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Short Review

Polycystic Ovary Syndrome: Facts beyond Reproduction. A Short Review

Suleiman Ghunaim and Ghina Ghazeeri*

Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, American University of Beirut Medical Center

***Corresponding author**
Ghina Ghazeeri, Division of Reproductive Endocrinology and Infertility, USA, Tel: 009611350000; Ext: 5618; Email: gg02@aub.edu.lb

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Abstract

Polycystic Ovary Syndrome (PCOS) is a common reproductive/gynecologic medical entity which often leads to an ovulatory state that could potentially lead to infertility. It is defined by the presence of two of the three following criteria: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. The majority of women with this condition are obese and have a higher prevalence of impaired glucose tolerance as well as insulin resistance which supports the fact that PCOS has a major role in the development of diabetes. Moreover, PCOS patients are at a higher risk of adverse cardiovascular outcomes, including a higher incidence of future development of hypertension, and dyslipidemia, early onset endothelial dysfunction, arterial stiffness, and formation of plaques which might compromise the integrity of the coronary arteries and potentially increase the risk of cardiovascular disease. It is imperative that gynecologists have a good understanding of the long term implications PCOS carry upon diagnosis and thus be able to provide a more general and complete clinical picture about the disease and aid in proper patient counseling.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a common reproductive/gynecologic medical entity which often leads to an anovulatory state that could potentially lead to infertility. It is defined by the presence of two of the three following criteria: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries [1]. Although the exact underlying mechanism of PCOS remains unclear, it is presumed to be complex and multifactorial. The hormone imbalance created by a combination of hyperandrogenism and/or insulin resistance plays an important role in the pathophysiology of PCOS. It is believed that a combination of genetic and environmental factors which may result in hormone disturbances with other factors such as obesity, ovarian dysfunction, and hypothalamic pituitary abnormalities all contribute to the etiology of PCOS [2].

The prevalence of PCOS may be different according to ethnic background. It was reported that women of South Asia may present at a younger age and even have more severe symptoms [3]. The risk of diabetes was increased by 4.4 folds in women with PCOS residing in Asia estimated that the Middle Eastern prevalence of PCOS is around 16% of the reproductive age female population thus it is regarded to be one of the most common endocrine disorders in women of reproductive age in our region [4,5].

Hyperandrogenism manifested by hirsutism, acne, and menstrual disorders may also be characteristic. The majority of women with this condition are obese and have a higher prevalence of impaired glucose tolerance as well as insulin resistance reported in around 65–80% of women independent of their obesity [6]. The prevalence of impaired glucose tolerance in patients with PCOS ranges from 23% to 35%, and another 4% to 10% of these women may present with undiagnosed type 2 diabetes [7]. The prevalence of impaired glucose tolerance was noted in body mass index (BMI)–matched patients to be 2.1-folds higher, non–BMI-matched 4.8-folds higher, lean-matched 4.4-fold higher, and overweight or obese–matched groups 2.5-fold higher [8]. After controlling for BMI, PCOS patients had a greater than threefold increased odds (95% confidence interval (CI) 1.2–8.0) of developing diabetes compared with normal-weight control subjects, which supportsthe fact that PCOS has a major role in the development of diabetes beyond the boundaries of contribution of BMI alone [9]. A large longitudinal study from Taiwan showed a significantly higher prevalence of diabetes in 4,595 women with PCOS compared with age-matched control women (2.4% vs. 1.4%) [10].

Sleep disorders, predominantly sleep apnea, have been reported with higher prevalence in women with CI PCOS, this may add to the metabolic baseline risk these patients have [11].

Furthermore, patients with PCOS are at a higher risk of adverse cardiovascular outcomes, including a higher incidence of future development of hypertension, and dyslipidemia [12,13].

It is imperative that gynecologists have a good understanding of the long term implications PCOS carry upon diagnosis and thus be able to provide a more general and complete clinical picture about the disease and aid in proper patient counseling. It is also important that all providers are aware of these increased risks and follow the current guidelines that recommend what and when to screen women with PCOS [13].

METABOLIC AND CARDIOVASCULAR RISKS

In a recent case control study, and in women below the age of 40 years, the incidence rates of prediabetes were 29.7 and 25.9 per 1,000 person-years for PCOS and healthy women, respectively, and the incidence rates of diabetes were 12.9 and 4.9 per 1,000 person-years for PCOS patients and controls, respectively over a median follow up time of 12.9 years [14].

Regarded as a non-modifiable risk factor for type II diabetes the Royal College of Obstetricians and Gynecologists recommends a 75g 2-hr oral glucose for screening women with PCOS for impaired glucose tolerance, as this has been proven to be more superior to fasting blood glucose measurement alone which can lead to the under diagnosis of type 2 diabetes in women with PCOS [15-17]. Moreover, the 2013 Endocrine Society guidelines recommends the use of 2-hour oral glucose tolerance test (OGTT) with a 2-hour glucose measurement to screen for impaired glucose tolerance, defined as a blood glucose ≥140 mg/dL [18]. Subsequent screening can be performed at 1–3 year intervals based on the presence of other risk factors for diabetes [13].

There is a strong correlation between PCOS and increased cardiovascular disease with an increased lifetime risk of CVD morbidity [19]. In an Australian longitudinal study on women's health, women with PCOS (n = 183) had a higher prevalence of hypertension than 4,638 control women aged 28–33 years; 5.1% vs. 1.0%; *P*<.001. However, as part of the multivariable model including BMI and DM, there was only a "clinical" trend toward an association between PCOS and hypertension however with no statistical significance (OR 1.6, 95% CI 0.9–2.6; *P* =.09) [20]. After controlling for age, BMI, and ethnicity, women with PCOS above the age of 40 years had higher rates of hypertension than control women (29.2% vs. 18.8%; *P* =.03) which shows the persistence of the effect of PCOS on the cardiovascular system [21].

