What is polycystic ovary syndrome?

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women of reproductive age, affecting around 7% of this group of women. The ovaries produce increased androgens, often leading to symptoms of androgen excess. PCOS is also associated with insulin resistance, dyslipidaemia, obesity, diabetes mellitus, CVD, anovulatory infertility, endometrial hyperplasia and carcinoma.

20% of women have appearances suggestive of polycystic ovaries on ultrasound but, unless they are symptomatic or fulfil the criteria for PCOS (see below), this doesn’t need treating.

When should I suspect PCOS?

Androgen excess affects the skin, hair and reproductive system. Consider PCOS if there is:

- Oligo-/amenorrhoea (indicating infrequent or absence of ovulation).
- Heavy, irregular or prolonged periods.
- Acne.
- Alopecia.
- Hirsutism.
- Obesity.
- Infertility.

Diagnosis of PCOS

Diagnosis is based on the Rotterdam criteria in which two out of the three following criteria should be present in PCOS:

- An-/oligo-ovulation (cycle >35d or <10 periods a year).
- Polycystic ovaries on ultrasound scan.
- Clinical or biochemical hyperandrogenism (acne, hirsutism, alopecia or raised free androgen index – see below).

This definition has been widely adopted. The diagnosis is one of exclusion, so means that, while PCOS can be suspected clinically, in practice we need to arrange tests to confirm the diagnosis and exclude other causes for the symptoms. (Hum Reprod 2004;19:41).

Biochemical hyperadrenogenism

An elevated free androgen index (FAI) of >5 suggests PCOS.

FAI is a measure of biologically active testosterone. Some labs calculate this for you; otherwise, it is calculated using the formula below from total testosterone and sex hormone binding globulin levels:

\[ \text{FAI} = \frac{\text{total testosterone} \times 100}{\text{SHBG}} \]

If symptoms are suggestive, the following tests will exclude other causes for menstrual disturbances:

- FSH.
- Prolactin.
- TFTs.

Red flags

Look out for the following red flags (NEJM 2005;352:1223):

- If total testosterone is high (>5), or there is evidence of rapid onset virilisation (e.g. with male pattern baldness, voice deepening, clitoromegaly), refer to endocrinologist.
- If congenital adrenal hyperplasia (CAH) is suspected (FH of infertility, more common in specific ethnicities: Eastern-European Jew, Yugoslav, Hispanic and those from Southern Mediterranean), a morning blood sample for 17-hydroxyprogesterone >5nmol/L is indicative. Refer to endocrinology.
- If there are symptoms suggestive of Cushing’s syndrome (high blood pressure, easy bruising, striae), a 24h urine free cortisol (UFC) or overnight dexamethasone suppression test (DST) can be done.

Physiology of the normal ovary

In the ovary there are two layers of cells:
Theca cells, where cholesterol is converted to androgen under the influence of LH.
Granulosa cells, where androgens are converted to oestradiol under the influence of FSH.

Production of these hormones leads to normal follicular growth and ovulation.

Pathophysiology of PCOS

A recent article outlines the physiology and management of PCOS (J Fam Plann Reprod Healthcare 2014;40:217).

There are three biochemical abnormalities associated with PCOS:

- Excess androgen production within the ovary.
- Hyperinsulinaemia stimulating more androgen production from the ovaries.
- Reduced binding (and inactivation) of androgen by sex hormone binding globulin caused by obesity.

Excess androgen production within the ovary

It is thought a genetic imbalance in LH to FSH levels drives increased androgen production in PCOS. Increased androgens promote the development of multiple small follicles AND inhibit larger follicular growth, and, with this, ovulation.

Hyperinsulinaemia encourages more androgen production from the ovaries

Insulin is also a co-factor that augments LH-induced androgen secretion. The hyperinsulinaemia associated with the insulin resistance often present in PCOS means that more androgen will be produced in the ovary.

Reduced binding of androgen by sex-hormone binding globulin

Sex-hormone binding globulin (SHBG) is a protein which binds androgens and so inhibits their action. SHBG is inversely related to weight, so as weight increases, so does androgen availability.
Management of PCOS

Management involves treating androgenic symptoms and preventing the long-term sequelae of the associated conditions. Women with PCOS may need referral to fertility services and should have their pregnancies monitored carefully.

Anxiety and depression are more common in women with PCOS, so it is important to enquire about emotional wellbeing (Evidence-based guideline for the assessment and management of PCOS – Australian Alliance 2011).

Symptom control

Lifestyle and weight loss

40–50% of women with PCOS are obese, so lifestyle is central to those with PCOS.

A loss of 10% body weight can increase fertility, ovulation rate and menstrual regularity, even when women remain obese (Hum Reprod 1995;10:2705).

A Cochrane review (2011, CD0075506) found that lifestyle interventions resulted in reduced weight and associated improvements in abdominal obesity, biochemical and clinical hyperandrogenism.

Even in the absence of weight loss, exercise improves PCOS. Encourage exercise!

There is a small amount of evidence that Orlistat may be effective in achieving weight loss in PCOS (J Hum Reprod Sci 2014;7:255).

