The many faces of polycystic ovary syndrome

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This opinion piece describes the diagnosis and management of polycystic ovary syndrome, a common, heterogeneous disorder that can have wide-ranging effects on a woman's appearance, fertility and cardiometabolic risk. Clinicians should treat the patient's immediate concern as well as addressing the longer-term implications of the diagnosis.

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder with the key features of irregular or anovulatory cycles and manifestations of androgen excess, with or without the appearance of polycystic ovaries on ultrasound examination.

Disagreement between clinicians and researchers has resulted in three sets of diagnostic criteria for PCOS (Table 1).[1-3] Of these, the Rotterdam criteria are the most inclusive, with women who meet either of the other two sets of criteria also meeting the Rotterdam criteria. Refinement of ovarian ultrasound sensitivity and changes in the techniques and standards for testosterone assays since the diagnostic criteria were first developed have further complicated the diagnostic process.

PCOS is a very prevalent condition in women of reproductive age.[4] Women may present at any age from teenagers through to mid-life and after menopause. The primary concern at presentation is equally variable and may change depending on the age of the patient. Younger women are often troubled by irregular menses, hirsutism, acne and weight gain. During the childbearing years, fertility may become a priority for the patient, whereas later the focus may shift to the management of cardiometabolic complications. It is important, therefore, for medical practitioners firstly to address what is concerning the patient and secondly to aim to prevent long-term health problems. Perhaps it is best to think of PCOS as an 'umbrella' diagnosis under which sits a range of phenotypes, patterns of biochemistry, risk profiles and ultimately genetic pathways (Figure 1).

Useful resources on PCOS, including current evidence-based Australian guidelines, are listed in the Box.[5-9]

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Key points

- **Women with polycystic ovary syndrome present with various issues, including menstrual cycle irregularity, symptoms of androgen excess, reduced fertility or metabolic problems such as obesity or glucose intolerance.**
- **A careful menstrual history and clinical examination are the most important components of assessment and diagnosis.**
- **Phenotype subclassification and a focus on the patient's primary concerns will help clinicians direct appropriate management.**

Diagnosis and phenotype subclassification

The most useful diagnostic 'tests' are a detailed history of menstrual function and a careful clinical examination. All other investigations are an adjunct to exclude other causes of the patient's

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symptoms and to identify other phenotypic features that may be present. For instance, patients may be lean or overweight, and may or may not have insulin resistance, dyslipidaemia, hypertension, a high dehydroepiandrosterone sulfate (DHEAS) level or a high ratio of serum luteinising hormone (LH) to follicle-stimulating hormone (FSH).

Menstrual irregularity

Normal menstrual cycles have a consistent cycle length, the average being 28 days (range 24 to 35 days).[10] It is considered that

Commentary from the Editor-in-Chief

Being a clinical syndrome, polycystic ovary syndrome (PCOS) is a challenge to define and to treat. This Feature Article by my colleague and expert in the field, Professor Bronwyn Stuckey and her coauthor Andrea Cussons, is highly practical and clinically based. I trust you will find it excellent and stimulating reading, as did I.

To aid in this topic of PCOS clinical care, the reader is also referred to the NHMRC clinical care guidelines on PCOS (*Evidence-Based Guidelines for the Assessment and Management of Polycystic Ovary Syndrome*), which remain current at the time of writing and can be found online (https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/ext_2_ext_0002.pdf).

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95% of girls will achieve regular ovulatory cycles within two years of menarche.[11] If this is not the case, especially if there are signs of androgenisation or a family history of PCOS, then the clinician should investigate. To gain an accurate history from adolescents it can be useful to recommend one of the smart phone apps developed to record menstrual cycle length. Weight gain in young adults often exacerbates menstrual irregularity, resulting in the patient presenting with features of PCOS. It is important at this time to exclude other causes of irregular or absent cycles, such as excessive dietary restriction or weight loss, hyperprolactinaemia and, depending on clinical findings, Cushing's syndrome.

