Long-term health outcomes in young women with Polycystic Ovary Syndrome: a narrative review

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Summary

Polycystic Ovary Syndrome (PCOS) has long been recognised as a common disorder in young women leading to reproductive and cutaneous sequelae. However, the associated health risks are now known to extend beyond these familiar manifestations to a range of longer-term comorbidities. Here we review the evidence for an association of PCOS with adverse long-term health outcomes, discussing the pathophysiological mechanisms involved in addition to opportunities for therapeutic intervention. Cross-sectional and longitudinal studies point to an increased risk of type 2 diabetes, hypertension and dyslipidaemia, with recent data confirming that these translate to an increased risk of cardiovascular events independently of obesity. Obstructive sleep apnoea, non-alcoholic fatty liver disease and endometrial cancer are also more prevalent, whilst mental health disorders, notably anxiety and depression, are common but under-appreciated associations. Uncertainties remain as to whether these risks are apparent in all patients with PCOS or are confined to particular subtypes, whether risks persist post-menopausally and how risk may be affected by ethnicity. Further work is also needed in establishing if systematic screening and targeted intervention can lead to improved outcomes. Until such data are available, clinicians managing women with PCOS should counsel patients on long-term health risks and invest in strategies that limit progression to metabolic and non-metabolic morbidities.

Introduction

PCOS is a common endocrine disorder, affecting 5-13% of premenopausal women.[1] The clinical manifestations of hyperandrogenism (hirsutism, acne, scalp hair loss) and menstrual disturbance are well-recognised. In contrast, the association with longer-term adverse health outcomes is less appreciated, despite a wealth of evidence pointing to an increased risk of metabolic and non-metabolic morbidities. Coupled with care that is often fragmented, this disconnect may lead to a management approach that is overly focused on symptom control, with consequent missed opportunities for prevention, screening and treatment of longer-term complications. In this review, we examine the evidence for long-term adverse health outcomes in young patients with PCOS, and consider the implications for clinical practice. We undertook this as a narrative exercise as there were insufficient studies in each area to conduct a systematic review.

Cardiovascular disease

Dyslipidaemia

Akin to the metabolic syndrome, patients with PCOS may display a pattern of dyslipidaemia which is characterised by reduced high-density lipoprotein cholesterol (HDL-C), increased

small, dense low-density lipoprotein cholesterol (LDL-C) particles, and increased fasting and post-prandial triglyceride concentrations (figure 1).[2] Whilst a number of pathological alterations may be in operation, insulin resistance appears to be key. Insulin resistance leads to increased hepatic very low-density lipoprotein (VLDL) triglyceride synthesis and variably increased hepatic apo B-100 production, leading to hypertriglyceridaemia and reduced HDL concentrations. Accelerated adipocyte lipolysis increases free fatty acid flux to the liver, whilst a relative reduction in lipoprotein lipase (LPL) activity may contribute to reduced VLDL breakdown. Reduced LPL activity may also affect the hydrolysis of chylomicrons, which transport diet-derived triglycerides to other tissues following a meal. Complement system dysregulation may also contribute to the dyslipidaemia present in PCOS: chylomicrons increase C3 activation, leading to increased triglyceride synthesis in adipocytes via cleavage of C3a (a product of C3 activation) to C3a(desArg). We, and others, have shown that C3 activation is increased in insulin-resistant patients with PCOS, and that regulation of this activation may be impaired post-prandially.[3]

In a meta-analysis of 30 studies in younger women (mean age <45 years), mean LDL-C, non-HDL-C and triglyceride concentrations were higher, and HDL-C concentrations lower in PCOS subjects (n>2000) compared with controls (n>2000), albeit that the absolute differences were only modest (mean differences: 0.23 mmol/l [LDL-C] and 0.41 mmol/ [non-HDL-C]) and typically within the reference range.[4] LDL-C concentrations appear to be increased across all body mass index (BMI) categories whereas differences from controls in triglyceride and HDL-C levels may only be apparent in overweight/obesity.[5]

