Continuum of polycystic ovary syndrome physiology

Polycystic ovary syndrome (PCOS) is defined by oligo-ovulation, hyperandrogenism, and/or ovaries with polycystic morphology. Amongst those who clearly meet PCOS Rotterdam criteria, the disorder remains heterogeneous and exists along a spectrum: patients may be completely amenorrheic or have 45 day cycles; may have ovaries with 30 antral follicles, or half this number; may suffer from severe hirsutism and high levels of testosterone; or only the mildest manifestations of these findings. Similarly, it is also clear that women who have never been diagnosed with PCOS or fail to meet formal criteria, may possess mild, sub-clinical manifestations of PCOS. However, what has not been known previously is whether these mild PCOS-like manifestations have clinical implications. Specifically, a gap in knowledge exists regarding whether presumably ovulatory women with subtle findings of PCOS, such as a robust ovarian reserve or mildly elevated androgens, also suffer from ovulatory inefficiencies or other effects that could impair fertility and early pregnancy.

In this issue, Sjaarda (1) report on a study that seeks to address this knowledge gap. The authors performed a secondary analysis of the Effects of Aspirin in Gestation and Reproduction trial (EAGR), which was a multi-center, randomized, double-blind, placebo-controlled trial of low-dose aspirin in women with a history of pregnancy loss. The study included 1,198 healthy, eumenorrheic women (defined as cycles between 21-42 days), ages 18-40 years with 1 to 2 prior confirmed losses. The authors asked whether women with the highest quartiles of testosterone (T) and antimüllerian hormone levels (AMH) might have differences in ovulation rates, time to pregnancy and pregnancy loss risk. The investigators assessed the first two study cycles. Ovulatory cycles were determined by a set of prioritized criteria, including a positive human chorionic gonadotropin level or an elevated urine pregnanediol 3-glucoronide $\geq$ 5 ug/mL, measured using samples collected and banked at home. When luteal pregnanediol 3-glucoronide was not available, a positive luteinizing hormone surge by a fertility monitored was considered.

The authors found an overall rate of anovulation in the cohort of 14.5% and found the high T/high AMH group had a 58% increased rate of anovulation when compared to the referent group (normal T/normal AMH) and the normal T/high AMH had a 39% higher risk (risk ratio 1.39; 95% confidence interval 1.0, 1.94). In contrast, those with a high T/normal AMH were not different. In regards to conception, time to pregnancy was similar across groups, though the high T/high AMH group had a marginally increased rate of pregnancy loss in comparison to other groups (risk ratio 1.39; 95% confidence interval 0.97,1.99). Given the increased prevalence of insulin resistance in PCOS, the authors were also interested in whether the metabolic profiles of the high T/high AMH group would differ. Notably, the high AMH/T group were of similar body weight and had no evidence of metabolic alterations compared to the rest of the cohort.

The findings have a number of implications. First, women without a PCOS diagnosis, but with subtle or occult PCOS-like findings, may suffer from ovulatory insufficiency, despite apparently normal cycle lengths. This suggests that aspects of PCOS physiology exist on a continuum and act in ways that could potentially impair reproductive function. Although this study was unable to definitively show an effect of high AMH/high T on time to pregnancy, one could hypothesize that in a larger and longer study, the lower rates of ovulation might translate to lower fecundity. Moreover, the slightly increased rates of pregnancy loss are provocative. Although PCOS has been associated with higher miscarriage rates, it has been difficult to tease apart whether this is related to obesity and/or its associated metabolic phenotype. Given the high T/high AMH group was lean and metabolically healthy, the results reported in this study raise the question of whether downstream effects of altered ovulatory dynamics could be a factor leading to pregnancy loss in PCOS.

Another provocative finding of the study is that the high AMH/T group was lean and did not show any differences in metabolic parameters. This would seem to suggest that if there is a continuum in the reproductive phenotype in PCOS, it is not necessarily paired with a similar continuum of metabolic disease. Indeed, these data seem consistent with the hypothesis that the initial ovulatory disturbance in PCOS stems from ovarian mechanisms, with metabolic alterations, such as insulin resistance, serving as a second hit that exacerbates this disturbance further.

These findings beg the question, what is it about the high AMH/high T phenotype that leads to altered ovulatory mechanisms in these otherwise normal women? Is there a direct impact from these elevated hormones or are we observing a bystander effect? The fact that the high AMH/normal T group also showed alterations, whereas the high T/normal AMH did not, could indicate a prominent pathophysiologic role for AMH. It is known that AMH reduces the sensitivity of granulosa cells to follicle-stimulating hormone in vitro, indicating a possible direct ovarian role (2). Intriguing new work has shown that AMH receptors are expressed on gonadotropin-releasing hormone neurons in both mice and humans, and, in mice, AMH increases gonadotropin-releasing hormone dependent luteinizing hormone pulsatility and secretion (3). Taken together, this work may indicate both a peripheral and/or central role for AMH in promoting ovulatory dysfunction.

The strength of this work is rooted in the rigorous followup of a well-characterized population. This report also confirms similar findings by this same group in a smaller population of women who were not seeking fertility (4). However, the study is not without its limitations. The somewhat idiosyncratic study population was originally recruited to answer a question regarding treatments to prevent miscarriage, and all subjects had had at least one prior pregnancy loss. In the future, study of a larger, nulliparous population seeking pregnancy would shed additional light on this question. Another understandable limitation relates to the documentation of ovulation, which is challenging in the best of circumstances. The somewhat surprising rate of anovulation (14% overall) noted by the authors, despite normal cycles lengths, raises

concern. In current practice, most clinicians would assume a patient with relatively normal cycle intervals is ovulatory. Improved methods of documenting ovulation would come as a welcome gift to both women attempting to conceive and their care providers and would be a boon for research as well. Indeed, an expert panel from the recent National Institutes of Health-sponsored Evidence-Based Methodology Workshop on PCOS recommended in a final report to improve the methods and criteria used to assess ovulatory dysfunction (5). The study by Sjaarda (1) highlights the importance of this recommendation.

Finally, in order to confirm and elaborate on these findings, more detailed examinations of cycle dynamics would be helpful. It would be interesting to know whether anovulatory cycles occurred due to sub-optimal follicular growth or a faulty ovulatory surge or both. Future studies that are better able to characterize ovulatory mechanisms across the cycle at multiple time points via both serum testing and ultrasound would shed greater light on where and how things go wrong with ovulatory machinery in various populations.

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