Polycystic ovarian syndrome (PCOS) is a common and complex syndrome that presents with a wide spectrum of clinical symptoms and is also associated with several other serious conditions. This article reviews the recommended management of PCOS and its associated symptoms in primary care and discusses when referral is necessary.

Prevalence
The general prevalence of PCOS is between 2 and 26 per cent, depending on the diagnostic criteria employed, with increased rates and severity of symptoms in south-east Asian women.1-3 Between 22 and 33 per cent of women will have evidence of polycystic ovaries on ultrasound scan but no associated symptoms; this is essentially a normal variant and does not require any further investigation or intervention.1,3 Approximately 40–50 per cent of patients with PCOS will be overweight (BMI >25),3 and a large majority will have a family history of PCOS.1

Pathophysiology
PCOS is named after the appearance of the ovaries on ultrasound scan. However, the ‘cysts’ described are normal ovarian follicles arrested in an immature state rather than physiological or pathological cysts (see Figure 1).

The normal menstrual cycle is characterised by predictable hormone fluctuations as depicted in Figure 2a. The ovarian follicles contain both granulosa and theca cells. The theca cells are stimulated by luteinising hormone (LH) and convert cholesterol to androgens. The granulosa cells then convert the androgens to oestradiol under the influence of follicle-stimulating hormone (FSH) and aromatase (see Figure 3a).
The cause of PCOS is currently unknown; however, it is likely to be multifactorial with both genetic and environmental influences.3,4 There are a number of theories that currently exist, including intrinsic ovarian dysfunction, insulin resistance and LH hyperstimulation.

**Intrinsic ovarian dysfunction**

Theca cells in women with PCOS produce increased androgens in response to similar levels of LH compared with normal theca cells.4,5

**Hyperinsulinaemia and insulin resistance**

Insulin resistance is present in 65–80 per cent of women with PCOS independent of obesity.1 Insulin works in synergy with LH to increase androgen production in theca cells and the adrenal glands leading to saturation of the pathway that converts androgens to oestradiol.4,6 This results in increased androgen output from the ovaries. Insulin also inhibits the production of sex hormone-binding globulin (SHBG), resulting in increased unbound active androgens. In addition, it inhibits the production of insulin-like growth factor 1 (IGF-1) binding protein, resulting in increased levels of free IGF-1 and further stimulation of theca cells (see Figure 3b).3-5

**LH hyperstimulation**

LH is elevated in approximately 40 per cent of women with PCOS and it is hypothesised that there is an increased LH pulse frequency and amplitude, resulting in increased androgen production in ovaries of women with PCOS (see Figure 3b).4,7

**Hormonal effects of PCOS**

Hyperandrogenism in PCOS results in hirsutism, acne and alopecia. Androgens may also stop follicular development and therefore cause anovulation.5 Testosterone is converted to oestradiol in peripheral adipose tissue.7 The arrested follicles also continue to produce oestradiol at a constant level. This suppresses FSH via negative feedback, and levels never peak, preventing the switch to positive feedback and hence follicle maturation and ovulation (see Figure 2b).

**Diagnosis**

Patients are likely to present with oligomenorrhoea/amenorrhoea, infertility or clinical signs of hyperandrogenism. The 2003 Rotterdam Consensus on diagnostic criteria for PCOS8 states that two out of the following three features need to be present:

- Oligo-anovulation or anovulation (characterised by oligomenorrhoea (cycles longer than 35 days) or amenorrhoea (cycles more than six months apart))
- Clinical and/or biochemical signs of hyperandrogenism (raised androgens or hirsutism, acne or alopecia)
- Polycystic ovaries: the presence of 12 or more follicles (measuring 2–9mm in diameter) in one or both ovaries and/or increased ovarian volume (>10ml)

It is essential to exclude other causes of hyperandrogenism and oligomenorrhoea/amenorrhoea, including simple obe-

---

**Figure 2.** The normal menstrual cycle (a); compared with the polycystic ovarian syndrome (PCOS) cycle (b)
Hypog-hypog is a central problem with the hypothalamus or pituitary gland characterised by impaired release of gonadotropins, typically seen in patients who have a low BMI, have experienced a sudden drop in weight or have undertaken excessive exercise. Primary ovarian insufficiency is a peripheral problem with the ovaries, in which the ovaries fail to release eggs and oestradiol in women under the age of 40 years old. The investigations described below help to distinguish between the causes of oligomenorrhoea/amenorrhoea.