Period regulation

CHC can reduce acne and regulate periods in women wishing to avoid pregnancy. CHC works by reducing LH secretion and increasing levels of SHBG.

Some features of PCOS may represent a relative contraindication for CHC use (e.g. obesity, DM, dyslipidaemia). But, in the absence of other risk factors, there is no evidence that women with PCOS are at increased risk with CHC compared with other women.

The progestogens in CHC vary in their androgenicity, and 3rd and 4th generation CHCs have less androgenic potential. There is currently no evidence for differences in effectiveness among the various progestogens. Drospirenone (the progestogen in Yasmin) is not considered to have a significant anti-androgenic action in the doses used in COCs (Fertil Steril 2012;97:28).

There are few studies looking at the metabolic effects of CHC in PCOS, but a Cochrane review (2007, CD005552) concluded that, based on limited evidence, CHC does not increase metabolic effect (Fertil Steril 2012;97:28).

Endometrial protection

Women with PCOS suffer with chronic anovulation, which means the absence of a cyclical progesterone production. This increases their risk of endometrial hyperplasia and cancer, due to unopposed oestrogen exposure.

- If amenorrhoeic and NOT using CHC, give a progestogen such as medroxyprogesterone acetate 10mg twice daily for 7–10d to induce a bleed 3–4 times a year.
- OR use an intrauterine progestogen-releasing device (IUS).
Hirsutism

This is a problem for many women with PCOS because androgens promote the transformation of vellus hair into terminal hair which is longer, thicker and more noticeable. This occurs in androgen-sensitive areas.

- Cosmetic treatments (shaving, waxing or depilatory creams) can be used and do not exacerbate hair growth.
- Laser and light-assisted hair removal have been shown to be effective in the short-term, although long-term efficacy is not known (Cochrane 2006;(4):CD004684).
- Vaniqa is topical eflornithine cream which has been shown to reduce hair growth during treatment, but not after stopping. It is expensive (cost to the NHS of £156–312 per year) so the DTB concludes it should only be considered where local treatments have been ineffective and systemic treatments are unsuitable (DTB 45(8):62 2007).

Acne

Androgens increase sebum production in the skin which contributes to the development of acne. Therapeutic options include:

- CHC.
- Anti-androgens.
- Topical/systemic acne preparations.
- In severe acne, isotretinoin can be beneficial but can occasionally cause alopecia.

Anti-androgens

Systemic anti-androgens are also effective in reducing hair growth, but should always be used with effective contraception due to the potential for teratogenicity. Cyproterone is often given as Dianette (ethinyloestradiol and cyproterone), and risk of thrombosis should be assessed before prescribing. Finasteride, spironolactone and flutamide are other options (Fertil Steril, 2012; 97:15), but probably under the supervision of a Consultant.

Fertility

Refer to fertility services if there are issues (see article on PCOS and pregnancy).

Cardiovascular risk

There is no clear evidence of increased cardiovascular mortality in PCOS (J Clin Endocrinol Metab 2010;95:2038). However, a subset of the Women’s Ischaemia Syndrome Evaluation (WISE) study confirmed increased cardiovascular events and deaths in post-menopausal women with PCOS (RCOG 2014, Green Top Guidance 33).

Consensus of expert opinion and the RCOG is that women with PCOS are at increased cardiovascular risk. However, there are no special cardiovascular risk calculators for use in PCOS.

In its Green Top Guideline, the RCOG recommends:

- Individual risk assessment (smoking, obesity, exercise, diet, etc.). We suggest that, in those over 40, you could also use QRISK2 as a starting point, but be aware it may underestimate risk.
- Screening for diabetes in women with PCOS if:
  - BMI >25.
  - >40y.
  - History of gestational diabetes.
  - Annual screening for those with impaired glucose metabolism (pre-diabetes, impaired fasting glucose, etc.).

Metformin

Metformin improves insulin sensitivity and reduces hyperinsulinaemia but is NOT generally recommended by the RCOG and is not licensed in the UK for PCOS.

- Metformin has been shown to have a beneficial short-term effect on insulin resistance and cardiovascular risk markers in women with PCOS.
- There is evidence metformin may reduce androgen levels by 11% compared with placebo.
- Modest reductions in BMI have been described in some studies.

However, overall, studies have not shown a convincing improvement in all women with PCOS, and its long-term effects are not known (RCOG 2014, Green Top Guideline 33).
Polycystic ovary syndrome

- PCOS is common.
- Diagnosis is made using the Rotterdam criteria.
- Treat symptoms and remember to consider endometrial protection.
- Discuss lifestyle and address cardiovascular risk factors.

How many women with PCOS are amenorrhoeic and not being offered endometrial protection? Is it worth identifying all women with PCOS who are not on CHC/have the IUS, and asking them to come to see you IF they have not had a period in the past 6m/y to discuss if they need a treatment to protect the lining of their womb? How many women with PCOS have had their cardiovascular risk factors assessed and been offered lifestyle advice? You may want to focus on weight and smoking in the first instance in younger women …

For patients:
www.verity-pcos.org.uk/home

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GP Update Limited
January 2017