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Polycystic Ovary Syndrome and Cardiovascular Disease: An Enigmatic Relationship

Roshan Dadachanji and Srabani Mukherjee*

Department of Molecular Endocrinology, National Institute for Research in Reproductive Health (ICMR), India

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***Corresponding author:** Srabani Mukherjee, Department of Molecular Endocrinology, National Institute for Research in Reproductive Health (ICMR), India, Tel: +91-22-24192009; Email: mukherjees@nirrh.res.in

Abstract

Polycystic Ovary Syndrome (PCOS) is a common endocrinopathy which affects women in reproductive age and is prominently associated with anovulatory infertility. This syndrome is a complex, heterogenous condition with classic manifestations being menstrual irregularities, hirsutism, acne, obesity, insulin resistance, raised LH: FSH ratio and the presence of bulky polycystic ovaries on ultrasound imaging. These women are more susceptible to developing both metabolic and gynecological anomalies including glucose intolerance, dyslipidemias, hypertension, type 2 diabetes Mellitus, and cardiovascular disorders along with endometrial and ovarian cancer. The metabolic milieu in combination with their obesity status and hormonal makeup increases the susceptibility of women with PCOS to critical cardiovascular events in future years. The disparities in CVD outcomes documented may be attributed to the differences in incidence of surrogate markers of cardiovascular disease in women with PCOS showing ethnic and phenotypic variability. The onset of cardiometabolic derangements may manifest in adolescence itself and early diagnosis and monitoring of markers of cardiovascular disease should be emphasized early on to prevent severe long term consequences.

Keywords: PCOS; CVD; Adolescent; Dyslipidemia

Abbrevations: Apo A-1: Apolipoprotein A-1; ApoB: Apolipoprotein B; BMI: Body Mass Index; CAC: Coronary Artery Calcium; CAD: Coronary Artery Disease; CHD: Coronary Heart Disease; CIMT: Carotid Intima-Media Thickness; CVD: Cardiovascular Disease; FMD: Flow-Mediated Dilation; FSH: Follicle Stimulating Hormone; GWAS: Genome-Wide Association Studies; HDL: High Density Lipoprotein; hsCRP: Highly Sensitive C-Reactive Protein; LDL: Low Density Lipoprotein; LH: Luteinizing Hormone; PCO: Polycystic Ovary; PCOS: Polycystic Ovary Syndrome; sdLDL: Small Dense Low Density Lipoprotein; VCAM-1: Vascular Cell Adhesion Protein 1

Introduction

Polycystic ovary syndrome (PCOS) is a multifactorial multigenic endocrinopathy with a complex pathophysiology. It is primarily considered a disorder associating androgen excess and insulin resistance to unfavorable reproductive and metabolic ramifications. PCOS is a heterogeneous condition characterized by oligo/amenorrhea, anovulatory infertility, hyperandrogenism of ovarian and adrenal origin, and bulky polycystic ovaries typified by multiple cystic follicles arrested at the pre-antral stage [1-3]. Other hallmark features include hyperinsulinemia, aberrant LH: FSH ratios, increased circulating androgen levels, obesity, and abdominal adiposity [1]. The pathophysiology of PCOS is not yet fully understood, but it may reflect an interaction between multiple predisposing genes and environmental factors in the manifestation of this disorder [4]. The undisputed wealth of information that has been gleaned from linkage based, candidate gene as well as genome-wide association studies (GWAS) has provided researchers with several markers which validate previously proposed theories of PCOS pathogenesis. Furthermore, revelation of hitherto unknown genetic loci has uncovered many new biological pathways to explore for their contribution to PCOS pathophysiology [5]. However, no etiologic factor alone can adequately elucidate the spectrum of abnormalities observed in PCOS. It has been hypothesized that the vicious cycle of insulin resistance and hyperandrogenemia is intrinsic to this syndrome, and may be a major player linking PCOS with potent risk factors such as dyslipidemia, hypertension and anatomical derangements which ultimately could signal onset of more serious metabolic disorders including type II diabetes, metabolic syndrome and cardiovascular disease (CVD) [1,6]. The frequency of metabolic syndrome, a known precursor to CVD, was found to be significantly increased in Australian women with PCOS, particularly in the obese group [7]. Nearly 42% of women diagnosed with coronary artery disease (CAD) presented with polycystic ovaries (PCOs) sonographically. Additionally, extent of CAD as well as positive family history was significant predictors of PCOs [8]. Conversely, another study reported that

merely presence of PCO was not a significant predictor of future CVD risk [9].

