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Polycystic ovary syndrome:

what do the new guidelines recommend?

ANJU E. JOHAM MB BS, FRACP
HELENA J. TEEDE MB BS, FRACP, PhD
ROBERT J. NORMAN MD, FRANZCOG, FRACPA, CREI

Polycystic ovary syndrome (PCOS) is a prevalent, chronic, heterogeneous condition with reproductive, metabolic and psychological features. Treatment focuses on relieving symptoms and preventing future complications with a strong emphasis on lifestyle intervention, augmented with targeted medical therapy. New national evidence-based guidelines are now available to help clinicians assess and manage women with PCOS.

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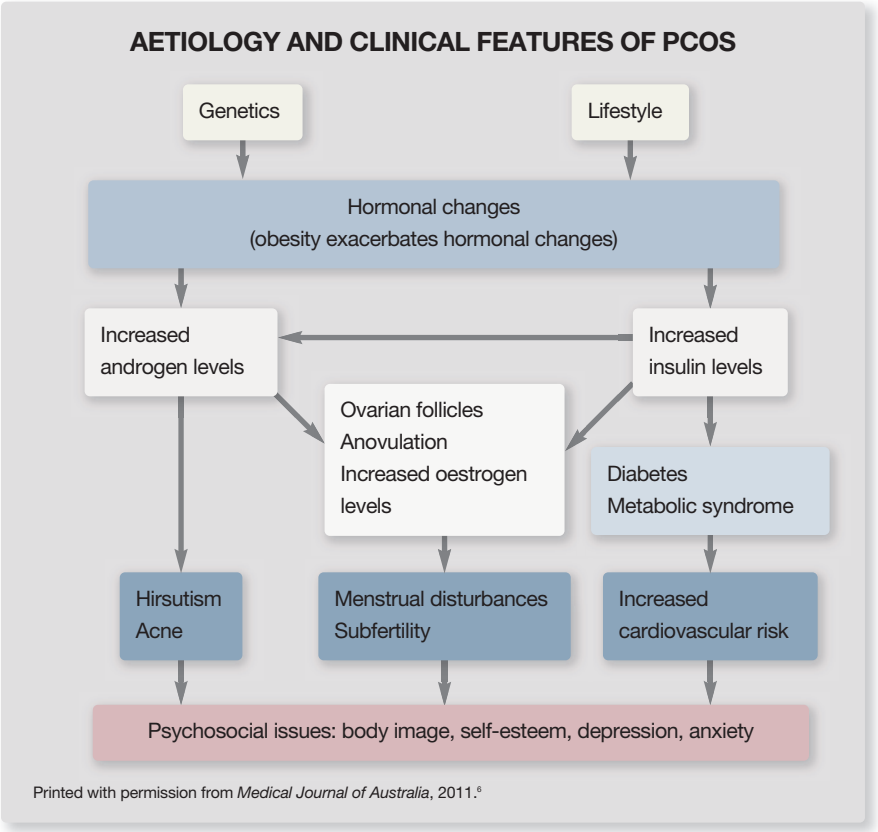
Dr Joham is a PhD student at the School of Public Health and Preventive Medicine, Monash University, Melbourne; and an Endocrinologist at Southern Health, Melbourne. Professor Teede is the Professor of Women's Health at the School of Public Health and Preventive Medicine, Monash University, Melbourne; an Endocrinologist at Jean Hailes for Women's Health, Melbourne; and Head at the Diabetes Unit, Southern Health, Melbourne, Vic.
Professor Norman is a Professor in Reproductive and Periconceptual Medicine and the Director of The Robinson Institute at The University of Adelaide; and a Senior Consultant in the Women's Health Centre, Royal Adelaide Hospital, Adelaide, SA.

Polycystic ovary syndrome (PCOS) affects 12 to 21% of women of a reproductive age in Australia, depending on the diagnostic criteria and population studied.[1] Healthcare costs related to PCOS are estimated at $400 million per year in Australia.[2] An estimated 70% of Australian women with PCOS remain undiagnosed,[1] and clinical practice, including diagnosis and management, is often inconsistent.[3] Most clinical services are unable to optimally address lifestyle issues, psychological issues and prevention of complications associated with PCOS[4] and often focus on infertility and expensive assisted reproductive technologies. GPs consistently highlight PCOS as an area of educational need. Given the prevalence, disease burden, healthcare costs and clear gaps in care, translation of evidence into clinical practice is vital for the most appropriate assessment and management of women with PCOS.

Greater clarity has been afforded by publication of the new evidence-based guidelines for the assessment and management of women with PCOS, developed by the National PCOS Alliance, auspiced by Jean Hailes for Women's Health.[5] These guidelines were funded by the Federal Government and were approved by the National Health and Medical Research Council (NHMRC). In approving these guidelines, the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines.

