PCOS: diagnosis and management of related infertility

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Abstract

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. It is characterised by a combination of hyperandrogenism (either clinical or biochemical), chronic oligo/anovulation, and polycystic ovaries. It is frequently associated with insulin resistance and obesity. PCOS receives considerable attention because of its high prevalence and possible reproductive, metabolic, and cardiovascular consequences. It is the most common cause of anovulatory infertility. Ovulation induction with an aromatase inhibitor or anti-oestrogen is the first-line medical treatment. The aim of ovulation induction is monofollicular growth to avoid multiple pregnancy. The second-line treatments include gonadotrophins and laparoscopic ovarian drilling. The role and benefit of metformin in ovulation induction is uncertain. Woman with PCOS undergoing IVF are at significant risk of ovarian hyperstimulation syndrome. Women with PCOS are also at an increased risk of developing gestational diabetes, pregnancy-induced hypertension, and pre-eclampsia.

Keywords clomifene; gonadotrophins; infertility; letrozole; metformin; ovulation induction; polycystic ovary syndrome

Definition

The most widely recognized Definition of PCOS was set during a consensus meeting of the American Society of Reproductive Medicine (ASRM) and European Society of Human Reproduction and Embryology (ESHRE) in Rotterdam in May 2003. This was recently endorsed by international evidence-based guidelines for the assessment and management of polycystic ovary syndrome (2018), published by the Centre for Research Excellence in Polycystic Ovary Syndrome (CREPCOS) in partnership with the ESHRE and ASRM, in collaboration with professional societies and consumer advocacy groups internationally.

The diagnosis of PCOS is made when two out of three of the following criteria are met:

1 Clinical and/or biochemical evidence of androgen excess after the exclusion of other related disorders,
2 Oligo-ovulation or anovulation,
3 Ultrasound appearance of the ovaries. The 2003 criteria mandated the presence of >12 follicles in each ovary measuring 2–9 mm and/or increased ovarian volume (>10 ml); in 2018 the cut-off for follicle number was raised to 20 or more in either ovary, to reflect improvement in ultrasound technology (transvaginal scanning with a frequency bandwidth including 8 MHz).

PCOS clinical presentation

(A) Anovulation in the context of PCOS is suspected from the history of oligomenorrhoea and/or amenorrhea. Anovulatory PCOS is the leading cause of secondary amenorrrhoea in patients attending fertility clinics and it is also a common cause of primary amenorrhoea.
(B) The patient's general appearance and body mass index (BMI) may give clues about systemic and endocrine problems including PCOS. About 40–50% of women with PCOS are overweight. Increased abdominal obesity and waist-to-hip circumference is correlated with reduced menstrual frequency and subfertility in association with insulin resistance.
(C) Signs of hyperandrogenism (e.g. acne, hirsutism, male-pattern balding) are also suggestive of PCOS. Virilization suggests a more profound disturbance of androgen secretion due to other causes such as androgen-secreting tumour, non-classical form of congenital adrenal hyperplasia (CAH), or Cushing's syndrome. Acanthosis nigricans is a sign of profound insulin resistance and is usually associated with PCOS and obesity.

Pathophysiology

The pathophysiology of PCOS usually includes excess ovarian androgen production with an abnormal degree of insulin-resistance being a non-essential but common aggravating factor. Hyperinsulinaemia augments LH-stimulated androgen production. The precise mechanism of follicular arrest and anovulation is uncertain but it is known that Anti-Müllerian Hormone (AMH) – which is elevated in PCOS - plays a restrictive role in follicular development.

Differential diagnosis

Other conditions with features similar to PCOS include thyroid dysfunction and non-classic congenital adrenal hyperplasia (CAH). Other causes of amenorrhoea and anovulation, such as hyperprolactinemia, are associated with oestrogen deficiency [WHO Type I, see Box 1]. Androgen-secreting ovarian and adrenal tumours, ovarian hyperthecosis, CAH or Cushing's syndrome need to be considered in women with severe hyperandrogenism and virilization.

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Endocrine causes of secondary amenorrhoea.

1. PCOS (characterised by normal or raised LH, normal FSH and oestradiol, normal or raised androgens, high AMH, and may be associated with mildly elevated prolactin)
2. Premature ovarian failure or insufficiency (characterised by very raised FSH, raised LH, low oestradiol and low AMH)
3. Hyperprolactinaemia (characterised by high prolactin, greater than 1000miu/l, with suppressed FSH/LH/oestradiol)
4. Weight-related and exercise-related amenorrhoea (characterised by very low LH, low FSH, low oestradiol and relevant lifestyle factors)
5. Hypogonadotrophic hypogonadism (consider a structural cause if very low LH/FSH/oestradiol with no relevant lifestyle factors)
6. Physiological: pregnancy and lactation **never forget these!**

Box 1

Laboratory findings

(A) One third of women with PCOS have elevated serum total testosterone concentration. If the value is greater than 5 nmol/L, it is then necessary to exclude other causes (see above). Free testosterone and free androgen index are thought to be sensitive methods of assessing hyperandrogenaemia. Overweight women with clinical hyperandrogenism may have a normal total testosterone but an elevated free testosterone as less is bound to sex hormone binding globulin (SHBG), which is suppressed by hyperinsulinaemia.