The risk for CVD development in PCOS has been widely acknowledged due to elevated prevalence of biochemical and morphological risk factors in affected women [10,11]. This risk is also found to be dependent on geographical, racial and ethnic differences [12-14]. In addition, PCOS sub-phenotypes, classified according to Rotterdam criteria, show varying degrees of insulin resistance and lipid abnormalities [15,16]. More adverse metabolic profiles are frequently recognized in women with classic PCOS presenting with hyperandrogenemia [16-21]. A recent meta-analysis conducted in women with PCOS after stratifying them according to types of CVD revealed that PCOS was significantly associated with increased of CHD [22].

Women with PCOS exhibit an array of potential biochemical and anatomical cardiovascular disease risk factors. Carotid intima-media thickness (CIMT), a non-invasive measure of the thickness of the intima media of carotid arteries, frequently used to detect subclinical atherosclerosis has been found to be elevated in women with PCOS [23]. On the other hand, ultrasonographic measure of the flow mediated dilation of brachial artery (FMD),a surrogate marker for endothelial dysfunction was reported to be reduced [24] in women with PCOS. Coronary artery calcification (CAC) scores, due to deposition of calcium which may impair vascular functioning, were found to be increased in women with PCOS presented with both oligomenorrhea and hyperandrogenism, contributing to increased risk of subclinical CVD [25]. A meta-analysis of serum levels of known CVD risk factors such as C- reactive protein (CRP), homocysteine, tumor necrosis factor-a, plasminogen activator inhibitor-1 (PAI-1), fibrinogen, interleukin-6, vascular endothelial growth factor, asymmetric dimethylarginine, endothelin-1, advanced glycationend-products, lipoprotein (a), in women with PCOS has revealed that although their concentrations are increased in women with PCOS compared to controls, their translational outcome is still under debate [26].

Women with PCOS commonly display proatherogenic lipid profiles and hypertension [27] and are frequently characterized by decreased high density lipoprotein (HDL) and apolipoprotein A-1 (ApoA-1) levels, with increased triglycerides, low density lipoprotein (LDL) and oxidized LDL levels [28,29]. Young women with PCOS are commonly reported to be afflicted with dyslipidemia, regardless of BMI [30-32]. Previously published data from our group has supported presence of dyslipidemia in women with PCOS as evidenced by raised serum levels of LDL and triglycerides coupled with diminished Apo-A1 and HDL levels [33]. Interestingly, when we classified our study population into lean and obese groups, only lean women continued to demonstrate low HDL and Apo-A1 levels with increased ApoB: sApoA-1 ratio compared to lean control women; however no significant difference in lipid variables were observed in the obese group [34]. Our lab has also investigated serum levels of oxidized LDL as well as activity of paraoxonase 1 (PON1), which have emerged as important non-traditional CVD risk factors. Oxidized LDL elicits the initiation and progression of endothelial dysfunction and subsequently cardiovascular disease [35]. What's more, we report significantly increased serum oxidized LDL levels in Indian PCOS women [34], similar to previous results [36]. The PON1 enzyme is an HDL-associated antioxidant enzyme has gained much attention due to its prohibitive effect on the oxidative modification of LDL cholesterol and subsequent impedance to the progress of cardiovascular disease. It decreases accumulation of lipid peroxides in LDL and atherosclerotic lesions, foam cell formation, while facilitating macrophage cholesterol efflux, and breakdown of oxidized phospholipids and homocysteine thiolactone [37]. Increased oxidative stress coupled with decreased PON1 activity contributes to pathogenesis of the metabolic syndrome in obese adolescents [38]. Reduced PON1 activity has been reported in Turkish [39,40], Saudi Arabian [41] and Egyptian [42] women with PCOS compared to controls. Our research has shown that PON1 activity is diminished in both lean and obese Indian women with PCOS compared to BMI-matched controls [34].

