Cardiometabolic Risk in Polycystic Ovary Syndrome

Current Guidelines

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KEYWORDS

• PCOS • Metabolic risk • Screening • Diabetes • Cardiovascular disease

KEY POINTS

- Women with polycystic ovary syndrome (PCOS) are at increased risk of obesity, impaired glucose tolerance, diabetes, dyslipidemia, hypertension, metabolic syndrome, venous thromboembolism, and subclinical atherosclerosis compared with women without POCS.
- Women with PCOS should be screened for these conditions at the time of diagnosis, and future screening should occur on a regular basis at intervals, depending on results and baseline risk.
- Despite the increased risk of traditional cardiovascular risk factors in women with PCOS, the true risk of cardiovascular events, such as myocardial infarction or stroke, in women with PCOS in unknown, although accumulating data suggest the potential for an association.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting 6% to 10% of women[1,2] and is associated with metabolic, reproductive, and psychological implications. Although the definition centers around 3 features—oligomenorrhea, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound—it is important for clinicians to counsel patients regarding the long-term health risks and the need for early screening and management. The metabolic complications of PCOS are numerous, including overweight/obesity, impaired glucose tolerance (IGT) and diabetes, dyslipidemia, hypertension (HTN), and metabolic syndrome (MetS). Even more concerning is the potential for subclinical atherosclerosis and cardiovascular events, including myocardial infarction (MI) and stroke. This article's objective is to outline the evidence for metabolic and cardiovascular comorbidities and discuss screening recommendations.

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OVERWEIGHT/OBESITY

Extent of the Problem

Approximately 60% of women with PCOS are obese,[3] and this risk appears to have a genetic predisposition.[4] Not only does obesity increase the risk of other metabolic complications associated with PCOS, such as dyslipidemia, type 2 diabetes mellitus (DM), HTN, and pregnancy complications, such as preeclampsia and gestational diabetes, but also it is one of the most common characteristics of PCOS that is cited by patients as a major concern.[5] Obesity also is related to increased risk of eating disorders, anxiety, and depression in women with PCOS.[6,7] Central obesity, often found in women with PCOS,[3] is known to be associated with more severe metabolic disturbances.[8]

There is a bidirectional relationship between PCOS and weight gain: women with PCOS are more likely to gain weight over time and weight gain predisposes to the risk of manifesting PCOS.[9,10] The risk of obesity varies by race, with white women having a higher odds of obesity compared with Asians (10.8-fold vs 2.3-fold, respectively; $P<.001$).[3] The risks for obesity and central obesity were similar irrespective of diagnostic criteria,[3] however, higher in the hyperandrogenic (HA) phenotypes (40% vs 11%, respectively; $P<.001$).[11] Both adolescents with PCOS[3] and older women with PCOS have increased risk of obesity.[12]

Screening Recommendations

Because weight gain in women with PCOS often starts in adolescence, early awareness of this risk and close monitoring are paramount in helping decrease weight gain trajectories. International guidelines recommend that women with PCOS should be monitored for weight changes every 6 months to 12 months (**Table 1**).[13,14] Given the association between negative body image and low self-esteem, it is important for providers to be tactful in discussing the risk of weight gain and obesity and participate in shared decision making about the frequency and manner of screening.

