Polycystic ovary syndrome: diagnosis and management of related infertility

Suresh Kini

Abstract
Polycystic ovary syndrome (PCOS) is one of the most common complex and heterogeneous endocrine disorder in women with uncertain aetiology. The syndrome is associated with a wide range of symptoms and the diagnosis is based on the Rotterdam criteria. This review describes the currently available evidence regarding the therapeutic challenges raised in these women. Before any intervention is initiated, pre-conceptional counselling should be provided emphasizing the importance of life style changes, especially weight reduction and exercise in overweight women. The recommended first-line treatment for ovulation induction remains clomifene citrate. Second-line interventions include exogenous gonadotropins and laparoscopic ovarian drilling. The recommended third-line treatment is in vitro fertilization. More patient-tailored approaches should be developed for ovulation induction based on initial screening characteristics of women with PCOS. Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction. Metformin use in PCOS should be restricted to women with glucose intolerance.

Keywords infertility; ovulation induction; PCOS

Introduction
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, yet its exact nature remains enigmatic. Women with PCOS can present with a wide range of features including reproductive (menstrual irregularity, hirsutism, infertility and pregnancy complications), metabolic features such as insulin resistance (IR), metabolic syndrome, prediabetes, type 2 diabetes and cardiovascular disease and finally psychological (poor self-esteem, anxiety, depression). Not all women demonstrate all symptoms and there is considerable heterogeneity. Presentation can also vary across the lifecycle. PCOS starts manifesting usually during adolescence with menstrual irregularity and symptoms of hyperandrogenism. Fertility problems manifest later on as PCOS remains the most common cause of anovulatory infertility (~75%). Despite its high prevalence (6–8% of women of reproductive age), there remains much controversy regarding its diagnosis, aetiology and most appropriate treatment strategy. The pathophysiology of PCOS appears to be multifactorial and although extra ovarian aspects have been suggested, ovarian dysfunction remains the central issue.

PCOS can be a frustrating experience for women, a complex syndrome for clinicians and a scientific challenge for researchers, as well as being a major public health concern. This review will present an overview of PCOS including a historical perspective, pathophysiology, diagnosis and various management options for PCOS.

Historical perspective
“Sclerocystic” ovaries were recognized as early as the mid-18th century. The PCOS (originally called the Stein–Leventhal syndrome), was originally described by two Americans (Irving F. Stein and Michael L. Leventhal) in 1935. They described their treatment of this condition, by using wedge resection of the ovaries to induce ovulation with remarkable success. However as medical treatment became available with the introduction of clomifene citrate (Greenblatt 1961), and subsequently the use of follicle stimulating hormone of pituitary (Kovacs and Norman 2012) and urinary sources (Wang and Gemzell 1980), surgical treatment became less often used. Interestingly, surgical treatment of resistant anovulation has had resurgence with the laparoscopic approach initially described by French gynaecologists, but popularized by Gjoanness (1984).

Pathophysiology
Factors involved in the development of PCOS can be divided into the following groups.

Aberration of gonadotropin secretion
Compared to normally cycling women, those with PCOS generally exhibit increased serum luteinizing hormone (LH) concentrations, low-normal follicle stimulating hormone (FSH) levels and increased LH: FSH ratios. The increase in serum LH levels results from abnormal LH secretory dynamics, characterized by an increase in LH pulse frequency and to a lesser extent, also in pulse amplitude. The decrease in FSH levels results from the increase in gonadotropin-releasing hormone (GnRH) pulse frequency, the negative feedback effects of chronically elevated oestrone concentrations (derived from peripheral aromatization of increased androstenedione) and normal or modestly increased levels of inhibin B (derived from small follicles). Increased circulating levels of oestrone may exert negative feedback effects on FSH, but probably do not have any important direct influence on LH secretion in women with PCOS. Whereas the lack of progesterone feedback resulting from anovulation undoubtedly contributes to the higher LH pulse frequency, as evidence suggests that the GnRH pulse generator is also less sensitive to the feedback inhibition of sex steroids. Studies suggest that excessive LH secretion or stimulation may be an important cause of disordered follicular development and anovulation, but is not the proximate cause of polycystic ovaries or of increased ovarian androgen production in women with PCOS.

