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ARTICLE

Pharmacological management of polycystic ovary syndrome

SUMMARY

Polycystic ovary syndrome is a common and frequently undiagnosed female endocrine disorder that is associated with diverse symptoms and features, and an increased risk of long-term chronic diseases such as type 2 diabetes and cardiovascular disease. Pharmacotherapy for polycystic ovary syndrome should be directed at the key concerns of the individual patient.

The combined oral contraceptive pill or metformin may be prescribed for irregular periods. The combined oral contraceptive pill is preferred over antiandrogens for treatment of hirsutism and acne.

Metformin is of benefit for reducing excess body weight and improving hormonal and metabolic outcomes in those with high metabolic risk (e.g. body mass index greater than 25 kg/m^2). Inositol appears to have limited benefits for metabolic outcomes, although it is associated with fewer adverse effects than metformin.

Modification of lifestyle factors is important as part of a holistic approach to managing polycystic ovary syndrome. Anti-obesity drugs may be considered for weight management in addition to lifestyle interventions.

Carolyn Ee
Principal Research Fellow[1]

Chau Thien Tay
Endocrinologist[2]
Research Fellow[3]

[1] NICM Health Research Institute, Western Sydney University, Penrith, NSW
[2] Monash Health, Melbourne
[3] Monash Centre for Health Research and Implementation, Monash University, Melbourne

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Introduction

Polycystic ovary syndrome (PCOS) is a common female endocrinopathy with reproductive, cardiometabolic, dermatological and psychological features. The key concerns of women with PCOS include subfertility, loss of feminine identity, irregular periods, excess body weight, hirsutism and acne, all of which can have a significant negative impact on the patient's emotional wellbeing.[1,2]

Despite affecting around 1 in 8 women globally with significant public health impacts,[3] women with PCOS have reported diagnostic delays, which are commonly due to a lack of knowledge about PCOS, particularly low awareness of diagnostic criteria, among primary care clinicians.[4,5] Even at the time of diagnosis, women are sometimes not provided with adequate information about PCOS and the initial information given can vary among medical practitioners.[6]

The International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023 integrates the best available evidence with multidisciplinary expertise and consumer preferences, to provide guidance on diagnosis, assessment of PCOS-related concerns and optimal treatment.[7] Nonpharmacological and lifestyle interventions are an essential part of management and are discussed in the international guideline. This article focuses on the current diagnostic criteria and key considerations for the pharmacological management of PCOS based on the guideline.

In this article, the term 'woman' is used to encompass all genders affected by PCOS and the term 'female' is used where biological sex is most relevant.

Diagnosis

The diagnosis of PCOS now includes using anti-Mullerian hormone concentration as an alternative to ultrasound in adults (Box 1). If used for diagnosis, ultrasound may be transabdominal or transvaginal; transvaginal ultrasound is the most accurate.[7]

The use of ultrasound or anti-Mullerian hormone concentration to diagnose polycystic ovaries is not recommended in adolescent females within 8 years of menarche because there is a risk of overdiagnosis.

Assessment for comorbidities

As PCOS is strongly associated with an increased risk of type 2 diabetes and cardiovascular disease, diagnostic assessment of women with PCOS should also include assessment of glycaemic status (preferably with an oral glucose tolerance test) and cardiovascular disease risk. Lifestyle interventions (exercise alone or combined with dietary measures and behavioural strategies) are recommended for all women with PCOS to improve their metabolic health, including reducing central adiposity and improving their lipid profile.

Women with PCOS should be informed about the increased premenopausal risk of endometrial cancer (twofold to sixfold), although the absolute risk is low and routine screening is not recommended. Informing women about this risk can help guide decisions regarding pharmacological treatment.[7]

Obstructive sleep apnoea is a common comorbidity in women with PCOS, and clinicians should assess patients for symptoms of obstructive sleep apnoea (e.g. snoring, waking unrefreshed, daytime sleepiness, fatigue).

Women with PCOS have a high prevalence of anxiety and depression, and assessment for psychological symptoms at the time of diagnosis is recommended.