Hypertension

A number of pathophysiological alterations may contribute to an increased risk of hypertension in patients with PCOS, including activation of the renin-angiotensin-aldosterone system, sympathoexcitation and reduced nitric oxide (NO) production (figure 1). Both insulin resistance (with consequent hyperinsulinaemia) and hyperandrogenism have been implicated. Women with PCOS have been shown to have higher prorenin, renin and aldosterone levels than age- and BMI-matched controls.[6-8] PCOS also emerged recently as a determinant of plasma prorenin levels in early pregnancy,[9] which might contribute to the increased risk of pre-eclampsia observed in this condition.[10] Evidence for sympathoexcitation comes from studies showing increased muscle sympathetic nerve activity, impaired heart rate recovery following exercise, and altered heart rate variability in women with PCOS compared with matched controls.[11] Increased sympathetic activity may be accompanied by activation of higher brain centres, notably the right orbitofrontal cortex, in an insulin-dependent manner.[12] Hyperandrogenism also appears to be mechanistically important: cross-sectional analysis in

a Taiwanese PCOS population showed that hyperandrogenism was associated with systolic and diastolic blood pressure, independently of age, obesity or insulin resistance.[13]

Two meta-analyses recently confirmed an increased risk of hypertension in young women with PCOS compared to controls,[14,15] although uncertainty remains as to the contribution of PCOS *per se* to this risk independently of obesity. In a large, longitudinal, community-based study in Australia, Joham *et al* found that women with PCOS were 37% more likely to develop hypertension than controls, independently of BMI or other confounders. The risk was present across all weight categories, although obesity compounded this risk (being 4-fold greater in women with a BMI ≥30 kg/m^2 compared to those with a healthy weight).[16] Obesity thus becomes an important target in identifying women with PCOS who are especially at risk, and where intervention may have benefit.

Surrogate markers of cardiovascular risk

Carotid intima media thickness (CIMT) is an ultrasound measure of the thickness of the inner layers of the carotid arteries and has been used as a surrogate marker of subclinical atherosclerosis. A meta-analysis of 19 studies showed a significant increase in CIMT in women with PCOS (n=1123) compared with controls, with a mean difference of 0.07 mm (for the highest quality studies).[17] In the general population, an increase of 0.1mm in CIMT equates to an 18% increased relative risk of stroke.[18] Surrogate marker studies have also reported an increase in endothelial dysfunction,[19] myocardial dysfunction,[20,21] arterial stiffness[22] and coronary artery calcification[23] in some studies of women with PCOS compared to controls, although other reports suggest that these differences may largely be driven by obesity and/or insulin resistance rather than PCOS *per se*.[24,25] Endothelial dysfunction as measured by flow-mediated dilation (FMD) predicts cardiovascular events in the general population, and in a meta-analysis of 21 studies was found to be 3.4% lower in women with PCOS compared with controls.[18]

Cardiovascular events

Whilst risk factors for the development of cardiovascular disease (CVD) appear to be increased in women with PCOS, high quality longitudinal studies examining clinical cardiovascular events are limited. A number of systematic reviews and meta-analyses have examined the risk of coronary artery disease, myocardial infarction and stroke in women with PCOS, with inconsistent findings.[15,26-31] Recent international guidelines restricting analysis to high quality studies only, found no difference in risk of myocardial infarction, stroke or cardiovascular mortality in women with PCOS,[32] although studies to date have likely been underpowered given the low absolute risk of CVD in this young female population. In a large longitudinal, population study of >170,000 women with PCOS, we recently demonstrated a

26% increased risk of major adverse cardiovascular events compared with age-, BMI category- and primary care practice-matched controls.[33] The risks were increased individually for myocardial infarction, angina and revascularisation, but not for stroke or cardiovascular mortality. Moreover, we identified weight increase, a diagnosis of type 2 diabetes and socioeconomic deprivation as significant predictors of progression to cardiovascular events, suggesting that the greatest benefits in minimising risk might be achieved by prevention of weight gain, prevention of progression to type 2 diabetes and targeting of resources to the most socially and materially deprived. In contrast, in a recent Mendelian randomisation study, no association was found between genetically-predicted PCOS and risk of coronary heart disease, type 2 diabetes or stroke.[34] Whilst these data suggest that PCOS *per se* may not exert a causal influence on risk of cardiometabolic disease, the study was limited by the relatively low number of single nucleotide polymorphisms (SNPs) available for analysis. Ongoing international efforts at discovering additional susceptibility SNPs will enhance power and allow for re-exploration of these associations. Furthermore, the findings do not exclude an influence of particular subphenotypes on risk, nor an effect confined to younger individuals. These questions are important for further study, since the syndrome may regress with age, accompanied by reduction in androgen levels and ovarian volume.[35] Since androgen levels have been causally implicated in cardiometabolic risk in women,[36] this reduction might lead to a reduced risk of CVD with aging and may suggest that efforts at cardiometabolic risk reduction are best targeted towards women with hyperandrogenism.