Hyperandrogenism

Hirsutism may be assessed by the modified Ferriman–Gallwey (FG) score (Figure 2).[8] Ethnicity should be taken into consideration in assessing hirsutism; Asian women may not be hirsute despite biochemical hyperandrogenism and women of Mediterranean descent may have widespread body hair without endocrine dysfunction. Androgenetic alopecia is less common in

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Table 1. Diagnostic criteria for polycystic ovary syndrome from different expert groups

National Institutes of Health (1990)[1*]	Rotterdam (2003)[2†]	Androgen Excess and PCOS Society (2006)[3]
• Chronic anovulation AND • Clinical and/or biochemical hyperandrogenism	• Two of the following three features: – chronic anovulation – clinical and/or biochemical hyperandrogenism – polycystic ovaries on ultrasound	• Clinical and/or biochemical hyperandrogenism • Plus either: – chronic anovulation OR – polycystic ovaries on ultrasound
• Exclude other causes of the reproductive disturbance (e.g. congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome, hyperprolactinaemia, hypothyroidism)		

Abbreviation: PCOS = polycystic ovary syndrome.

* The US National Institutes of Health have recently adopted the Rotterdam criteria for PCOS.

† Women who meet the National Institutes of Health or the Androgen Excess and PCOS Society criteria for PCOS also meet the Rotterdam criteria.

younger women and often reflects hair follicle sensitivity to androgens rather than elevated circulating androgens. Acne is so common in adolescents that it is not considered a discriminating symptom, but severe acne may be an alert for hyperandrogenism.

Biochemical hyperandrogenism is not always seen in PCOS. Immunoassay of testosterone is notoriously unreliable in women.[12] Assay by liquid chromatography–mass spectrometry is more accurate, but reference ranges are not well established and the test is not yet widely available.[13] The current recommendation is to measure total testosterone and sex hormone binding globulin (SHBG) and to calculate the free androgen index. Measurement of 'minor' androgens should be considered if there is suspicion of an adrenal contribution to androgen excess (e.g. late-onset congenital adrenal hyperplasia) or an androgen-secreting tumour. Biochemical tests should include measurement of serum LH, FSH, oestradiol and progesterone levels to confirm that the test is being done in the follicular phase of the menstrual cycle. This is not always predictable in a patient with variable cycle length.

Useful resources for PCOS

Australian PCOS guidelines

- Teede HJ, Misso ML, Deeks AA, et al; Guideline Developments Group. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. Med J Aust 2011; 195(6): S65-S112. [Erratum in Med J Aust 2011; 195: 585].[5]
- *Evidence-Based Guidelines for the Assessment and Management of Polycystic Ovary Syndrome.* Melbourne: Jean Hailes for Women's Health on behalf of the PCOS Australian Alliance; 2015. (Available online at: https://jeanhailes.org.au/contents/documents/Resources/Tools/PCOS_evidence-based_guideline_for_assessment_and_management_pcos.pdf)[6]

Resources for doctors

- Jean Hailes for Women's Health. *PCOS.* (Available online at: https://jeanhailes.org.au/health-a-z/pcos)[7]
- Ferriman–Gallwey score diagram (Figure 2)[8]

Resources for patients

- PCOS Australia Alliance, Jean Hailes for Women's Health. *Polycystic Ovary Syndrome. All You Need To Know.* (Available online at: https://jeanhailes.org.au/contents/documents/Resources/Booklets/PCOS_All_you_need_to_know.pdf)[9]

Figure 1. Polycystic ovary syndrome is a heterogeneous disorder that is perhaps best regarded as an 'umbrella' diagnosis that includes a range of phenotypes. Women may be lean or overweight and may or may not have any of a range of biochemical and hormonal abnormalities.