Hyperandrogenemia characterized by augmented total [43] and free [44] testosterone, were found to be closely linked to markers of sub-clinical CVD, thereby aggravating cardiometabolic repercussions. Obesity, impaired glucose tolerance and cigarette smoking have also been reported to exacerbate CVD risk [45] in affected women. Evidence from a principal components analysis study highlighted that risk factors may be clustered into three main groups relating to insulin resistance, dyslipidemia and hyperandrogenemia, which in turn, may contribute to the variability in CVD risk in women representing different PCOS phenotypes [46].

A few groups have focused on evaluating the putative risk of development of CVD in women with PCOS in their later years. However, the findings across various studies have yielded contradictory results. Very early retrospective studies conducted in Swedish women with PCOS have shown later age of menopause onset, with increased prevalence of diabetes and hypertension [47]. Swedish women with PCOS present with 7.4 fold increased risk of developing myocardial infarction compared to controls [48]. Women with PCOS who had undergone ovarian wedge resection were found to have significantly increased risk for non-insulin dependent diabetes mellitus and coronary artery disease compared to control women between the ages of 45-59 years [49]. A large scale prospective cohort study over 14 years revealed that women reporting menstrual cycle irregularity had nearly 50% increased risk for coronary heart disease including nonfatal myocardial infarction or fatal CHD, in contrast to healthy women with regular cycles; however only a non-significant upward trend in stroke and ischemic stroke risk was noted [50]. Non-diabetic menopausal women showed increasing risk of CVD concomitant with increased reporting in number of typical PCOS traits, including oligomenorrhea, premenopausal clinical or biochemical hyperandrogenism, infertility, central obesity and

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insulin resistance [51]. Interestingly, a recent meta-analysis has stated that women with PCOS presented with nearly 2-fold risk of cardiovascular events, irrespective of BMI adjustment [52]. This suggests that both lean and obese women with PCOS are predisposed to cardiovascular disease, and suitable lifestyle and therapeutic management strategies need to be employed. Past hospitalization records have revealed a greater likelihood of PCOS women being admitted for hypertension related anomalies, ischemic heart disease, cerebrovascular disease and arterial and venous diseases [53]. Collectively, these findings indicate that women with PCOS show increased propensity to cardiovascular maladies in later life.

On the other hand, early studies have concluded that women with PCOS in the United Kingdom do not have increased tendency to development of CVD despite presence of markedly higher cardiovascular risk factors [54,55] or non-fatal cerebrovascular disease [55] associated with the syndrome. Telephonic interviews with lean Dutch women with PCOS revealed significantly increased prevalence of hypertension and diabetes, but very low incidence of cardiac complaints compared to Dutch female population [56]. Follow-up of Norwegian PCOS women after ovarian wedge resection surgery showed that CVD risk remained unaffected, though the authors state that this was insufficiently powered [57]. Similarly, a recent follow-up study in Swedish post-menopausal PCOS women did not show any significant association of adverse cardiometabolic risk profiles with increased incidence of cardiovascular complications [58]. Another retrospective cohort study conducted in a group of Minnesota women collected information on cardiovascular events and its associated mortality as well as CVD risk factors. They found that women with PCOS were significantly overweight compared to controls but did not display markedly higher levels of CVD risk factors such as dyslipidemia, impaired glucose metabolism or hypertension, nor significantly higher rate of cardiac events, thus concluding that there is no considerable prevalence of CVD in PCOS [59]. Chang *et al*. [60] too failed to show any association of increased incidence of symptomatic CVD characterized by CAC and abdominal aortic plaque formation among a group of multiethnic participants with PCOS from the Dallas Heart Study compared to healthy control women [60]. Therefore, to date the studies which have attempted to evaluate the impact of PCOS on CVD outcomes are inconsistent and a definitive risk assessment with additional follow-up studies is warranted.