Metabolic Risk

Overweight/Obesity

Obesity is a common comorbid condition in women with PCOS (figure 1). In a meta-analysis of over 100 studies, the pooled prevalence of obesity was 61%.[37] The prevalence of overweight was also increased compared to non-PCOS populations, as was central obesity, with Caucasians having a higher relative risk than Asians. Magnetic resonance imaging studies have shown that fat accumulation is generalised, with no predilection for the visceral compartment compared with BMI- and fat-mass matched controls,[38] despite differences in insulin sensitivity. Genetic studies have recently unpicked the directionality of this association, with bidirectional Mendelian randomisation studies consistently demonstrating a causal effect of BMI on PCOS, but not of PCOS on BMI.[39-42] These findings are consistent across Caucasian[39,41,42] and East Asian[40] populations, and emphasise the importance of weight management in disease prevention and treatment. Prevention of weight gain in early adulthood may be particularly important in light of data identifying this period as a time when weight increase has a significant effect on PCOS emergence.[43]

Insulin resistance, impaired glucose tolerance and type 2 diabetes

PCOS is now well-recognised as a metabolic disorder characterised by reduced insulin sensitivity, involving tissue-specific insulin receptor and post-receptor cellular signalling alterations.[44] Genetic evidence also implicates insulin resistance as an independent risk factor for the development of PCOS.[41,42] Insulin resistance, and the accompanying hyperinsulinaemia, contribute to the metabolic and reproductive sequelae of the syndrome through altered gonadotrophin secretion, increased ovarian androgen production and lowered sex hormone binding globulin (leading to increased free androgen levels). Conversely, androgens may themselves be metabolically deleterious in PCOS. Emerging data point to the importance of adrenal-derived 11-oxygenated C19 steroids, which represent a high proportion of the total serum androgen pool in women with PCOS, and which correlate closely with markers of insulin resistance.[45] Adipose tissue is also a major source of androgen excess in PCOS: *in vivo* and *ex vivo* studies identified the androgen-activating enzyme aldoketoreductase type 1C3 (AKR1C3) as a significant driver of lipogenesis and insulin resistance, offering a potential new target for therapeutic intervention.[46]

A systematic review and meta-analysis of euglycaemic-hyperinsulinaemic clamp studies, the gold standard method of assessing insulin sensitivity, confirmed a significant (27%) reduction in insulin sensitivity in women with PCOS.[47] This was independent of BMI, although elevated BMI exacerbated this reduction and did so to a greater extent than in controls. Data also suggest that PCOS subphenotype may have an influence on risk of insulin resistance: clamp studies have shown that insulin resistance is most marked in women with the 'classic' or 'complete' phenotype, and less apparent in women with normoandrogenic or ovulatory phenotypes[48], although the effect of diagnostic criteria (Rotterdam versus NIH) is minimal.[47]

Consistent with clamp study data, meta-analyses have confirmed an increased risk of impaired glucose tolerance (IGT) and type 2 diabetes in young women with PCOS compared with controls (figure 1).[49,50] In the later of these analyses[49], the odds of IGT was threefold greater overall in women with PCOS, although this was influenced by ethnicity (5.2-fold, 4.4-fold and 2.6-fold for Asian, North/South American and Europeans, respectively) and body weight (4.4-fold and 2.5-fold for lean-matched and overweight/obesity-matched groups, respectively). For type 2 diabetes, there was a 4.4-fold and 4.7-fold increased risk in women with PCOS living in Asia and the Americas, respectively.[49] A family history may also influence risk: in a retrospective analysis of a large database of women with PCOS, a family history of type 2 diabetes was associated with a significantly increased risk of IGT or type 2 diabetes, and of adverse metabolic characteristics in women with normal glucose tolerance.[51] In our analysis of electronic health record data of >50,000 UK women with PCOS and corresponding

controls, we reported an adjusted hazard ratio for incident type 2 diabetes of 1.75.[52] The risk was increased across all BMI categories, although weight gain was an important determinant of progression to a new diagnosis of diabetes, with a 1% increase in BMI leading to a 2% increase in risk. Consistent with these observations, genetically higher testosterone has been shown to be metabolically harmful in women.[36] These, and studies in other populations, collectively confirm an increased risk of IGT in younger women with PCOS and progression to type 2 diabetes up to and beyond the menopause.[53] These risks are evident in lean as well as overweight/obese women, and highlight the importance of screening for type 2 diabetes in long-term management.

