Basic Infertility Including Polycystic Ovary Syndrome

Maryse Brassard, MD\textsuperscript{a}, Youssef AinMelk, MD\textsuperscript{b}, Jean-Patrice Baillargeon, MD, MSc\textsuperscript{a,}\textsuperscript{*}

\textsuperscript{a}Division of Endocrinology, Department of Medicine, Université de Sherbrooke, 3001, 12th North Avenue, Sherbrooke, QC J1H 5N4, Canada

\textsuperscript{b}Department of Obstetrics and Gynecology, Université de Sherbrooke, 3001, 12th North Avenue, Sherbrooke, QC J1H 5N4, Canada

Infertility is the inability of a couple to conceive after 12 months of unprotected and frequent intercourse. It affects about 10% to 15% of couples \[1\]. Cycle fecundability is the probability that a single cycle will result in pregnancy and is approximately 20% in normal couples \[2\]. It typically decreases with age. The fertility rate in developed countries has declined in recent years and can be attributed mainly to delayed childbearing.

The effect of aging on female fertility is clear: In women, the fertility peak is between the ages of 20 and 24 years, decreases slightly by age 32, and then declines progressively and more rapidly after age 40 \[3,4\]. Decreasing fertility is associated with increasing pregnancy wastage. Spontaneous miscarriage increases from 10% in younger women to 40% at age 40, even with assisted reproductive technology. This increase is due to progressive follicular depletion and a high incidence of abnormalities in aging oocytes, mainly aneuploidy.

In addition to age, other factors that influence fertility include lifestyle (smoking, alcohol, caffeine, drugs, and body mass index) and the timing and frequency of intercourse. Normal sperm can survive at least 3 days, but an oocyte can be fertilized for only 12 to 24 hours.

The major causes of infertility include tubal and peritoneal pathology (30%–40%), ovulatory dysfunction (15%), and male factor (30%–40%) \[5\]. Uterine and cervical factors are uncommon. Patients without an

\textsuperscript{This work was supported by Personal Award \#12131 to Jean-Patrice Baillargeon from the Fonds de la recherche en santé du Québec.}

\* Corresponding author.

\textit{E-mail address:} jp.baillargeon@usherbrooke.ca (J-P. Baillargeon).
identifiable cause are classified as unexplained infertility (10%). Ovulatory dysfunction and unexplained infertility have the best prognosis. This article reviews the evaluation and treatment of female infertility.

**Initial evaluation**

The evaluation should be initiated after 12 months of unprotected intercourse, at which time 85% of couples attempting conception will have been successful [6]. In women between 35 and 40 years of age, assessment should be considered after 6 months. In such females with oligomenorrhea or amenorrhea, or a history of pelvic infection or chemotherapy [1], assessment should be considered sooner.

Initial evaluation includes a complete medical history, physical examination, and screening tests for cervical dysplasia and sexually transmitted infections, including gonorrhea and chlamydia. Basic testing consists of semen analysis, documentation of ovulation (eg, midluteal phase progesterone level above 6.5 ng/mL followed by menstrual bleeding within 2 weeks), and a hysterosalpingogram to assess possible tubal factors. If an obvious cause, such as oligoanovulation, is determined during initial clinical evaluation, semen analysis and hysterosalpingogram can be postponed until after resolution of this condition, assuming that infertility persists. The next steps in the evaluation of female infertility are based on the most probable causes initially identified. These are discussed in this article and summarized in Fig. 1.

**Tubal and peritoneal pathology**

**Tubal factors**

Approximately 20% of female infertility results from tubal disease. This disease can be suspected by a history of pelvic infection disease (PID), tubal or pelvic surgery, or ectopic pregnancy. Infection by *Chlamydia trachomatis* is one of the main causes of tubal injury, which can ultimately lead to tubal occlusion or adnexal adhesions. Subclinical salpingitis is even more common than symptomatic PID, and can occur despite appropriate antibiotic therapy. The incidence of tubal disease is 10% after one episode of PID and 54% to 75% after three episodes [7]. The mechanism involves anatomic abnormalities in the tubes that prevent the union of sperm and ovum.

The classic methods for evaluation of tubal patency are hysterosalpingography (HSG) and laparoscopy with chromotubation. HSG is performed by injecting water-soluble contrast through the cervix into the uterus. HSG images the uterine cavity and reveals the internal architecture and patency of the tubal lumen. Laparoscopy is regarded as the definitive test for the evaluation of tubal factors. It provides more detailed information, such as
pelvic anatomy, adhesions, and endometriosis. Laparoscopy also offers the opportunity to treat disease at the time of diagnosis. Chlamydia antibody testing has been shown to be as predictive as HSG, or even laparoscopy, for the detection of tubal pathology [8]. The role of chlamydia antibody tests in the evaluation of the infertile women has not yet been defined, but may prove useful as a pretest to select women who warrant earlier or more detailed evaluations [2,9].

The treatment options for tubal factors include reconstructive surgery and in vitro fertilization (IVF). In selected cases, a microsurgical procedure, such as fimbriolysis and fimbrioplasty, may be used. In most cases, especially in older women, IVF is more efficient and more effective [10].

**Uterine factor**

Abnormalities of the uterine cavity are a relatively uncommon cause of infertility. Abnormalities include congenital malformations, such as a septum or bicornuate uterus, leiomyomas, intrauterine adhesions (Asherman’s syndrome), and endometrial polyps. Uterine abnormalities more commonly affect pregnancy outcome than fertility. Assessment of the uterine cavity can be obtained by HSG, transvaginal ultrasound (for uterine malformations

---

**Fig. 1. Algorithm for investigation and treatment of infertile women.** IUI, intrauterine insemination; IVF, in vitro fertilization; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone.
and myomas), sonohysterography (for submucosal myomas and endometrial polyps), hysteroscopy (the definitive method for diagnosis and treatment of intrauterine pathology), MRI, and laparoscopy.