This article summarises key aspects of the guidelines. A comprehensive clinical summary of the guidelines was recently published in the *Medical Journal of Australia*[6] and the full guidelines, along with details about NHMRC approval, are available online (see: www.managingpcos.org.au/pcos-evidence-based-guidelines).



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DIAGNOSTIC CRITERIA FOR PCOS[6,9,10]

Rotterdam diagnostic criteria

Requires two of the following:

- Oligo-anovulation or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries and exclusion of other aetiologies, such as hypothyroidism, hyperprolactinaemia, congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome

National Institutes of Health diagnostic criteria

Requires both of the following:

- Oligo-anovulation or anovulation
- Clinical and/or biochemical signs of hyperandrogenism; and exclusion of other aetiologies, such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome

AETIOLOGY

The pathophysiology of PCOS is not yet fully understood. Hyperandrogenism and insulin resistance are the key hormonal disturbances underpinning PCOS (see the flowchart on this page).[6] Hyperandrogenism is detected in about 60 to 80% of cases and insulin resistance in about 50 to 80%.[6,7] Insulin resistance is a significant contributor to the reproductive and metabolic complications of PCOS,[8] especially in women who are overweight. Hormonal imbalances, combined with genetic and environmental factors, such as lifestyle and obesity, contribute to the development and severity PCOS.

DIAGNOSIS AND ASSESSMENT

The diagnosis of PCOS can be challenging. The 1990 National Institutes of Health (NIH) diagnostic criteria have been superseded by the 2003 Rotterdam criteria (see the box on this page).[6,9,10] PCOS is a diagnosis of exclusion and other conditions, including thyroid dysfunction and hyperprolactinaemia, should be excluded biochemically. Rarer conditions may initially be excluded clinically.

There is considerable controversy on the optimal criteria for the diagnosis of PCOS. The various criteria create three main diagnostic reproductive phenotypes of PCOS: NIH hyperandrogenic anovulatory PCOS; nonNIH hyperandrogenic ovulatory PCOS; and non-hyperandrogenic anovulatory PCOS.[11] This heterogeneity can present barriers to diagnosis; however, in all phenotypes women display reproductive disturbances and have greater metabolic abnormalities than women without PCOS. Women with PCOS diagnosed by the NIH criteria have the greatest metabolic risk.[11]

There is no single diagnostic test for PCOS. Measurement of free androgen levels (testosterone, calculated free testosterone or free androgen index, including sex hormone binding globulin) should be performed. Other investigations may include a pelvic ultrasound for ovarian morphology and endometrial thickness (in women over 18 years of age and who are sexually active). Ovarian ultrasound should be performed in the first week following a menstrual period, if possible. There should be at least 10 small antral follicles in each ovary; a unilateral polycystic ovary is rare but still clinically significant.

PCOS is also associated with elevated circulating and follicular levels of anti-müllerian hormone (AMH), an inhibitor of follicular recruitment and maturation.[12,13] Serum AMH levels may be a surrogate marker of the ovarian antral follicle number and may be useful in the diagnosis of PCOS in situations where accurate ultrasonographic data are not available.[14]

Although not part of the diagnosis, given the high risk of glycaemic abnormalities and metabolic syndrome associated

with PCOS, the national guidelines recommend an oral glucose tolerance test (rather than measurement of fasting blood glucose levels)[15] and measurement of lipid profiles in all women at diagnosis. These should be repeated every one to two years based on risk factors including excess weight or other risk factors for diabetes or cardiovascular disease. Insulin levels should not be measured in clinical practice because of assay variability, difficulty of interpretation and inaccuracy.[7] Presence of the metabolic syndrome, increased waist circumference and body mass index (BMI), low sex hormone binding globulin levels and abnormal glucose metabolism best reflect insulin resistance in this population.[7]

Diagnosis of PCOS in adolescents is challenging because cycles can take two years postmenarche to stabilise.[5] Polycystic ovaries on ultrasound are common and this imaging technique lacks specificity for PCOS in adolescents, hence, in this group, diagnostic assessment should ideally occur two years after menarche and be based on the NIH criteria (see the box on page 59).[5] To optimise treatment and prevention of future complications, women should ideally be assessed before starting the oral contraceptive pill (OCP) as this masks features of PCOS.[5]

CLINICAL FEATURES

PCOS is a chronic condition with significant and diverse clinical implications, including reproductive (hyperandrogenism, anovulation, subfertility), cosmetic (hirsutism, acne), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes, adverse cardiovascular disease risk profiles), and psychological features (increased anxiety and depression and body image concerns).[7] There is considerable heterogeneity in clinical presentation with highly variable phenotypic expression, depending on genotype, ethnicity, life stage and environmental factors, including bodyweight and lifestyle.[7] Women from Asia generally have more marked metabolic features and less incidence of hirsutism, even if they have a low bodyweight. Mediterranean women generally have more androgenic features and Caucasian women are more commonly overweight.

