Polycystic ovary syndrome: is obesity a symptom?

"The amount and distribution of body fat is recognized as a major contributor to the significant variation in the severity and expression of the polycystic ovary syndrome phenotype…"

Women's HEALTH

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Polycystic ovary syndrome (PCOS) is a common and complex disorder characterized by an excess of androgen, oligoanovulation and enlarged polycystic ovaries on ultrasound [1]. PCOS is closely linked with obesity. Although obesity is not universally observed in PCOS, many women with PCOS are obese. The amount and distribution of body fat is recognized as a major contributor to the significant variation in the severity and expression of the PCOS phenotype, and increased adiposity exacerbates reproductive, metabolic and psychological features of PCOS. Nevertheless, the underlying mechanistic basis for the association of PCOS and obesity is far from being fully understood.

Several studies have focused on the question of whether women with PCOS are more obese compared with their healthy counterparts. A meta-analysis of 35 studies, including women with PCOS, reported a 2.8- and 1.7-fold increased risk for obesity and central obesity, respectively, in PCOS, with significant heterogeneity among the studies. The prevalence of obesity in PCOS ranged from 12.5 to 100% (pooled estimated prevalence of 49%), whereas the prevalence rates of central obesity were between 20 and 85.5% (pooled estimated prevalence of 54%), both significantly higher compared with those women without PCOS [2]. The risk of obesity was up to six-times greater in adolescents with PCOS. The studies included in this meta-analysis, similar to many others in the literature, evaluated women with PCOS presenting at the clinic compared with healthy women, using a cross-sectional study design.

In order to investigate the prevalence of obesity in unselected women with PCOS, representing the background population, we have analyzed data from 675 women in the USA who have participated in two populational studies that assess the prevalence of PCOS according to NIH criteria. We found that the prevalence rates of PCOS were 9.8, 9.9 and 9.0% in normal weight, overweight and obese women, respectively. Prevalence rates did not show a significant difference according to body weight, even though they were as high as 12.4% in women with a BMI between 35–40 kg/m^2 and 11.5% in women with a BMI over 40 kg/m^2 [3]. In the same study, data from 746 untreated PCOS patients presenting at the same clinic between 1987 and 2002 demonstrated that the average BMI of PCOS patients rose from 31.3 kg/m^2 in 1997 to 37.3 kg/m^2 in 2000–2002, in line with the similar increase of body weight in the surrounding population. However, the mean age at presentation was approximately 27 years and did not show any significant change over the 15 years [3].

In another study of 392 unselected women between the ages of 18 and 45 years representative of the background of the Turkish population, with an average age of 33 years and an average BMI of 24.2 kg/m^2, we reported prevalence rates of PCOS as 6.1, 19.9 and 15.3% according to NIH, Rotterdam and AE-PCOS Society criteria, respectively [4]. PCOS was more common in obese women compared with nonobese (15, 30 and 22.5% according to NIH, Rotterdam and AE-PCOS Society criteria, respectively). Alternatively, while 10.2% of the whole group had a BMI over 30 kg/m^2, prevalence rates of obesity in women with PCOS were 25, 15.4, and 15% when NIH, Rotterdam and AE-PCOS Society criteria were applied, respectively [4].

These two studies show some differences regarding the link between PCOS and obesity. The data from the USA indicate that obesity only moderately increases the risk of PCOS and the prevalence of obesity in PCOS mostly reflects environmental factors, similar to the general background of the US population where the prevalence rates of obesity and morbid obesity are already high. On the other hand, the data from Turkey, where the background population is relatively lean, demonstrates that PCOS is more common in obese women and obesity is more common in women with PCOS, both with an

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increase between 1.5- and 2.5-fold depending on the diagnostic criteria applied. Taken together, it is evident that obesity rates of the background population significantly influence the expression of the inter-relation between PCOS and obesity.