Genetics and PCOS
PCOS appears to be inherited as a complex, polygenic trait. The familial clustering of PCOS cases and the accumulating evidence about the interaction between multiple genetic and
environmental factors necessary for the development of the syndrome has led to the initiation of genetic studies on PCOS. These studies have focused on genetic polymorphisms, and investigating their possible positive or negative correlation with the syndrome. Studies in large families have suggested an autosomal-dominant inheritance, with premature balding as the male phenotype. Other studies of siblings and parents of women with PCOS have observed a high prevalence of hyperinsulinaemia and hypertriglyceridaemia, associated with premature balding of male trait. The syndrome clusters in families and prevalence rates in first degree relatives are five to six times higher than in the general population. Nearly 50% of sisters of women with PCOS have elevated total or bioavailable testosterone concentrations, and approximately 35% of mothers are also affected. The first degree relatives of women with PCOS also exhibit other metabolic abnormalities such as dyslipidaemia, which may predispose to an increased risk for cardiovascular disease. These observations further suggest a genetic predisposition or susceptibility. Although several genes have been postulated as responsible for the aetiology of this disorder, no single gene has been confidently identified to play a predominant role in the pathogenesis of PCOS. Despite the progress that has been made in the elucidation of the genetic mechanisms of the PCOS, the genetic studies on the syndrome still face many challenges. Further studies are needed, in order to shed new light on the pathogenesis of the syndrome.

Hyperinsulinaemia and insulin resistance
Insulin resistance is a condition in which endogenous or exogenously administered insulin has less than normal effects on fat, muscle and the liver. Decreased glucose utilization and increased hepatic gluconeogenesis (which insulin normally inhibits) result in increased blood glucose concentrations and a compensatory hyperinsulinaemia. The importance of insulin resistance (IR) and hyperinsulinaemia in the pathogenesis of PCOS was first suggested by a study conducted in 1980 and appears to be more common in obese PCOS patients. Increased circulating insulin levels cause or contribute to hyperandrogenism by stimulating ovarian androgen production and by inhibiting hepatic sex hormone binding globulin (SHBG) secretion. Insulin also potentiates LH induced androgen production by the ovarian stroma. High insulin concentrations also inhibit hepatic SHBG production, as do high androgen concentrations yielding increased free androgen concentrations, which then aggravate insulin resistance. Ultimately, these conditions foster a self-propagating positive feedback loop that can increase in severity over time. Insulin resistance and hyperinsulinaemia are undoubtedly an important part of the pathophysiology of PCOS. However, it is important to emphasize that 25–50% of women with PCOS have no demonstrable insulin resistance. Moreover, among all women with IR, the prevalence of PCOS is relatively low (approximately 15%). Therefore, insulin resistance and hyperinsulinaemia may not be the only pathogenic factors in women with PCOS.

Diagnosis
Diagnosis of PCOS (Table 1) can only be made when other factors contributing to anovulation have been excluded (thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinaemia, androgen secreting tumours and Cushing syndrome). Hyperandrogenic features are often most common among adolescents, whereas fertility issues are more prominent among women in their 20s–30s and metabolic challenges mostly have their effects in later years. The propensity to weight gain and psychological challenges affect all ages, and metabolic features can occur early, especially among those who are overweight.

Racial difference in expression
The highest prevalence of PCOS has been reported in around 52% women among South Asian immigrants in Britain, of whom 49% had menstrual irregularity. South Asians women with anovulatory PCOS have greater IR and more severe symptoms compared to anovulatory white Caucasians with PCOS and tend to express symptoms at an earlier age. On the other hand, compared with Caucasians, Chinese women and Middle Eastern women with PCOS usually have a lower risk of metabolic syndrome.

Signs and symptoms
PCOS has a variety of clinical manifestations, not all of which may be present, including:

Menstrual abnormalities
The majority of women with PCOS (approximately 60–70 %) exhibit gross menstrual dysfunction. The most common abnormalities are oligomenorrhoea and amenorrhoea. Polymenorrhoea is very uncommon, observed in less than 2%. Approximately 25% of the patients have regular periods.

Symptoms of hyperandrogenism
These include hirsutism, acne persisting beyond adolescence, oily skin and male pattern alopecia. Hirsutism is the growth of terminal hairs on the face or body in a male pattern. Hirsutism is the most important feature of PCOS, affecting 65–75% of women.