Obesity increases the incidence, prevalence and severity of PCOS and weight loss improves reproductive and metabolic features of PCOS.[16] BMI is the primary predictor of risk of PCOS.

Reproductive features

It is important to note that not all women with polycystic ovaries on ultrasound have PCOS. Clinical features of androgen excess primarily include hirsutism, acne and male pattern alopecia.[17] Acne is a common feature of PCOS but is not diagnostic of hyperandrogenaemia.

Reproductive features usually manifest as oligomenorrhoea/amenorrhoea, resulting from chronic oligo-ovulation/anovulation,[18] which may result in endometrial hyperplasia and increased risk of endometrial cancer.[19] PCOS causes subfertility, exacerbated by obesity, and it is the most common cause of anovulatory infertility. Women with PCOS can be fertile but the time it takes them to conceive is often increased.[18] Age and BMI have a critical role in the risk of infertility in women with PCOS. Early family initiation (before the age of 35 years), combined with strategies to optimise BMI, are therefore very important in the management of women with PCOS.

Metabolic features

Metabolic complications increase with age in women with PCOS, but diabetes and cardiovascular risk factors are often present in young women, particularly if they are obese. Metabolic complications of PCOS include dyslipidaemia, abnormal glucose metabolism and increased cardiovascular risk factors. Dyslipidaemia is common in women with PCOS compared with weight-matched controls,[20-23] occurs independent of BMI,[21,24] and leads to higher triglycerides levels and lower high-density lipoprotein cholesterol levels.[21]

Insulin resistance leading to hyperinsulinaemia occurs in most women with PCOS, especially in overweight women and those with more severe phenotypes of PCOS. Insulin resistance also occurs more often in lean women with PCOS[25] than in weight-matched controls.[26] There is also an increased risk of developing impaired glucose tolerance and type 2 diabetes (2.54 and 4.00 times increased risk in women with PCOS, respectively, compared with women without PCOS).[27] Women with PCOS have an earlier onset of glycaemic abnormalities and may more rapidly convert from impaired glucose tolerance to type 2 diabetes.[28] They also have a greater risk of gestational diabetes (2.94 times increased risk compared with those without PCOS).[29] Lipid abnormalities, impaired glucose tolerance and diabetes are associated with increased risk of cardiovascular disease,[30] but no well-designed studies have yet addressed the risk of cardiovascular disease in women with PCOS.

Psychosocial features

Psychological complications, such as poor self-esteem, body image issues, and high rates of depression and anxiety, are common in women with PCOS.[5] Obesity, acne, excess hair and infertility can challenge feminine identity and body image. Psychological features, particularly anxiety and depression, should be screened for. A simple evidence-based screening tool has been developed and is available in the PCOS guidelines.[5]

MANAGEMENT

The focus of management of women with PCOS should be on a healthy lifestyle, with targeted medical therapy if necessary (see the box on page 62).[6,7,31-34] To improve quality of life and facilitate effective and sustainable lifestyle change, psychological features need to be screened for, acknowledged and discussed, and counselling

SUMMARY OF TARGETED TREATMENT OPTIONS IN PCOS[6,7]*

Oligomenorrhoea/amenorrhoea

- Lifestyle change (5 to 10% weight loss in addition to structured exercise)
- Oral contraceptive pill† (OCP; low-dose oestrogen – e.g. 20 µg – may have less impact on insulin resistance)[31]
- Cyclic progestins (e.g. 10 mg medroxyprogesterone acetate 10 to 14 days every two to three months)
- Metformin† (improves ovulation and menstrual cyclicity)

Hirsutism[32]

Choice of options depends on patient preference, impact on well-being, access and affordability.[32] Nonpharmacological therapy includes:

- self-administered and professional cosmetic therapy (as a first-line option laser is recommended)
- eflornithine cream, which can be added to cosmetic therapy and may induce a more rapid response

If cosmetic therapy is ineffective/inaccessible/unaffordable, pharmacological therapy can be considered if the patient is concerned. It should be trialled for at least six months before any changes in dose or medication type are made. Pharmacological therapy includes:

- OCP† (monitor glucose tolerance in women at risk of diabetes)
- antiandrogen monotherapy (e.g. spironolactone or cyproterone acetate); however, these should not be used without adequate contraception
- combination therapy (if six months or more of the OCP has been tried and is ineffective) by adding an antiandrogen (spironolactone >50 mg twice daily or cyproterone acetate 25 mg daily to the OCP on days 1 to 10 of a woman's cycle)