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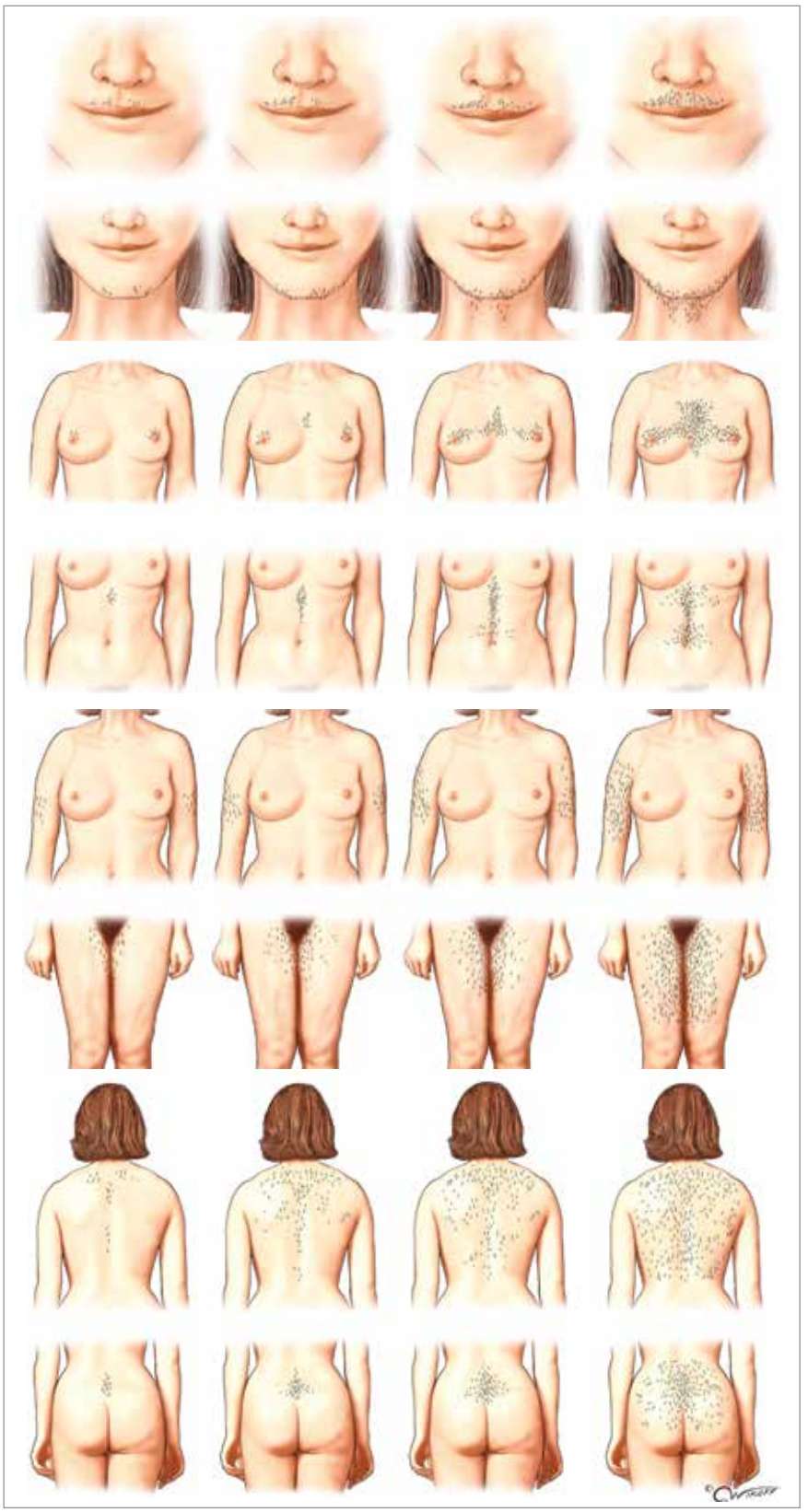

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Figure 2. Modified Ferriman–Gallwey score for hirsutism. Each of these nine areas is scored 0 to 4. A total score greater than 6 is considered mild hirsutism, and a total score greater than 15 as severe hirsutism.