Metabolic syndrome

Since PCOS is associated with an increased risk of dyslipidaemia, hypertension, obesity and insulin resistance, it is not surprising that the risk of metabolic syndrome is also increased in this condition (figure 1). The risk appears to be more than two-fold in excess of controls and is present even after adjustment for age and BMI.[50,54] As with insulin resistance, PCOS subphenotype may have an important influence, with a greater risk reported in studies in whom patients were diagnosed by the NIH rather than Rotterdam or AE-PCOS criteria.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD), or metabolic dysfunction-associated fatty liver disease (MAFLD), is the commonest chronic liver disease in Western societies and is associated with significant morbidity. Both PCOS and NAFLD are characterised by a similar set of risk factors, including insulin resistance and metabolic syndrome. Insulin resistance results in increased adipose tissue lipolysis, leading to increased fatty acid efflux to the liver and consequent hepatic steatosis. Owing to these metabolic similarities, a growing body of evidence has recognised an increased risk of NAFLD in women with PCOS (figure 1). In a large, retrospective longitudinal cohort study in the UK, Kumarendran and colleagues confirmed a 2.2-fold increased risk of NAFLD in young women with PCOS after adjustment for BMI or dysglycaemia.[55] They extended their findings to show an association of raised total testosterone and lowered sex hormone binding globulin (SHBG) with NAFLD risk. These observations have been replicated in other studies,[56-58] suggesting that hyperandrogenism contributes to NAFLD development and that screening for NAFLD (if undertaken) might be best considered in PCOS patients with androgen excess. However, studies are still needed to establish whether hyperandrogenism is a risk factor for progression of NAFLD to steatohepatitis and fibrosis, and whether anti-androgens can reduce risk.

Obstructive sleep apnoea and sleep disturbance

Obstructive sleep apnoea (OSA) is a common disorder characterised by intermittent upper airway obstruction during sleep and consequent hypoxia. Left undiagnosed and untreated, OSA is associated with an increased risk of cardiovascular events.[59] Since obesity is a risk factor that is common to both PCOS and OSA, OSA may be a common comorbidity in PCOS. In a recent systematic review and meta-analysis, Kahal *et al* identified a 35% prevalence of OSA in women with PCOS.[60] This was significantly higher than controls (odds ratio 3.8), was unaffected by variation in PCOS definition, and was markedly higher in obese than lean patients (figure 1). However, a number of uncertainties remain since many of the studies which informed this analysis were hampered by selection bias, failure to adjust for confounders, and restriction to more significant degrees of obesity. Disturbances in sleep patterns and sleep quality are also more apparent in women with PCOS. Community-based studies have shown that sleep disturbances may be twice as common in women with PCOS compared with non-PCOS subjects, even after adjustment for BMI and depression.[61,62] Difficulty in falling asleep and maintaining sleep are more prevalent, although obesity and depressive symptoms may be important mediators of the latter. [61]

Cancer

Endometrial Cancer

Multiple mechanisms have been proposed as drivers for a potential excess risk of endometrial cancer amongst women with PCOS. Chronic anovulation may expose the endometrium to prolonged unopposed oestrogenic stimulation, which promotes endometrial hyperplasia. Hyperandrogenism may also be a risk factor: both androgen receptors and 5 alpha-reductase are expressed in endometrial tissue, and overexpression of endometrial androgen receptors has been demonstrated in some women with PCOS.[63] Moreover, genetically-higher testosterone has been shown to increase the risk of endometrial cancer.[36] Hypersecretion of LH has also been proposed as a contributing factor.[63]

Several meta-analyses have confirmed an increased risk of endometrial cancer in young women with PCOS,[64-66] with the most recent showing a 2.8-fold increased risk compared with controls (figure 1).[65] However, these observations are limited by the small number of events (reflecting the low incidence in young women in the general population), self-reported diagnosis, case-control designs and a failure to adjust for important confounders such as obesity, which is a risk factor for endometrial cancer in its own right. Indeed, in a population-based study in Australia, adjustment for BMI attenuated the association between PCOS status and endometrial cancer risk to a non-significant difference from controls.[67] Despite these uncertainties, clinicians and patients should be aware of a potentially increased risk of endometrial carcinoma in women with PCOS and seek to prevent endometrial hyperplasia

especially in patients with prolonged time intervals between cycles. Studies also suggest that endometrial dysfunction is evident in women with PCOS,[68] which may additionally contribute to the increased risk of miscarriage and pregnancy complications compared to non-PCOS populations.[10]

Other Cancers

Several studies have examined the risk of other reproductive cancers in women with PCOS. Counter to null findings from earlier, small studies,[65] the Ovarian Cancer Association Consortium reported a reduced risk of invasive ovarian cancer among women with PCOS, although the validity of these findings is uncertain due to diagnosis being made on the basis of self-reporting.[69] Mendelian randomisation studies have since confirmed this reduced risk, not only overall but also specifically for the endometrioid subtype,[70,71] even after adjustment for BMI, parity and oral contraceptive use. Potential mechanisms may involve reduced ovulation (with less damage/repair) or hormonal factors such as hyperandrogenism, as evidenced by a reduced effect on ovarian cancer risk of genetically-higher testosterone.[36]