IMPAIRED GLUCOSE TOLERANCE AND TYPE 2 DIABETES MELLITUS

Extent of the Problem

Women with PCOS have increased risks of IGT and type 2 DM (odds ratio [OR] 3.26; 95% CI, 2.17–4.90; and OR 2.87; 95% CI, 1.44–5.72, respectively; meta-analysis of 40 studies).[15] Women living in the Asian subcontinent (5.2 fold) and North/South Americans (4.4 fold) had the highest risk of IGT, whereas the risk was moderate in Europe (2.6 fold). Similar ethnic distributions and risks were seen when evaluating for the risk of DM.[15] US studies show that Hispanic and black women have higher degrees of insulin resistance compared with non-Hispanic whites.[16,17] The increased prevalence of IGT was noted in body mass index (BMI)-matched (2.1 fold), non–BMI-matched (4.8 fold), lean-matched (4.4 fold), and overweight or obese–matched groups (2.5 fold).[15] On the contrary, Kakoly and colleagues[15] did not find an increased risk of DM in subgroups matched on BMI (OR 1.13; 95% CI, 0.83–1.54; 7 studies), perhaps due to the small numbers in this subanalysis and a young mean age (30 years). Another study reported a higher risk of DM in nonobese women with PCOS compared with nonobese controls (OR 1.5; 95% CI, 1.1–2.0; $P = .007$; 5 studies), although they had less stringent inclusion criteria for the diagnosis of PCOS in their meta-analysis.[18]

Two longitudinal studies[19,20] conducted over 10 years found a higher incidence of DM in the PCOS cohort compared with controls. They each had limitations, however, including self-report of PCOS diagnosis[19] or use of administrative codes for PCOS

Table 1
Screening recommendations for women with polycystic ovary syndrome

Metabolic Morbidity	Who Should be Screened?	Screening Recommendations	Screening Intervals	Special Considerations
Obesity	All women at time of PCOS diagnosis	• Weight and height to calculate BMI • Ideally, waist circumference	Every 6–12 mo	
IGT, type 2 DM	All women at time of PCOS diagnosis	• Fasting glucose or HbA_{1c} in low risk women or • OTT in higher risk women (BMI >25 kg/m^2 or in Asians >23 kg/m^2, history of abnormal glucose tolerance, or family history of diabetes)	Every 1–3 y based on risk factors for DM	• An OGTT should be offered in all women with PCOS who are planning pregnancy or seeking fertility treatment. • If not performed preconception, an OGTT should be offered at <20 wk gestation and all women with PCOS should have an OGTT at 24–28 wk gestation.
Dyslipidemia	All women (regardless of weight) after age 20[3] Adolescents who are overweight or obese at time of PCOS diagnosis	• Fasting lipid profile (cholesterol, LDL, HDL, and TG levels)	Repeat measurement should be guided based on results or global CVD risk. ACC/AHA guidelines recommend at least every 4–6 y	
HTN	All women at time of diagnosis	• Blood pressure	Annually or more frequently based on global CVD risk.	

Data from Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril.* 2018; 110(3):364-379 and Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* 2019;74(10):e177-e232.

and/or hirsutism.[20] Population-based studies also have shown higher rates of DM in women with PCOS,[21–24] some of which also adjusted for BMI.[22,23]

A large cross-sectional study found higher rates of insulin resistance in the HA PCOS phenotypes but no difference in rates of hyperglycemia in PCOS phenotypes.[11] Similarly, a recent large cross-sectional study of PCOS identified from a hospital-based cohort in China (N = 2436) showed that all 4 Rotterdam phenotypes had a similar prevalence of DM.[25]

There are few data on prevalence of IGT and DM in adolescents. The meta-analysis by Kakoly and colleagues[15] included 7 studies with subjects less than 20 years, 5 of which were higher quality. Three showed a nonsignificant increase in IGT in adolescents with PCOS and 2 had no cases of IGT/DM in either the PCOS or the control group. The small number of subjects in each study limits the ability to draw firm conclusions in this age group.[15] In a systematic review, the authors' group previously reported that 7 of 10 studies reported an increased prevalence of IGT and/or DM in women with PCOS over age 40 years.[12] More recently, 2 longitudinal studies have examined the risk of DM in older women; 1 showed an increased risk (mean age at follow-up: 52 years),[26] but the other reported an increased risk in younger (<40 years), but not older, women with PCOS.[27]

Overall, the data support that reproductive-aged and perimenopausal/menopausal women with PCOS are at an increased risk of IGT and DM. Furthermore, cross-sectional studies demonstrate the increased risk of IGT is independent of obesity. Although cross-sectional studies do not show an increased risk of DM independent of BMI, multiple larger population-based and longitudinal studies have demonstrated an increased risk of DM even after adjusting for BMI.[19,22,23,27] Future studies should focus on evaluation of the risk of IGT/DM in adolescents.

