Do women with PCOS have a unique predisposition to obesity?

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Women with PCOS are often obese and there is debate in the literature regarding whether women are obese because of their PCOS status or if those who become obese are more predisposed to PCOS. There is support for a predisposition to obesity by some data indicating impaired metabolism in PCOS women compared to weight matched controls but this data is limited. Contrary data also exist that adiposity rates do not vary between women with PCOS and those without, and that differences in obesity rates between countries are more likely due to environmental and lifestyle factors. Until further data are available, lifestyle recommendations for weight reduction in women with PCOS should be similar to those for women without PCOS. (Fertil Steril® 2012;97:13–7. ©2012 by American Society for Reproductive Medicine.)
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While, there is considerable evidence that obesity plays a negative role in the pathophysiology of PCOS (1), it is not clear if women with PCOS harbor a unique predisposition to obesity, or if obesity is a secondary factor exacerbating the condition. It has been estimated that as many as 38–88% of women with PCOS are overweight or obese (2, 3). Indeed, the rates of obesity across all populations worldwide have increased significantly in the last 30 years (4, 5). In the United States, the majority of the adult population is now overweight or obese (6). Reasons for the continued growth in obesity prevalence are multifaceted. Energy intake has significantly increased in the last several decades, particularly the consumption of more calorie dense food. This increase is paralleled by a corresponding decline in energy expenditure through daily activity and physical exercise (7). The conditions that contribute to increased obesity prevalence impact women both with and without PCOS, making the relative contribution of obesity predisposition in PCOS difficult to assess.

Obesity has been a common feature of PCOS since the original description of the Stein-Leventhal syndrome in the 1930s (8). However, obesity is not a defining feature of the syndrome as PCOS is seen in both normal weight and obese women. There is nonetheless evidence that obesity, particularly abdominal obesity, worsens both the clinical and endocrine features of the syndrome. Variation in the prevalence of obesity in the syndrome across different populations has been attributed to lifestyle factors as well as genetic factors (9).

Obesity in PCOS has a marked impact on the features of the syndrome. In addition to the metabolic consequences including a high prevalence of type 2 diabetes in obese women with PCOS (10), the reproductive consequences of obesity in PCOS include a higher prevalence of irregular menses and menorrhagia, an increase in serum androgen concentrations, and a significantly reduced response to ovulation induction regimens as well as reduced success of fertility treatments when compared to lean women with the condition (11, 12). This review examines the evidence both for and against the predisposition towards obesity in women with PCOS.

Pro: Women with Obesity have a Unique Predisposition to Obesity—Kathleen M. Hoeger, M.D., M.P.H.

Given the impact of obesity in PCOS, the question as to whether women with PCOS have a unique predisposition to obesity is critical to our understanding of the pathophysiology of the condition, as well as insight into the best treatment options. While all individuals with obesity face potential barriers to effective weight management, it is possible that women with PCOS face additional barriers. Women with PCOS who are enrolled in a lifestyle program demonstrate high rates of failure to lose weight and dropout from these studies. Dropout rates in excess of 40% are noted in these studies (13, 14).

As stated above, there is some evidence that prevalence of obesity is increased in PCOS populations when compared to general populations. In

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the North Finland birth cohort, a study of over 2000 women born in 1966 and followed prospectively, women were contacted at ages 14 and 31. If individuals were obese at age 31 there was an increased relative risk of self reported symptoms of PCOS of 1.44. If there was obesity present at both 14 and 31 years of age the relative risk of PCOS increased to 1.71 (15). In an unselected Spanish cohort, the prevalence of PCOS in an obese population was 28.3% which was significantly increased over the rate of PCOS in the general population (16). However in an unselected US population the rate of PCOS in lean women with BMI <25 kg/m^2 did not differ from that in women with BMI 35 kg/m^2 or higher (9.8% versus 12.5%, NS) (17). This may reflect however a smaller portion of women in the higher BMI categories with a trend noted to increased diagnosis of PCOS in those with BMI over 35 kg/m^2.

Obesity itself is associated with an increase in androgen concentration in children. While this is not clearly associated with an increase in the diagnosis of PCOS, premenarchal obesity is associated with significantly higher androgen concentrations in early puberty (18). It is not possible from these studies to interpret whether a predisposition to obesity is associated with PCOS early in development but it is suggested that obesity primarily is associated with elevated ovarian androgen production which may predispose to PCOS.