The management of uterine myoma in infertile women must be individualized. The decision for surgical treatment varies depending on age and duration of infertility after excluding other infertility factors [11]. It appears that submucous myomas can lower the rate of pregnancy and implantation [12]. In one study, myomectomy for a submucous myoma increased the pregnancy rate from 27.2% (no treatment) to 43.3% (myomectomy), though there was no improvement in the pregnancy rate following myomectomy in locations outside the uterine cavity.

For intrauterine adhesions (ie, synechiae), predisposing events can usually be identified, such as pregnancy termination or postpartum curettage. The presence of adhesions can be confirmed by HSG, though hysteroscopy is considered the preferred technique for diagnosis and treatment [13]. Hysteroscopy is also appropriate for diagnosis and treatment of uterine septum.

Cervical factor

Cervical mucus is important in the reproductive process. Estrogen stimulates cervical mucus while progesterone inhibits its production and permeability. The traditional postcoital test, the Sims-Hühner test, has a poor predictive value for infertility and its utility has been debated. Routine postcoital testing is not recommended [6]. Because there is no good method for diagnosing infertility due to cervical factor, that diagnosis is usually a one of exclusion when ovulation and semen analyses are normal and the tubes are patent. It is usually included in unexplained infertility (see Fig. 1). Common treatments for cervical factor infertility bypass the cervix and include intrauterine insemination and IVF.

Endometriosis

There is a higher incidence of endometriosis in infertile women (25%–48%) as compared with all women in the reproductive age group (3%–10%) [2]. Despite this association, a causal link between endometriosis and infertility has not been clearly demonstrated and management of infertility associated with endometriosis remains challenging. In severe endometriosis, pelvic adhesions can clearly distort the relationship of the tubal fimbria and ovarian follicles with resulting infertility. In minimal and mild endometriosis, mechanisms that cause reproductive failure are subtler and remain controversial. They include alterations in peritoneal fluid as a result of inflammatory factors (macrophages, cytokines, and growth factors). Such alterations can affect ovum maturation, fertilization, or implantation. Endocrine and ovulatory abnormalities are among other mechanisms that may cause reproductive failure in minimal and mild endometriosis [14,15].
Fecundity in women with untreated endometriosis is only 2% to 3% per cycle, far below the normal monthly rate of 20%. The medical treatment of endometriosis with a period of ovulation suppression does not improve subsequent fecundity and fertility [2].

Conservative surgical therapy, such as ablation of endometriosis implants, can improve the fecundity in patients with severe disease by up to 50%, but is still controversial in patients with mild endometriosis. A randomized trial of laparoscopic ablation treatment for minimal or mild endometriosis demonstrated a significant increase in the rate of pregnancy [16]. Thirty-six weeks after surgery, 29% of treated women achieved an ongoing pregnancy compared with 17% of those who were not treated. However, a smaller Italian trial with similar design and laparoscopic ablation therapy showed no effect on live birth rate [17]. Other approaches to consider for treatment of endometriosis are expectant management, superovulation with intrauterine insemination for young patients (<35 years old), or IVF for older women (>35 years old). For more advanced cases, IVF preceded by 3 months of medical treatment for endometriosis is suggested.

Ovulatory dysfunction

Ovulatory dysfunction is associated with infertility and is usually manifested either by oligomenorrhea, defined as eight or fewer menstrual periods per year, or amenorrhea, defined as the absence of menstrual bleeding. This lack of menstrual periods may be classified as primary or secondary. Primary amenorrhea refers to absence of menses by the age of 14 years in the absence of secondary sexual characteristics or by the age of 16 years in the presence of secondary sexual characteristics. Secondary amenorrhea applies to women who have not menstruated for at least 6 months but who have previously menstruated. Furthermore, it is estimated that about 10% of “normal” menstrual cycles of 35 days or less are actually anovulatory. The causes of ovulatory dysfunction are discussed below.

Hypogonadotrophic hypogonadism

Hypogonadism is defined as an abnormal decrease in the functional capacity of the gonads and is classified as hypergonadotrophic or hypogonadotrophic, depending on whether the disease is of gonadal or pituitary/hypothalamic origin. In the presence of abnormal sex hormones and gamete production, low levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are indicative of hypogonadotropic disease, whereas high levels reflect a hypergonadotropic hypogonadism. Causes of hypogonadotropic hypogonadism are listed in Box 1.

Patients with Kallmann syndrome have hypogonadotropic hypogonadism along with anosmia. The clinical feature of anosmia relates to the embryologic development of gonadotrophin-releasing hormone (GnRH)
neurones. Kallmann syndrome is a genetically heterogeneous condition and affects 1 in 70,000 females [18]. In addition to anosmia, other possible features of Kallmann syndrome include unilateral renal agenesis, synkinesia (mirror movements), hearing loss, midline facial defects, cryptorchidism, and bone abnormalities [19–21]. Recently, scientists have isolated the KAL gene as a cause of at least some forms of Kallmann syndrome [22–25].

Functional hypothalamic amenorrhea is one of the most frequently encountered forms of ovulation dysfunction. This endocrine disorder is due to a deficiency of pulsatile GnRH secretion unrelated to hypothalamic-pituitary organic lesions nor endocrine or systemic diseases [26,27]. Based on the degree of GnRH suppression, these women can present with different clinical profiles that vary from an inadequate luteal phase, to anovulation with menstrual irregularity, to hypothalamic amenorrhea [27]. The incidence of functional hypothalamic amenorrhea ranges from 15% to 48% [28,29] of women with secondary amenorrhea. In clinical practice, functional hypothalamic amenorrhea is often associated with stressors (metabolic, physical, or psychologic), with weight loss due to decreased caloric intake, or with intensive physical exercise [26]. Statistics show that the prevalence of reproductive dysfunction is 6% to 79% in athletic women [30].