(B) An increase in LH pulse frequency results in the frequent observation of elevated LH. FSH is not increased, probably because of negative feedback of chronically elevated oestradiol levels. High serum LH levels are associated with menstrual cycle disturbance, reduced chance of conception, and an increased risk of miscarriage.

(C) AMH is elevated in PCOS. Serum AMH measurement indicates the size of the follicle pool, including pre-antral and small antral follicles (<2 mm), which are harder to detect by ultrasound. However, serum AMH is not currently recommended as a stand-alone diagnostic tool.

(D) Other biochemical investigations should be arranged based on the clinical presentation and suspicion of other aetiologies of anovulation. The common causes of secondary amenorrhoea and related anovulation are listed in Box 1. Thyroid disorders, particularly hyperthyroidism, can cause menstrual irregularity but it is rare for this to be the presenting symptom. Mildly elevated serum prolactin is found in 10–15% of women with PCOS. Women with the most common form of CAH (21-hydroxylase deficiency) will have an elevated serum 17-hydroxyprogesterone concentration.

(E) A progesterone concentration of greater than 30 nmol/L in the middle of the luteal phase is indicative of ovulation. However, it can be difficult to know when to take a blood sample if the patient has an erratic menstrual cycle, and a lower level of progesterone does not confirm anovulation. In general a cycle length <42 days suggests ovulation'. As part of general fertility investigations, it is important to check for other contributing factors (additional pre-treatment investigations may include semen analysis and assessment of tubal patency) and to undertake a pre-pregnancy review (e.g. confirmation of rubella immunity, screening for impaired glucose tolerance/diabetes).

Ultrasound findings

(A) The polycystic ovary is characterised by at least one of the following: either 20 or more follicles measuring 2–9 mm in diameter or increased ovarian volume (>10 ml). Typically there is increased central stroma with peripherally-arranged follicles. However, the subjective appearance of PCO should not be substituted for the Definition given above.

(B) Ultrasound scanning (USS) is also an important diagnostic tool to check for other pathologies in the pelvis, which might be contributing factors to infertility and can therefore modify the management plan.

(C) Diagnosis can be made without USS in women with features of hyperandrogenism and ovulatory dysfunction and in adolescents, but is helpful in patients presenting with subfertility.

Practice points

- PCO describes the morphological appearance of the ovary.
- PCOS is only appropriate when PCO is found in association with menstrual disturbance and/or the complications of hyperandrogenism.

Management

Management of PCOS-related infertility is outlined in Figure 1.

Weight loss

(A) The patient's BMI correlates with increased rate of cycle disturbance and anovulation secondary to insulin metabolism. At least 50% of patients diagnosed with PCOS are obese (BMI >30 kg/m^2). These women are at higher risk of developing type II diabetes or impaired glucose metabolism, and should be screened for diabetes mellitus and encouraged to lose weight. The optimal screening tool is uncertain (fasting glucose, HbA1C, or oral glucose tolerance test may be used). Studies show that even modest weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment.

(B) Lifestyle modification is the first-line therapy for weight control, followed by pharmacological treatment and weight loss surgery. Lifestyle recommendations include decrease in daily caloric consumption and regular physical exercise. The safety of any pharmacological agent used to achieve weight loss in PCOS patients should be taken into consideration, as fertility is the main target and early pregnancy need to be considered. Metformin is not in itself a weight loss agent.

(C) If the above measures do not resolve morbid obesity, bariatric surgery needs to be considered.