Screening Recommendations

Given the increased prevalence of IGT and DM in women with PCOS, close monitoring is necessary. In the general population, those with IGT at baseline develop DM at a yearly rate of 5.7%.[28] In a study of women with PCOS in Thailand (N = 400), BMI greater than 23 kg/m^2 and impaired fasting glucose at baseline were 2 important predictors in the development of DM after 5 years of follow-up.[29] The international guidelines recommend screening for IGT/DM at time of diagnosis and every 1 year to 3 years thereafter based on risk (see **Table 1**). Screening for low risk women can consist of a fasting glucose or hemoglobin (Hb) A_{1c}, but higher risk women (BMI >25 kg/m^2 or, in Asians, BMI >23 kg/m^2; history of IGT;or family history of DM) and women who are seeking pregnancy or fertility treatment should be offered an oral glucose tolerance test (OGTT).[14]

Although discussion of treatment is beyond the scope of this article, the guidelines recommend starting metformin, in addition to lifestyle recommendations, in women with PCOS who have IGT or DM. The guidelines also suggest considering the use of metformin in women with PCOS with BMI greater than or equal to 25 kg/m^2 without IGT/DM,[14] Metformin has been shown to decrease progression from IGT to DM in the general population[30] and to decrease BMI in women with PCOS.[31]

DYSLIPIDEMIA

Extent of the Problem

In a meta-analysis of 30 studies,[32] women with PCOS were found to have a higher mean serum low-density lipoprotein (LDL) cholesterol (LDL-C), non–high-density lipoprotein (HDL) cholesterol (non–HDL-C), and triglyceride (TG) levels and lower HDL-C

levels compared with women without PCOS, although overall differences were small (ie standardized mean difference [SMD] between groups: 12 mg/dL for LDL-C), raising the question of clinical significance. In studies that matched on BMI, the association between PCOS and elevated LDL-C and non–HDL-C persisted.[32] The HA phenotype is associated with a higher risk of dyslipidemia with low HDL-C in women with HA-PCOS.[11] Among women with PCOS, non-Hispanic black women may have a lower prevalence of dyslipidemia compared with both Hispanics and non-Hispanic whites.[16,17] In a meta-analysis in adolescents with PCOS, there were no significant differences in TG and HDL-C levels, however. this study was limited by low numbers (6 of 7 studies included <70 PCOS subjects).[33] A few large studies examining the risk of dyslipidemia in older women (>40) also have shown an association with PCOS.[12] Future studies should assess the prevalence of dyslipidemia in women of all ages independent of BMI.

Screening Recommendations

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend screening for lipid disorders in all patients aged 20 years to 45 years every 4 years to 6 years.[34] International PCOS guidelines recommend a fasting lipid profile at the time of PCOS diagnosis in overweight and obese women regardless of age (see **Table 1**). These guidelines suggest that the interval for repeat testing should be based on results of initial testing and global risk of cardiovascular disease (CVD).

HYPERTENSION

Extent of the Problem

In a meta-analysis,[35] the overall pooled prevalence of HTN was higher in women with PCOS compared with controls (15% vs 9%, respectively). When evaluating non–population-based studies separated by age, this association was seen only in studies of reproductive-aged women (OR 1.5; 95% CI, 1.2–1.8) and not menopausal women (OR 1.5; 95% CI, 0.91–2.3), although there were fewer studies of older women. The investigators did not report findings adjusted for BMI.[35] Daan and colleagues[11] found a higher prevalence of HTN in the HA PCOS phenotypes in unadjusted but not adjusted analysis. Among women with PCOS, non-Hispanic white women have the lowest prevalence of HTN.[16,17]

Two longitudinal studies also did not report significant differences in HTN[36,37] In adolescents with PCOS a higher systolic blood pressure but not diastolic blood pressure was reported compared with controls (SMD 5.0; 95% CI, 1.3–8.7; and SMD 3.5; 95% CI, 0.5–8.6, respectively).[33]

In summary, the reported prevalence of HTN varies considerably. Most studies do not show a continued risk of HTN, independent of BMI, after menopause.[12] and data in adolescents are limfited.