Investigations
Table 1 lists the recommended blood tests in patients with suspected PCOS. A pelvic ultrasound scan should also be performed (see Figure 4). However, the results should be interpreted with caution in teenagers where a polycystic picture is often seen.9

Anti-Müllerian hormone (AMH) is another test that is usually performed in secondary or tertiary care. AMH is produced by granulosa cells. It is used as a marker for ovarian reserve and can be measured at any time in the menstrual cycle as the levels do not fluctuate. AMH levels are significantly elevated in patients with PCOS, indicating good ovarian reserve. However, studies are currently investigating the implications of raised AMH in the pathophysiology of PCOS.4 AMH testing may be

### Table 1. Recommended blood tests in patients with suspected polycystic ovarian syndrome (PCOS)1,3

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Normal range</th>
<th>Levels in PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>For PCOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total testosterone</td>
<td>0.5–3.5nmol/L</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Sex hormone-binding globulin</td>
<td>40–140nmol/L</td>
<td>Normal or low</td>
</tr>
<tr>
<td>Free androgen index</td>
<td>&lt;5.0</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Luteinising hormone</td>
<td>Reproductive age 1–12.5IU/L:</td>
<td>Normal or high in PCOS High in primary ovarian insufficiency Low in hypog-hypog</td>
</tr>
<tr>
<td></td>
<td>● follicular phase 1–12.5IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● luteal phase 1–12IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postmenopausal &gt;25IU/L</td>
<td></td>
</tr>
<tr>
<td>Follicle-stimulating hormone</td>
<td>Reproductive age 2–11IU/L</td>
<td>Normal in PCOS High in primary ovarian insufficiency Low in hypog-hypog</td>
</tr>
<tr>
<td></td>
<td>● follicular phase 2–11IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● luteal phase 2–9IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postmenopausal &gt;25IU/L</td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>≤500mU/L</td>
<td>Mildly elevated in PCOS High in prolactinomas</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone</td>
<td>0.4–4.5mU/L</td>
<td>Normal in PCOS High/low in thyroid dysfunction</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>Reproductive age 70–1350pmol/L:</td>
<td>Not recommended Normal/high in PCOS Low in hypog-hypog Low in primary ovarian insufficiency</td>
</tr>
<tr>
<td></td>
<td>● follicular phase 70–500pmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● midcycle 250–1350pmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● luteal phase 100–800pmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postmenopausal ≤170pmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Key: Hypog-hypog = hypogonadotrophic hypogonadism

Figure 3. Hormone synthesis in normal ovaries (a); and polycystic ovaries (b)

(sanity, nonclassical congenital adrenal hyperplasia, Cushing’s syndrome, androgen-secreting tumours, hyperprolactinaemia, hypothyroidism, hypothalamic amenorrhoea (hypogonadotrophic hypogonadism or hypog-hypog), primary ovarian insufficiency and drug-related causes.1,5

Hypog-hypog is a central problem with the hypothalamus
useful in the diagnosis of PCOS and when reassuring patients of their fertility potential.

**Prognosis and complications**

Patients with PCOS have good overall fertility potential with simple interventions required to induce ovulation. However, PCOS is a systemic condition carrying an increased risk of impaired glucose tolerance, type 2 diabetes, dyslipidaemia and endometrial cancer (if oligomenorrhoeic/amenorrhoeic) secondary to unopposed oestrogen exposure. There is also limited evidence of associations with cardiovascular disease and sleep apnoea.

**Management**

**Nonpharmacological**

Overweight patients (BMI >25) should be advised that lifestyle measures are first-line treatment and weight loss is likely to improve their symptoms of hyperandrogenism and oligomenorrhoea/amenorrhoea. A reduction of 5 per cent body weight reduces insulin resistance and testosterone levels as well as improving body composition and cardiovascular risk markers. The patient should be advised regarding calorie counting (<1500 calories per day) and, if necessary, referred to a dietitian. Patients should be regularly screened for impaired glucose tolerance (see Table 2), type 2 diabetes, cardiovascular risk factors (blood pressure, waist circumference, BMI, lipid profile) and evidence of sleep apnoea, either every year or two years depending on previous results and risk factors.

<table>
<thead>
<tr>
<th>Yearly OGTT</th>
<th>Two-yearly OGTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous abnormal OGTT or</td>
<td>Normal initial OGTT</td>
</tr>
<tr>
<td>Risk factors:</td>
<td>No risk factors for diabetes</td>
</tr>
<tr>
<td>• Strong family history of diabetes</td>
<td></td>
</tr>
<tr>
<td>• BMI &gt;30 (&gt;25 in Asian women)</td>
<td></td>
</tr>
<tr>
<td>• History of gestational diabetes</td>
<td></td>
</tr>
</tbody>
</table>

**Pharmacological treatment in primary care**

The pharmacological treatment options for use in primary care are summarised in Table 3.

