Polycystic ovary syndrome and increased cardiometabolic risk

ANJU JOHAM MB BS, FRACP
HELENA TEEDE MB BS, FRACP, PhD

Although women with PCOS have more cardiovascular risk factors (abdominal obesity, impaired glucose tolerance, type 2 diabetes and dyslipidaemia), the long-term risk of cardiovascular disease in these women remains unclear.

Key points

- **Polycystic ovary syndrome (PCOS) is a common heterogeneous condition underpinned by insulin resistance and associated with significant metabolic sequelae and an adverse cardiovascular risk profile.**
- **Despite the increased prevalence of cardiovascular risk factors and early indicators of atherosclerosis in women with PCOS, the long-term risk of cardiovascular disease in these women remains unclear.**
- **Appropriate screening and management of risk factors is crucial in women with PCOS.**
- **Lifestyle change to prevent weight gain and reduce weight in those who are overweight should be first-line PCOS therapy.**
- **Medical therapy is targeted to specific symptoms and does not supersede lifestyle therapy. The oral contraceptive pill regulates menstrual cycles and improves hyperandrogenism, and insulin sensitisers (primarily metformin) reduce insulin resistance**.

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Dr Joham is an Endocrinologist at Southern Health, Melbourne; and a PhD student, Monash Applied Research Stream, School of Public Health and Preventive Medicine, Monash University, Melbourne. Professor Teede is Professor of Women's Health and Director of the Monash Applied Research Stream, School of Public Health and Preventive Medicine, Monash University; Head of Diabetes and Vascular Medicine Unit at Southern Health, Melbourne, Vic; and an NHMRC Fellow.

Polycystic ovary syndrome (PCOS) affects between 12 and 18% of reproductive-aged women in Australia, depending on diagnostic criteria and the population studied. This common, complex and chronic condition has considerable health and economic costs, and presents many diagnostic and management challenges for clinicians.

PCOS has significant and diverse clinical implications, including reproductive features (hyperandrogenism, oligo- or anovulation and subfertility), metabolic features (insulin resistance, impaired glucose tolerance, type 2 diabetes, adverse cardiovascular risk profiles and possible increased cardiovascular disease [CVD]) and psychological features (see the box on page 30).[1] Excess weight is common in women with PCOS and increases the prevalence of the condition as well as exacerbating the severity of clinical features. Overall, there is considerable heterogeneity in the clinical presentation of PCOS, the highly variable phenotypic expression depending on genotype, ethnicity, life stage and environmental factors, including body weight and lifestyle.[1]

Reproductive features are well recognised in PCOS, and hence management has mainly been concerned with short-term reproductive outcomes. Recently, however, significant metabolic features and longer-term complications of the condition have been recognised. Insulin resistance is a key pathophysiological feature in PCOS, is present independent of and exacerbated by obesity, and contributes to reproductive and metabolic complications.[2,3] Insulin resistance is an independent predictor of cardiovascular disease, and this risk is potentially further amplified in PCOS by the presence of additional cardiovascular risk factors.[4] The coexistence of insulin resistance and other cardiovascular risk factors and a high prevalence of obesity is well recognised in women with PCOS. This article focusses on the increased cardiometabolic risk in women with PCOS.

Features of polycystic ovary syndrome

Reproductive features
- Hirsutism and other indicators of hyperandrogenism
- Oligo/amenorrhoea, resulting from chronic oligo/anovulation
- Subfertility

Metabolic features
- Insulin resistance
- Gestational diabetes
- Impaired glucose tolerance
- Type 2 diabetes
- Lipid abnormalities
- Metabolic syndrome

Psychological features
- Increased anxiety
- Depression
- Poor self-esteem
- Body image issues
- Worsened quality of life

Diagnostic assessment

PCOS is a diverse and heterogeneous condition and diagnosis can be challenging. Its diagnosis using the current 2003 Rotterdam criteria is based on the presence of two of three features: oligo- or amenorrhoea, clinical or biochemical hyperandrogenism, and polycystic ovaries on ultrasound.[5]

Secondary causes such as hypothyroidism, hyperprolactinaemia and nonclassical congenital adrenal hyperplasia need to be excluded biochemically; androgen-secreting tumours and Cushing's syndrome can usually be excluded on history and examination alone. It is important to note that although approximately 25% of reproductive-aged women have polycystic ovaries on ultrasound, not all women with polycystic ovaries have PCOS.[1]

Metabolic features of PCOS

Although the metabolic complications of PCOS increase with age, diabetes and cardiovascular risk factors can be present even in the very young, especially where obesity and other risk factors such as ethnicity are involved. Metabolic complications of PCOS include dyslipidaemia, impaired glucose tolerance, type 2 diabetes, metabolic syndrome, gestational diabetes and increased CVD risk.

