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Cardiovascular disease risk in women with PCOS

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ABSTRACT

Cardiac disease is the number one killer in women. Adolescents and reproductive age women with PCOS have an increased prevalence of cardiovascular risk factors. These include obesity, impaired glucose tolerance, diabetes, hypertension, mood disorders and metabolic syndrome. There is sufficient evidence to confirm the presence of subclinical atherosclerosis in women with PCOS compared to age matched controls. There are, however, few prospective studies examining non-fatal and fatal cardiac events in women with well-defined PCOS. Future directions of research should include longitudinal studies in peri- and post-menopausal women with prospectively defined PCOS to better estimate the risk of cardiac morbidity and mortality in this high-risk population. In the meantime, regular screening for risk factors and timely early interventions are critical to reduce the overall risk burden.

1. Introduction

Women with PCOS have a high prevalence of several traditional risk factors for cardiovascular disease (CVD). These include controllable risk factors such as dyslipidemia, diabetes, hypertension and obesity [1]. CVD is not just a man's disease. In fact, one in three women die of CVD and more women die of CVD than the next five causes of death. In the worldwide INTERHEART study of patients from 52 countries, nine potentially modifiable risk factors accounted for over 94% of the population-attributable risk of a first myocardial infarction (MI) in women [2]. These factors included smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors (e.g., depression, perceived stress, life events), daily consumption of fruits and vegetables, regular alcohol consumption, and regular physical activity. Collectively, these findings underscore the need for regular CV screening in women with PCOS to allow for early interventions to decrease the overall cardio metabolic burden.

2. Assessment of CV risk

Tools available for CV risk stratification include multivariate risk models such as the Framingham risk score which provides a 10-year coronary heart disease (CHD) risk based on age, HDL-C, total cholesterol, smoking status and hypertension [3]. The sex-specific Framingham CHD prediction performs well among whites and blacks and can also be applied to other ethnic groups [4]. In 2008, a sex-specific multivariable risk factor algorithm derived from 4522 women between 30–74 years of age was published and can be used to assess general CVD risk and risk of individual CVD events including coronary, cerebrovascular, peripheral arterial disease and heart failure. The estimated absolute CVD event rates can be used to quantify risk and to guide preventive care. The presence of PCOS identifies a high-risk group that may benefit from early CV risk assessment and timely interventions. Currently, the National Cholesterol Education Panel (NCEP) on detection, evaluation and treatment of high blood cholesterol (Adult Treatment Panel, ATP III) recommends assessing risk in subjects with two or more traditional CV risk factors [5]. However, it is very likely that these recommendations may change to include subjects with one or more risk factors in future guidelines such as ATP IV. Moreover, in reproductive age women with PCOS the risk is usually low as there are negative or zero points for age less than forty. Also assessments that stratify patients according to the number of defined risk factors can identify high-risk women, but they may falsely reassure those with a low risk score who have multiple borderline abnormalities. For example, based on the Framingham risk score women with less than 10% likelihood of CHD are considered at low risk. However, this approach does not consider lifetime risk, which might be substantially higher especially in PCOS and amenable to aggressive risk factor reduction. The Androgen Excess (AE)-PCOS society has published guidelines for assessment of CVD risk in women with PCOS [1]. Based on the presence of established risk factors for CVD but not including age, women with PCOS can be stratified as being at risk or at high risk for CVD.

3. Traditional cardiovascular disease risk factors in PCOS

Although we do not have validated tools to assess life-time risk, the increased prevalence of many cardio-metabolic risk factors in

Abbreviations: CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; AE-PCOS, Androgen Excess PCOS.

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young women with PCOS has been well documented. Obesity prevalence is known to differ according to age, ethnicity and geographic regions in the general population. A meta-analysis ($n = 35$ studies, 15,129 women) showed that women with PCOS had increased prevalence of overweight [RR (95% CI): 1.95 (1.52, 2.50)], obesity [2.77 (1.88, 4.10)] and central obesity [1.73 (1.31, 2.30)] compared with women without PCOS. The increased risk of being overweight and obese for women with PCOS was independent of PCOS diagnostic criteria, age and geographic region. The Caucasian women with PCOS had a greater increase in obesity prevalence than the Asian women with PCOS compared with women without PCOS [10.79 (5.36, 21.70) versus 2.31 (1.33, 4.00), $p < 0.001$) [6]. In another meta-analysis by the same authors, obesity significantly worsened all metabolic outcomes when compared to normal weight women with PCOS [7]. Given the high prevalence of overweight and obesity in PCOS it is imperative to determine if the increased prevalence of associated CV risk factors are due to the underlying obesity or independent of obesity.

Increased risk of impaired glucose tolerance (IGT) and type 2 DM has been reported in women with PCOS from all over the world. A meta-analysis of 11 studies including 835 women with PCOS and 568 controls, showed an increased prevalence of IGT (OR 2.48, 95% CI 1.62–3.77) using either the World Health Organization (WHO) or American Diabetes Association (ADA) definitions for IGT. In a sub-group analysis of BMI-matched studies, the OR was 2.54 (95% CI 1.54–4.47) and in another sub-group analysis of studies with only lean subjects (BMI < 25 kg/m^2), the OR was 3.22 (95% CI 1.26–8.24) [8]. The same authors performed a meta-analysis of 12 studies reporting that women with PCOS ($n = 12{,}102$) compared to controls ($n = 56{,}959$) had an increased prevalence for type 2 diabetes (DM), with an OR of 4.43 (95% CI 4.06–4.82). Again BMI matched studies ($n = 6$) showed an increased prevalence in PCOS, OR 4.0 (95% CI 1.97–8.1). Collectively, these studies demonstrated that PCOS is associated with a significantly higher prevalence of IGT and DM independent of BMI.