**Hormonal treatment**

If the patient has not had a menstrual bleed in more than three months then a withdrawal bleed should be induced to protect the endometrium against hyperplasia. This is achieved with 14 days of progestogen treatment to decidualise the endometrium. Following this, a transvaginal ultrasound scan should be performed to check endometrial thickness (see Figure 5). If the endometrium is >10mm or abnormal in appearance then an endometrial biopsy is required to exclude pathology and a gynaecological referral is warranted. If the endometrium is <10mm and appears normal then ongoing endometrial protection is required.

There are three suitable options for endometrial protection and the choice will depend on the patient’s individual circumstances:

- **Cyclical progestogen** (as described above) every three months
- **Combined hormonal contraception (CHC):** pills, patches or contraceptive vaginal ring
- **Progestogen-only contraception:** pills, injection, implant or levonorgestrel-releasing intrauterine system (Mirena).

CHC will provide endometrial protection, achieve regular cycles and may be beneficial in treating hyperandrogenism. The progestogen in CHC suppresses LH levels and thus ovarian androgen production, and the oestrogen increases SHBG thus reducing bioavailable androgens. Some preparations contain progestogens with antiandrogenic properties, due to their antagonist effects on androgen receptors and/or inhibition of 5-alpha reductase, eg Dianette (containing cyproterone acetate 2mg) or Yasmin (containing drospirenone 3mg). These preparations may improve acne and hirsutism symptoms to a greater degree than other CHC. Effects on hyperandrogenism will take three to six months to achieve and are often only mild to moderate improvements.

Progesterone-only contraception may be used as an alternative to CHC for endometrial protection. It works by thinning the endometrial lining, causing a cervical mucus plug and, depending on the preparation and method of administration, suppressing ovulation to a certain degree.

If the patient is trying to conceive then hormonal contraception should be avoided, and cyclical progesterone would be the recommended option.

When prescribing any contraceptives, consider any contraindications by referring to the Faculty of Sexual and Reproductive Health (FSRH) clinical guidelines, particularly as PCOS patients may be overweight and have cardiovascular risk factors.

**Topical treatment for hirsutism**

Vaniqa cream (11.5% efomithine) is a topical treatment used for facial hirsutism. It is an antiprotozoal drug, which inhibits the enzyme ornithine decarboxylase in hair follicles to reduce hair growth. Efficacy is low and if there is no improvement
<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Mode of action</th>
<th>Effectiveness</th>
<th>When to prescribe (primary care)</th>
<th>Side-effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclical progesterone (14 days/3-monthly: norethisterone or medoxy-progesterone)</td>
<td>Endometrial protection</td>
<td>Endometrial decidualisation</td>
<td>Good efficacy</td>
<td>No menstrual period for 3 or more months</td>
<td>Unlikely given short course</td>
<td>History of liver tumours, Genital or breast cancer, Acute porphyria</td>
</tr>
<tr>
<td>Combined hormonal contraception</td>
<td>General:</td>
<td>General:</td>
<td>Good efficacy:</td>
<td>Oligo/amenorrhoea</td>
<td>Breast tenderness</td>
<td>Extensive contraindications, See FSRH UK MEC for information</td>
</tr>
<tr>
<td></td>
<td>endometrial protection</td>
<td>LH suppression</td>
<td>• mild to moderate improvement in acne/hirsutism</td>
<td></td>
<td>Bloating, Headaches, Nausea, Vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cycle control</td>
<td>SHBG increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined hormonal contraception</td>
<td>Dianette/Yasmin:</td>
<td>Dianette/Yasmin:</td>
<td>Good efficacy:</td>
<td></td>
<td>Breast tenderness</td>
<td>Current breast cancer, See FSRH UK MEC for information</td>
</tr>
<tr>
<td></td>
<td>antiandrogenic effects</td>
<td>antiandrogenic effects</td>
<td>• endometrial protection</td>
<td></td>
<td>Bloating Administration-specific side-effects; see FSRH guidelines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• cycle control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progestosterone-only contraception</td>
<td>Endometrial protection</td>
<td>Endometrial decidualisation</td>
<td>Good efficacy:</td>
<td>Oligo/amenorrhoea</td>
<td>Breast tenderness</td>
<td>Current breast cancer, See FSRH UK MEC for information</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• endometrial protection</td>
<td></td>
<td>Bloating Administration-specific side-effects; see FSRH guidelines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• cycle control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaniqa cream (11.5% eflornithine cream)</td>
<td>Facial hirsutism</td>
<td>Inhibits ornithine decarboxylase in hair follicles</td>
<td>Poor efficacy:</td>
<td></td>
<td>Acne, Skin rash/sensitivity</td>
<td>Pregnancy, Breastfeeding</td>
</tr>
<tr>
<td>Topical retinoids</td>
<td>Acne</td>
<td>Local anti-inflammatory effect</td>
<td>Good efficacy:</td>
<td>Mild/moderate acne</td>
<td>Local skin irritation/peeling</td>
<td>Pregnancy (adequate contraception must be prescribed)</td>
</tr>
<tr>
<td>Topical benzoyl peroxide/azelaic acid</td>
<td>Acne</td>
<td>Antimicrobial agent</td>
<td>Good efficacy:</td>
<td>Mild/moderate acne</td>
<td>Local skin irritation</td>
<td>None</td>
</tr>
<tr>
<td>Oral antibiotics tetracycline/doxycycline</td>
<td>Acne</td>
<td>Antibiotic</td>
<td>Good efficacy:</td>
<td>Mild/moderate acne</td>
<td>Nausea, Vomiting</td>
<td>Pregnancy, Breastfeeding, Children</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Weight loss</td>
<td>Gastrointestinal lipase inhibitor</td>
<td>Good efficacy:</td>
<td>BMI &gt;30 or BMI &gt;28 plus risk factors in conjunction with weight loss programme</td>
<td>Oily leakage, Flatulence, Faecal urgency, Liquid/oily stools, Faecal incontinence, Abdominal distention/pain</td>
<td>Chronic malabsorption syndrome, Cholestasis, Breastfeeding, Caution in Pregnancy</td>
</tr>
</tbody>
</table>

