Polycystic Ovary Syndrome

Novel Insights into Causes and Therapy.

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Cardiovascular Risk and Subclinical Cardiovascular Disease in Polycystic Ovary Syndrome

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Abstract

In addition to its effects on reproductive health, it is now well recognized that polycystic ovary syndrome (PCOS) is a metabolic disorder, characterized by decreased insulin sensitivity which leads to an excess lifetime risk of type 2 diabetes and cardiovascular disease. PCOS patients are often obese, hypertensive, dyslipidemic and insulin resistant; they have obstructive sleep apnea and have been reported to have higher aldosterone levels in comparison to normal healthy controls. These are all components of an adverse cardiovascular risk profile. Many studies exploring subclinical atherosclerosis using different methods (flow-mediated dilatation, intima media thickness, arterial stiffness, coronary artery calcification) as well as assessing circulating cardiovascular risk markers, point toward an increased cardiovascular risk and early atherogenesis in PCOS. The risk and early features of subclinical atherosclerosis can be reversed by non-medical (normalization of weight, healthy lifestyle) and medical (metformin, thiazolidinediones, spironolactone, and statins) interventions. However, the long-term risk for cardiovascular morbidity and mortality as well as the clinical significance of different interventions still need to be properly addressed in a large prospective study.

Besides the clinical features of oligomenorrhea, hirsutism and infertility, polycystic ovary syndrome (PCOS) patients are often insulin resistant (IR), obese, they have arterial hypertension, dyslipidemia, an increased prothrombotic state, impaired glucose tolerance (IGT) or frank type 2 diabetes (T2D). High prevalence of cardiovascular risk factors in PCOS is assumed to be associated with accelerated cardiovascular disease (CVD). Since PCOS is highly prevalent in female population of the reproductive age accounting for 7–10% when applying National Institutes of Health 1990 criteria or even 15–20% by Rotterdam 2003 criteria, it represents a potential health

The first two authors should be regarded as joint first authors.
economic burden. However, clear data from large end point trials to answer the question about cardiovascular morbidity and mortality in PCOS are currently lacking. Of note, there are plenty of data on early occurrence of subclinical, potentially reversible atherosclerosis in women with PCOS, and many controlled clinical trials did show its amelioration with treatment and/or lifestyle changes.

**Epidemiology of Cardiovascular Disease in PCOS**

In one of the first studies addressing CVD, the association between polycystic ovaries (diagnosed by ultrasound only) and extent of coronary artery disease in 143 women having cardiac catheterization for assessment of chest pain or valvular disease was explored [1]. Polycystic ovaries were found in 42% of women, and those women had more extensive coronary artery disease than women with normal ovaries. The Nurses’ Health Study included 82,439 female nurses who provided information in 1982 (at ages 20–35 years) on prior menstrual regularity and were followed through 1996 for cardiovascular events [2]. Incident reports of nonfatal myocardial infarction, fatal coronary heart disease (CHD), and nonfatal and fatal stroke were made. Compared with women reporting a history of very regular menstrual cycles, women reporting usually irregular or very irregular cycles (as a surrogate marker for PCOS) had an increased risk for nonfatal or fatal CHD.

Women’s Ischemia Syndrome Evaluation study evaluated the risk of cardiovascular events in 390 postmenopausal women [3]. Hundred and four among them had clinical features of PCOS defined by a premenopausal history of irregular menses and current biochemical evidence of hyperandrogenemia. Women with clinical features of PCOS were more often diabetic, obese, with the metabolic syndrome and had more angiographic signs of coronary artery disease compared to women without clinical features of PCOS. Cumulative 5-year cardiovascular event-free survival was lower for women with clinical features of PCOS than for women without PCOS.

Three additional studies gave further support to the association between PCOS and CVD. The Rancho Bernardo cross-sectional study of 713 postmenopausal women (mean age, 73.8 years) showed that non-diabetic women with clinical and biochemical features of PCOS had significantly higher prevalence of CVD compared to women without that phenotype (RR 1.36, CI 1.05–1.76) [4]. A case-control study of 414 postmenopausal women (mean age, 60.4 years) reported an increased odds ratio for coronary vascular disease in women with premenopausal menstrual irregularity (as a putative sign of PCOS) [5]. In another study, increased waist/hip ratio and hirsutism were associated with confirmed coronary artery disease in women aged 60 years or older who underwent coronary angiography.