Box 1 Diagnostic criteria for polycystic ovary syndrome[7]

Diagnosis of polycystic ovary syndrome in **adult** females requires **two** of the following criteria after exclusion of other aetiologies:

- oligo-anovulation or anovulation [NB1]
- clinical and/or biochemical hyperandrogenism [NB2]
- polycystic ovaries on ultrasound or elevated anti-Mullerian hormone concentration. [NB3]

Diagnosis of polycystic ovary syndrome in **adolescent** females requires **both** of the following criteria after exclusion of other aetiologies:

- oligo-anovulation or anovulation [NB1]
- clinical and/or biochemical hyperandrogenism. [NB2]

NB1: Anovulation is a condition in which the ovary does not produce and release an egg each menstrual cycle. Oligo-anovulation refers to irregular cycles lasting less than 21 days or more than 35 days, less than 8 periods per year, or an absence of raised serum progesterone 7 days before a period.

NB2: Clinical hyperandrogenism includes acne, female pattern hair loss (adults only) and hirsutism. Biochemical hyperandrogenism refers to elevated serum androgens such as total serum testosterone or elevated free androgen index; reference ranges vary depending on the assay used – seek advice from the laboratory.

NB3: The polycystic ovarian morphology threshold is a follicle number per ovary of 20 or more and/or an ovarian volume of 10 mL or more (with transvaginal ultrasound), or follicle number per section of 10 or more and/or an ovarian volume of 10 mL or more (with transabdominal ultrasound). Reference ranges for anti-Mullerian hormone concentration are population- and assay-specific – seek advice from the laboratory.

Table 1 Pharmacological management of symptoms of polycystic ovary syndrome[7]

Symptom	First-line therapy	Second-line therapy	Third-line therapy
irregular periods	combined oral contraceptive pill	metformin	–
excess body weight and metabolic effects (e.g. insulin resistance)	metformin	anti-obesity drugs	inositol
clinical hyperandrogenism, including hirsutism and acne	combined oral contraceptive pill	antiandrogens	–

Following initial assessment, women with PCOS should be monitored for these comorbidities based on their individual risk factors.

Principles of pharmacological management

Effective pharmacotherapy for symptoms of key concern to women with PCOS focuses on patient-centred care, where treatments are tailored to individual needs, goals and preferences.[7] Monitoring of response to treatment, identifying adverse reactions and adjusting therapy will support patients in achieving their desired health outcomes. Discussions around management of PCOS and related concerns should be conducted in a sensitive manner. For example, clinicians should be aware of their own potential biases about weight and aim to promote and adopt weight-inclusive practices that advocate for the acceptance of, and respect for, people of all body sizes.

The recommended preferences for pharmacological therapies for irregular periods, excess body weight and metabolic effects, and clinical hyperandrogenism are summarised in Table 1 and discussed in more detail in the individual sections on each therapy below.

Subfertility can be a key concern in women with PCOS; however, not all women with PCOS will experience subfertility. Women should be reassured that pregnancy can often be successfully achieved either naturally or with assistance. The management of subfertility in women with PCOS requires optimising healthy lifestyle behaviours and metabolic health before conception. If pharmacological management of subfertility is required, patients should be referred to a specialist. Contraception should be considered in women with PCOS who do not wish to conceive.

Combined oral contraceptive pill

The combined oral contraceptive pill (COCP) is usually the first-line treatment to ameliorate symptoms of irregular periods or clinical hyperandrogenism, such as hirsutism or acne, in women with PCOS.[7] The COCP can improve symptoms through multiple pathways including:

- direct inhibition of ovarian androgen production
- increased hepatic production of sex hormone–binding globulin, which reduces free androgen availability
- direct antiandrogenic effects of newer progestins.[8,9]

Despite the common perception that the COCP is the first-line treatment for any woman with PCOS, the COCP should only be used in patients who have concerns about irregular periods or clinical hyperandrogenism, or who are already on a COCP for another indication.

General population guidelines should be followed when prescribing the COCP for women with PCOS. Formulations containing low-dose estrogen are preferred as high-dose estrogen formulations do not confer additional clinical benefits. Apart from minimising the use of preparations containing cyproterone acetate because of its less favourable adverse effect profile (e.g. increased risk of venous thromboembolism), no specific types of COCP are recommended as none of them have demonstrated superiority in the context of PCOS. [7-9]

Progestogen-only oral contraceptives may be considered for endometrial protection in women with contraindications to, or who are intolerant of, the COCP. Evidence of other benefits, such as regulating menstrual cycles or improving clinical hyperandrogenism, in women with PCOS is limited.