In contrast to ovarian cancer, the risk of breast cancer may be increased in women with PCOS. Whilst previous meta-analyses found no association between PCOS and breast cancer risk,[65,66,72] a series of recent genetic studies have shown that genetically-predicted PCOS[73-75] and genetically-determined increased testosterone[36] are both associated with an increased risk of oestrogen receptor (ER) positive but not ER negative breast cancer. This is consistent with an increased appreciation of the importance of androgen receptor signalling in breast cancer development.[76]

Mental health and neurological disease

Depression and anxiety

Cross-sectional studies using screening tools, such as the Beck Depression/Anxiety Inventory or the Hospital Anxiety and Depression Scale, have identified an increased prevalence of depression and anxiety in women with PCOS (figure 1), a risk which persists even if only moderate-to-severe symptoms are considered and when diagnosis is validated by a psychiatrist.[77] Longitudinal studies in the UK, Taiwan and Australia have also demonstrated an increased incidence of depression and anxiety compared with matched controls.[78-80] A number of mechanisms may be contributory. Obesity could explain some of this risk since this is itself associated with depression and anxiety. However, the increased risk of symptoms persists even when women with PCOS are matched by BMI with controls.[77] The cutaneous manifestations of PCOS (hirsutism, acne and scalp hair loss) are emotionally distressing, whilst fertility may be another major concern, albeit that depression and anxiety scores remain

higher than in controls where this has been considered.[77] Women with PCOS may feel less satisfied with their appearance and body size; this negative body image has been strongly associated with depression even after adjustment for any confounding influence of weight.[81] Furthermore, emotional well-being may be compromised by psychosexual dysfunction, which is more common in women with PCOS than in the general population, and associated with reduced quality of life.[82] Additional factors merit consideration: a Swedish registry study identified a higher risk of a range of psychiatric disorders not only in women with PCOS but also their siblings.[83] These observations may be explained by alterations in androgen production[84] or steroidogenic pathways,[85] which are present in the sisters and brothers respectively of women with PCOS. Alternatively, shared familial factors may be in operation, including psychosocial factors in childhood and/or common genetic predisposition. Indeed, Mendelian randomisation studies suggest that genetic variants associated with depression may play a causal role in PCOS, although these links may be explained in part by BMI, since BMI pathways are causally implicated in both PCOS and depression.[42]

Eating disorders

The prevalence of eating disorders and disordered eating appears to be increased in women with PCOS. Population-based studies and a systematic review have reported an increased risk of eating disorders compared with matched controls.[78,83,86] The risks appear to be increased for bulimia nervosa and binge eating disorder, but not anorexia nervosa. This may reflect a higher prevalence of identified risk factors for disordered eating in women with PCOS, including obesity, anxiety, depression, low self-esteem and impaired body image.

Other mental health disorders

Some studies have suggested that the risk of mental health disorders in women with PCOS may be broader than previously appreciated. Population-based studies have variably confirmed increased odds of bipolar disorder, personality disorders, tics, autism spectrum disorder and schizophrenia in women with PCOS compared with controls,[78,83] although further studies are needed to verify these associations. Valproate therapy could in part explain the association with bipolar disorder since symptoms in keeping with PCOS have been reported in women with bipolar disorder treated with this medication. However, the association, whilst slightly attenuated, persists when women treated with valproate are excluded from analysis,[78,83] suggesting that factors other than shared drug exposure must be in operation.

Cognitive function

Metabolic risk states such as diabetes and prediabetes have been shown to associate with poorer cognition and smaller brain volumes. Investigators have thus begun to explore whether