Suppression of gonadotrophin release may occur when there is acute [31,32] or chronic [33,34] systemic disease, which can acutely suppress the hypothalamic-pituitary-gonadal (HPG) axis. Chronic systemic illnesses most associated with hypothalamic-pituitary dysfunction include chronic renal failure and AIDS. Acute illnesses, in turn, may lead to transient forms of either hypogonadotropic or hypogonadotropic hypogonadism [35,36]. In fact, suppression of the GnRH pulse generator in response to the physiologic stress of any severe illness inhibits the release of pituitary gonadotropins [31,32] in the same way that excessive exercise does.

A few drugs are incriminated in the pathogenesis of hypogonadotrophic hypogonadism. Opioid use is the most common cause of iatrogenic hypogonadism, and it may have a toxic effect on the reproductive axis. The mechanism of amenorrhea in opioid users is probably attributable to

**Box 1. Causes of hypogonatotropic hypogonadism**

- Kallmann syndrome
- Functional hypothalamic amenorrhea, including eating disorders, intense exercise, stress from systemic disease
- Iatrogenic causes from drugs, pituitary surgery, cranial radiation
- Tumors of the central nervous system
- Sheehan’s syndrome, trauma
- Infiltrative disorders of the pituitary
- Hyperprolactinemia
opioid-induced hypothalamic GnRH suppression [37]. Other drugs causing infertility are certain psychotropic drugs, such as phenothiazines and risperidone, which block prolactin-inhibiting dopamine release [38,39]. Also, anabolic androgenic steroids can cause hyperandrogenism and menstrual irregularity.

Most central causes of hypogonadism that are organic in nature can be attributed to pituitary and hypothalamic lesions. Other causes of structural etiology include infiltrative diseases, such as sarcoidosis, histiocytosis, and hemochromatosis; head trauma; pituitary apoplexy; and cranial irradiation or surgery. Tumors of the central nervous system, such as craniopharyngiomas, germinomas, and other extrasellar germ cell tumors, may interfere with FSH secretion and lead to ovulatory function failure. Patients who have low levels of other hormones, symptoms of a pituitary tumor (such as frontal headache or reduced visual fields), or increased prolactin levels not due to medication, warrant pituitary MRI. Pituitary imaging is also required when drug-related hyperprolactinemia is associated with one of these factors.

The impact of elevated prolactin on the gonads is hypothesized to result from disruption of normal GnRH pulsatility and consequent alterations in the secretion of FSH and LH [40]. The clinical expression is anovulation, with either amenorrhea or oligomenorrhea in most women, as well as galactorrhea and decreased libido. Hyperprolactinemia can be divided into pituitary and nonpituitary causes. Pituitary causes include prolactin-secreting adenomas, nonsecreting pituitary tumors or cysts, and idiopathic hyperprolactinemia. Any disruption of the pituitary stalk, usually by macroadenomas, can lead to failure of the normal hypothalamic suppression of prolactin by dopamine. Nonpituitary causes of hyperprolactinemia are common and include pregnancy, hypothyroidism, and dopamine-antagonist drug therapy (eg, phenothiazines and metoclopramide). Some women with polycystic ovary syndrome (PCOS) have mild hyperprolactinemia [41]. Treating prolactinomas or idiopathic hyperprolactinemia with dopamine agonists reduces tumor size and prolactin levels, normalizes abnormal sexual function, and improves fertility.

**Hypergonadotropic hypogonadism**

Premature ovarian failure (POF) is diagnosed when sex steroid deficiency, elevated gonadotropins, and amenorrhea are found in women under the age of 40 [42–44]. Spontaneous 46,XX POF is not a rare condition. The age-specific incidence is approximately 1 in 250 women by age 35 and 1 in 100 by age 40 [43]. In around 10% of patients, the disorder is familial [45].

POF most commonly presents as secondary amenorrhea, though it may present rarely as primary amenorrhea with variable degree of secondary sexual characteristics. As estrogen deficiency progresses, vasomotor symptoms and symptoms of atrophic vaginitis eventually become prominent. Women suffering from POF are at increased risk of developing a variety
of comorbidities [46,47] and nearly double their age-specific mortality risk [48]. They are deficient in sex steroids and therefore have a significantly increased risk of osteoporosis [49,50], particularly in those who have developed POF before achieving peak adult bone mass. The risk of cardiovascular disease in POF sufferers is also significantly increased [51,52], which is probably caused by lower high-density lipoprotein cholesterol and higher insulin resistance than those of age-matched premenopausal women [53].

The most troublesome aspect of the disorder for these young women is infertility [54]. Previously, they were considered as irreversibly sterile. However, accumulating evidence has demonstrated that the infertility associated with POF is not absolute. Up to 50% of young women with 46,XX spontaneous POF have remaining follicles in their ovaries [55,56] and are probably more affected by follicular dysfunction than follicular depletion. Studies in women with POF have demonstrated that up to 20% of patients ovulate spontaneously during 4 months of observation, nearly 50% have intermittent ovarian follicle function (as defined by serum estradiol > 50 pg/mL) [56], and 5% to 10% unexpectedly became pregnant some time after diagnosis [57,58]. But ovulations are unpredictable, making appropriate timing of intercourse or insemination impossible. There is no evidence that such treatments enhance the pregnancy rate in patients with POF [57].

There are a variety of causes of POF: chromosomal and genetic abnormalities, autoimmune disease, viral infections, and iatrogenic therapies, such as pelvic surgery, chemotherapy, and radiotherapy. In the majority of cases, however, no etiologic factor can be identified [59]. In fetuses with 45,XO karyotype (Turner’s syndrome), ovaries develop normally in utero. Due to the absence of the second X chromosome, accelerated follicle atresia occurs from week 18 of pregnancy onwards or over the first few postnatal months and years, leading to POF [60,61]. Mosaicism, typically 45,XO/46,XX or 46,XX/47,XXX, is more common and characterized by a milder clinical phenotype [62]. Other genetic mutations have also been associated with POF [63,64].

