Ovarian reserve in polycystic ovary syndrome: more, but for how long?

It has long been assumed that women affected by polycystic ovary syndrome (PCOS) tended to reproduce later in life. This belief stems from the fact that PCOS women have higher ovarian reserve parameters and their ovulation disorder often normalizes in late reproductive years. It is indeed a lingering die-hard belief that women with PCOS enjoy an extended window of fertility as compared to their regularly ovulating counterparts. However, actual facts, sparse for reasons explained below, speak differently.

In a long-term follow up study, Hudecova et al. (1) showed that there was no higher incidence of childlessness in women affected by PCOS, as compared to regularly ovulating women. In a different study, West et al. (2) at first glance confirmed the findings of Hudecova et al. (1). West et al. (2) conducted a lifetime study of reproductive success based on Finland's birth cohort. Women who self-reported oligomenorrhea and hirsutism were compared to symptom-free controls (2). In this latter study (2), women harboring symptoms of PCOS had similar rates of having given birth. Remarkably however, the Finland study revealed that PCOS women delivered at the same age as controls. Furthermore, as it could have been expected, women with PCOS symptoms had more often consulted for infertility than their matched controls. Ultimately however, PCOS women had a lower rate of having ≥ 2 deliveries than their cycling counterparts thus, ending up with smaller families. These findings therefore challenge the concept that ultimate fecundity is unaltered in PCOS and that just its accomplishment is delayed.

The same belief exists with assisted reproductive technology (ART), where it has been assumed that the higher ovarian reserve parameters encountered in PCOS result in better outcome particularly, in aging women. There too, data seem to contradict the myth. Using the Society for Assisted Reproductive Technology database, Kalra et al. (3) reported that the higher oocyte yield obtained in PCOS indeed resulted in higher pregnancy rates in PCOS women. There was however a similar age-related decline in outcome in PCOS and controls. Moreover in the >40 years-old group, clinical pregnancy and live-birth rates were similar in PCOS and women whose infertility was related to tubal factor. These data indicate that the slight edge in ART outcome observed in younger women, linked to the increased oocyte yield, is lost when women are over the age of 40 years. This again contradicts the wishful thinking proclaiming that PCOS women enjoy an extended window of fertility also in ART.

Studies on aging in PCOS are rendered complex by the fact that the PCOS phenotype changes over time, as reported by Laven's group (4). Typically, a decrease in the degree of expression of the PCOS phenotype is observed as women age (4). This tempering of PCOS characteristics includes a reduction in the excess of ovarian follicles, androgen levels, and insulin resistance (4). Symptoms change too as women age, with an increasing fraction of PCOS women starting to ovulate regularly in later years (4). Practically therefore, these age-related changes result in the fact that many known PCOS women start failing to fulfill the Rotterdam criteria as they reach the ages of 35-40 years. Cross-sectional studies therefore fail to provide an accurate picture of the situation pertaining to PCOS and aging, as only the most severe members of the PCOS cohort meet the diagnostic criteria for PCOS when they become older. This cogent point stresses the importance of having cohort rather than cross-sectional studies for studying PCOS aging.

The scarcity of badly-needed cohort studies on PCOS aging, gives particular credence and interest to the data reported by Ahmad et al. (5) in this issue of *Fertility and Sterility*. The longitudinal follow up of ovarian reserve parameters was conducted in women with documented PCOS on inclusion, as per Rotterdam criteria (5). Interestingly, 9% of the patients who initially met the Rotterdam criteria no longer did at the follow-up visit when their mean age was still <35 years of age. In Ahmad et al.'s (5) observation, antimüllerian hormone (AMH) and antral follicle count declined more abruptly in the PCOS population, as compared to normal cycling controls.

Ahmad et al.'s data (5) underscore several facts of marked clinical relevance in our daily management of PCOS women seeking infertility treatment. Women who once belonged in the PCOS category may not be identified anymore based on either Rotterdam or Androgen Excess and PCOS society criteria because of age-related changes in the PCOS phenotype. Indeed, using the classical criteria for diagnosing PCOS in a snap-shot manner, cross-sectional studies and instant analysis, leads us to ignore a progressively increasing fraction of PCOS women. Stated bluntly, a rising numbers of PCOS women disappear from the radar screens as they get in the later years of their reproductive life. Women undertaking infertility treatments, notably ART, should be identified as being PCOS not based on their actual menstrual history, but rather by taking into account the symptoms that prevailed in their twenties. Hence, the interpretation of an AMH value in a woman who used to be an oligo-anovulator, even if she is not anymore, should be put in the perspective of the more rapid decline reported by Ahmad et al. (5). Women whose AMH is high despite being >35 years of age, whether fulfilling PCOS criteria now or in the past, should not be told that they have 20-year old ovaries. Such comment and particularly the underlying thinking that there is time is not just erroneous, it is more importantly misleading. Based on Ahmad et al.'s (5) and other data, we have to consider that women with PCOS have a more rapid decrease of their ovarian reserve parameters and similar age-related decrease in fecundity compared to normal controls. The urgency to treat infertility in PCOS should thus take into account Ahmad and colleagues' data.

The lesson that ovarian reserve parameters decrease more rapidly in PCOS (5) women should be heard loud and clear

together with the awareness that the extended window of fertility may not exist in PCOS.

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