similar observations are apparent in PCOS, with variable results. Whilst some studies have shown subtle deficits in reaction time, word recognition tasks, verbal tasks, manual dexterity and visuospatial memory in women with PCOS compared with unaffected controls, these have been limited by remote assessments and/or a failure to match for BMI.[87,88] Udiawar *et al* compared cognitive performance and brain white matter microstructure in women with PCOS and age-, BMI- and IQ-matched controls. PCOS women displayed subtle but significant reductions in performance across a range of cognitive domains, accompanied by reduced axial diffusivity (representing diffusion along the main axis of white matter fibres) throughout the mean white matter skeleton.[89] Other studies have suggested that dysglycaemia, rather than PCOS *per se*, may influence cognitive function in reproductive age women.[90] If confirmed, these observations raise the possibility that PCOS is an early life risk state for later cognitive decline. However, larger and longer-term studies are needed to establish whether any subtle neuropsychological alterations lead to a clinically meaningful impact on brain health.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) is largely a disease which affects obese reproductive age women. Phenotypic characteristics overlap with PCOS, with some studies suggesting that the prevalence of IIH may be greater in women with PCOS than in matched controls.[91,92] Hyperandrogenism has been implicated in younger-onset cases.[93] However, in a recent study O'Reilly *et al* showed that the androgen signature in women with IIH is distinct from those with PCOS or simple obesity, and is characterised by increased serum testosterone and increased cerebrospinal fluid (CSF) testosterone and androstenedione.[94] Furthermore, in a cell-based model they demonstrated the potential for androgens to increase CSF secretion, suggesting that targeting androgen excess may offer a novel therapeutic approach in IIH.

Opportunities for intervention

Screening

In light of the increased long-term risk of multi-morbidity in women with PCOS, consideration should be given to screening, early intervention and risk factor modification. However, the case for adoption of a systematic approach to screening is controversial. For example, for CVD, whilst the relative risk of cardiovascular events is increased, the absolute risk is still low in this young, pre-menopausal population. Screening would thus only be beneficial if it led to earlier identification of risk factors which were amenable to modification, and if risk factor modification in turn led to improved outcomes. Whilst screening might well improve CVD outcomes in women with PCOS, there is currently no evidence to confirm this nor is there evidence of the most effective method of risk assessment. Uncertainties also remain as to the importance of PCOS subphenotype and patient-related factors, such as ethnicity, on CVD risk.

Nevertheless, international position statements and guidelines recognise the increased lifetime cardiovascular risk burden in women with PCOS and recommend regular assessment of cardiovascular risk factors and global CVD risk.[32,95] Similar gaps in the evidence base for screening for other long-term morbidities are also recognised, for which assessments should nevertheless be considered on an individualised basis.

Cardiometabolic disease

Weight increase was noted as an independent risk factor for progression to type 2 diabetes and cardiovascular events in two large population studies.[33,52] Monitoring for weight change should thus be undertaken at each clinic visit, or at least annually. Calculation of BMI, and ideally waist circumference, is recommended, adopting ethnicity-specific cut-offs to determine risk (table 1). Assessment for cardiovascular risk factors should include an enquiry about cigarette smoking, physical activity and family history of premature CVD (defined in [95] as a male <55 years or female <65 years), in addition to measurement of blood pressure, fasting lipid profile (comprising total cholesterol, LDL-C, HDL-C and triglycerides) and an assessment of glycaemic status. International PCOS guidelines recommend that the latter be assessed by oral glucose tolerance test (OGTT), fasting plasma glucose (FPG) or HbA1c, with the exception that high risk patients (BMI >25 kg/m^2 or >23 kg/m^2 in Asians, history of gestational diabetes, impaired fasting glucose or impaired glucose tolerance (IGT), hypertension, high-risk ethnicity, family history of type 2 diabetes) undergo OGTT.[32] This recommendation balances the potential benefits of identifying IGT from an OGTT in higher risk subjects with the added inconvenience and cost if OGTT was adopted on a universal basis. Moreover, data do not suggest any particular benefit of OGTT in normal weight, non-pregnant women with PCOS, who are at low risk of type 2 diabetes.[96] This is in keeping with its limited use in screening for prediabetes or diabetes in non-PCOS populations. These baseline evaluations will help establish global cardiovascular risk and should inform subsequent screening intervals (table 1), with glycaemic status assessed every 1-3 years dependent on the presence or not of diabetes risk factors.

Adoption of healthy lifestyle behaviours, including regular physical activity and healthy eating, should be encouraged in all women with PCOS, with lifestyle intervention recommended in overweight/obese women in order to reduce weight and improve insulin sensitivity (table 1). A target of 5-10% weight loss within 6 months is achievable and associated with significant reproductive, metabolic and psychological benefits. Since there is presently no evidence that specific dietary macronutrient approaches confer long-term advantages, a balanced diet reducing energy intake is recommended, with an energy deficit of 30% (500 – 750 kcal/day) prescribed to achieve weight loss.[32] Behavioural change strategies may also need to be

considered, alongside assessment of any body image concerns, disordered eating and psychological factors such as anxiety or depression. For adults, physical activity should comprise at least 150 minutes/week of moderate intensity exercise or 75 minutes/week at high intensity, including muscle strengthening activities, to prevent weight gain and maintain health.[32] However, greater exercise volume may be required to achieve weight loss (table 1).