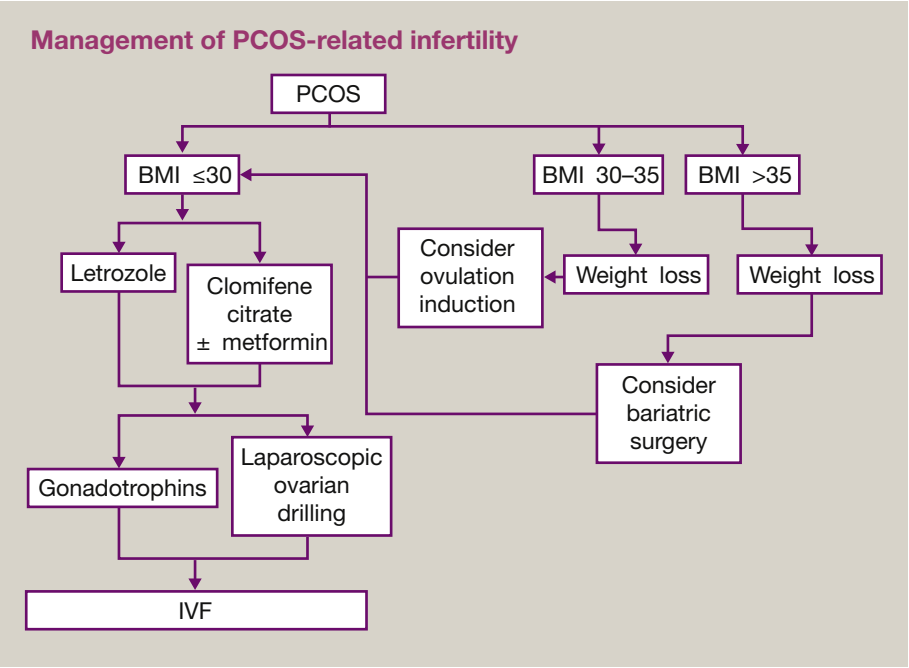

Figure 1 Management of PCOS-related infertility.

Pharmacological treatments for ovulation induction

(A) Clomifene Citrate

Anti-oestrogen therapy with clomifene citrate (CC) has for many years been used as first-line therapy for anovulatory PCOS. CC is thought to bind and block the oestrogen receptors in the hypothalamus for prolonged periods, thereby decreasing the normal ovarian-hypothalamic feedback. This blockade increases GnRh pulsatility, leading to increased pituitary secretion of gonadotrophins which promote ovarian follicular development.

The aim of ovulation induction is to mimic a physiological menstrual cycle with monofollicular ovulation. The starting dose of CC is 50 mg/day orally for five days beginning on day 2 −5 of the menstrual cycle. The dose should be increased to 100 mg if there is no response or decreased to 25 mg/day if there is exuberant response. Discontinuation of CC should be considered if the patient is anovulatory after the dose has been increased.

CC will induce ovulation successfully in 70−80% of selected patients. Among anovulatory infertile woman who respond to CC treatment, the pregnancy rate per cycle is approximately 15%. Cumulative pregnancy rates of 67% can be expected over 6 months in woman who have no other subfertility factors. When pregnancy is not achieved within 3 cycles, the infertility investigations should be reviewed, including any factors not yet evaluated. It is appropriate to offer the couple assisted conception if pregnancy has not occurred after 6 to 12 ovulatory cycles, taking into account the woman's age.

CC is associated with 6−11% risk of multiple pregnancy, so careful monitoring with ultrasound to assess ovarian response is recommended. Ultrasound monitoring is also used to advise couples on optimal timing of intercourse, to assess endometrial development (which may be suboptimal, due to the anti-oestrogenic effect of CC), and confirm ovulation.

Side effects of CC include visual disturbances (stop drug immediately), hot flushes, abdominal distension, mood swings, breast tenderness, dizziness, and nausea. CC is currently licensed for 6 months' use.

(B) Aromatase Inhibitors

Letrozole is now recommended as a first-line pharmacological treatment for ovulation induction and may soon replace CC. Recent studies indicate an improvement in pregnancy and live birth rates without affecting miscarriage or multiple pregnancy rates compared to CC. However, aromatase inhibitors are not licensed in the UK for use in ovulation induction.

The mechanism of action is to inhibit the aromatization of androgen to oestrogen and thus release the hypothalamic −pituitary axis from negative feedback. Unlike CC these drugs do not have anti-oestrogenic effects on the endometrium or cervical mucus. Dosage is 2.5 up to 7.5mgs daily for five days and ultrasound monitoring is advised as for CC.

(C) Metformin

Metformin is an insulin sensitiser which can be used for ovulation induction, usually in a dose of 1500 mg daily, either alone or in combination with Letrozole or CC. Recent meta-analysis suggests that metformin alone may be useful for OI, and does not require ultrasound monitoring, although it is associated with gastro-intestinal side-effects. Combination therapy of metformin with CC shows improved ovulation and clinical pregnancy rates compared with either agent alone. Metformin may be useful for patients with pre-diabetes who are at risk of gestational diabetes, and can be continued in pregnancy.