Revised diagnostic criteria for PCOS

<table>
<thead>
<tr>
<th>National Institutes of Health (NIH) 1990 criteria (both 1 and 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic anovulation</td>
</tr>
<tr>
<td>• Clinical and/or biochemical signs of hyperandrogenism and</td>
</tr>
<tr>
<td>exclusion of other aetiologies</td>
</tr>
<tr>
<td>The Rotterdam ESHRE/ASRM consensus revised 2003 criteria (2</td>
</tr>
<tr>
<td>out of 3)</td>
</tr>
<tr>
<td>• Oligo- and/or anovulation</td>
</tr>
<tr>
<td>• Clinical and/or biochemical signs of hyperandrogenism</td>
</tr>
<tr>
<td>• Polycystic ovaries and exclusion of other aetiologies</td>
</tr>
<tr>
<td>(congenital adrenal hyperplasias, androgen secreting tumours,</td>
</tr>
<tr>
<td>Cushing’s syndrome)</td>
</tr>
</tbody>
</table>

The Rotterdam ESHRE/ASRM consensus on diagnostic criteria for PCOS.

Table 1
and varies with ethnicity. The modified Ferriman–Gallwey score is the most common method for grading the extent of hirsutism. The prevalence of acne among white women with PCOS is 12–14% and like hirsutism varies with ethnicity. Androgenic alopecia, describing scalp hair loss in women in PCOS affects less than 5% of patients.

Sub-fertility

Chronic oligo or anovulation is very common in women with PCOS and PCOS accounts for approximately 75% women with anovulatory sub-fertility. Hypersecretion of LH is found in 40% of women with PCOS and is associated with a reduced chance of conception and an increased risk of miscarriage in both natural and assisted conception. Obese women with PCOS have increased rate of cycle disturbance and sub-fertility which is secondary to disturbance in insulin metabolism.

Metabolic symptoms

Obesity is often associated with PCOS (approximately 35–60%), but many with PCOS are of normal weight. Women with PCOS have a greater truncal abdominal fat distribution as demonstrated by a higher waist: hip ratio which is an indication of insulin resistance. Acanthosis nigricans is another marker of insulin resistance occurring in 1–3% of women and manifests as dark pigmented areas of skin commonly affecting axillae, perineum or extensor surfaces of the elbow and knuckles. Insulin resistance combined with abdominal obesity is thought to account for the higher prevalence of type 2 diabetes (~15%) in PCOS. Women with PCOS are also at increased risk of developing gestational diabetes and manifestations of dyslipidaemia.

Endocrinological features

The most frequently found endocrine abnormalities in PCOS include hyperandrogenism, elevated serum concentration of LH, LH: FSH ratio ≥ 2 and hyperinsulinaemia. Increased testosterone >2.5 nmol/l (~70%), increased Free androgen index (FAI) >5 (~75%) and decreased sex hormone binding globulin (SHBG) (~50%) may be seen in women with PCOS. A large proportion of circulating testosterone is bound to a protein called SHBG that is decreased in women with PCOS leading to increased free testosterone. The FAI is a simple method of estimating the circulating free testosterone and is calculated as: FAI = [total testosterone] divided by [SHBG] × 100. Although raised LH more than 10 IU/l (~60%) with a normal FSH and LH:FSH ratio more than 2 (~95%) may be found in PCOS, it is important to note that the measurements of gonadotropins no longer form part of the diagnostic criteria. Some women with PCOS may demonstrate biochemical features of increased insulin (>20 mU/ml) (~50%) and increased blood prolactin (~30%).

Ultrasound features of PCOS

The ESHRE/ASRM Rotterdam consensus (2003) recommended polycystic ovaries (PCO) should be considered as one of the possible criteria for PCOS. The criteria fulfilling sufficient specificity and sensitivity to define PCO are the following: presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume (>10 cm³). Only one ovary fitting this definition is sufficient to define PCO (Figure 1).

Although 35% women have PCO on transvaginal ultrasound, only 10% of these meet the criteria for PCOS.