However, in the past 3 decades, much evidence has accumulated to suggest that autoimmune mechanisms are involved in pathogenesis of up to 30% of cases of POF [65,66]. Autoimmune lymphocytic oophoritis is a clearly established mechanism of 46,XX spontaneous POF, which can present in an isolated manner or as part of the autoimmune polyendocrinopathy syndrome, type 1 [67].

Women less than 40 years old with 4 or more months of amenorrhea should have an FSH measured with a repeat in 1 month if it is elevated. If two levels are in the menopausal range (> 40 IU/L by radioimmunoassay), POF is diagnosed. These women should have a karyotype [44] and thyroid function studies [68] performed. Hypothyroidism, as well as adrenal insufficiency, is associated in 3% of cases [69]. Other invasive procedures do not change management or prognosis.
Providing hormone replacement to induce regular menses is probably indicated in these women to normalize symptoms and decrease the risk of osteoporosis associated with estrogen deficiency, to reduce the risk of adenocarcinoma with an effective progestin replacement, and possibly to improve chances of spontaneous pregnancy [70]. However, the effectiveness of this strategy to improve fertility has not been confirmed [71].

**Ovulatory dysfunction without hypogonadism**

**Polycystic ovary syndrome**

*Introduction.* Defined by Stein and Leventhal [72] in 1935, PCOS is now thought to be the most prevalent endocrine disorder in young women, affecting 6% to 10% [73–77] of women of childbearing age and accounting for 70% of anovulatory subfertility [78]. In a British population study, 37% of amenorrheic and 90% of oligomenorrheic women treated for infertility had PCOS [79]. Also, PCOS is one of the major causes of infertility overall, affecting up to 20% of infertile couples in some studies [80,81]. Its diagnosis is important not only for the short-term fertility issue, but also for long-term considerations, such as metabolic or insulin resistance syndrome and its associated consequences.

*Diagnosis and clinical presentation.* Based on criteria established during the European Society of Human Reproduction & Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) consensus conference in Rotterdam in 2003 [82], PCOS is diagnosed in the presence of two factors among the following: menstrual irregularity, hyperandrogenism (clinical or biochemical), and polycystic ovaries after excluding other secondary causes of hyperandrogenism, such as congenital adrenal hyperplasia (CAH), Cushing’s syndrome, hyperprolactinemia, or an androgen-secreting tumor. This definition has been revised in a published Androgen Excess Society guideline, which recommends that hyperandrogenism be mandatory for the diagnosis of PCOS [83].

Menstrual irregularity typically manifests at the time of menarche in women with PCOS, and menarche may be delayed. Some may have normal menses at first and then develop menstrual irregularity later in life, often after weight gain. Affected women are typically anovulatory with resulting oligomenorrhea or amenorrhea. Heavy bleeding in this situation is typical of anovulatory menses. Infertility in PCOS is mostly related to this chronic absence or low rate of ovulation, but also to an increased rate of early pregnancy loss.

Hyperandrogenism is usually a presenting feature of the syndrome, manifested clinically by hirsutism (excess pigmented body hair with a male distribution), acne, and male-pattern alopecia. Evidence of virilization, such as clitoromegaly, increased muscle mass, and deepening of the voice should raise concern for androgen-secreting neoplasm of the ovary or
adrenal gland, but can also be the result of hyperthecosis, a rare and extreme form of PCOS. Circulating androgens, especially testosterone and androstenedione, are found to be elevated in 50% to 90% of patients, depending upon the androgen measured and technique employed [84]. The ultrasound criteria for polycystic ovaries [82] are based on the presence of 12 or more 2- to 9-mm follicles in each ovary, or ovarian volume greater than 10 mL.

A recent prospective systematic study screened 400 unselected reproductive-aged women in the United States to determine the prevalence of PCOS and performed a phenotyping of the women involved [77]. The proportion of overweight and obese women with PCOS seems to be the same as in the general population. Though the proportion of women with the syndrome is similar in normal and obese patients, obese women often have more severe hormonal and metabolic abnormalities [85]. Indeed, obesity increases the degree of insulin resistance typically found in PCOS women, which plays a key role in PCOS pathophysiology, as discussed below.

**Pathogenesis.** The pathogenesis of PCOS has been controversial. Most experts agree that hyperandrogenemia is the central feature of PCOS [83]. Studies found that greater than 60% of the circulating levels of androgens were of ovarian origin, and about 40% were of adrenal source [86]. Furthermore, increased adrenal and ovarian androgen responses to stimulation by LH [87,88] or corticotropin [89,90], respectively, were found in vivo in women with PCOS.

Insulin resistance is also a common characteristic of PCOS, both in obese and nonobese affected women [91]. Insulin resistance primarily refers to impaired action of insulin on glucose metabolism, in the presence of normal insulin binding [92]. In turn, the resulting compensatory hyperinsulinemia [91–99], or increased insulin action, leads to exaggerated effects of insulin on other actions, including stimulation of androgen secretion by ovarian and adrenal cells [88,100–104]. Insulin can also directly inhibit sex-hormone-binding globulin (SHBG) production [105], increasing the active testosterone fraction.

The ovarian and adrenal androgenic hyperresponsiveness to LH and corticotropin that characterizes PCOS women may result from increased chronic insulin stimulation. Indeed, this androgenic hyperresponsiveness has been shown to persist after prolonged LH or corticotropin suppression [88,106,107], but to improve after insulin sensitization (with weight loss, metformin, or peroxisome proliferator-activated receptor γ agonists) [108–112]. Moreover, our group found that PCOS women, who were nonobese, normoinsulinemic, and normally insulin-sensitive, normalized their hyperandrogenemia with a pure insulin-lowering agent (diazoxide) [113]. These results demonstrated that even normal insulin levels contribute to PCOS hyperandrogenemia.