The prevalence of CVD risk factors have been found to increased right from early age of PCOS onset. A prospective study showed a positive relationship between patterns of menses delay in adolescent phase with adult onset of glucose dysmetabolism [61]. Measures of insulin resistance and inflammation including insulin levels, glucose: insulin ratio, homeostatic model assessment (HOMA) and PAI-1, were found to be significantly increased in adolescent girls with PCOS compared to controls [62]. Menstrual irregularity was also reported to be associated with hyperandrogenemia in Finnish adolescent girls and girls with higher free androgen index (FAI) showed dyslipidemia [63]. Therefore, early evaluation of glucose intolerance and lipid parameters is necessitated in adolescent and younger women with PCOS, with timely lifestyle intervention to impede progress to full-fledged cardiovascular events in later life [64]. Obesity was reported to further worsen insulin resistance [65,66] and dyslipidemia typically characterized by increased triglycerides and ApoB levels [67], in adolescent girls and may be a major precursor to metabolic and cardiovascular derangements [68]. Along similar lines, we have observed that obese Indian adolescent girls were more hirsute and presented with increased 2-hour glucose and insulin levels, low SHBG levels, along with elevated blood pressure [69]. Metabolically unhealthy obese Caucasian PCOS adolescents presented with atherogenic lipoprotein profiles and markedly reduced insulin sensitivity and beta cell function [70]. A closer look at lipoprotein sub types demonstrated increased LDL particle number attributed to increased sdLDL particles in serum of adolescents with PCOS [71]. Newer putative surrogate markers of subclinical atherosclerosis were investigated in PCOS adolescents. Augmented levels of vascular cell adhesion protein 1 (VCAM-1) reflecting endothelial dysfunction, and hsCRP, a known marker of inflammation [72], granzyme B [73], a cytotoxic molecule produced by activated atherogenic CD4+CD28null T cells, and antioxidant thiols [74] were observed. Conversely, no significant difference in serum copeptin, a C-terminal part of the precursor pre-provasopressin and pentraxin 3, an inflammatory mediator, levels [75] were noted. Additionally, anatomical markers of CVD including increased CIMT, beta stiffness with decreased arterial compliance [76] as well as increased pulse wave velocity [72] were shown in PCOS adolescents, indicating that the foundations of vascular abnormalities were laid early on. Hart *et al*. [77] concluded that the risk for metabolic syndrome was higher in Australian PCOS adolescent girls classified according to NIH compared to Rotterdam criteria, with significant positive correlation of testosterone levels with insulin resistance [77]. Hyperandrogenic Italian adolescents were found to be more predisposed to metabolic syndrome and subsequently to potential CVD in adulthood [78] and another study by the same group has shown that metformin beneficially modified adverse metabolic parameters [79]. A careful weight loss management routine followed over a year has been found to be associated with regularizing menses, alleviating total testosterone and insulin levels, improving SHBG levels and CIMT measures in adolescent PCOS girls [80]. Therefore suitable and personalized management at early stages will promote favorable long term outcomes.

Conclusion

While only a few studies have shown positive correlation of cardiovascular disease in women with PCOS in later life, the presence of aberrant biochemical and anatomical markers definitely calls for a thorough examination of the functional

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impact of these altered sub-clinical surrogate markers in order to confirm their role in onset of CVD in PCOS. As PCOS is a heterogenous disorder with phenotypic and ethnic variability, it would therefore also be advantageous to assess CVD risk in phenotypically diverse women with PCOS. More long-term studies detailing the occurrence of cardiovascular events in women with PCOS in adulthood, with concomitant evaluation of cardiovascular risk factors in early years would be advantageous in accurately elucidating the CVD risk in these women. These markers are inherent in PCOS women, regardless of age and obesity status, and cannot be ignored. What is particularly interesting to note is that several studies have strongly indicated that these markers take root in early age itself, thus it is imperative to evaluate their efficacy in formulation of diagnostic, prognostic and therapeutic strategies suited to this distinct PCOS adolescent population. This would be beneficial in mitigating the metabolic ramifications commonly encountered in adult life.

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