Screening Recommendations

International guidelines recommend that all women with PCOS have blood pressure measured annually (see **Table 1**).[14]

METABOLIC SYNDROME

Extent of the Problem

MetS is a cluster of metabolic disturbances, including central obesity, hyperglycemia/insulin resistance, dyslipidemia, and HTN. In young adults with PCOS, the mean prevalence of MetS is estimated to be 30% (95% CI, 27–33; 46 studies)[38] with a 2-fold to 3-

fold increased odds of MetS compared with controls.[18,39–41] In sensitivity analyses, Lim and colleagues[40] demonstrated that this increased prevalence persisted in BMI-matched studies (OR 1.8; 95% CI, 1.3–2.3) and in overweight or obese women (OR 1.88%; 95% CI, 1.16–3.04) but not in lean women (OR 1.45; 95% CI, 0.35–6.12). When evaluating geographic differences, all regions had increased odds of MetS in women with PCOS (Europe: 2.6-fold, Americas: 5.2-fold, Asia: 3.5-fold; and Australia and New Zealand: 3.6-fold). These studies on phenotype are limited, however, by not controlling for BMI. Hispanic women with PCOS had a higher prevalence of MetS compared with non-Hispanic black women in some[16] but not all studies.[17] Several meta-analyses have suggested a relationship between PCOS phenotype and prevalence of MetS.[39,40,42] In a meta-analysis specifically evaluating phenotype, Yang and colleagues[42] found increased odds of MetS in women with HA phenotype compared with women with PCOS without HA (OR 2.21; 95% CI, 1.88–2.59). The risk of MetS in older women with PCOS is less clear. The prevalence of MetS increases with use of OCPs in overweight/obese women with PCOS and can be mitigated by lifestyle modifications.[43]

In summary, the risk of MetS clearly is higher in adolescent and reproductive-aged women with PCOS in several regions of the world.

Screening Recommendations

MetS is associated with an increased risk of DM, cardiovascular disorders, coronary heart disease, stroke, and mortality[44]; thus, as with its individual components, appropriate screening and diagnosis are paramount.[45] Frequent assessment in overweight/obese women with PCOS prescribed combined hormonal contraceptives allows early detection of metabolic risk factors.

CARDIOVASCULAR DISEASE: SUBCLINICAL ATHEROSCLEROSIS

Extent of the Problem

In addition to the traditional risk factors for CVD, discussed previously, evidence of subclinical atherosclerosis has been shown associated with CVD events, including stroke and MI. Common methods of evaluating subclinical atherosclerosis are measuring carotid artery intima media thickness (C-IMT) endothelia dysfunction, measured by comparing changes in arterial flow-mediated dilation (FMD); and coronary artery calcium (CAC) scores, which are measured with the use of cardiac computerized tomography or magnetic resonance imaging. In the general population, increases in C-IMT, lower FMD, and higher CAC scores are associated with increased risks of CVD events.[46–50]

A meta-analyses showed that women with PCOS have a higher C-IMT compared with controls (SMD 0.072 mm; 95% CI, 0.040–0.105; $P<.0001$; meta-analysis of 19 studies).[51] In the general population, for every 0.1-mm incremental increase in mean C-IMT, the hazard of stroke increases by 18% and the hazard of MI increases by 15%.[47] In another meta-analysis, women with PCOS had a 3.4% lower pooled mean FMD (95% CI, 1.9–4.9; meta-analysis of 21 studies) than control women. Their results remained significant after matching on age and BM.[52] Most women in these studies were in the second or third decade of life, suggesting that evidence for subclinical atherosclerosis can be detected at a young age. CAC scores also have been reported to be higher in some small studies of young women with PCOS[53,54] but not in others.[55]

An evaluation of phenotypic differences in risk of atherosclerosis is limited because none of the meta-analyses evaluated phenotype. Also, no differences based on race

are reported.[17] Studies on subclinical atherosclerosis in older women with PCOS are mixed, with most not showing a higher prevalence.[12] This leaves the question open as to whether women with PCOS potentially develop atherosclerosis at a younger age than women without PCOS but that women without PCOS catch-up, such that at older ages there is no longer a difference.