Increased risk of dyslipidemia including elevated LDL-C, elevated triglycerides (TG) and low HDL-C has also been shown in PCOS. In a meta-analysis by Wild et al., TG levels were significantly lower in control women (−26.39 95% CI −35.5, −17.2), HDL-C levels were significantly higher in control women (6.41 95% CI 3.68, 9.14) and LDL-C levels were significantly lower (−12.6 95% CI −15.6, −9.51) compared to women with PCOS [9]. Two large studies in different ethnic populations have recently shown higher ApoB/ApoA1 ratios in women with PCOS [10,11]. In the INTERHEART study, the top quintile of ApoB/ApoA1 significantly related to the risk of acute myocardial infarction [2]. These findings support the AE-PCOS and American College of Obstetrics and Gynecology (ACOG) guidelines to screen all women with PCOS with a complete lipid panel [1,12]. Routine apolipoprotein measurements are not routinely recommended and may be premature in clinical practice.

The co-occurrence of metabolic risk factors for both type 2 DM and CVD (abdominal obesity, hyperglycemia, dyslipidemia, and hypertension) suggests the existence of a ''metabolic syndrome''. In a meta-analysis including 2256 PCOS women and 4130 controls, the prevalence of metabolic syndrome using different definitions was 2.88 (95% CI 2.4–2.45) and in a BMI-matched population the OR was 2.2 (95% CI 1.36–3.56). Identification of women with PCOS and metabolic syndrome identifies a high-risk group that will benefit from aggressive life style intervention.

Family history is an independent risk factor for CHD, particularly among younger individuals with a family history of premature heart disease [2]. An increased risk of MI and stroke in fathers of women with PCOS has been demonstrated [13]. In this study, 11.3% of fathers of women with PCOS had a history of MI compared to 5.3% of fathers of subjects from the NHANES registry ($p < 0.01$). Also, 3% of fathers of women with PCOS had a history of stroke compared to 1% of fathers from the NHANES registry ($p < 0.002$). Moreover, fathers of women with PCOS had an elevated 10-year risk for CHD (11.5 versus 9.9% in NHANES, $p = 0.03$).

Both ACOG and the AE-PCOS society provide recommendations for screening women with PCOS for cardio metabolic risk factors [1,12].

4. What is the evidence for subclinical atherosclerosis in PCOS?

In asymptomatic women with PCOS the presence of subclinical atherosclerosis has been determined using a number of modalities such as endothelial function, carotid intima media thickness (CIMT) and coronary artery calcium (CAC) scores. The presence of endothelial dysfunction indicates early evidence of atherosclerosis and can be measured in a laboratory setting as a research tool. The endothelium modulates platelet adhesion, macrophage migration and lipid transport [14]. Insulin has a potent vasodilatory effect on the endothelium secondary to the release of endothelium-derived nitric oxide (NO). Endothelial function can be measured by examining flow mediated dilatation (FMD) of arteries and is modified by a variety of factors including smoking, hypercholesterolemia, hypertension and poorly controlled type I and II diabetes. In subjects from the multi-ethnic study of atherosclerosis (MESA) with no CVD, baseline abnormal brachial artery FMD was significantly predictive of cardiovascular events at 5 years [15]. In a recent meta-analysis ($n = 21$ studies) with 908 PCOS subjects and 281 controls, the pooled brachial artery FMD was found to be 3.4% lower (CI 95% 1.9–3.9) in women with PCOS compared to controls. After controlling for age, BMI and smoking, the pooled FMD remained low in women with PCOS, 4.1% (CI 95% 2.7–5.5).

Another method of evaluating subclinical atherosclerosis is measurement of CIMT. In adult population studies, there was a moderate, graded positive relationship between CIMT and the presence of coronary atherosclerosis [16]. Increased CIMT also correlated with a graded increase in the risk of future cardiovascular events, but the magnitude of the relationship lessened when traditional risk factors were taken into account. The age- and sex-adjusted overall estimate of the RR of MI was 1.15 (95% CI, 1.12–1.17) per 0.10-mm CIMT difference [17]. The age- and sex-adjusted RR of stroke was 1.18 (95% CI, 1.16–1.21) per 0.10-mm CIMT difference. In a meta-analysis of studies examining CIMT, ($n = 19$ studies, 1123 women with PCOS and 923 controls) mean difference in CIMT in women with PCOS and controls was 0.072 mm (95% CI 0.04, 0.105, $p < 0.001$) for highest quality studies [18].

Both electron beam and multislice computed tomography (CT) are used to noninvasively measure CAC as a marker of total coronary atherosclerosis burden [19]. This marker can be used to assess the risk of having a MI or sudden cardiac death [20], and has been shown to independently predict all-cause mortality [21]. Compared to assessment of endothelial function and CIMT, fewer studies have measured CAC in the asymptomatic PCOS population (Table 1). Shroff et al. studied a young, obese premenopausal population, with a mean age of 32 ± 6.5 years, and BMI of 36 ± 5.4 kg/m^2 in the PCOS group. The prevalence of CAC in the PCOS group was 33% compared to 8% in the control group. After matching for age, BMI and other CV risk factors, the risk of any CAC was higher in the PCOS group compared to controls OR 5.5 (95% CI 1.03, 29.45) [22]. In the two largest studies, there is conflicting evidence regarding the prevalence of CAC in PCOS. Talbott et al., found a significant increase in the prevalence of CAC in PCOS women compared to controls (63.1% versus 41%) while Chang et al. found no difference (5% versus 6.3%) [25,26]. The cohort in the Talbott study had a higher mean age (48 years) compared to the Chang et al. study (41 years). The higher prevalence of CAC in the Talbott study