Infertility

- Advise women to take folate supplements, cease smoking, be of an optimal weight and exercise regularly
- Advise women to optimise family initiation because of age-related infertility
- Appropriate therapies may include clomiphene, metformin, gonadotrophins and surgery

Cardiometabolic risk

- Lifestyle change (>5% weight loss in women who are overweight will reduce the risk of diabetes by about 50 to 60% in high-risk groups)[33]
- Consider use of metformin† (reduces the risk of diabetes by about 50% in adherent high-risk groups)[33]

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† Metformin and the OCP are not currently approved for management of PCOS by many regulatory bodies. The OCP is indicated for contraception and metformin for diabetes. However, their use for PCOS is supported by evidence and is recommended by international and national specialist societies.[34]

considered if necessary. Treatment options should be tailored to individual presentations and should focus on the clinical features of PCOS, in addition to the short- and long-term reproductive, metabolic and psychological complications.[7]

Lifestyle interventions

Lifestyle interventions are effective in improving clinical features of PCOS and in reducing long-term glycaemic abnormalities and cardiovascular complications in the general population.[35] Women with PCOS have a higher rate of weight gain and the clinical expression of PCOS is largely dependent on weight;[35] hence, lifestyle change enabling prevention of weight gain in all women and weight loss in overweight women should be first-line therapy for PCOS.[36,37] Even a 5 to 10% weight loss has significant clinical benefits, improving psychological, reproductive and metabolic features. Behavioural lifestyle change with small achievable goals results in clinical benefits even if women remain overweight.[38] The advantages of specific dietary approaches, including low glycaemic index diets, over that of caloric restriction alone are still unclear.

Incorporating simple moderate physical activity, including structured exercise (at least 30 minutes/day), and optimising incidental exercise augments weight loss and improves clinical outcomes in women with PCOS compared with diet alone.[39] Exercise alone also improves clinical outcome even without a significant weight change. Goals for exercise should focus on overall health benefits. Weight maintenance strategies to prevent weight gain are vital in managing PCOS generally and include women self-monitoring with regular weighing[40-43] and appropriate action if weight increases even marginally.

Pharmacological management

There is currently no ideal medical therapy that fully reverses the underlying hormonal disturbances and treats all clinical features of PCOS. Medical therapy does not supersede lifestyle therapy in PCOS.

Infertility is a common problem in women with PCOS (see the guidelines for more detail) but full management of this problem is outside of the scope of this article. Treatment of hirsutism is guided by current recommendations and focuses on recognition of the psychological impact of hirsutism and the use of cosmetic therapy (see the box on this page). Cycle regulation and endometrial protection can be provided by intermittent progestin use or use of the OCP. Hirsutism can

also be treated by use of the OCP, which reduces the levels of free androgens, induces regular cycles and protects the endometrium. Some studies suggest that the OCP can increase insulin resistance and worsen glucose tolerance.[31] Low-dose OCP preparations may be a preferable alternative, but more research is needed.[31] Acne may respond to the OCP or other hormonal interventions.

Use of metformin improves ovulation and cycle regulation with positive cardiometabolic effects, but does not reduce weight.[34,44] It has a role in the prevention and treatment of diabetes, if lifestyle therapy is inadequate or if prediabetes or diabetes is present.[43] It also has a role in women experiencing infertility issues,[44] but is less effective than clomiphene. Side effects of metformin include gastrointestinal side effects, such as nausea and diarrhoea, vitamin B_{12} deficiency with long-term use and, rarely, lactic acidosis in those with other chronic illness, in particular renal impairment. Use of metformin is generally safe in otherwise healthy women with PCOS.

Metformin and the OCP are not currently approved for use in the management of women with PCOS. However, their use is evidence based and is recommended by international and national specialist societies.[34]

CONCLUSION

PCOS is a common heterogeneous condition in women and is associated with psychological, reproductive and metabolic features with manifestations across the lifespan. Hyperandrogenism and insulin resistance both contribute to the pathophysiology of PCOS.

Comprehensive assessment of women with PCOS is important and management should focus on support, education and addressing psychological factors with a strong emphasis on a healthy lifestyle and targeted medical therapy as required. A focus on lifestyle measures and an aggressive lifestyle-based multidisciplinary approach is the mainstay of treatment for most women with PCOS. This strategy will also target management and prevention of the long-term complications of PCOS. Although further research is needed, new comprehensive evidence-based guidelines aid consumers and clinicians in optimal assessment and management of women with PCOS. MT

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