Altogether, these findings suggest that women may develop PCOS because of increased sensitivity of their androgenic pathway to insulin,
and not just hyperinsulinemia. This increased sensitivity might be improved with insulin sensitization or reduction [114]. It is probable that only a minority of women with PCOS have a defect severe enough to cause a typical syndrome without insulin resistance. Most women with PCOS must develop insulin resistance with compensatory hyperinsulinemia to further aggravate insulin stimulation of androgen production and express the syndrome. Thus, classical insulin resistance and compensatory hyperinsulinemia are not necessary to develop PCOS, but they favor the clinical expression of PCOS and may result from the same factors as for the general population, which are obesity and a genetic predisposition to insulin resistance.

As shown in Fig. 2, the combination of elevated levels of androgens and obesity is thought to lead to increased formation of extraglandular estrogen, termed estrone. This hormone exerts a positive feedback on LH secretion and negative feedback on FSH secretion. Studies have provided conflicting results on the ability of insulin to increase the pulsatory rate of GnRH [115–121]. It is possible that PCOS women have a higher sensitivity to insulin-stimulated LH production, but that this defect is attenuated in obese women because of other factors, such as leptin resistance, other adipokynes, and higher testosterone levels. In some studies, circulating concentrations of FSH are within the normal range in women with PCOS [122–124], but the normal intercycle rise in serum FSH levels is lacking. The increased level

---

Fig. 2. Proposed mechanism for the initiation and perpetuation of chronic anovulation in the PCOS. (Adapted from Mishell Jr DR, Davajan V, editors. Reproductive endocrinology, infertility, and contraception. 2nd edition. Philadelphia: Davis; 1986; with permission of Blackwell Publishing; and from Yen SCC, Jaffe RB, Barbieri RL, et al, editors. Reproductive endocrinology. 4th edition. Philadelphia: Saunders; 1999; with permission of Elsevier Health.)
of LH can lead to hyperplasia of the ovarian stroma and theca cells and increased ovarian androgen production, which in turn provides more substrate for peripheral aromatization and perpetuates the chronic anovulation. Deregulation of local follicle regulatory systems by androgens and other factors impedes normal follicular growth, resulting in follicular arrest at the 4- to 8-mm diameter size [125]. A dominant follicle (ie, 18–25 mm in diameter) does not develop, and therefore ovulation does not occur.

Complications. In addition to infertility, patients with PCOS are at risk for many other complications. The overall risk of type 2 diabetes mellitus (T2D) is increased in PCOS, particularly in women with a first-degree relative with T2D [126–129]. In a study of 122 obese women with PCOS, 45% had either impaired glucose tolerance (35%) or T2D (10%) [130]. All obese women with PCOS should have frequent assessment of glucose tolerance. This association is less clear in lean women. Fasting plasma glucose for detecting abnormal glucose tolerance was shown to be insensitive in women with PCOS as compared with oral glucose tolerance test (OGTT) [131]. Thus, we recommend performing an OGTT to screen this population. This recommendation was recently stated in an Androgen Excess Society position article, which also recommends repeating OGTTs every 2 years [132].

A recent meta-analysis comparing the risk of pregnancy and neonatal complications in women with PCOS to controls found that those with PCOS demonstrated a significantly higher risk of developing gestational diabetes (odds ratio [OR] 2.94), pregnancy-induced hypertension (OR 3.67), preeclampsia (OR 3.47) and preterm birth (OR 1.75). Their babies have significantly higher perinatal mortality (OR 3.07), unrelated to multiple births [133]. Most of these complications have been strongly associated with obesity in the general population, as recently demonstrated in large register study [134]. The importance of weight loss before conception should therefore be strongly emphasized, not only to increase pregnancy rates but also to prevent deleterious effects on the pregnancy outcome.

Clinical management of PCOS

Lifestyle modifications. Women with obesity and PCOS demonstrate improved ovulation and menses with weight reduction, which may be considered as primary therapy for infertility before the use of ovulation-inducing agents [135]. In many overweight and obese women with PCOS, weight loss alone is often associated with a reduction in serum-free testosterone concentrations, resumption of ovulation, and pregnancy [136–139]. This is likely related to improvement of the hyperinsulinemic state, concomitant with an increase in SHBG levels, as shown in most of the studies that reported these parameters [140–143].

Lifestyle modification, including a weight-reducing diet and exercise, is recommended as first-line therapy for all obese women with PCOS. A small weight loss of 5% to 10% of total body weight was shown to be effective for
inducing ovulation in many women [139]. Pharmacologic therapy should ideally be considered only if lifestyle modifications fail to resolve spontaneous ovulatory cycles after 3 to 6 months [144].

**Ovulation-induction agents.** Clomiphene citrate (CC) was the first ovulation inductor and is still the most common one used for ovulation induction. It is a nonsteroidal selective estrogen receptor modulator that releases estrogen inhibition on FSH production at the pituitary level. By increasing FSH levels, it favors follicle recruitment, induction of FSH receptors at the cell surface of granulosa cells, and eventually selection of one or multiple dominant follicles. This drug is taken for 5 days starting on the third or fifth day of the menstrual cycle, following either a spontaneous or induced bleeding with progesterone withdrawal. CC is initially begun at a dose of 50 mg daily for 5 days and, if ovulation does not occur in the first cycle of treatment, the dose is increased to 100 mg and, subsequently, to a maximum of 150 mg. The couple should be advised to have intercourse at least every other day for 1 week beginning the last day of medication. The response to treatment should be monitored. Conversion of a uniphasic to a biphasic basal temperature curve suggests ovulation has occurred, but this should not be used by the couple as an indicator for beginning to have frequent intercourse as the temperature rise occurs up to 4 days after ovulation. The occurrence of ovulation can also be accurately confirmed by a midluteal serum concentration greater than 6.5 ng/mL (ideally greater than 10 ng/mL). Adding transvaginal ultrasonographic monitoring and urinary LH testing is costly and does not appear to improve pregnancy rates significantly [145]. Transvaginal ultrasound monitoring may be done in the very first CC cycle to exclude hyperresponse [146]. CC is indicated as first-line therapy for women with PCOS desiring pregnancy. Based on a meta-analysis in PCOS women, CC doubles the odds of clinical pregnancy as compared with no treatment or placebo [147,148]. Indeed, a cumulative pregnancy rate of up to 73% can be achieved in women with PCOS when CC is repeated for up to nine ovulatory cycles [149].