Ovarian ultrasound

The usefulness of ovarian ultrasound examination and the associated diagnostic implications are questionable. A large proportion of young women with regular menstrual cycles have 'polycystic' ovaries on ultrasound that would fulfil the Rotterdam diagnostic criteria.[14] In adolescents, ovarian ultrasound examination often shows 'cystic' change, reflecting the presence of a high number of antral follicles in this age group. A 'polycystic' appearance has become more visible with the improved resolution of newer ultrasound machines and may lead to overdiagnosis.[15]

The serum concentration of anti-Müllerian hormone (AMH), which is secreted from antral follicles, may be viewed as a surrogate for the follicle count in PCOS (Figure 3). However, AMH level is high in adolescents and discriminates poorly in this age group.[16]

Ovarian ultrasound examination and AMH measurement become more useful in women undergoing in vitro fertilisation treatment, as a high follicle count or high AMH level may indicate potential hyperstimulation during ovulation induction. AMH measurement is not covered by Medicare.

Exclusion of disorders that may mimic PCOS

Cushing's syndrome has a similar phenotype to PCOS and should be considered in women with suspected PCOS. Violaceous striae are a clue but may not be obvious early in Cushing's syndrome, and an initial diagnosis of PCOS may require revision if they appear. Hypothyroidism may lead to irregular and heavy menses and lower SHBG levels, leading to a rise in bioavailable androgen. A high prolactin level disturbs the regular menstrual cycle, but hirsutism is usually not marked in hyperprolactinaemia. Late-onset congenital adrenal hyperplasia closely mimics PCOS and should be considered, particularly in the presence of a high LH:FSH ratio. Lastly, a recent onset of hirsutism and irregular cycles in a woman with previously normal menstrual function, especially if accompanied by signs

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of virilisation (deepening voice, clitoromegaly) and markedly elevated testosterone level should prompt a search for an androgen-secreting tumour. Investigations to exclude disorders that may mimic PCOS are summarised in Table 2.

Other PCOS features (not included in current diagnostic criteria)

High LH:FSH ratio

A high LH:FSH ratio is seen less often with the newer highly specific LH immunoassays, but when it does occur it is commonly in women with the lean PCOS phenotype.[17] An elevated LH:FSH ratio is secondary to increased pulse frequency of gonadotrophin releasing hormone (GnRH), which favours LH rather than FSH secretion. It is thought to be set by early androgen exposure and may suggest the possibility, albeit less common, of late-onset congenital adrenal hyperplasia.[18]

Disordered glucose metabolism

More than 60% of the variance in PCOS phenotype is related to insulin resistance.[19] Hyperinsulinaemia stimulates ovarian androgen production, reduces hepatic SHBG production and thereby increases bioavailable androgen. This pattern is seen particularly in overweight women with PCOS and increases the risk of gestational and type 2 diabetes. An oral glucose tolerance test (OGTT) is recommended as part of the screening investigations for women diagnosed with PCOS, with repeats of the OGTT or measurement of glycosylated haemoglobin (HbA_{1c}) in at-risk individuals every two years.

Cardiometabolic risk

The elements of cardiovascular risk in PCOS reside mostly, but not entirely, with the subtype displaying insulin resistance, obesity and the metabolic syndrome. Women with PCOS are four times more likely than the general population to have metabolic syndrome, and this prevalence increases with age and weight gain.[20] PCOS is associated with nontraditional markers of cardiovascular risk, such as abnormal vascular function, markers of inflammation and oxidative stress. Although some uncertainty remains regarding the incidence of cardiovascular events in PCOS, a meta-analysis found an increased risk of coronary heart disease and stroke for patients with PCOS, which remained significant when studies were adjusted for body mass index (BMI).[21] Further long-term research, with a focus on the possible effect of PCOS phenotype on cardiovascular outcomes, is needed in this area.