Management of infertility in PCOS

Life style interventions: lifestyle management (single or combined approaches of diet, exercise and/or behavioural interventions) for weight loss, prevention of weight gain or for general health benefits should be recommended in women with PCOS. Lifestyle management targeting weight loss (in women with a body mass index (BMI) ≥25 kg/m² (overweight/obese)) and prevention of weight gain (in women with a BMI 18.5–24.9 kg/m² (lean)) should include both reduced dietary energy (caloric) intake and exercise should be first line therapy for all women with PCOS. Face to face, tailored dietary advice, including education, behavioural change techniques and ongoing support should be provided to women with PCOS and a BMI ≥25 kg/m². Simple strategies, including self-monitoring, pedometers and time management techniques should be encouraged. Exercise participation of at least 150 minutes per week should be recommended to all women with PCOS, especially those with a BMI ≥25 kg/m², given the metabolic risks of PCOS and the long term metabolic benefits of exercise. Of these 150 minutes, 90 minutes per week should comprise of aerobic activity at moderate to high intensity (60%–90% of maximum heart rate) to optimize clinical outcomes. Lifestyle management, including diet and exercise programmes, should be used throughout the lifespan in women with PCOS to optimize health benefits generally and also to alleviate symptoms such as infertility. In women with PCOS and BMI ≥30 kg/m² (obese) due consideration should be given to age-related infertility, and intensive (frequent multidisciplinary contact) lifestyle modification alone (and not in combination with pharmacological ovulation induction therapy) should be considered as the first line therapy for 3 to 6 months duration to determine whether ovulation can ensue spontaneously. Weight loss of just 5–10% has been shown to reverse the deleterious effects of obesity on ovarian function and can restore reproductive function in a majority of women within 6 months of weight reduction. Pharmacological ovulation induction should not be recommended as first line therapy in women with PCOS who are morbidly obese (BMI ≥35 kg/m²).
until appropriate weight loss has occurred either through diet, exercise, bariatric surgery or other appropriate means. Psychological factors should be considered and managed in infertile women with PCOS, to optimize engagement and adherence to lifestyle interventions.

**Anti-obesity pharmacological agents:** the available literature supports the adjuvant use of pharmacological agents for weight loss treatment of obesity in PCOS. Orlistat, blocks intestinal absorption of fat whereas sibutramine, acts as an appetite suppressant and both have been shown to significantly reduce body weight and hyperandrogenism in women with PCOS.

**Pharmacological management of infertility in PCOS**

**Clomifene**

Clomifene citrate (CC) should be the first-line pharmacological therapy to improve fertility outcomes in women with PCOS and anovulatory infertility with no other infertility factors.

**Mechanism of action:** clomifene is a non-steroidal synthetic oestrogen that acts as a selective oestrogen receptor modulator (SERM), having both oestrogen agonist and antagonist properties. Structural similarity to oestrogen allows clomifene to compete with endogenous oestrogen for nuclear oestrogen receptors at the hypothalamic-pituitary level; clomifene blocks the negative feedback effect of oestradiol on GnRH secretion, thus triggering increased GnRH pulse amplitude leading to increased serum levels of both FSH and LH from the pituitary which, in turn, drives ovarian follicular development. In successful treatment cycles, one or more follicles emerge and grow to maturity.

**Clomifene treatment regimens:** clomifene (CC) administered orally, in the early follicular phase, can be used in different regimens; the most commonly used is administration of clomifene stating on day 2 of the menstrual cycle for 5 days after the onset of a spontaneous or progestin-induced menses. Ovulation and conception rates and pregnancy outcomes are similar when treatment starts anywhere between cycle days 2 and 5. Obese women often require higher doses of clomifene treatment, the results achieved ultimately are similar to those observed in lean women. Treatment usually starts with a single 50 mg tablet daily for 5 days, increases by 50 mg increments in subsequent cycles until ovulation is achieved. Lower oestrogen levels rise progressively, ultimately triggering an LH surge and ovulation. In addition to its desirable central actions, clomifene can exert less desirable anti-oestrogenic effects at peripheral sites; at endocervix which could lead to decreased quality and quantity of cervical mucus production and at the endometrium- where it could lead to impaired growth, but there is no compelling evidence to indicate that such effects have important clinical consequences in most doses. Most women who respond to clomifene will respond to either 50 mg (52%) or 100 mg (22%). It is recommended that at least the first cycle of ovulation induction with clomifene, should be monitored with a combination of serial ultrasound scans and serum progesterone. Although the treatment with clomifene induces ovulation in 70–80% of patients but only 40–50% conceive. The cumulative conception rate is 67% over six months with multiple pregnancy rate of <10%, and there is very small risk of ovarian hyperstimulation syndrome (OHSS). The response rate decreases with increasing age and BMI and with the extent of any associated hyperandrogenaemia in anovulatory women. There may be benefit in using CC for up to 12 cycles as cumulative pregnancy rates continue to rise after six treatment cycles before reaching a plateau, comparable to that of the normal fertile population. The treatment with doses up to 150 mg is reasonable before considering alternatives. Anovulatory women who do not ovulate while receiving the 150 mg dose of CC are considered to be resistant to the drug.