Side effects are infrequent, dose-dependent, and rarely interfere with therapy. They include hot flashes, blurred vision, exaggerated symptoms of ovulation, and inhibition of estrogen-mediated endometrial growth. The most significant risk with CC is multiple pregnancy, which occurs in up to 6% of pregnancies [147]. CC has been the preferred fertility treatment in PCOS women for decades because of its low cost, few side effects, and simplicity of administration.

The aromatase inhibitor letrozole is another ovulation-inductor drug that is gaining popularity because its side effects appear to be less severe than those of CC. For example, with letrozole, patients experience less of a decrease in cervical mucus, less thinning of the endometrial lining, and less emotional irritability. At the doses usually used for ovulation induction, side effects can include hot flashes, nausea, and vomiting.

**Insulin-sensitizing agents.** Insulin sensitizers, namely metformin and thiazolidinediones, are beneficial in controlling both short- and long-term
issues in PCOS. However, thiazolidinediones are contraindicated during pregnancy because they were found to decrease progesterone levels and impair fetal growth in animal studies.

Metformin is a biguanide whose primary mechanism of action is the reduction of hepatic gluconeogenesis, which pathologically increases in insulin-resistant states and thereby produces fasting hyperinsulinemia. Recent studies in women with PCOS have suggested that this may be a safe and effective means of improving the metabolic profile and reproductive function in both lean and obese women with PCOS. The favorable effect of metformin on hyperandrogenemia and ovulation in PCOS may stem from metformin-induced reduction of insulin levels, which reduces ovarian and adrenal secretions of androgens, reduces pituitary secretion of LH, and increases SHBG levels [114].

Accumulating evidence has shown that the rationale for metformin use in PCOS makes sense, and it has been shown to improve ovulation rates in women with PCOS [150,151]. A randomized trial comparing the effectiveness of metformin to CC administration as first-line treatment in nonobese anovulatory women with PCOS found ovulation rates were not different between the groups, whereas the pregnancy rate was significantly higher in the metformin group (15.1% versus 7.2%) [152]. Ovulation and pregnancy rates with the use of metformin increased steadily during the 6 months of the study with a number needed to treat of three for inducing a pregnancy. In contrast, CC showed higher efficacy initially, but this declined over time [113]. More recently, the same investigators did another head-to-head randomized controlled trial of CC versus metformin as first-line treatment in infertile anovulatory patients with PCOS. They reported treatment with CC or metformin for 6 months resulted in cumulative pregnancy rates of 49% with CC and 63% with metformin, a difference that was not significant [153]. Furthermore, use of metformin during early pregnancy has been shown to reduce first-trimester pregnancy loss [154,155], which can be as high as 30% to 50% in women with PCOS [156,157]. Finally, metformin induces normal ovulation, such that the risk of multiple gestation is no more than in the general population [147]. Despite such promising initial results, further studies are needed to confirm whether metformin has any benefit over CC as an initial treatment in PCOS.

The recent Pregnancy in Polycystic Ovarian Syndrome (PPCOS) study [147] brought additional controversy to the subject. In this study, 626 infertile women with PCOS received CC plus placebo, extended-release metformin plus placebo, or a combination of extended-release metformin and CC for up to 6 months. The results suggested that the live birth rate achieved with CC was higher for women who received CC alone (22.5%) or in combination with metformin (26.8%) than for women who received metformin alone (7.2%). Unfortunately, the PPCOS study used an extended-release formulation that demonstrated none of the expected metabolic benefits of this insulin sensitizer, especially the absolute change
in plasmatic insulin concentration and homeostasis model assessment of insulin resistance, both from baseline and compared with CC. The change in body mass index was statistically significant but minor (−0.6 [ ± 2.2]; 95% CI, −0.9—0.2 [P < .001]). In the absence of the expected metabolic improvements with metformin, it is not surprising that fertility parameters did not improve. The cumulative rate of ovulation after 6 months in the metformin group was only 29%, as compared with 63% and 55% in the two studies from Palomba and colleagues [152,153] and 58% after 3 to 6 months in a meta-analysis of four randomized controlled trials [150]. Thus, the PPCOS study should probably not be considered the definitive study for the choice of the best pharmacologic first-line therapy in PCOS anovulatory women.

In summary, the first-line agent for the treatment of PCOS should be chosen by the physician after considering the discussed available data and consulting with the patient. There is no firm recommendation as to which agent should be used for initial therapy. We generally prefer metformin as a first treatment, as it intervenes at the source of the disease and treats the metabolic abnormalities in PCOS. Even more importantly, metformin acts more slowly and tends to reduce appetite, which allow for lifestyle changes and weight loss before pregnancy.