In summary, younger women have an increased prevalence of subclinical atherosclerosis, but this risk is unclear past the reproductive years. Longitudinal studies with well-phenotyped women with PCOS are needed to evaluate persistent risk in the perimenopause and beyond.

Screening Recommendations

There are no specific recommendations for screening for evidence of subclinical atherosclerosis in women with PCOS. CAC scores have not been incorporated into current CVD risk assessment algorithms although they may improve risk stratification.

CARDIOVASCULAR DISEASE: VENOUS THROMBOEMBOLISM

Extent of the Problem

Women with PCOS have risk factors for venous thromboembolism (VTE), including obesity, DM, dyslipidemia, and HTN. In addition, first-line treatment of PCOS is combined oral contraceptive pills (COCs), which also can increase the risk of VTE. A meta-analysis of 3 studies (mean age 30 years), which controlled for BMI, demonstrated that women with PCOS had an increased risk of VTE compared with controls (adjusted OR 1.9; 95% CI, 1.6–2.2). These population-based studies used *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes for obesity to control for BMI using either propensity scores or regression models; however, prevalence of obesity in the populations were low (1%–13%), suggesting there could be residual confounding and underestimation of the impact of BMI on VTE risk.

Data are mixed on the effect of concurrent COC use on VTE risk, with 1 study showing increased risk for VTE in women with PCOS taking COCs[56] and another showing a decreased risk[57] Given the young age of these populations, the absolute risk of VTE among women with PCOS is low, ranging from 6.3 to 28.3 per 10,000 person years.[56–58]

Screening Recommendations

International guidelines for use of COCs in women with PCOS recommend use of the lowest effective estrogen doses (such as 20–30 μg of ethinyl estradiol or equivalent)[14] to minimize risk of VTE.

CARDIOVASCULAR DISEASE EVENTS: MYOCARDIAL INFARCTION OR STROKE

Extent of the Problem

Studies in women with PCOS examining CVD outcomes use the following endpoints: CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina.[59] There are several limitations in the current studies. First, CV events are rare in young women, such that large numbers of women are needed to have sufficient power to detect differences at a young age. Second, diagnosis of PCOS is difficult to establish in older women and is subject to recall bias, because symptoms, such as menstrual irregularity and hirsutism, improve with age.[60,61] Despite these limitations, there are multiple meta-analyses attempting to evaluate the association between PCOS and CV events.[62–64] Unfortunately, included studies had limitations, such as a presumed diagnosis of PCOS based on menstrual irregularity only[37,65] or inclusion of non-Rotterdam

criteria, such as infertility, history of miscarriage, obesity, or insulin resistance.[66,67] A meta-analysis performed for the international guidelines attempted to include only quality studies[14] and did not find a difference in risk of MI (OR 1.21; 95% CI, 0.68–2.14; $P = 0.5$; 3 studies), stroke (OR 1.64; 95% CI, 0.92–2.93; $P = 0.1$; 4 studies), CVD-related death (OR 1.81; 95% CI, 0.55–5.88; $P = .3$; 2 studies), or coronary artery/heart disease (OR 2.44; 95% CI, 0.88–6.74; $P = .09$; 2 studies).[14] They did include a study,[68] however, where all of the women with PCOS had a history of a wedge resection. It is unclear how this would bias their results because perhaps the women in this study had a more severe PCOS phenotype necessitating treatment or, by contrary, the surgery may have resulted in subsequent improvement in androgens or oligomenorrhea, thereby mitigating their future CVD risks. The 2 other studies had very low numbers (<35 women with PCOS).[24,69]

Given the small numbers of subjects and young age of participants (mean ages of women in the 2 largest studies included in this analysis were <40 years at follow-up) and the absolute risk of a CVD event being very low in this population, it is likely that these studies are underpowered. Thus, the question of a true association between PCOS and CVD is unanswered by these meta-analyses of cross-sectional studies.