On the other hand, some studies have reported no association between the presence of PCOS and cardiovascular events. One of the population studies in the UK on 786 PCOS patients followed up for 30 years showed no increase in cardiovascular deaths.
compared to the national rate. A subsequent study by the same group found no difference in CHD morbidity and mortality between PCOS patients and age-matched controls [6]. Similarly, there was no difference in cardiac complaints between 346 PCOS patients and 8,950 controls, although the mean age of this cohort was only 39 years [7].

Even the most recent data are still contradictory. A large study (456,298.5 person-years of follow-up) reported an association between menstrual irregularity and increased age-adjusted risk for cardiovascular mortality [8]. However, this association was not statistically significant after adjustment for body mass index (BMI). These data are in conflict with another recent meta-analysis that showed a 2-fold risk for arterial disease in patients with PCOS as compared to women without PCOS [9]. BMI adjustment did not affect this finding.

The present epidemiological data suggest more frequent CVD in classical PCOS (as diagnosed by NIH criteria), mostly mediated through increased total and abdominal adiposity, and perhaps interacting with PCOS-related hyperandrogenism. In fact, both extremes of androgen levels in postmenopausal women, in either direction, are associated with increased risk of CVD. Several studies have indicated that low levels of testosterone are associated with more carotid atherosclerosis compared to higher, but normal levels of testosterone [10]. On the other hand, in the Multi-Ethnic Study of Atherosclerosis, 1,947 women were evaluated for subclinical atherosclerosis according to their circulating androgens. Testosterone levels correlated positively with carotid intima media thickness, independently of BMI and IR [11]. In the analysis of the Rancho Bernardo population, women in the highest quintile of circulating testosterone had an increased incidence of CVD over 20 years of follow-up (RR 1.96, CI 1.13–3.41) compared to women in the middle quintile, independent of age, BMI, smoking and central adiposity [4]. However, according to several other trials, the contribution of coexisting risk factors to CVD in women with higher androgen levels should always be taken into account.

In conclusion, women with PCOS often have an adverse cardiovascular risk profile. However, data on long-term risk for cardiovascular morbidity and mortality are inconsistent, and this issue has not been properly addressed by a large prospective study yet.

Cardiovascular Risk Factors in PCOS

Data on CVD and cardiovascular mortality in women with PCOS are thus insufficient. This paucity of data is, in part, due to the fact that most studies in this population are conducted at a time when women are young, before an age when CVD would be expected to develop. Due to the lack of outcome studies, a wealth of traditional as well as less traditional surrogate risk markers is very important and points toward an increased cardiovascular risk in women with PCOS.

It has long been established that obesity, particularly of visceral origin, plays a crucial role in both the development and maintenance of PCOS, and significantly influences
the severity of cardiovascular risk profile. In most large series, at least 30% of women with PCOS are obese, and in some series, up to 75% are obese. About 50–60% of women with PCOS have central body fat distribution whereby a disproportionate quantity of adipose tissue is distributed in the visceral depot. Visceral fat is the main source of free fatty acids and inflammatory cytokines causing IR and consequent CVD. Furthermore, mean arterial blood pressure and the risk of preeclampsia are higher in women with PCOS. Lipid abnormalities are encountered in up to 70% of PCOS patients.

Beyond the traditional CVD risk factors, more recently identified risk markers are also more prevalent in women with PCOS. In a recent meta-analysis looking into the relationship between PCOS and CVD, various risk markers were analyzed [12]. Women with PCOS had significantly elevated high-sensitivity C-reactive protein (hsCRP), homocysteine, plasminogen activator inhibitor-1 and its activity, vascular endothelial growth factor, asymmetric dimethylarginine, advanced glycation end products (AGEs), and lipoprotein(a) concentrations compared with controls, yet with significant between-study heterogeneity [12].

AGEs have been shown to be increased in PCOS women, independent of obesity and insulin resistance. In postmenopausal women, higher levels of AGEs were positively associated with higher androgen levels suggesting a potential pathophysiological mechanism contributing to higher prevalence of cardiovascular events in postmenopausal women with higher androgen levels. Endothelin-1, a marker of abnormal vascular reactivity, was also increased in women with PCOS compared with the age-matched controls, independently of the presence of obesity. A positive correlation of endothelin-1 with free testosterone levels and a negative correlation with insulin sensitivity were also observed.