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Another important question is whether obesity rates differ in patients with PCOS presenting to the clinic from those women with PCOS in the population. A PCOS patient seeking medical care might be influenced by several factors including, but not limited to, the degree of concern for symptoms, awareness of the disorder and access to medical care. The phenotype(s) of PCOS may show a variation depending on whether the patient is presented to a clinic or identified in an unselected background population, reflecting a certain degree of referral bias. For example, a study from Spain has reported a 28.3% prevalence rate of PCOS among 113 overweight or obese women who were referred to an endocrinology clinic for weight loss [5], whereas the populational prevalence was 6.5% among 154 Spanish female blood donors [6]. Similarly, in a study of 292 PCOS patients referred to a tertiary care health center, 64 PCOS patients and 563 healthy controls who were identified through a pre-employment physical screening in the USA, we reported 2.3- and 2.5-times greater estimates for the prevalence rates of obesity and severe obesity in referral PCOS [7]. These prevalence estimates and mean BMIs were similar for unselected PCOS and unselected controls. In addition to an increased body weight, PCOS patients presented at the clinic had higher hirsutism scores and higher androgen levels [7]. Overall, these data indicate a referral bias for PCOS at a clinical setting driven by obesity and the severity of disease burden.

Obesity, particularly of the abdomen, has a significant impact on androgen excess and oligoanovulation of PCOS through various mechanisms [8]. It is well established that excess body weight is associated with a more severe presentation of clinical and biochemical androgen excess, menstrual irregularities, infertility, insulin resistance, glucose intolerance and dyslipidemia [9]. A recent meta-analysis of 30 studies demonstrated that obese women with PCOS have decreased sex hormone-binding globulin, increased testosterone, fasting glucose, fasting insulin and a worsened lipid profile. According to the results of this meta-analysis, obesity significantly worsens all metabolic and reproductive outcomes in PCOS except for hirsutism compared with normal weight women with the syndrome [10].

Furthermore, it is becoming clearly evident that obese women with PCOS are at an increased risk of psychological disturbances, including depression and anxiety, compared with patients with normal weight [11,12]. Interestingly, depression scores in obese women with PCOS appear to be correlated with components of metabolic syndrome, including insulin resistance and dyslipidemia [12].

Ethnicity and age are among several factors influencing the amount of excess body fat in PCOS. Caucasian women with PCOS are likely to be more obese than Asian women with PCOS. South Asian women usually have central obesity rather than an increase in BMI [2]. Ethnicity-specific BMI cutoff points need to be performed in patients with PCOS from different ethnic backgrounds.

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Older women with PCOS have higher levels of obesity and there is an increase in waist circumference with aging [13]. Moreover, increased insulin resistance with aging in PCOS patients appears to be mainly attributable to an increase in obesity [14]. However, it should be noted that the increased risk of women with PCOS being overweight and obese is independent of age and geographic region [2].

Several studies, using clinical anthropometric measurements, ultrasonography, dual x-ray absorptiometry or computerized tomography, reported that abdominal adiposity is present in most PCOS patients, even those with a normal BMI [8]. The subphenotype of PCOS modifies the expression of central obesity, thus resulting in ovulatory women with PCOS exhibiting smaller quantities of abdominal fat compared with anovulatory PCOS, and having less evidence of adipocyte dysfunction [15]. Interestingly, recent studies evaluating body fat deposits by MRI in women with PCOS and age- and BMI-matched controls reported that the volume and distribution of abdominal adipose tissue are similar between these two groups [16,17], suggesting that

insulin resistance and other metabolic abnormalities observed in PCOS women compared with healthy women of similar age and BMI might not be explained by differences in visceral obesity. Further comparative research is needed in PCOS to precisely characterize the amount of body fat and its distribution in well-characterized populations using sensitive methods.

Overall, both obesity and central obesity are common in patients with PCOS presenting to the clinic, which worsens the phenotype of the syndrome. The prevalence of obesity in unselected women with PCOS from relatively lean background populations appear to be increased by all available diagnostic criteria albeit at different levels. Obesity is evident in PCOS beginning at puberty and it increases with age. Many questions remain unanswered regarding the complex interaction between PCOS and obesity. Among these are whether women with PCOS have a predisposition to gain weight, whether PCOS and obesity are causally related and the potential role of adipose tissue dysfunction in PCOS. Identifying and addressing these questions appear to be essential for a better understanding of the syndrome and will undoubtedly have a critical role to play before successful strategies for screening, evaluation and management of obesity in PCOS can be implemented.

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