A study by Mani and colleagues,[70] not included in the meta-analysis, discussed previously, compared women with PCOS (N = 2301) diagnosed in an endocrinology clinic to age-matched control women. They reported that women with PCOS had higher odds of MI than controls in all age groups greater than age 45 years.[70] Most meta-analyses did not include any registry or population-based studies given the limitations of using *ICD-9* codes. In the absence of definitive data from other sources, however, population-based studies can be helpful in evaluating the risk of CV events because they allow for large sample sizes, long follow-up times, and, in some cases, adjusting for confounders, such as BMI.

There are 6 population-based studies evaluating CVD events in women with PCOS, some of which followed women for more than 10 years. Four showed increased odds of CVD events in women with PCOS, 3 of which adjusted for BMI.[21,22,71,72] These studies are limited by potential inaccuracies with PCOS diagnosis[71,72] or inclusion of only hospitalized women.[22] Two studies did not show increased rates of VD events; however, the mean ages were less than 30 years.[23,73] There is 1 meta-analysis evaluating just population studies, which found a higher odds of CV events and mortality due to CV events in women with PCOS (OR 1.8; 95% CI, 1.5–2.1; and OR 1.8; 95% CI, 1.5–2.1; respectively)[64]

Taken together, there is a suggestion of an increased prevalence of CVD events in women with PCOS when evaluating a combination of cross-sectional, cohort, and population-based studies, although most studies have limitations. The ideal study would include a large cohort of reproductive-age women with well characterized PCOS phenotype and follow-up data for several decades. Long duration of follow-up is needed, given the low prevalence of CV events in premenopausal women.

Screening Recommendations

Clinicians can use the ACC/AHA calculator for computing the 10-year risk of an atherosclerotic CVD event, in women over the age of 40.

SUMMARY

In conclusion, all women with PCOS need to be counseled regarding their increased risks of obesity, IGT, DM, dyslipidemia, HTN, MetS, VTE, and subclinical atherosclerosis. Screening for these conditions should be conducted at the time of diagnosis and

repeated based on risk factors to facilitate early identification and treatment of metabolic conditions. Due to several limitations in the current studies, it is not clear if the risks observed in the reproductive years persist into the perimenopause and menopausal period. Data support that the risk of both obesity and DM continues at older ages, confirming the need for frequent screening. Management of PCOS should be comprehensive and include a multidisciplinary model of care to treat comorbidities associated with PCOS, including cardiometabolic, psychological, dermatologic, and infertility. Future studies should focus on better elucidating the risk of CVD in women with PCOS specifically in the postmenopausal years so that women can be counseled accurately. In the meantime, risk stratification should occur based on known risk factors for CVD and prediction models created for the general population.

CLINICS CARE POINTS

- Adolescents and women with PCOS are at an increased risk for obesity and should be monitored for weight gain and counseled regarding weight management strategies.
- Reproductive-aged women with PCOS are at an increased risk for IGT and diabetes and should be screened at the time of diagnosis irrespective of their weight; follow-up screening can occur at regular intervals based on other risk factors.
- The prevalence of metabolic risk factors appears to be higher in the HA PCOS phenotypes as defined by the Rotterdam criteria.
- Risk of VTE in women with PCOS can be minimized by starting with oral contraceptives that contain the lowest effective estrogen doses.
- It is important to be aware of early screening recommendations as for many conditions often starts at younger ages than recommended for the general population.

DISCLOSURES

The authors have nothing to disclose.

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