**Other endocrine or metabolic disorders**

**Congenital adrenal hyperplasia.** CAH is an inherited recessive disorder of adrenal steroidogenesis, usually resulting from deficiency of one of the five enzymes required for synthesis of cortisol in the adrenal cortex. The clinical manifestations reflect the severity of the enzymatic defects. The most prevalent disorders are caused by 21-hydroxylase deficiency (~90% of cases [158–161]), followed by 11β-hydroxylase deficiency and 3β-hydroxysteroid dehydrogenase deficiency accounting for most of the remaining cases. The adrenal precursors produced proximal to the enzymatic defect accumulate and are converted into androgens, resulting in symptomatic hyperandrogenism. Nonclassical or late-onset 21-hydroxylase deficiency is one of the most common autosomal-recessive diseases and is more frequent than cystic fibrosis. It ranges in prevalence from 1% to 10%, depending on the ethnicity of the patient [162]. Nonclassical forms of CAH have clinical features similar to those of patients diagnosed with PCOS (ie, menstrual irregularity, hyperandrogenism, infertility, and polycystic ovaries). Consequent anovulation, in association with sexual dysfunction [163], is responsible for impaired fertility in these women. Another explanation for their subfertility is high glucocorticoid levels in treated women [164,165]. Finally, CAH women often develop insulin resistance, due to high levels of androgens or exogenous glucocorticoids, with superimposed PCOS. Patients with mild forms of 21-hydroxylase deficiency might ovulate with adequate cortisol replacement and conceive spontaneously. Nevertheless, in more severe forms of CAH, fertility and childbirth rates are compromised despite treatment [163,165–167].
In nonclassical CAH women, follicular early-morning measurement of serum 17-hydroxyprogesterone concentration is the most likely to show an elevation. Levels greater than 800 ng/dL (24 nmol/L) are diagnostic of 21-hydroxylase deficiency, whereas patients with levels greater than 400 ng/dL (12 nmol/L) and less than 800 ng/dL should be addressed with a provocative test with corticotropin (250 μg intravenously) [65]. A lower cutoff 17-hydroxyprogesterone level of 200 ng/dL (6 nmol/L) for CAH screening may be more appropriate if early-morning samples cannot be obtained. The diagnosis of 21-hydroxylase deficiency is then made if 17-hydroxyprogesterone levels are greater than 1000 ng/dL (30 nmol/L) 1 hour after administration of corticotropin. The other enzymatic defects that result in nonclassical CAH can be similarly tested with measurements of corticosteroid products proximal to the blockade following provocative testing [168].

The fundamental aim of endocrine therapy for CAH is to provide replacement of the deficient hormones, especially in the severe classical forms. Dexamethasone is the corticosteroid of choice for all forms of CAH [169]. CC and other assisted reproduction techniques may be added if glucocorticoid therapy alone is ineffective in restoring fertility [170].

**Virilizing tumors.** Both benign and malignant adrenal tumors can produce androgens, including testosterone, many steroid intermediates, and, rarely, cortisol. Approximately 50% to 60% of adrenal cancers are functional. The most frequent presentation is Cushing’s syndrome with or without virilization. Androgen-secreting adrenal tumors are more frequently malignant than benign. Nearly all patients have very high serum dehydroepiandrosterone sulphate concentrations and the values do not fall in response to high-dose dexamethasone. Ninety-five percent of adrenal carcinomas are larger than 5 cm in diameter. Androgen-producing carcinomas lead to virilization in women: male-pattern baldness, deepening voice, breast atrophy, clitoral hypertrophy, increased libido, oligomenorrhea or amenorrhea, total testosterone concentrations over 200 ng/dL, and characteristic ultrasound or CT findings. Ovarian virilizing tumors typically secrete predominantly androstenedione and are thus characterized by a disproportionate elevation of plasma androstenedione relative to testosterone, resulting in anovulation. When a virilizing tumor is suspected, confirmatory imaging is required and the treatment is surgical resection.

**Adrenal failure and Cushing’s syndrome.** Both adrenal failure and Cushing’s syndrome may cause infertility. If adrenal insufficiency is suspected, the 250-μg corticotropin stimulation test should be performed as a screening measure. The maximal plasma cortisol level following acute corticotropin stimulation should be 20 μg/dL or above [171]. Hormonal supplementation with hydrocortisone generally permits restoration of fertility. Puerperal mortality/morbidity in women with adrenal failure can be prevented by
both mineralo- and glucocorticoid replacement with higher doses during stressful periods, such as labor, delivery, and surgery.

In Cushing’s syndrome, the excess cortisol and androgen levels suppress gonadotropin secretion, impair LH response to GnRH [172,173], and, in some cases of Cushing’s disease due to pituitary tumor, also result in hyperprolactinemia, which suppresses ovulatory LH surge [174–176]. The insulin resistance due to cortisol excess may also cause a typical PCOS. Cushing’s syndrome can be diagnosed, when the clinical suspicion is high, with the administration of 1 mg of dexamethasone at 11 PM and measurement of serum cortisol at 8 AM the next morning [177], which should be less than 2 ug/dL in normal subjects [178]. Twenty-four–hour urinary cortisol excretion also provides a direct and reliable practical measure of cortisol secretion [179,180]. Concern should be raised if the result is a two-fold increase compared with normal laboratory values. Cause-specific treatment has a high likelihood of improving fertility, as well as improving maternal and perinatal outcomes in case of Cushing’s syndrome diagnosed during pregnancy.

Other endocrine disorders. Overt hypo- or hyperthyroidism may result in oligomenorrhea, amenorrhea, and anovulatory infertility, whereas subclinical hypothyroidism may result in menorrhagia and luteal phase defect. Subclinical hypothyroidism is defined as thyroxine and tri-iodothyronine levels in the normal range with thyroid-stimulating hormone (TSH) above the upper limit of the reference value, typically greater than 3.5 IU/L. Surprisingly, subclinical or mild hyperthyroidism is rarely associated with infertility [181], but more severe hypothyroidism can cause infertility. According to routine screening studies in infertile populations, 2.3% to 5.1% have abnormal thyroid function tests in this more severe range [182,183]. Thyroid hormones have direct effects on granulosa cells, luteal cells, and oocytes, indicating a direct interference with normal ovarian function [184]. Several studies confirmed that subclinical hypothyroidism or euthyroidism in patients with thyroid antibodies may also adversely affect the mother or fetus [185,186], and substitutive treatment with levothyroxine has been shown to lower the chance of miscarriage and premature delivery in these particular women [187]. Women with subclinical hypothyroidism should then be treated before pregnancy, aiming for a TSH of 2.5 IU/L or less to optimize fertility and ensure normal thyroid hormone levels for the fetus.

Diabetic women have a higher incidence of secondary hypogonadotropic amenorrhea, more so if body mass index is low and glycosylated hemoglobin (HbA1c) is higher than normal [188]. In women with diabetes mellitus desiring pregnancy, prepregnancy counseling is essential and adequate glycemic control before conception is critical to diminish the risk of spontaneous abortion [189,190], fetal abnormalities, macrosomia, and other pregnancy complications [191,192]. Thus, diabetic women should aim for an HbA1c below 6%, or below 7% if the risk of hypoglycemic episodes is
too high, before getting pregnant. The possibility of associated PCOS should also be questioned in this population.