**Side effects of CC:** clomifene has cumulative side-effects which occur as a result of its use in consecutive cycles. The main side effects of clomifene are related to its anti-oestrogen effects. Common side effects of clomifene include hot flushes, headaches, abdominal bloating and pain, nausea and vomiting, mood changes, and breast tenderness. Visual symptoms such as blurring, double vision or seeing spots occur in 1–2 percent of women, and usually resolve when treatment stops. Most studies do not show an increased risk of birth defects, miscarriage, or learning disability in children of women who took clomifene. There is no increased risk of breast cancer or uterine cancer. There may be a slightly increased risk of ovarian cancer if more than 12 cycles of clomifene are used. Cumulation of clomifene in hypothalamus-pituitary-ovarian-uterine-cervical axis causes: irregularities in FSH secretion and follicular development, irregularities in LH secretion resulting in premature luteinization of the developing follicle (20–30%) and inappropriate endometrial development and dry secretions from the cervix.

**Tamoxifen citrate (TMX)**

TMX is another non-steroidal selective oestrogen receptor modulator. It is safe and effective alternative to CC for anovulatory infertility in women with PCOS. Unlike clomifene, tamoxifen acts as an agonist on the oestrogen receptors of the endometrium. It is used in a similar way to CC for 5 days in the early follicular phase with a starting dose of 20 mg that can be increased to 40 mg and then 80 mg in subsequent cycles if ovulation is not achieved. There are no substantial differences in ovulation rates between tamoxifen and clomifene. Limited data on pregnancy rates and outcomes showed no significant differences between the treatments.

**Letrozole**

Aromatase inhibitors were first proposed as new ovulation-inducing agents in anovulatory women with PCOS (with an inadequate response to CC) in 2001. The most commonly used aromatase inhibitors in ovulation induction are letrozole and anastrozole, with letrozole being the most widely used.

**Mechanism of action:** the enzyme aromatase catalyzes the conversion of androgens to oestrogens. Therefore, aromatase inhibitors inhibit oestrogen biosynthesis, thereby releasing the hypothalamus/pituitary axis from oestrogenic negative feedback and increasing the secretion of FSH by the pituitary. The increasing oestradiol levels secreted by the multiple developing ovarian follicles which first appear on day 7 results in normal negative feedback on FSH secretion later in the follicular phase, resulting in most cases, in single follicle ovulation.
Usage: Letrozole is typically administered for 5 days in the early follicular phase at doses of 2.5–7.5 mg per day with 2.5 mg increments.

Advantages: Letrozole may be very effective for ovulation induction in cases of CC resistance. When used together with FSH injections, letrozole resulted in a significant reduction in the FSH dose needed for controlled ovarian hyperstimulation. Aromatase inhibitors likely increase ovarian sensitivity to FSH and may be useful in poor responders and in women undergoing ovarian stimulation for in vitro fertilization (IVF). Letrozole avoids some of the adverse effects of CC including the peripheral anti-oestrogenic effects on the endometrium and cervical mucus and the increased risk of multiple pregnancies. Letrozole is not licensed for use in UK and Europe due to controversial reports of fetal anomalies; further large randomized trials are needed to confirm this.

Metformin: the association of IR contributing to anovulation in PCOS has led to the introduction of insulin-sensitizing drugs in an attempt to restore ovulation and enhance pregnancy. The early studies examining its effects on the reproductive system effects in women with PCOS showed promising results but most of these studies had relatively small sample sizes. An extremely variable large target dose of 1500–2550 mg per day in divided doses was proposed. If one is considering using metformin alone to treat women with PCOS who are anovulatory, have a BMI ≥ 30 kg/m² (obese), and are infertile with no other infertility factors, CC should be added to improve fertility outcomes. In women with PCOS who are CC resistant, metformin can be combined with CC to improve fertility outcomes. The recent Cochrane review showed that metformin was associated with improved clinical pregnancy rate but there was no evidence that metformin improves live birth rates whether it was used alone or in combination with clomifene, or when compared with clomifene. Therefore, the role of metformin in improving reproductive outcomes in women with PCOS appears to be limited.