If women with PCOS have an increased risk of obesity compared to women without PCOS, it is possible that this may manifest as a difference in either basal metabolic rate (BMR) or in utilization of calories after consumption. There have been only a few studies that have attempted to assess the basal metabolic rate and postprandial thermogenesis in women with PCOS compared to control women matched for body weight. The studies available in the literature were all performed with indirect calorimetry and show mixed results. Segal and Dunaif studied 10 obese women with PCOS and 9 obese controls and compared to lean controls. They demonstrated decreased resting metabolic rate in obese versus lean control women but there was no difference between obese with and without PCOS (19). Robinson et al., however, found decreased postprandial thermogenesis in women with PCOS compared to control women in both obese and lean PCOS (20). More recently a study of 62 women with PCOS and 23 control women matched for body weight demonstrated decreased basal metabolic rate in all PCOS women compared to controls, although women with PCOS who were classified as insulin resistant had the lowest BMR (21). Overall these studies suggest that there are differences in caloric utilization in women with PCOS when matched for body weight. Unfortunately there are no studies that examine metabolic rates in women with PCOS using more rigorous methodology and carefully controlled direct observation of dietary intakes, leaving the question of basal metabolic rates in PCOS unresolved.

It is possible that either energy intake or energy expenditure differ between women with and without PCOS. With respect to energy intake, a study of 84 women with PCOS and 79 controls, part of a long-term PCOS cohort study in Pittsburgh, suggested that lean women (BMI <25 kg/m^2) with PCOS restricted calories significantly more than BMI matched control women to maintain the same weight (1398 versus 1792 kcal/day) (22). This relationship was not seen in the overweight and obese women, as similar caloric intake was seen between the cases and controls in women with BMI >25 kg/m^2. In that study there was no difference in physical activity scores between the groups as measured in a survey questionnaire. In a contrary study looking a prospective food diary collection, Douglas et al studied 30 overweight women with PCOS compared to weight matched controls (BMI 29 kg/m^2) and did not show any difference in caloric intake between the groups, but women with PCOS consumed more foods with high glycemic content (23). It is possible that differences in caloric intake and BMI may be most revealing however in women with normal body weight. Unfortunately there are no studies with a large enough lean population of PCOS women to adequate answer the question as to whether maintaining a normal body mass index in PCOS requires either more dietary restriction or increased energy utilization.

There is evidence that obesity prevalence varies between different ethnic populations of women with PCOS (9). This may indeed be due to the impact of different lifestyle characteristics within different geographic areas but may also reflect genetic predisposition to obesity within populations. While there are yet no definitive genetic markers that define PCOS, it is possible that genes for obesity may track in PCOS populations and therefore predispose women with PCOS to obesity. Evidence for this was reported with the fat mass and obesity associated gene (FTO) which has been shown to influence susceptibility to type 2 DM through a substantial impact on BMI and adiposity in a general European population (24). Barber et al. studied a variant of FTO, rs9939609 in 436 women with PCOS and 1336 controls. They found a significant association between this FTO genotype and PCOS status (25). There was no association however with androgens in that study. This study would need to be expanded to other populations to assess the possibility of increased prevalence of obesity genes in women with PCOS.

Androgen excess itself may predispose to abdominal fat deposition. In women androgen excess has been associated in some studies with increased risk of metabolic syndrome (26). Coviello et al. (27) reported higher prevalence of metabolic syndrome in PCOS adolescents than in the general population. They demonstrated a higher prevalence of metabolic syndrome using pediatric standards with increasing levels of testosterone. Interestingly this was independent of both obesity and insulin resistance, although abdominal adiposity specifically was not examined. Given the dysregulation of sex steroids in PCOS as demonstrated by androgen excess, this may play a fundamental role in the development and expression of obesity phenotypes as well as metabolic dysfunction.

An area of relatively new investigation is the influence of prenatal exposures on adult diseases. It is possible that predisposition to obesity begins antenatally. The intrauterine environment, particularly over nutrition prenatally, may predispose to adult diseases (28). For instance, there is evidence that maternal obesity predisposes to risk for childhood metabolic syndrome. In a study of children at 11 years of age, maternal obesity predicted presence of metabolic syndrome in childhood, independently of gestational diabetes, a known risk factor for metabolic dysfunction in childhood (29). It is