Metformin

In women with PCOS, metformin is used off label as first-line treatment for excess body weight and metabolic effects. Metformin can improve the underlying insulin resistance that is characteristic of PCOS. Its action primarily involves improving insulin sensitivity in the liver and peripheral tissues, and reducing hepatic glucose production.[10]

Metformin has demonstrated significant efficacy in improving various anthropometric outcomes, including reducing body weight, waist–hip ratio and body mass index (BMI), in addition to improving metabolic parameters (e.g. blood glucose concentrations, lipid profile).[7,10] These therapeutic effects are particularly pronounced among adults with a BMI greater than 25 kg/m^2.[7] Combining metformin with lifestyle interventions has demonstrated better outcomes compared with lifestyle interventions alone, suggesting synergistic effects.[10]

Additionally, metformin may exert beneficial effects of restoring menstrual cyclicity and ovulation, and can be considered in preference to the COCP in women wishing to conceive.

There is conflicting evidence on whether metformin use in pregnant women with PCOS can prevent gestational diabetes, late miscarriage, hypertension, pre-eclampsia or macrosomia; however, there is evidence that metformin reduces gestational weight gain and decreases the risk of preterm delivery. These effects warrant further research and clinical consideration in this context.[7]

Inositol

Inositol is a nutrient supplement that acts as an insulin sensitiser and is thought to promote glucose uptake and reduce androgen production in ovarian granulosa cells.[11] In Australia, inositol is available without a prescription and is a 'listed' medicine on the Australian Register of Therapeutic Goods, meaning it has not been assessed for efficacy.

A 2024 systematic review and meta-analysis reported inconclusive evidence of benefit for inositol in women with PCOS.[11] The most commonly used forms of inositol, myo-inositol and D-chiro-inositol, may have limited benefit for some metabolic outcomes in PCOS, including reduced fasting insulin concentration and increased insulin sensitivity. Metformin appears to be superior to inositol for hirsutism and central adiposity, although metformin has more adverse effects such as gastrointestinal effects. It is unclear if there is any benefit in adding inositol to metformin. Specific types, doses or combinations of inositol cannot currently be recommended because of a lack of high-quality evidence.

Clinicians should discuss with patients the potential benefits and harms of using inositol, including cost and the relative lack of regulation, while acknowledging and respecting the individual's values and preferences.

Anti-obesity drugs

There is limited evidence for the efficacy of anti-obesity drugs, such as orlistat and glucagon-like peptide-1 (GLP-1) receptor agonists (e.g. liraglutide, semaglutide), specifically in women with PCOS, including for reproductive outcomes.[12] However, based on guidelines in the general population, orlistat and GLP-1 receptor agonists can be considered for management of excess body weight in adults with PCOS alongside lifestyle interventions.[13]

Concurrent effective contraception is required if pregnancy is possible because there is insufficient safety data on the use of GLP-1 receptor agonists in pregnancy. Gastrointestinal adverse effects, such as diarrhoea and vomiting, are common with GLP-1 receptor agonists and gradual dose escalation is recommended. Women should be counselled about the lack of long-term safety data and the high risk of weight regain after discontinuation.

Anti-obesity drugs are not recommended in adolescents as no evidence for efficacy or safety was identified in this age group.[7]

Antiandrogens

Antiandrogens play a role in managing clinical hyperandrogenism in PCOS via diverse mechanisms, such as:

- competitive inhibition of androgen receptors
- suppression of androgen synthesis
- inhibition of 5-alpha-reductase activity, which converts testosterone to its active metabolite, 5-alpha-dihydrotestosterone.[14]

Spironolactone is the most frequently prescribed antiandrogen because finasteride, flutamide and bicalutamide have an increased risk of causing liver toxicity. Prolonged use of cyproterone acetate is associated with development of meningioma.[7]

While there is some evidence for antiandrogens in managing hirsutism,[14] they are reserved for cases where the COCP is contraindicated, or where there is suboptimal response after a minimum of 6 months of the COCP or cosmetic therapy.[7] This cautious approach stems from potential teratogenicity of antiandrogens, which can cause hypovirilisation of male fetuses. Concurrent use of effective contraception is imperative for women taking antiandrogens in whom pregnancy is possible.

Although evidence in treating female pattern hair loss in PCOS is limited, the combination of antiandrogens with the COCP should be considered given the significant psychological impact of alopecia on affected patients.[7]

Conclusion

Management of PCOS requires a comprehensive patient-centred approach, incorporating education, empowerment and shared decision-making to optimise the patient's experience and health outcomes. The International Evidence-based Guideline for the Assessment and Management of PCOS 2023 provides guidance on nonpharmacological and pharmacological management of PCOS. Choice of pharmacotherapy is driven by the individual patient's symptoms and may include the COCP, metformin, inositol, anti-obesity drugs and antiandrogens. <

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