Insulin Resistance in PCOS

IR is highly prevalent, occurring in 60–80% of women with PCOS and in 95% of obese women with PCOS. It is most prevalent and severe in classic PCOS phenotype with hyperandrogenism and chronic anovulation. IR is intrinsic to the disorder and additive with that of obesity. PCOS and obesity act synergistically to impair insulin sensitivity. In vivo insulin action is profoundly decreased in skeletal muscle secondary to signaling defects, but hepatic IR is present only in obese women with PCOS. There is a defect in insulin postreceptor signaling, namely increased serin/threonin phosphorylation of insulin receptor substrates (IRSs) instead of tyrosine phosphorylation, and consequent proteosomic degradation of IRSs.

IR plays a central pathogenetic role in the development of metabolic derangements of the syndrome like IGT, T2D, atherogenic dyslipidemia, chronic inflammation and others. IGT and T2D are highly prevalent among PCOS adolescents, and up to 40% of women with classic PCOS develop IGT or T2D by the fourth decade of life, with age and weight gain worsening the glycemic control [13].
In the arterial wall, IR is associated with reduced synthesis and release of nitric oxide (NO), enhanced inactivation of NO after its release from endothelial cells and enhanced synthesis of vasoconstricting agents. Increased vascular stiffness and impaired vasodilatory action of insulin ex vivo was demonstrated in patients with PCOS suggesting an abnormal insulin-regulated endothelial NO production in the vasculature [14]. In addition, it has been demonstrated that hyperinsulinemia exerts a direct hypertrophic effect on the vascular endothelium and the smooth muscle cells. In the arteries of skeletal muscles, insulin can stimulate both endothelin-1 and NO production, and an imbalance between the release of these two substances may be involved in the pathophysiology of endothelial dysfunction. More accurately, phosphatidylinositol 3 kinase (PI3 kinase)-dependent insulin-signaling pathway which stimulates NO production in the endothelium shares striking similarities with the metabolic pathway in the skeletal muscle that promotes glucose uptake. Other distinct nonmetabolic pathway of insulin-signaling (mitogen-activated protein kinase, MAP kinase, pathway) stimulates secretion of the vasoconstrictor endothelin-1 in the endothelium. IR is characterized by pathway-specific impairment in PI3 kinase-dependent signaling, leaving MAP kinase pathway unaffected, which in endothelium may cause imbalance between production of NO and secretion of endothelin-1. Increased endothelin-1 levels have already been demonstrated in PCOS population [15].

It has also been suggested that inflammatory markers such as hsCRP directly promote the atherosclerotic processes and endothelial cell inflammation leading to atherothrombosis. Furthermore, IR is linked to the endothelial dysfunction also by other mechanisms, such as increased oxidative stress, increased activity of the renin-angiotensin system and the action of hormones and cytokines secreted by the adipose tissue.

**Arterial Hypertension**

Hypertension is a significant contributor to the risk of CVD. Although hypertension has been an inconsistent finding, several studies suggest its increased prevalence in women with PCOS compared with the general population. The prevalence of hypertension in PCOS ranges from 10 to 40% [16]. In addition, there are some data to suggest that the nocturnal decrease in blood pressure characteristic of healthy vasculature is absent in adolescent and adult women with PCOS and that pregnant women with PCOS have a greater risk of pregnancy-induced hypertension and preeclampsia than pregnant women without PCOS. Obesity may have a major influence on blood pressure in PCOS. In the studies that did adjust the analyses for BMI, the association between hypertension and PCOS was not always clear. However, there are several other mechanisms potentially involved in the pathogenesis of hypertension in PCOS. Increased blood pressure may be secondary to enhanced sodium retention occurring in the setting of IR. Hyperandrogenemia has been associated with hypertension in...
PCOS independent of obesity and hyperinsulinemia. Greater sympathetic activity has also been implicated in the etiology of hypertension in this population.

Given the association of hypertension with all of the common PCOS manifestations, treating the manifestations of PCOS may treat concomitant hypertension or the risk for hypertension as well. Lifestyle modifications and other methods of weight loss were shown to improve hypertension. The response to oral contraceptives has been inconsistent. There are data to suggest that the effect of spironolactone is beneficial [17]. Antihypertensives are indicated for blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic. Reducing blood pressure to 120/80 mm Hg is optimal for long-term CVD prevention. Some authors favor angiotensin-converting enzyme inhibitors and angiotensin receptor blockers over diuretics and beta-blockers. It would be prudent to avoid using agents that impair insulin sensitivity (atenolol, metoprolol). All above-mentioned antihypertensives are contraindicated in pregnancy and require contraception.

