian tissue is feasible, but reimplanting ovarian tissue brings the potential risk of implanting tumor cells as well [30].

Because of the indolent behavior of the disease, *recurrence* and death can occur 20 years or more after diagnosis [31]. For most relapses, surgery alone is the treatment of choice. Chemotherapy is indicated for patients with invasive recurrences or rapid tumor growth.

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B.C.J.M. Fauser, A.R. Genazzani (eds.), *Frontiers in Gynecological Endocrinology: Volume 2: From Basic Science to Clinical Application*, ISGE Series, DOI 10.1007/978-3-319-09662-9