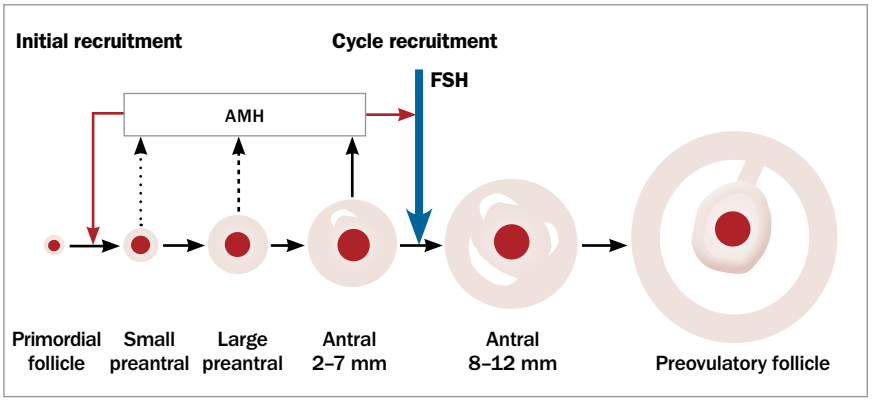

Figure 3. In women with polycystic ovary syndrome (PCOS), there is so-called 'follicular arrest'. A number of ovarian follicles reach the early antral stage (5 to 7 mm), but they seldom reach preovulatory size (16 mm or more). Anti-Müllerian hormone (AMH) is secreted from preantral and early antral follicles and reflects the ultrasound follicle count in women with PCOS. AMH inhibits excessive follicular recruitment by follicle-stimulating hormone (FSH). This diagram is useful to show patients the relative dimensions of the 'cysts' in PCOS.

Management

When a clinician makes a diagnosis of PCOS, they can easily lose sight of the patient's main concerns and concentrate on long-term, perhaps theoretical, consequences. The patient who presents with distressing hirsutism will not benefit, in the short term at least, from dietary and lifestyle advice for that particular symptom. The concerns of individual patients may vary and range from hirsutism, weight and fertility to long-term health or simply wanting a diagnosis.

Hirsutism, acne and alopecia

The degree of hirsutism as measured by the FG score does not necessarily correlate with the distress experienced by the patient. Pharmacological management of hair follicle growth necessarily takes at least three months to have any effect, and advice on local therapies is often forgotten.[22] For hirsutism, shaving, waxing and depilatory

Table 2. Investigations to exclude disorders that may mimic PCOS

Condition	Investigation
Cushing's syndrome	24-hour urinary free cortisol, late night salivary cortisol, 1 mg dexamethasone suppression test (if not on OCP)
Hypothyroidism	Thyroid-stimulating hormone level
Hyperprolactinaemia	Resting prolactin level
Late-onset congenital adrenal hyperplasia	17-Hydroxyprogesterone level (follicular phase)
Androgen-secreting tumour	Testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS) levels

Abbreviations: OCP = oral contraceptive pill; PCOS = polycystic ovary syndrome.

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creams are effective in the short term, whereas photoepilation and electrolysis result in more permanent hair reduction. Eflornithine cream retards the regrowth of hair, once removed by whatever means.