The Androgen Excess and Polycystic Ovarian Disease Society recommends a screening blood pressure measurement in women with PCOS at every visit and that prehypertension and hypertension are detected and treated, given the potential benefit of lowering blood pressure for the prevention of CVD [13].

**Dyslipidemia**

PCOS is frequently, but not always, associated with dyslipidemia. Dyslipidemia in PCOS can present with different patterns: lower levels of high-density lipoprotein cholesterol (HDL cholesterol) and higher levels of triglycerides, total and low-density lipoprotein cholesterol (LDL cholesterol) [18]. Different types of dyslipidemia are probably the net result of interfering influences of hyperandrogenism, IR and additional environmental influences (diet, exercise) and genetics. Obese PCOS patients most frequently have the so-called atherogenic type of dyslipidemia with low HDL cholesterol, small dense LDL particles and elevated triglyceride levels, which is typical for states with IR. Because the pathophysiologic processes of obesity and IR overlap, this form of dyslipidemia most often presents in obese PCOS patients (which represent 70% of the PCOS population in the USA). However, in countries with lower average BMI, this association is less frequent [18]. A form of dyslipidemia with high LDL cholesterol was reported in PCOS, but is less frequent, less obesity correlated and more hyperandrogenism correlated [19; see the chapter on dyslipidemia and oxidative stress by Macut et al., pp. 51–63].

**The Renin-Angiotensin-Aldosterone System in PCOS**

Many experimental and clinical data show that aldosterone is an important risk factor for CVD [20]. Aldosterone accelerates fibrosis in the myocardium and blood vessels,
negatively affects the compliance of arteries, remodeling of the heart muscle and causes perivascular inflammation. The main etiopathogenetic event behind these cardiovascular changes could be an immunostimulatory state, characterized by oxidative stress, inflammation and profibrogenic genotype. Data on association of aldosterone with IGT, T2D and metabolic syndrome are also accumulating. Even values of aldosterone in the upper normal range are associated with arterial hypertension, although the deleterious effects of aldosterone on cardiovascular system are independent of its effects on blood pressure.

One of the first papers studying the renin-angiotensin-aldosterone system in PCOS reported higher levels of renin in PCOS patients compared to the control group, which was explained by greater activity of intrinsic renin-angiotensin-aldosterone system in ovaria. Other studies also reported higher levels of angiotensin II, although not all the data are consistent.

In a later report that included 50 PCOS patients and 50 healthy controls, plasma concentration of aldosterone in association with cardiovascular risk factors was studied [21]. Aldosterone but not renin levels were significantly increased in the PCOS group. In PCOS, a significant direct correlation between plasma aldosterone and fasting insulin concentration, homeostasis model assessment index of IR (HOMAIR), hsCRP, intima media thickness (IMT), and mean blood pressure was found. This was later confirmed by other studies.

Regarding the renin-angiotensin-aldosterone system, the question of medical intervention arises. Namely, low-dose spironolactone (an antimineralocorticoid and antiandrogenic drug) treatment without any relevant hemodynamic effect significantly improved survival and endothelial function in patients with chronic heart failure. This finding revolutionized the treatment of heart failure several years ago. Since spironolactone is routinely used for treating hyperandrogenism in PCOS patients, it could have additional beneficial effect in lowering cardiovascular risk. Our group was the first to report that it improved endothelial dysfunction in non-obese, non-insulin-resistant PCOS patients [22]. However, it was also shown that spironolactone worsened endothelial function in type 2 diabetic patients, probably due to worsening of glycemic control and an increase in angiotensin II [23]. Since many of the PCOS patients have IGT or T2D, they most probably represent a subgroup in which the beneficial effect of spironolactone is less likely. Before firmer instructions on therapy can be stated, further research in this area is needed.

**Obstructive Sleep Apnea in PCOS Women**

Adult (but not adolescent) PCOS patients were reported to have at least 5-fold higher risk for obstructive sleep apnea (OSA) as similarly obese women without PCOS. OSA is an independent risk factor for CVD. It is associated with activated pathways that lead to IR, hypertension and increased levels of a