There is no good evidence available on the long-term use of statins (alone or in combination) for the management of PCOS.

Gonadotropins
Gonadotropins may be used as a second line treatment in patients with clomifene resistance or for those who fail to conceive despite ovulating with clomifene. Human menopausal gonadotropin (hMG) is a purified extract from human post-menopausal urine; it contains both FSH and LH. FSH alone is available in a variety of preparations, which are either derived from human menopausal urine or as a recombinant peptide (rFSH) produced by cultured cells. These are equally effective in inducing ovulation and potentially easier to monitor. The ‘step-up’ gonadotropin regimen is well established in fertility practice. This approach results in a monofollicular ovulation rate of ~70%, a pregnancy rate of 20% per cycle and low incidence of multiple pregnancies (~5%) and OHSS (<1%).

Risks: the sensitivity to gonadotropin therapy is increased in PCOS with multiple follicular development and cycle cancellation. Ovulation induction with gonadotropins is expensive, requires regular monitoring and often results in the development of multiple mature follicles with a potential risk of multiple pregnancies and OHSS.

Surgical management of infertility in PCOS
Laparoscopic ovarian drilling
Laparoscopic ovarian diathermy or ‘ovarian drilling’ (LOD) was first described in 1984 with minor variations in the procedure described since then. LOD carried out with either electro surgery (Figure 2) or laser has been demonstrated to lead to a resumption of menstrual cycles and ovulation in a significant proportion of women. This is also associated with a fall in serum androgen and LH levels.

Indication: LOD is a second line of therapy for women with PCOS, who are either CC resistant or do not conceive. LOD can

![Figure 2 Laparoscopic ovarian drilling](image-url)
also be considered first-line treatment if laparoscopy is indicated for another reason in infertile women with PCOS.

The mechanism of the effect of LOD is believed to be due to the damage to the ovarian androgen producing tissue leading to a correction in the pituitary—ovarian feedback mechanism, since treatment of only one ovary is believed to be as effective as treating both. A fall in serum concentrations of androgens and LH and an increase in FSH concentrations have been demonstrated after LOD. Several factors have been found to influence the response to LOD. The presence of pre-treatment elevated LH (in excess of 10 IU/l) has been associated with favourable response to LOD while the presence of an increased BMI (≥35 kg/m²), marked hyperandrogenism (testosterone ≥ 4.5 nmol/l or FAI ≥ 15) and long duration of infertility (>3 years) have been found to predict resistance to treatment. Response to LOD has been found to be dependent on the amount of energy delivered to the ovary where ovulation rates increase with an increase in the dose of energy. Obviously this needs to be balanced against the potential harm that can result from the use of excess energy levels leading to ovarian damage. The procedure includes penetration of the ovarian capsule by monopolar electrocautery making four punctures per ovary at a power setting of 30 W (150 J) applied for 4 seconds per puncture (600 J/ovary). The site of application should be away from the ovarian hilum and fallopian tube.

Outcome: the ovulation rate after LOD in CC-resistant PCOS women was approximately 80%. Approximately two thirds of PCOS women treated with LOD respond to treatment with resumption of regular cycles for a variable length of time. Live births were reported in 34% of women in the LOD groups. In patients remaining anovulatory 8 weeks after LOD or those who subsequently became anovulatory, adjuvant therapy with CC or gonadotropins was required to achieve equivalent pregnancy and live birth rate. A recent Cochrane review found that there was no evidence of a significant difference in rates of clinical pregnancy, live birth or miscarriage in women with clomifene resistant PCOS undergoing LOD compared to other medical treatments. Compared to gonadotropin therapy, LOD can lead to monofollicular development and has the advantage of being associated with a lower risk of multiple pregnancies. An economic evaluation has shown that the cost of a live birth after LOD in CC-resistant PCOS women appears to be approximately one-third lower than the equivalent cost of gonadotropin treatment. In contrast, ovulation induction with gonadotropins is expensive and requires regular monitoring, with risks of multiple pregnancy and OHSS. However, laparoscopic surgery, especially in overweight women, is associated with intra-operative risks (i.e., difficulty with access to abdominal cavity and manipulation of surgical instruments, reduced operative field exposure) and postoperative risks (i.e., bleeding, infection, thromboembolism, pulmonary atelectasis/hypoxaemia, and wound complications). LOD can be associated with the occurrence of adhesions in a significant number of patients. Furthermore there is also a concern that LOD may damage the ovarian reserve as evidenced by lower concentrations of anti-mullerian hormone (AMH) and lower antral follicle counts following the procedure. However this evidence is not conclusive and there is little research addressing the long-term complications of LOD. These potential risks suggest minimizing ovarian trauma during the procedure.