Pharmacological management of hirsutism and androgenetic alopecia begins with the use of the oral contraceptive pill (OCP). The OCP reduces ovarian androgen production and also reduces androgen bioavailability by increasing SHBG. Formulations containing antiandrogenic progestins (cyproterone acetate and drospirenone) have added benefit. There are currently no strong data showing metabolic harm with the use of the combined OCP in women with PCOS.[23] There is evidence of worsening of insulin resistance with progestin-only contraception, and this should be avoided.[24]

Additional antiandrogen therapy such as spironolactone, an androgen-receptor blocker, or cyproterone acetate, an antiandrogenic progestin, may be considered in women who are using adequate contraception (usually the OCP).[25]

Disordered glucose metabolism in PCOS

Insulin resistance in PCOS may manifest clinically as amenorrhoea, overweight and obesity, particularly upper body obesity, acanthosis nigricans and skin tags. The NHMRC guidelines on PCOS recommend an OGTT should be performed in all women with PCOS at diagnosis.[6] This is even more important in all overweight women, as even young teenagers with this condition may already have type 2 diabetes.

Lifestyle advice

The treatment of 'insulin-driven' PCOS should start with dietary advice, supplemented by advice on exercise to maintain a healthy weight. Regardless of dietary composition, weight loss in overweight women improves the metabolic features of PCOS. However, a low glycaemic index diet is beneficial for menstrual regularity and quality of life.[26]

What is the role of metformin in PCOS?

The use of metformin in PCOS arose from its original use in women with PCOS and type 2 diabetes, and has spread to its off-label use in nondiabetic women with PCOS. A meta-analysis of clinical trials showed that metformin may increase ovulation rates and improve androgen levels.[27] Based on results of the Diabetes Prevention Program, one might predict that it could also be useful for preventing the progression to diabetes.[28] However, its efficacy in cycle regulation in PCOS is not restricted to overweight women. Studies have shown that metformin has a direct effect on signalling within the ovary, independent of its role in glucose metabolism, and that it improves ovulatory rates in women with PCOS regardless of BMI.[29] Studies using immediate-release formulations seem to report better outcomes than those using slow-release formulations, but there are no head-to-head studies. The most widely agreed role of metformin is in the setting of fertility treatment, where it has been used as monotherapy or as an adjunct to clomiphene therapy.

Fertility and contraception

Women with PCOS often believe that they never ovulate and cannot become pregnant without ovulation induction. This is not the case. An unwanted pregnancy can occur from a sporadic ovulation and may not be recognised for months. For this reason, advice on contraception is important.

For those requiring fertility, the maintenance of a healthy weight and/or prevention of weight gain is a first step in women with PCOS. Metformin may improve menstrual regularity in women desiring a pregnancy. Further than that, clomiphene and letrozole have been used as ovulation induction agents. However, these are best left in the hands of an experienced reproductive specialist.

Endometrial cancer risk

The risk of endometrial cancer is increased in women with untreated PCOS. This is attributed partly to long-term unopposed oestrogen production in the setting of anovulation, but the presence of hyperinsulinaemia and obesity are considered to be major contributors.[30] It is worth noting that the incidence of endometrial cancer is increased in obese women in general, irrespective of the presence of PCOS.[31] The risk of endometrial cancer is reduced by the use of the OCP and by weight loss.

Genetics of PCOS

It is apparent that PCOS is an inherited condition or, at least, an inherited predisposition that may be unmasked by lifestyle factors. It is not particularly helpful for patients to gain the impression that their reproductive problems are their own doing, even though they may be able to ameliorate them with lifestyle changes. Genome-wide association studies have identified several candidate genes associated with PCOS. Some of these are in pathways one might expect to be involved, such as the *INSR* (insulin receptor) or *FSHR* (FSH receptor) genes. Others such as the *THADA* (thyroid adenoma associated) gene, which is strongly associated with PCOS, would not be expected in pathways influencing reproductive derangement.[32] It is hoped that advances in our understanding of the genetics of PCOS may lead to advances in treatment.

Conclusion

PCOS is a heterogeneous cluster of different clinical and biochemical phenotypes and genotypes. Careful clinical history taking and examination are the most accurate means of identifying the condition. Biochemical and other tests are an adjunct to subclassification of aetiology and long-term risk. Treating the patient's immediate concern should come first before addressing the longer-term implications of the diagnosis. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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