Obesity

About 70% of women in Australia with PCOS are overweight or obese. Obesity exacerbates the incidence, prevalence and severity of PCOS, and weight loss improves its reproductive and metabolic features.[1] Obesity is also a recognised risk factor in the development of glycaemic abnormalities, dyslipidaemia, hypertension and CVD. The Nurses' Health Study demonstrated a relative risk of 3.4 for CVD in obese individuals with a body mass index (BMI) greater than 30 kg/m^2.[6]

Distribution of adiposity is also an important factor, and abdominal (central) obesity is well recognised as an independent predictor of cardiovascular risk.[7] Central obesity also has an important role in the pathogenesis of metabolic syndrome, compounding the effects of insulin resistance, dyslipidaemia and hypertension.[4]

Insulin resistance and glycaemic abnormalities

Insulin resistance and resulting hyperinsulinaemia occur in most women with PCOS and are more prominent in overweight or obese women and those with a more severe phenotypic expression of PCOS. Insulin resistance occurs in about 50 to 80% of women with PCOS, is independently associated with PCOS and occurs independent of obesity.[1,3] Lean women with PCOS often, but not always, have abnormalities of insulin secretion and action, compared with weight-matched control subjects.[8] A recent meta-analysis suggests an approximate 2.5-fold increase of impaired glucose tolerance and a fourfold increased risk of type 2 diabetes in women with PCOS compared with controls.[9] Women with PCOS have an earlier onset of glycaemic abnormalities and may demonstrate a more rapid conversion from impaired glucose tolerance to type 2 diabetes.[10] Women with PCOS also have greater risk of gestational diabetes, with a recent meta-analysis reporting a 2.9-fold increased risk in women with PCOS.[11]

Insulin resistance and cardiometabolic features are common in women with PCOS, but are not required for diagnosis, in part because of the lack of accurate methods to measure insulin resistance.[12] However, given the high risk of diabetes and metabolic syndrome, screening has been prioritised in a recent national PCOS evidence-based guideline, including an oral glucose tolerance test (OGTT) and lipid profile at baseline in women with PCOS.[13] Testing for cardiovascular risk factors should be repeated every one to two years, with frequency of testing informed by metabolic risk (e.g. body weight, age, family history, ethnicity). An OGTT, rather than measurement of fasting glucose levels, should be performed as impaired fasting glucose is a poor predictor of impaired glucose tolerance in women in general and particularly in PCOS.[10,14,15] Insulin levels need not be measured in clinical practice because of assay variability and inaccuracy.[1] Insulin resistance in this population is best reflected by waist circumference, BMI, the presence of metabolic syndrome or abnormal glucose metabolism.[1]

Lipid metabolism

Dyslipidaemia is more common in women with PCOS than in weight-matched controls with higher triglyceride levels and lower high-density lipoprotein cholesterol levels.[16,17] The dyslipidaemia occurs independent of BMI;[17] however, there is a synergistic deleterious effect of obesity and insulin resistance in women with PCOS analogous to that seen in individuals with type 2 diabetes.[4]

The aetiology of dyslipidaemia in PCOS is multifactorial. Insulin resistance appears to have an important role, mediated in part by altered expression of lipoprotein lipase and hepatic lipase and stimulation of lipolysis.[17]

Hypertension

Studies of blood pressure in women with PCOS have found inconsistent results.[4] Some studies show no difference in 24-hour ambulatory blood pressure measurements between women with PCOS and age- and sex-matched controls.[16,18] Another study found higher mean ambulatory blood pressures and higher daytime systolic blood pressures in women with PCOS than in BMI-matched controls, with differences in blood pressure persisting after adjustment for adiposity and insulin resistance.[19] Potential mechanisms for hypertension in women with PCOS may include insulin resistance or, in later life, the increased arterial stiffness seen in obese PCOS women compared with controls, which in turn may be multifactorial including endothelial dysfunction as well as insulin resistance.[4,16]