Bariatric surgery

Bariatric surgery could be considered second line therapy to improve fertility outcomes in adult women with PCOS who are anovulatory, have a body mass index ≥35 kg/m² and who remain infertile despite undertaking an intensive structured lifestyle management programme involving reduced dietary energy intake, exercise, behavioural and/or drug interventions for a minimum of 6 months. A structured weight management programme should continue even postoperatively. The patient should be made aware of the risk of pre-and post-operative nutritional deficiencies and should be managed in a specialist interdisciplinary care setting, including a bariatric surgeon, a dietician and/or other multidisciplinary staff trained to work with patients who have had bariatric surgery. Pregnancy should be avoided during periods of rapid weight loss and patients should be counselled to avoid pregnancy for at least 12–18 months after bariatric surgery.

Assisted reproduction techniques: IVF

IVF treatment is recommended either as a third-line treatment or in the presence of other infertility factors. IVF is a reasonable option, because the number of multiple pregnancies can be kept to a minimum by transferring small numbers of embryos. The optimal stimulation protocol is still being debated. At present, there are no randomized controlled trials upon which to base any practice recommendations regarding in vitro maturation (IVM) of immature oocytes before IVF for women with PCOS. The available published data is reassuring that the pregnancy rates in women with and without PCOS are similar. The increase in the cycle cancellation rate in women with PCOS appears to be due to absent or limited ovarian response or due to increased OHSS. The Cochrane review found no evidence that metformin treatment before or during assisted reproductive technique cycles improves live birth or pregnancy rates. However the risk of OHSS was reduced with metformin.

Conclusion

PCOS is the most prevalent endocrine disorder in women of reproductive age and by far the most common cause of anovulatory infertility. Lifestyle change alone is generally considered as the first-line treatment for the management of infertile anovulatory women with PCOS who are overweight or obese. CC should be considered as a first-line pharmacological therapy to improve fertility outcomes. Second-line medical treatments may include ovulation induction with gonadotropins (in CC resistant or CC failure women) or laparoscopic ovarian drilling (in CC-resistant women) or possibly with metformin combined with CC (in CC-resistant women). IVF treatment is recommended either as a third-line treatment or in the presence of other infertility factors.
Fritz MA, Speroff L. Clinical gynaecologic endocrinology and infertility. 8th edn. Philadelphia: Lippincott Williams & Wilkins, 2011 (Chapter 12).

**Practice points**

- PCOS is the most common endocrine disorder affecting 6–8% of women of reproductive age
- PCOS is the most common cause (≈75%) of anovulatory infertility
- The pathophysiology of PCOS appears to be multifactorial and polygenic
- The diagnosis is based on Rotterdam ESHRE/ASRM revised 2003 criteria (2 out of 3)
  - Oligo- and/or anovulation
  - Clinical and/or biochemical signs of hyperandrogenism
  - Polycystic ovaries
- Life style management targeting weight loss (in women with BMI ≥ 25 kg/m²) and prevention of weight gain (in women with normal BMI) should be the first line therapy for all women with PCOS
- More patient-tailored approaches should be developed for ovulation induction based on initial screening characteristics of women with PCOS
- The recommended first-line treatment for ovulation induction remains the anti-oestrogen CC. The cumulative conception rate with CC continues to increase until 12 cycles, then plateaus
- Recommended second-line intervention should CC fail to result in pregnancy is either exogenous gonadotrophins or LOD
- The use of gonadotrophins is associated with increased chances for multiple pregnancy and intense monitoring of ovarian response is therefore required
- LOD can lead to monofollicular development and has the advantage of being associated with a lower risk of multiple pregnancies
- Recommended third-line treatment is IVF
- Metformin use in PCOS should be restricted to women with glucose intolerance. The role of metformin in improving reproductive outcomes in women with PCOS appears to be limited as there was no evidence that metformin improves live birth rates whether it is used alone or in combination with other ovulation induction
- Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction