

CARDIOMETABOLIC RISK IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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Introduction

Polycystic ovary syndrome (PCOS) is a condition that was first described by Drs. Stein and Leventhal in 1935, when they described a group of women with amenorrhea, hirsutism, obesity, and enlarged ovaries [1]. Over subsequent years, PCOS has become recognized as a common endocrine disorder which affects 6-12% of reproductive-aged women in most populations, making it the one of the most common endocrine disorders. The exact prevalence varies in different populations and according to the definitions used, but has been reported to be as high as 28.3% among overweight and obese women from Spain [2]. In Asian populations such as Chinese, hirsutism may not be a prominent feature [3], though a recent study in southern Chinese reported a prevalence of 2.2% among women of reproductive age [4].

Diagnostic Criteria of PCOS

Initial research in the field of PCOS was hampered by the use of different definitions among investigators. This was partially resolved in 1990 when a conference held at the National Institutes of Health (NIH) gave rise to a consensus set of diagnostic criteria: oligo- or anovulation, biochemical or clinical evidence of hyperandrogenism, along with exclusion of other causes of hyperandrogenism. This last point is important, since several conditions such as Cushing's syndrome, late-onset congenital adrenal hyperplasia, and androgen-secreting tumors may mimic PCOS, and therefore need to be excluded before making a diagnosis of PCOS [5]. The more recent Rotterdam criteria proposed in 2003 broadened the definition and proposed that the diagnosis requires 2 of the following 3 criteria: oligo- or anovulation, biochemical or clinical signs of hyperandrogenism, and characteristic appearance of polycystic ovaries [6]. Use of the recent Rotterdam criteria is likely to lead to a further increase in the prevalence of PCOS [7].

Cardiometabolic Complications in PCOS

Although the definition of PCOS has focused on androgen excess and the reproductive phenotype, there has been increasing interest in the metabolic abnormalities in women affected by PCOS [8]. It is now recognized that women with PCOS have a marked increase in the risk of type 2 diabetes. Both obese and lean women with PCOS have increased insulin resistance and impaired β -cell function when compared to age- and body mass index-matched controls. Even among lean patients with PCOS, 31% have impaired glucose tolerance (IGT) and 7.5% have type 2 diabetes [9]. The conversion from IGT to diabetes is also accelerated in PCOS [10]. It has been noted that in most populations, including Caucasians and Chinese, use of fasting glucose alone is not adequate for the diagnosis of diabetes in subjects with PCOS, and it is recommended that affected women should undergo regular screening with an oral glucose tolerance test [3,9-11].

In addition to increased risk of diabetes, PCOS is also associated with atherogenic dyslipidemia [12], hypertension [13], low grade inflammation [14], and endothelial dysfunction [15]. It is now recognized that women with PCOS have peripheral insulin resistance, which is characterized by a 35-40% decrease in insulin-mediated glucose uptake, and is independent of obesity [16].

The prevalence of metabolic syndrome (MES) in PCOS women shows a marked variation between countries and ethnic groups, probably due to differences in diet, lifestyle, genetic factors, as well as cut-offs for waist circumference. Using the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria, the prevalence of MES was reported to be 1.6% [17], 8.2% [18], and 43% [19] in Czech, Italian, and US women with PCOS, respectively. There has been only limited data available regarding prevalence of metabolic syndrome among Asian patients with PCOS. This is further complicated by the fact that Asian patients need use of ethnic-specific cut-off for waist circumference [20], as use of the ATP III criteria will underestimate the risk in Asian subjects [21]. This can be addressed by using the modified version of the ATP III criteria proposed by the American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) in 2005 [22], or by using the criteria proposed by the International Diabetes Federation (IDF) [23], both of which utilize ethnic-specific cut-offs for waist circumference, though recent data suggest that the IDF criteria may be less useful in identifying diabetic subjects at high risk of subsequent cardiovascular events [24].

In one of the first major studies from Asia examining metabolic syndrome among subjects with PCOS, 295 premenopausal Chinese women with PCOS diagnosed by the Rotterdam criteria and 98 control subjects without PCOS were evaluated for presence of MES and cardiovascular risk factors. Metabolic syndrome according to the ATP III criteria was present in 18.1% of the subjects with PCOS, though the proportion with MES increases substantially to 24.9% if the updated ATP III 2005 criteria are adopted [22]. The frequency of MES increases with increasing age of the subjects, but was consistently higher among subjects with PCOS compared to controls (Figure 1). The frequency of each MES component, in decreasing order, was central obesity (53.1%), elevated blood pressure (29.4%), reduced HDL-C (28.6%), increased TG (21.4%), and impaired fasting glucose (21.4%). Increasing age, higher BMI, and diagnosis of PCOS were found to be independent predictors of metabolic syndrome in multivariate logistic regression analysis, with PCOS associated with a 5-fold increase in the risk of MES (OR 4.90; 95% CI: 1.35-17.84) even after adjustment for age and BMI [25]. In another

recent study involving 170 Asian women with PCOS, MES according to the IDF criteria was present in 35.3% of the subjects [26]. The alarming prevalence of cardiometabolic risk factors among young women with PCOS suggests this is a problem with significant public health impact. Increased awareness, along with early and regular screening for metabolic abnormalities, is warranted in all individuals with PCOS.

Role of Obesity and Insulin Resistance

Although women with PCOS may be overweight, obesity is not one of the diagnostic criteria for PCOS. Nevertheless, women with PCOS have significantly greater insulin resistance when compared to age- and BMI-matched control women [16,27]. The presence of obesity often further exacerbates the reproductive as well as metabolic phenotype of subjects with PCOS [28-30]. Obesity is associated with increased insulin resistance, which is believed to play a central role in the pathogenesis of PCOS. Furthermore, obesity is associated with decreased levels of sex hormone binding globulin (SHBG), which will lead to increased fraction of free androgens being delivered to target sensitive tissues, thereby contributing to the effects of androgen excess [30].

Although the pathogenesis of PCOS is not entirely clear, it is increasingly recognized that insulin resistance plays a central role in its development. The central role of insulin resistance in the pathogenesis of PCOS is highlighted by the beneficial effects on the metabolic and reproductive phenotype following weight loss [30] and use of agents which improve insulin sensitivity [31,32]. It is believed that the hyperinsulinemia that accompanies insulin resistance in PCOS acts with luteinizing hormone (LH) within the theca cells of polycystic ovaries, leading to activation of the enzyme responsible for ovarian androgen synthesis, P450c17 α , and increased androgen production, as well as arrest of ovarian follicle development, leading to anovulation [33]. This contrasts with impaired metabolic and vascular effects of insulin, which may reflect tissue-specific insulin resistance, resulting in glucose intolerance, dyslipidemia, hypertension, and endothelial dysfunction among subjects with PCOS [34,35].

The pathogenesis of insulin resistance among lean subjects with PCOS is still a matter under much debate. One theory is that there is a propensity to deposit fat in visceral and abdominal subcutaneous depots [36-38], sites known to be associated with insulin resistance as well as metabolic disturbances [39,40]. Furthermore, when comparing women with and without PCOS, the increase in insulin resistance in women with PCOS becomes attenuated if the two groups are matched for abdominal adiposity rather than BMI [41]. Indeed, recent studies in women with PCOS have indicated that women with PCOS have a tendency to an android body fat distribution, and the amount of central fat closely correlate with metabolic abnormalities and indices of inflammation [42-45]. Other abnormalities that may contribute to insulin resistance in PCOS include enhanced catecholamine-induced lipolysis in visceral fat cells [46].

Implications for Clinical Management

The increasing appreciation of the role of insulin resistance in PCOS has led to a new approach to management of PCOS, and much enthusiasm in exploring agents that improve insulin resistance as possible therapeutic agents for treatment of the various complications relating to PCOS. However, the widespread use of insulin sensitizers for PCOS is not supported by current evidence [47]. For clinicians who manage patients with PCOS, a high degree of awareness

regarding their cardiometabolic risk, and regular screening of metabolic abnormalities, including an oral glucose tolerance test, is warranted.

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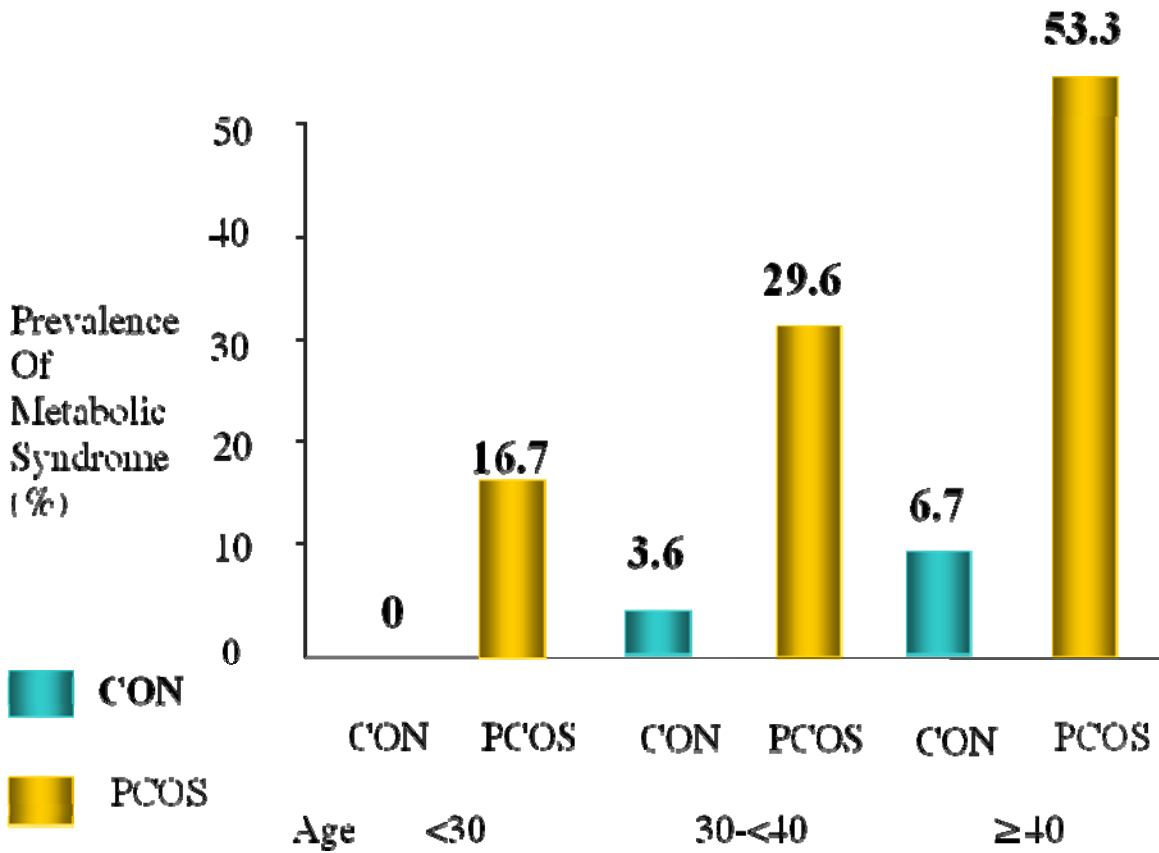


Figure 1. Prevalence of metabolic syndrome (MES) according to the criteria proposed by the American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) in 2005 among 295 Chinese subjects with PCOS and 98 control subjects without PCOS stratified according to the different age groups. On multivariate logistic regression, the presence of PCOS conferred a 5-fold increase in risk of MES (OR 4.90; 95% CI: 1.35-17.84) even after adjustment for age and BMI. CON-control subjects, PCOS-subjects with PCOS