Key: FSRH UK MEC = Faculty of Sexual and Reproductive Healthcare UK Medical Eligibility Criteria; SHBG = sex hormone-binding globulin

Table 3. Pharmacological treatments used in primary care.1,3,14,16,20
after four months of treatment, it should be discontinued.\textsuperscript{14} Nonpharmacological methods of hair removal, including shaving, waxing and plucking, electrolysis and laser hair removal, are not available on the NHS but can be recommended to patients.\textsuperscript{16}

**Treatments for acne**

Initial treatment for acne should be with a topical retinoid or benzoyl peroxide. Retinoids cause redness and skin peeling. They should not be used in pregnancy and should be prescribed with adequate contraception. Benzoyl peroxide also causes skin irritation initially.\textsuperscript{14,17} If these treatments are poorly tolerated then topical azelaic acid can be prescribed, which is less likely to cause irritation. It has antimicrobial and anticomedomonal properties. In more severe cases, an oral antibiotic can be added to treatment. Whenever an underlying endocrinological or gynaecological cause is suspected, the patient should be referred for further management. Unresponsive or severe acne should be managed by a dermatologist.\textsuperscript{17}

**Treatments for weight loss**

A weight-loss programme should be monitored for three months; however, if unsuccessful or if BMI remains $>$30, consider prescribing orlistat (a gastrointestinal lipase inhibitor). Orlistat reduces absorption of dietary fat from the gastrointestinal tract. Studies show that treatment with orlistat leads to a significant reduction in BMI in women with PCOS (12.9 per cent at 24 weeks).\textsuperscript{18} Side-effects include oily rectal leakage, flatulence, oily stools, incontinence and abdominal distention or pain. It is contraindicated in chronic malabsorption syndrome and cholestasis. It should be used with caution in pregnancy and avoided in breastfeeding.\textsuperscript{14}

If the patient has a BMI $>$40, or $>$35 with another high-risk obesity-related co-morbidity, they should be considered for referral for bariatric surgery.\textsuperscript{1}

**Treatment initiated in specialist care**

If the patient would benefit from metformin treatment (see below), is unresponsive to the treatments described above for hirsutism or acne, has significant alopecia or wants to pursue fertility management then a referral for specialist care is warranted (see Figure 6).

**Metformin**

Metformin (a biguanide) is an insulin-sensitising drug that decreases gluconeogenesis and increases peripheral utilisation of glucose. It is licensed for use in patients with type 2 diabetes; however, it is also used off-licence in patients with PCOS for symptomatic management.\textsuperscript{14} Treatment in patients with PCOS should be initiated by a specialist. Gastrointestinal side-effects are common initially and if they persist, a slow-release preparation may be beneficial. Additionally, metformin can rarely provoke lactic acidosis (most commonly in patients with pre-existing renal impairment).\textsuperscript{14}