General diagnostic approach of anovulatory disorders

Anovulatory infertility should be suspected in all women who have oligomenorrhea or amenorrhea and have not been able to conceive despite unprotected and timely intercourse. The use of a questionnaire is a key element of the evaluation (Box 2), in addition to a thorough physical examination, including calculation of the patient’s body mass index and assessment for signs of potential causes of infertility. Patients should be evaluated for abnormalities of the thyroid gland, galactorrhea, and signs of androgen excess (hirsutism, acne, male-pattern baldness). All women should typically have FSH, LH, prolactin, TSH, and fasting glucose levels checked. Women with signs of androgen excess or menstrual irregularity should be tested with levels of total and calculated free testosterone, as well as 17-hydroxyprogesterone or dehydroepiandrosterone sulphate levels to rule out CAH or androgen-secreting tumors (Fig. 3). Screening tests for Cushing’s syndrome (24-hour urinary cortisol excretion or 1-mg dexamethasone suppression test) should be reserved for cases with high clinical suspicion. Glycemic control should be assessed in diabetic women with HbA1c.

Box 2. History taking in infertile women

Fertility history: duration of infertility, prior pregnancies (including miscarriage), previous infertility testing and/or treatment, frequency of intercourse

Gynecologic history: pelvic inflammatory disease, fibroids, endometriosis, cervical dysplasia; surgery of the cervix, ovary, uterus, fallopian tube or abdomen; prior contraceptive use (including intrauterine device); uterine abnormalities

Menstrual history: age at menarche, cycle length, regularity and bleeding heaviness; presence of symptoms suggestive of menopause or hyperandrogenism (see text)

Change in body weight, galactorrhea, Cushing’s symptoms, symptoms of dysthyroidism

Family diseases: birth defects, reproductive failure, hyperandrogenism

Other medical and surgical history: radiation or chemotherapeutic agents

Regular medications, drug use (including tobacco, alcohol, other recreational drug use), occupational exposures, exercise, and dietary habits
Unexplained infertility is defined as the failure to conceive for a couple in whom no definitive cause for infertility can be found. In such cases, basic tests for ovulation, fallopian tube patency, and semen analysis are normal. It is a state of relative inability to conceive. In such cases, the need to include a diagnostic laparoscopy in the basic tests is controversial [2,193].

The incidence of unexplained infertility varies with the population studied and the criteria used. It ranges from 10% to 30% in all infertile couples. The cycle fecundity in unexplained infertility is about 2% to 4%, which is far below the normal rate of 20%. With increasing age of the female partner and increasing duration of infertility (>3 years), conception is even less likely.

The proposed treatments of unexplained infertility are empiric. The goal of treatment is to increase monthly fecundity and hasten pregnancy by increasing the gamete density (superovulation). Recommended treatments have included controlled ovarian hyperstimulation with CC (even in ovulatory female) for 3 to 6 months, alone or with intrauterine insemination, or by gonadotropins with or without intrauterine insemination. The cycle fecundability varies from 8.3% with CC plus intrauterine insemination to 17.1% with gonadotropins plus intrauterine insemination [193,194]. IVF can be the last resort of treatment, but caution about the increased risk of multiple births and ovarian hyperstimulation syndrome should be applied with these treatments.
Assisted reproductive technology

Assisted reproductive technology procedures can be divided into several categories, namely IVF, intracytoplasmic sperm injection, gamete intrafallopian transfer, cryopreserved embryo transfer, and donor oocyte or embryo.

The indications for IVF are tubal factor infertility, endometriosis, male factor infertility (IVF or intracytoplasmic sperm injection), unexplained infertility, ovarian failure, and diminished ovarian reserve [147]. The main problem with the accessibility of IVF is the high cost with less than 10% of infertile couples undergoing such treatment [195]. The risk of multiple gestation is increased in assisted reproductive technology cycles. In 2006 in the United States, 33% of multiple gestations in women under 35 were a result of IVF. Of these multiple gestations, approximately one third were twins. During the use of assisted reproductive techniques, the risk for spontaneous abortion is about 17% and for ectopic pregnancy 2% [195]. It is recommended that no more than two embryos be transferred in women under 35 and more than two only in older women. In Europe, many in the field have suggested that multiembryo transfers be discouraged for all women, no matter the age. The success rate of assisted reproductive technology varies with age. In 2003 in the United States, the percentage of cycles resulting in live births were 37% for women younger than 35 years, 30% for women age 35 to 37 years, 20% for women age 38 to 40 years, and 11% for women age 40 to 41 years [195]. In Canada in 2003, the clinical pregnancy rates per cycle started were 31% in IVF–intracytoplasmic sperm injection cycles [196]. It was estimated that the number of IVF–intracytoplasmic sperm injection cycles cycles per million population per annum is 269 in the United States, 270 in Canada, 784 in France, and 1791 in Denmark [196].

Summary

Infertility is a common disorder that has major consequences on women’s well-being. Affected women eagerly seek answers and effective therapy. The most common cause of medically treatable infertility is the polycystic ovary syndrome. This syndrome is common in young women and is the cause of anovulatory infertility in 70% of cases. It is therefore an important condition to screen and manage in primary care medical settings. In the past 10 years, insulin sensitization with weight loss or metformin has been shown to be a safe and effective treatment for PCOS infertility that eliminates the risk of multiple pregnancy and may reduce the risk of early pregnancy loss as compared with ovulation-inductor drugs. The authors believe metformin should be considered as first line therapy because it has the advantage to allow for normal single ovulation, for reduced early pregnancy loss, and, most importantly, lifestyle modifications and weight loss before pregnancy. Losing weight not only improves fertility but also reduces adverse pregnancy outcomes associated with obesity.
References