Cardiovascular risk

Although evidence for CVD in reproductive-aged women with PCOS is limited, current data suggest an increased risk of CVD.[20] As noted, women with PCOS often have multiple risk factors for CVD, including metabolic syndrome, abdominal obesity, glycaemic abnormalities, dyslipidaemia and hypertension.[20-22] Given that large longitudinal cohort studies have reported that up to 65% of CVD deaths occur in people with impaired glycaemic states and that the prevalence of impaired glucose tolerance and type 2 diabetes is increased in women with PCOS, it would be expected that those with PCOS would have an increased CVD risk, although clear clinical outcomes are lacking.[23]

Alongside the clustering of conventional cardiovascular risk factors, women with PCOS also have increased novel cardiovascular risk factors (inflammation, oxidative stress and impaired fibrinolysis).[24] Some studies show increased early clinical and subclinical markers of atherosclerosis (endothelial dysfunction, increased carotid intima media thickness, presence of carotid plaque and increased coronary artery calcification) in women with PCOS, which are further exacerbated by obesity.[16,25]

The high prevalence of cardiovascular risk factors and early markers of atherosclerosis in women with PCOS suggests that there may be higher rates of CVD in postmenopausal women with a history of PCOS.[20] However, studies of the association between PCOS and CVD risk have had inconsistent results.[26,27] Some studies support an increased risk of CVD in PCOS – for example, a recent study in postmenopausal women with premenopausal features of PCOS noted a higher prevalence of angiographically-demonstrated coronary artery disease (odds ratio, 1.7) and worsened cardiovascular event-free survival.[28] Nevertheless, despite the increased prevalence of cardiovascular risk factors and early indicators of atherosclerosis in women with PCOS, the long-term risk of CVD in women with a history of PCOS remains unclear. There is currently a lack of long-term studies to appropriately address CVD risk in those with PCOS, and further research is needed in this area.[1]

Management

Given the high prevalence of cardiovascular risk factors and increased risk of cardiovascular events, appropriate screening and management of risk factors is crucial in women with PCOS. This is endorsed in the recent national evidence-based guideline for assessment and management of PCOS produced by the Jean Hailes Foundation for Women's Health on behalf of the PCOS Australian Alliance.[13]

The clinical expression of PCOS is largely dependent on weight and lifestyle interventions that improve metabolic abnormalities, reduce long-term glycaemic abnormalities and improve cardiovascular risk factors.[1] Hence, lifestyle change to prevent weight gain and reduce weight in those who are overweight should be first-line PCOS therapy.[1] Weight loss of even 5 to 10% of body weight has significant clinical benefits, improving metabolic, reproductive and psychological features. Behavioural lifestyle change with small achievable goals results in clinical benefits even when women remain in the overweight or obese range.[29]

There is currently no ideal medical therapy that fully reverses the underlying hormonal disturbances in PCOS and treats all the clinical features. Medical therapy for PCOS is targeted to specific symptoms and does not supersede lifestyle therapy. The oral contraceptive pill is used to regulate menstrual cycles and improve hyperandrogenism, and insulin sensitisers (primarily metformin) are used to reduce insulin resistance.[30]

There are some concerning data that suggest that the oral contraceptive pill can increase insulin resistance and worsen glucose tolerance.[1] Studies are inadequate but the cardiometabolic effects of medical therapy should also be considered, and low-dose oral contraceptive preparations may be preferable.[30]

Metformin improves ovulation and menstrual cycle regulation with positive cardiometabolic effects but does not reduce weight.[12,31] Metformin has a role in the prevention of diabetes if lifestyle therapy is inadequate or where prediabetes or diabetes is present.[12] Thiazolidinediones (pioglitazone and rosiglitazone) are relatively contraindicated in reproductive-aged women as animal studies have raised concerns about adverse effects on the fetus.

Conclusion

PCOS is a common heterogeneous condition in women, underpinned by insulin resistance and associated with significant metabolic sequelae and an adverse cardiovascular risk profile. Women with PCOS have CVD risk factor-clustering, including metabolic syndrome, abdominal obesity, impaired glucose tolerance, type 2 diabetes and dyslipidaemia; however, the long-term risk of CVD remains unclear. Women with PCOS should be appropriately screened for metabolic complications, and preventive and management strategies employed as appropriate. A focus on lifestyle measures and a targeted multidisciplinary approach is the mainstay of treatment for most women with PCOS, with the aim of management and prevention of long-term complications. **ET**

References

A list of references is available on request to the editorial office.

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