Metformin is recommended as first-line treatment in women with PCOS who have type 2 diabetes or impaired glucose tolerance and in whom lifestyle modification has failed, or second-line in women who have menstrual disorders and who cannot take or tolerate CHCs.\textsuperscript{13} Metformin has been associated with weight loss in some studies.\textsuperscript{13,18} A Cochrane review showed an improved ovulation rate (odds ratio (OR) 1.81), no difference in live birth rate, reduced testosterone levels (mean reduction 0.60nmol/L), no effect on BMI or miscarriage risk and a reduction in systolic BP (mean reduction 3.59mmHg) with metformin compared with placebo.\textsuperscript{19}

**Specialist treatment for hyperandrogenism**

If hirsutism has failed to respond to treatment in primary care, it may respond to systemic treatments such as antiandrogens (cyproterone acetate, spironolactone) or a 5-alpha reductase inhibitor (finasteride).\textsuperscript{16}

**Fertility – ovulation induction**

Anovulatory infertility as seen in PCOS can be treated with clomifene citrate (a selective oestrogen-receptor modulator (SERM)). This induces gonadotropin release by blocking the oestrogen receptors in the hypothalamus, thereby interfering with hypothalamic-pituitary-ovarian (HPO) axis feedback mechanisms.\textsuperscript{14} It can be used for up to six cycles and the patient should be monitored for ovulation, multiple ovulation and ovarian hyperstimulation syndrome (OHSS) via ultrasound scans during the first cycle. A live birth rate of 23 per cent has been demonstrated with clomifene treatment; however, multiple pregnancy occurs in 4–8 per cent of cases.\textsuperscript{20} If the patient has not fallen pregnant after six months then the treatment should be discontinued due to the theoretical risk of ovarian cancer.

Letrozole (an aromatase inhibitor) is an alternative to clomifene citrate for ovulation induction. It prevents the conversion of androgen to oestrogen and therefore prevents the constant and excessive feedback of oestrogen on the HPO axis, thereby facilitating ovulation.\textsuperscript{20} Studies have suggested reduced multiple ovulation, reduced multiple pregnancy rates and improved live birth rates compared with clomifene.\textsuperscript{20}
Figure 6. Management of polycystic ovarian syndrome (PCOS) in primary care – and when to refer

1. Patient attends with oligo/amenorrhoea and suspected PCOS
   - Screen for PCOS and to exclude other causes of symptoms

2. PCOS confirmed
   - Other diagnosis suspected
   - Refer to relevant specialist

3. Screen for associated co-morbidities, IGT, type 2 diabetes, cardiovascular risk factors

   a. >4 menstrual periods per year:
      - Offer CHC for cycle control
   b. BMI <25:
      - Maintain healthy weight and lifestyle
   c. No hirsutism:
      - Maintain healthy weight and lifestyle
   d. No acne:
      - Maintain healthy weight and lifestyle
   e. No alopecia:
      - Maintain healthy weight and lifestyle
   f. Patient not currently trying to conceive:
      - Maintain healthy weight and lifestyle

   - <4 menstrual periods per year:
     - Withdrawal bleed
     - TVUSS scan
     - Ongoing endometrial protection

   - BMI >25:
     - Weight loss
     - BMI >30 – orlistat
     - BMI >40 – bariatric referral

   - Hirsutism:
     - CHC
     - Vaniqa cream
     - Nonpharmacological interventions
     - Refer to gynaecology if inadequate response

   - Acne:
     - CHC
     - Topical preparations
     - Oral antibiotics
     - Refer to dermatology if inadequate response

   - Alopecia:
     - CHC
     - Refer to dermatology

4. Patient wishes to conceive
   - Refer to gynaecology

Revisit screening for associated co-morbidities and changes in individual circumstances

Key: IGT = impaired glucose tolerance
TVUSS = transvaginal ultrasound scan
CHC = combined hormonal contraception

Prescriber November 2016
prescriber.co.uk
Conclusion

PCOS is a common and complex syndrome with a large spectrum of clinical symptoms and wider reaching systemic implications. The mainstay of management in primary care is screening for associated conditions, lifestyle and weight loss management, hormonal contraception, and topical preparations for acne and hirsutism. Patients not responding to these measures or wishing to pursue fertility management should be referred for specialist gynaecological care.

References

14. NICE. BNF. Available at: https://www.evidence.nhs.uk/summary/lnf/current [Accessed June 2016]
15. Faculty of Sexual and Reproductive Healthcare of the RCOG. UK medical eligibility criteria for contraceptive use (UKMEC). July 2016. Available at: https://www.fsrh.org/documents/ukmec-2016/

Declaration of interests

None to declare.

Dr Graham is an ST3 in community sexual and reproductive health at King’s College Hospital, and Mr Hamoda is a consultant gynaecologist and subspecialist in reproductive medicine and surgery at King’s College Hospital NHS Trust