Metformin has been used off-label as an insulin sensitiser in the management of PCOS for several decades. In non-PCOS populations, it may limit weight gain, prevent progression to type 2 diabetes and reduce micro- and macro-vascular disease in patients with type 2 diabetes. Evidence of benefit with respect to clinically important outcomes, such as progression to type 2 diabetes or CVD, in women with PCOS is lacking, yet systematic review has shown modest benefits compared with placebo on weight, BMI, waist:hip ratio, testosterone and triglyceride levels, with stronger evidence for metabolic benefits in women with elevated BMI.[32] Metformin, in addition to lifestyle intervention, may thus be considered for the treatment of weight and metabolic outcomes, especially in women with BMI >25 kg/m^2 and those with diabetes risk factors, IGT or higher-risk ethnicity (table 1).[32] There is less evidence for a benefit of anti-obesity agents, such as sibutramine or orlistat, on metabolic outcomes in women with PCOS, although use may be considered in line with general population recommendations, dependent on regulatory status, availability, cost and contraindications.[32] Glucagon-like peptide 1 (GLP-1) receptor agonists exert beneficial effects on weight loss and glycaemic control in patients with type 2 diabetes, with some demonstrating benefits in CVD prevention. In a recent systematic review and meta-analysis of seven randomised trials involving overweight/obese women with PCOS, GLP-1 receptor agonists showed greater improvements than metformin on reduction of BMI and insulin resistance.[97] However, the quality of evidence was low and further studies are needed before these agents can be considered for this purpose in routine clinical practice. Finally, statin therapy and anti-hypertensives may need to be considered on an individual basis, taking into consideration an assessment of global CVD risk, in addition to desire for pregnancy (where statins and some anti-hypertensives are contraindicated) (table 1).[32,95]

Non-alcoholic fatty liver disease

Whilst data increasingly support a heightened risk of NAFLD in patients with PCOS, it is unclear whether screening for NAFLD should form part of the evaluation of a woman with PCOS. The case for screening in the general population is similarly contentious, with European guidelines recommending screening for NAFLD in patients with obesity, metabolic syndrome or type 2 diabetes,[98] whilst others recommend against this on the basis of insufficient data to demonstrate the cost-effectiveness of such an approach. The value of

screening has also been questioned on the grounds of the low predictive value of non-invasive tests, the risks of liver biopsy and the absence of effective disease-specific treatments. National Institute of Health and Care Excellence (NICE) guidelines in the UK recommend that clinicians retain an 'increased awareness' of NAFLD in patients with type 2 diabetes and metabolic syndrome but screening is not advocated due to a lack of evidence.[99] Until further data are available on the clinical- and cost-effectiveness of screening, it would seem reasonable to follow such guidelines in women with PCOS, with an offer of lifestyle modification and hepatology review if fatty liver is identified incidentally (table 1).

Obstructive sleep apnoea

Although there may be a high prevalence of OSA in women with PCOS, international guidelines recommend clinical screening only in patients with suggestive symptoms, where treatment benefits have been shown in the general population (table 1).[32] Screening with the intention of improving cardiometabolic risk is not advocated since there is inadequate evidence for benefits in either PCOS or in the general population.

Cancer

The relative risk of endometrial cancer in women with PCOS may be increased although the absolute risk is low, hence routine ultrasound screening for endometrial hyperplasia or cancer is not justified. However, investigations (transvaginal ultrasound +/- endometrial biopsy) should be considered in patients with risk factors (prolonged amenorrhoea, abnormal vaginal bleeding), and weight loss encouraged as this is in itself a risk factor for endometrial cancer. Furthermore, in patients with amenorrhoea or significant oligomenorrhoea (cycles >90 days), the risk of endometrial hyperplasia should be minimised by use of cyclical progestogen therapy, the combined oral contraceptive pill or an intra-uterine system containing a progestogen (table 1). No additional screening is required for breast cancer, but women should be encouraged to participate in national population-based breast screening programmes as appropriate.

Mental health

The high prevalence of depressive and anxiety symptoms in women with PCOS justifies routine screening in all patients at diagnosis,[32] yet this is often under-appreciated and poorly performed. Assessment should comprise an initial symptomatic enquiry followed by additional screening using validated tools (such as the General Anxiety Disorder Scale [GAD-7] or Patient Health Questionnaire)[32] and/or referral to an appropriate professional if any of the initial responses are positive (table 1). If pharmacotherapy is being considered, care is needed in avoiding agents with the potential to exacerbate symptoms, including weight gain. Clinicians

should also be aware of the potential negative consequences of PCOS on body image, psychosexual function and disordered eating, for which psychological therapy may be required, informed by local guidelines.