Dyslipidemia is common in young women with PCOS [22]. Historically, authors looked at the changes of triglycerides and HDL-Cholesterol in patients with PCOS as part of associated metabolic investigation [23]. yet, a large number of studies have found an increase of LDL-Cholesterol levels in women with PCOS. In a recent met analysis, triglyceride levels were 26 mg/dL (95% CI 17–35) higher and HDL-cholesterol concentrations 6 mg/dL (95% CI 4–9) lower in women with PCOS. The LDL-cholesterol concentration was higher in PCOS by 12 mg/dL (95% CI 10–16) [24]. In general, there are few studies reporting the persistence of dyslipidemia beyond the age of 40 years. Hudecova et al. reported a persistently higher triglyceride levels in women with PCOS compared to non PCOS patients (mean age 43 ± 5.8 y) even after controlling for BMI although both were in the normal range.

Therefore, the American College of Obstetricians and Gynecologists (ACOG) guidelines have recommended that women with PCOS should have a complete fasting lipid and lipoprotein evaluation as part of their cardiovascular risk assessment. [25].

Furthermore, PCOS patients tend to suffer from an early onset endothelial dysfunction, arterial stiffness, and formation of plaques which might compromise the integrity of the coronary arteries and potentially increase the risk of CVD [26]. In a recent meta-analysis, Meyer et al. reported a mean difference in Carotid artery Intima-Media Thickness (C-IMT) among women with PCOS compared with controls was 0.072 mm [95% confidence interval (CI) 0.040, 0.105, *P* < 0.0001], for every 0.1 mm incremental increase in mean C-IMT, the hazard of stroke increases by 18% and the hazard of myocardial infarction MI increases by 15% [27,28]. This was even demonstrated to be persistent even among patients beyond the age of 45 [29].

Serum triglycerides and high-density lipoprotein cholesterol (HDL) are also associated with insulin resistance, have day-to-day variability, and do not add additional cost as they are already recommended for screening of lipid abnormalities in PCOS [30].

All patients with PCOS should be offered regular monitoring for weight changes. Monitoring could be at each visit or at a minimum 6–12 monthly [13]. Although the available evidence is in favor of an increased CVD risk above the general population, there is not yet an established verified risk calculator that could be of reliable use by the treating physician, thus clinical judgment along with established proper history taking which includes personal history of smoking, cardiovascular or metabolic disease as well as family history of metabolic, cardiovascular, or endocrine diseases, along with a physical exam which includes blood pressure (BP) measurement (at least annually) [13], BMI and waist circumference based on individualized assessment may prompt further investigation including measurement of cholesterol and triglyceride levels.

MANAGEMENT

Diabetes mellitus, insulin resistance, and metabolic abnormalities are all significantly lower in lean women (BMI<25kg/m^2) with PCOS [31] and even many physicians do not prefer to use the term "insulin resistance" in the absence of obesity [32]. Although the issue of a lower incidence of insulin resistance per se remains debatable in the literature with a reported prevalence of 6-22% among lean PCOS patients [33]. The recommended first line management of high risk PCOS women defined as obese (BMI>30kg/m^2) women, or women with already existing metabolic disorder, or at a significantly higher risk above the general population of developing a metabolic disorder [34], is the implication and maintenance of lifestyle modification plans which include a healthy diet, exercise and weight loss. A reduction of as little as 5% of total body weight in overweight/obese women has been shown to enhance sensitivity to insulin and reduce testosterone levels which in the end may improve the overall cardiovascular risk [35]. This entitles a multidisciplinary approach from doctors, nurses, dieticians, and health fitness specialists to establish the goal of improved lifestyle and help maintain it [36]. The utilization of behavioral change and the utilization of cognitive behavioral therapy over an 8 week period resulted in a significant weight drop (-0.35 kg/wk 95% CI −0.47 to −0.23), vs. -0.16 kg/wk in controls (95% CI −0.28 to −0.04) *p=0.033*) in addition to improvement in the quality of life [37]. According to the National Institute for Health and Clinical Excellence guidelines, failed lifestyle modification strategies , and those patients with a BMI of 40 kg/m^2 or more or who have a BMI of 35 kg/m^2 or more with a high-risk obesity-related condition (such as hypertension or type II diabetes) should be considered for bariatric surgery [16].

The 2013 Endocrine Society guidelines suggest the use of metformin as a second-line therapy in young PCOS women with hyperglycemia, defined as impaired glucose tolerance or type 2 diabetes [18].

Although considered in women with PCOS undergoing lifestyle management regimes [38], in recent literature, there is still no strong evidence in the benefit from the use of insulin sensitizing agents such as Metformin in women with PCOS especially when addressing its efficacy among different BMI's with evidence that women with a BMI above 37kg/m^2 have a poorer response to Metformin [39,40].

According to the Joint British Societies' guidelines, hypertension should be treated, and persistent blood pressures greater than or equal to 140 mmHg systolic and/or 90 mmHg diastolic, not responding to lifestyle measures, need to be considered for drug therapy (patients with diabetes or other high-risk factors with blood pressure greater than 130 mmHg systolic and/or 80 mmHg diastolic may require drug therapy [41]. Pharmacological treatment modalities are beyond the scope of this review.

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