Does the risk of diabetes and heart disease in women with polycystic ovary syndrome lessen with age?

Polycystic ovary syndrome (PCOS) is a highly inheritable complex genetic trait and one of the most prevalent endocrine-metabolic-reproductive disorders of humans, clinically evident in 10%–15% of reproductive-age women. It is the single most common cause of ovulatory infertility in women and of subfertility overall in Western societies. Fundamentally, most patients with PCOS, particularly those with hyperandrogenic phenotypes, also demonstrate underlying metabolic dysfunction and subclinical chronic inflammation, leading to insulin resistance and compensatory hyperinsulinemia. These features result in, among other morbidities, an increased risk for vascular abnormalities and glucose intolerance. Notably, women with PCOS have been reported to have a 5–7-fold higher risk for type 2 diabetes (T2DM) compared with age-matched control subjects. However, notwithstanding the high prevalence of the disorder and the fact that many of us have been following patients with PCOS for >30 years, little is known concerning the impact of aging and menopause on the risk of metabolic or vascular disease in these women. Kazemi Jaliseh et al. now provides us, in a well designed study, insight on how aging may affect the risk of T2DM in PCOS (1).

The investigators used a unique resource, the Tehran Lipid and Glucose Study, a large-scale long-term prospective population-based study initiated in 1998 aimed at exploring the prevalence and risk factors of chronic diseases in the region. The study included 178 women with PCOS (10.5% of the total and consistent with previous estimates of PCOS prevalence) and 1,524 women without PCOS. Among other evaluations, all participants aged ≥20 years who were not diabetic on medication underwent a 2-hour 75-g oral glucose tolerance test every 3 years. Overall, there were little differences between women with PCOS and without PCOS, including in the prevalence of prediabetes and T2DM, at the start of the study. Median follow-up was 12.9 years, with most subjects exceeding the 10-year follow-up mark.

The investigators calculated the incidence rates and hazard ratio of diabetes and prediabetes events, and observed that the adjusted hazard-ratios for T2DM and prediabetes in women with PCOS ≤40 years of age were almost 4.9 and 1.7, respectively. In contrast, there was little difference between the two groups regarding the incidence rates of T2DM and prediabetes after the age of 40 years. Thus, the results of this study suggest that although premenopausal and perimenopausal women with PCOS have an increased risk of T2DM, compared with body mass index (BMI)– and age-matched control subjects, this difference appears to lessen, and even disappear, with age.

Importantly, the study by Kazemi Jaliseh et al. is strengthened by the fact that it avoided the bias inherent to studies that examine women retrospectively or from medical clinics. However, we should note that the investigators used the more restrictive National Institutes of Health 1990 criteria for diagnosing PCOS in their study. Consequently, all PCOS subjects included in the study demonstrated either phenotype A (hyperandrogenism [HA] + oligoanovulation [OA] + polycystic ovarian morphology [PCOM]; i.e., the so-called "full PCOS phenotype") or phenotype B (HA + OA, but not PCOM) of PCOS. These phenotypes, as opposed to phenotype C (HA + PCOM; i.e., "ovulatory PCOS") or phenotype D (OA + PCOM; the "nonandrogenic PCOS"), carry with them a higher risk of metabolic dysfunction. Therefore, we would expect to find an even lower risk of glucose intolerance in PCOS women with phenotypes C and D, further supporting the investigators' conclusions.

We should also note that the mean BMI of the PCOS women studied did not differ from the women without PCOS in this study, a finding that is consistent with other studies carried out in nonmedically biased populations (2). And in contrast to that observed in other countries, notably the United States, the mean BMI of women in the study was in the normal weight range (25–26 kg/m^2). Therefore, it is possible that the risk of T2DM and prediabetes would be higher in countries with greater rates of obesity.

Do other studies support the conclusion that the risk of T2DM in PCOS lessens, and even disappears, with age? Dahlgren et al. reported on 33 women aged 40–59 years with ovarian histopathology typical of PCOS, 22–31 years after having undergone wedge resection, and 132 age-matched referents, and observed that perimenopausal women with PCOS had an increased risk of T2DM compared with referents (15% vs. 2.3%, respectively; $P<.05$) (2). However, and in support of the findings by Kazemi Jaliseh et al., in a follow-up report of 35 PCOS women (aged 61–79 years) and 120 age-matched control subjects performed 21 years after the initial study, Dahlgren's team observed that PCOS women had a prevalence of T2DM similar to control subjects of similar BMI (3). Wild et al., in a retrospective cohort study of 319 postmenopausal women diagnosed with PCOS in the United Kingdom before 1979 and 1,060 age-matched control women, reported an odds ratio (OR) of 2.2 (95% confidence interval [CI] 0.9–5.2) for T2DM after adjustment for BMI, a difference that did not reach significance ($P<.08$) (4).

That the risk of T2DM and prediabetes in older or postmenopause patients with PCOS is not higher compared with BMI- and age-matched control subjects may not be an isolated finding. A significantly greater prevalence of risk factors for cardiovascular (CV) disease in premenopausal women with PCOS is consistently observed, yet there are limited data demonstrating a definitive increase in CV events (e.g., myocardial infractions) in these individuals as they age. For example, in a study of 295 postmenopausal women enrolled in the Women's Ischemia Syndrome Evaluation (WISE) study, where 8% of the women had clinical features consistent with PCOS, we observed that women with clinical features of PCOS trended toward demonstrating more evidence of angiographic coronary artery disease than women without these features (5). Raw mortality rates were 28% for women with clinical features of PCOS versus 27% for women without clinical

features of PCOS, and 20% versus 17% for CV-associated deaths. Overall, PCOS was not a significant predictor of all-cause or CV mortality rates.

Wild et al., in their long-term retrospective cohort study, reported higher levels of several CV risk factors in women with PCOS, but a history of coronary heart disease, after adjustment for BMI, was not significantly more common in women with PCOS versus control subjects (4). That study was able to observe, however, that the crude OR for cerebrovascular disease was higher in PCOS patients compared with control subjects (2.8, 95% CI 1.1–7.1; $P<.02$). Likewise, in the follow-up study by Schmidt et al., postmenopausal PCOS women (aged 61–79 years) had a higher prevalence of hypertension and elevated triglyceride levels, but similar prevalences of myocardial infarction, stroke, cancer, overall mortality, and, as mentioned above, T2DM compared with age-matched control subjects of similar BMI (3).

Overall, taken together these data suggest that after menopause, antecedent PCOS may not be as strong a risk factor for the development of T2DM or CV events as previously thought, after accounting for differences in BMI. Why may this be the case? Provocatively, it may reflect a protective effect of antecedent PCOS on the risk of developing these morbidities in the face of other risk factors. However, it may more likely reflect the much stronger impact that aging has, compared with PCOS, on the development of these morbidities. It is also possible that the results reflect the need for better follow-up data, including well designed larger longer-term prospective studies, such as the ongoing CARDIA (Coronary Artery Risk Development in Young Adults) study, as well as the Tehran Lipid and Glucose Study already mentioned in the current report (1). The results of these studies will allow us to better counsel and manage patients with PCOS long term and develop appropriate public health policies and strategies.

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