Does body weight affect cardiometabolic risk in women with polycystic ovary syndrome?

Polycystic ovary syndrome (PCOS) is a heterogeneous and common endocrine disorder in reproductive-age women that is associated with significant variation in diagnosis and management and leads to dissatisfaction among patients. The diagnosis of PCOS is based on three criteria, namely, irregular menses, clinical or biochemical hyperandrogenism, and polycystic morphology of the ovaries, resulting in four different phenotypes (1). The presentation also varies with age, and diagnosis in adolescents can be challenging owing to overlap with symptoms that present during the normal transition through puberty. In addition to making an accurate and timely diagnosis, it is critical that all women with PCOS are appropriately counseled regarding the risk of long term comorbidities (2). The most common comorbidity is weight gain, resulting in a high prevalence of obesity associated with this syndrome seen worldwide. Other complications include a higher risk of prediabetes, type 2 diabetes, dyslipidemia, hypertension, anxiety and depressive symptoms, obstructive sleep apnea, nonalcoholic fatty liver disease, and possibly cardiovascular disease (CVD). Do these complications occur at the same rate in all PCOS phenotypes and ethnicities? Because many of these conditions are exacerbated by weight gain, it is also critical to ask whether these comorbidities are independent from obesity. Identification of a threshold body mass index (BMI) associated with higher risk would enable targeting interventions to high-risk groups and allow appropriate counseling and management of the normal- and overweight subset of women with PCOS.

Because the prevalence of obesity is high in women with PCOS, there are few studies that have examined cardiometabolic risk exclusively in normal- and overweight subjects. Most publications on the association of PCOS with cardiometabolic risk include a subanalysis in BMI-matched groups. Although we do not have precise data on the prevalence of obesity in women with PCOS, studies in the United States indicate a prevalence as high as 70% and much lower rates are reported in other countries. Moreover, referral populations have a higher prevalence of obesity, whereas in unselected groups the BMI appears to be similar to control subjects. In this issue of *Fertility and Sterility*, Zhu et al. (3) report, in a meta-analysis that specifically included studies with nonobese women (Caucasians with BMI <30 kg/m^2 and Asians with BMI <25 kg/m^2), an increased risk of impaired glucose tolerance (IGT; odds ratio [OR] 3.42, 95% confidence interval [CI] 1.56–7.52, four studies) and type 2 diabetes (OR 1.47, 95% CI 1.11–1.93, five studies) associated with PCOS. The risk of IGT and type 2 diabetes was increased when examining only Caucasians and when diagnosis was established using either National Institutes of Health or Rotterdam criteria. There was heterogeneity in the studies evaluating risk of dyslipidemia and hypertension, with no significant differences. Another metric that indicates an increased risk of developing type 2 diabetes and CVD is metabolic syndrome, a composite risk including dyslipidemia, hypertension, and glucose impairment. Zhu et al. also report a higher risk of metabolic syndrome in nonobese women with PCOS (OR 2.57, 95% CI 1.30–5.07, six studies). What is the risk in women with a normal BMI? In a subanalysis of only lean subjects (BMI <25 kg/m^2) an earlier meta-analysis reported a higher risk of IGT (OR 4.37, 95% CI 1.66–11.54, two studies), but the authors were unable to evaluate the risk of type 2 diabetes, because only one study met the inclusion criteria (4). The risk of metabolic syndrome was not increased in lean women (four studies).

Systematic reviews and meta-analyses can be useful for counseling patients and guiding therapy. However, their results depend on the number and quality of studies that meet the inclusion criteria. The above-mentioned meta-analyses are limited by the small number of studies examining each outcome, limiting the ability to confirm the robustness of the results. Compared with studies including obese women, it is clear that there is limited information on the nonobese PCOS phenotype concerning cardiometabolic risk. Despite these limitations, the current data suggest that nonobese women with PCOS are at an increased risk of IGT, type 2 diabetes, and metabolic syndrome. There is also good evidence in the literature that progression of all these conditions can be delayed by early screening and lifestyle and pharmacotherapeutic interventions. Therefore, the recently published international PCOS guidelines (1) include a clinical consensus recommendation that all women with PCOS should be assessed for global CVD risk. Glycemic status should be assessed at the initial visit by means of fasting plasma glucose or glycosylated hemoglobin. In high-risk women (obesity, history of impaired fasting glucose, IGT, gestational diabetes, family history of type 2 diabetes, hypertension, or high-risk ethnicity), an oral glucose tolerance test is recommended. A fasting lipid profile should be performed in all overweight and obese women at their initial diagnosis. In addition, blood pressure should be checked annually and weight checks should be offered at all visits.

In our attempts to understand the true cardiometabolic risk in normal- and overweight women with PCOS, the relationship between BMI and the various cardiometabolic outcomes may not be linear. Furthermore, it is important to examine the risk in different PCOS phenotypes, because earlier studies have indicated that hyperandrogenic women (phenotypes A, B, and C) have a higher prevalence of metabolic syndrome compared with nonhyperandrogenic women (phenotype D). Metabolic risk also varies with ethnicity; we compared the risk of metabolic syndrome and its components in five countries, namely, the United States, India, Brazil, Norway, and Finland, and reported differences in both overall metabolic syndrome risk and clustering of components of metabolic syndrome based on race and ethnicity (5). Although Zhu et al. (3) performed a sensitivity analysis, the majority of the studies included Caucasians only, and only two studies included east Asian women and one included Indian women. Studies from the Scandinavian and Nordic regions show a low prevalence of cardiometabolic risk in lean and overweight women with PCOS, calling into question the cost-effectiveness of universal

screening. There is a clear need for studies examining cardiometabolic risk and long-term CVD outcomes in lean women with PCOS including different ethnic populations and PCOS phenotypes. Until more data are available in the nonobese population, it seems appropriate to follow the screening guidelines suggested by the international consortium, because a large majority of the patients referred for care will be obese.

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https://doi.org/10.1016/j.fertnstert.2018.11.001

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