(D) Gonadotrophins

Gonadotrophin ovulation induction is a second−line therapy, indicated in those patients who failed to ovulate and were resistant to oral agents. It is also indicated in those who have intolerable side-effects with other treatments or a response that is likely to reduce their chances of conception (hypersecretion of

LH or antioestrogenic effect on cervical mucus and endometrium). It is important to start with low doses of gonadotrophins (37.5–75iu daily by subcutaneous injection) and monitor the response carefully by USS. Different regimens have been reported (step up, low-dose step-up, step down) to minimize the risk of multiple pregnancy and OHSS.

Multiple pregnancy has been reported in up to a third of patients, but this risk is minimized by low-dose regimens. Treatment should be suspended if 3 or more follicles >14 mm develop as the risk of multiple pregnancy obviously increases.

PCOS patients are at risk of ovarian hyperstimulation syndrome (OHSS), which occurs if many follicles are stimulated leading to symptoms of abdominal distension, discomfort, nausea, vomiting, and in its severe form, difficulty breathing with ascites and sometimes pleural and pericardial effusions.

Laparoscopic ovarian drilling (LOD)

LOD has been shown to have similar efficacy to gonadotrophins in the treatment of clomifene-resistant PCOS. Furthermore it is free of the risks of ovarian hyperstimulation and multiple pregnancy. The exact mechanism of action is not known. The favoured method is to use monopolar diathermy at 4 points per ovary for 4 s at 40 W.

Patients with high LH are more likely to benefit and respond to LOD while those with marked hyperandrogenism, obesity, or long duration of infertility are more likely to be resistant. LOD is particularly appropriate in women who need laparoscopic assessment of their pelvis or who are unable to attend the frequent monitoring required for gonadotrophin therapy.

The surgical procedure, the small risk of postoperative adhesions and the theoretical risk of damaging ovarian reserve deserve careful consideration and discussion with the patient. It is also important to note that response to LOD is not permanent and it is not used to treat other sequelae of PCOS (e.g. hirsutism, obesity).

In vitro fertilization (IVF)

IVF is not necessary for anovulatory infertility and is not the first-line treatment for PCOS. However, patients may be referred for IVF either because they fail to conceive despite ovulation induction or because there is an additional reason for infertility (for example, male factor).

IVF outcomes in women with PCO compared with controls show the development of more follicles, higher serum oestradiol concentration, and more eggs but often lower fertilization rates. Patients with PCOS have a significantly increased risk of OHSS (5–10%). Strategies to reduce the risk of OHSS in PCOS patients undergoing IVF include the use of a GnRH antagonist protocol, using low doses of gonadotrophins, careful monitoring during stimulation to adjust the gonadotrophin dose, and giving an agonist trigger. OHSS is worsened by pregnancy, so in women at high risk, embryo transfer should be deferred and embryos cryopreserved.

In vitro maturation (IVM) has been suggested as an alternative to conventional IVF in young women with PCOS or history of prior OHSS. The maturation of retrieved immature oocytes in the laboratory minimises gonadotrophin stimulation. However, pregnancy rates are low and this technique is not widely used.

Pregnancy and PCOS

(A) Polycystic ovary syndrome (PCOS) has been linked to an increased risk of miscarriage. The exact mechanism remains unclear, but has been attributed to insulin resistance, hyperinsulinaemia and hyperandrogenaemia.

(B) PCOS patients are at increased risk of developing gestational diabetes. This risk is greatest in women with high BMI especially those who required ovulation induction to conceive. These women should be screened for gestational diabetes before 20 weeks of pregnancy and referred to a specialist obstetric diabetic service if abnormalities are detected.

(C) Women with PCOS are also at increased risk of developing pregnancy-induced hypertension and pre-eclampsia with related complications of prematurity.

(D) Obesity itself increases the risk of miscarriage, congenital anomalies, and obstetric complications, and this reinforces the need for weight loss prior to fertility treatment.

Long-term consequences of PCOS

It is important to inform women with PCOS of the possible long-term risks to health. Long-term consequences of metabolic dysfunction include type 2 diabetes, risk of sleep apnoea, hypertension and hyperlipidaemia.

PCOS patients with oligo-amenorrhoea due to anovulation are predisposed to endometrial hyperplasia and later carcinoma. Regular induction of withdrawal bleeding is advisable, using cyclical or intermittent progestogen or a combined oral contraceptive pill where medically appropriate, or control with the levonorgestrel intrauterine system. ◆

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Practice points

Ovulation induction [OI]:

- Oral agents are the first line treatment for OI.
- Letrozole may provide a higher live birth rate per cycle of treatment compared with clomifene
- Multiple pregnancy is a significant risk and ideally all OI cycles should be monitored by ultrasound.
- Metformin can be used alone or in combination with Clomifene/Letrozole.
- Gonadotrophin therapy and laparoscopic ovarian drilling are second-line treatments