Conclusions

Evidence increasingly points to a much wider range of adverse long-term outcomes associated with PCOS than previously appreciated. These observations underscore the importance of recognising the syndrome as a metabolic disorder, with an impact that extends beyond its well-recognised reproductive sequelae. Screening for major morbidities thus forms an important part of the comprehensive long-term care package that should be offered to women with PCOS. Further data are now needed to establish which patients are most at risk of adverse long-term outcomes, whether screening programmes are clinically- and cost-effective, and which interventions offer greatest benefits in preventing progression to multi-morbidity.

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Figure legend

Figure 1. Major long-term health risks associated with Polycystic Ovary Syndrome.

Abbreviations. RAA: renin-angiotensin-aldosterone; NO: nitric oxide; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol.

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829 **Table 1.** Suggested programme for the identification, prevention and management of long-term health risks in women with PCOS

Morbidity	**Baseline assessments**	**Follow-up**	**Intervention(s)**
Overweight/obesity	Weight BMI[a] Waist circumference[a]	Re-assess every 6-12 months.	If overweight, target 5% weight loss within 6 months. Recommend reduced energy diet with energy deficit of 30% (500-750 kcal/day) to achieve weight loss. Consider behavioural change strategies. Recommend 150 minutes/week of moderate intensity exercise or 75 minutes/week at high intensity, including muscle strengthening activities for weight maintenance. For weight loss, recommend 250 minutes/week at moderate intensity or 150 minutes/week at high intensity.
Prediabetes/T2DM	OGTT, FPG or HbA1c. High risk patients[b]: OGTT.	Re-assess every 1-3 years dependent on presence of diabetes risk factors.	Consider metformin in addition to lifestyle intervention in women with BMI >25 kg/m^2 and in those with diabetes risk factors, IGT or higher-risk ethnicity.
Cardiovascular disease	BMI +/- waist circumference, assess glycaemic status *plus*: Enquire re: CV risk factors (cigarette smoking, physical activity, family history of premature CVD[c]). Blood pressure. Fasting lipids (total cholesterol, LDL-C, HDL-C and triglycerides).	Re-assess every 6-12 months.	Advise smoking cessation. Lifestyle intervention (as above) if overweight/obese and/or limited physical activity. Consider anti-hypertensive therapy dependent on global CVD risk assessment and inidividual circumstances (e.g. desire for pregnancy). Consider statin therapy dependent on degree of hyperlipidaemia, global CVD risk assessment and inidividual circumstances (e.g. desire for pregnancy).
NAFLD	Be aware of increased risk in patients with metabolic syndrome/T2DM but routine screening not recommended.	Routine review not currently recommended.	Lifestyle modification +/- hepatology review if identified incidentally.
Obstructive sleep apnoea	Clinical screening only in patients with suggestive symptoms. Routine screening not recommended.	Annual symptomatic review.	If suggestive symptoms, consider specialist referral alongside lifestyle modification.
Endometrial cancer	Consider TV US +/- endometrial biopsy if prolonged amenorrhoea and/or abnormal vaginal bleeding.	Annual symptomatic review.	Lifestyle intervention (as above) if overweight/obese. If menstrual cycle length >90 days, consider cyclical progestogens, COCP or IUS with progestogen.
Mental health	Symptomatic enquiry +/- validated questionnaire[d].	Apply clinical judgement, guided by risk factors, life events and comorbidities.	Consider specialist referral, psychological therapy +/- pharmacological therapy, informed by local guidelines.

			If relevant, address any effects on body image, psychosexual function and disordered eating.

Abbreviations: BMI: body mass index; OGTT: oral glucose tolerance test, FPG: fasting plasma glucose; IGT: impaired glucose tolerance; GDM: gestational diabetes; T2DM: type 2 diabetes; CVD: cardiovascular disease; TV US: transvaginal ultrasound; COCP: combined oral contraceptive pill; IUS: intrauterine system

[a]Adopt ethnicity-specific cut-offs to assess risk. [b]High risk patients: BMI >25 kg/m^2 [or >23 kg/m^2 Asians], history of GDM, impaired fasting glucose or IGT, hypertension, high-risk ethnicity, family history of T2DM. [c]Defined as male <55 years or female <65 years. [d]For example, Patient Health Questionnaire (PHQ) and General Anxiety Disorder Scale (GAD-7).