Diminished ovarian reserve and poor response to stimulation are not reliable markers for oocyte quality in young patients

Today, four decades into the history of assisted reproductive technology (ART), ovarian stimulation (OS) stands as the most effective measure ever taken to increase the yields—implantation and pregnancy rates—of ART. In the classic form of OS, physicians adjust the OS parameters by assessing the ovarian reserve, including a pretreatment count of antral follicles and a measure of the levels of antimüllerian hormone and baseline (day-3) follicle-stimulating hormone. Generally, the OS response is assessed by taking into account the woman's age and the postcycle oocyte yield results. In each of those two categories, the group who underperforms has been categorized as diminished ovarian reserve (DOR) patients or poor responders (PR), with a reported prevalence of up to around 6.3% in infertile women younger than 35 years, as reported by Hu and colleagues (1) in this issue of *Fertility and Sterility*.

OOCYTE QUANTITY AND OOCYTE QUALITY

In ART there is an erroneous belief that oocyte quality and quantity are inherently linked. This stems from the fact that age induces a parallel downturn of both parameters. We know now that both depletion of the ovarian reserve and reduction in oocyte quality are physiologic events determined by aging, and that both the age-related decrease in implantation rates and increase in miscarriages are principally, if not solely, due to a decrease in oocyte quality. Indeed, the deterioration in the reproductive potential of women as they become older—lower pregnancy rates and increased miscarriage rates—is only seen in autologous ART. Thus, if accelerated deterioration in blastulation rate, aneuploidy rate, and pregnancy outcomes occurs in parallel with DOR/PR in younger patients, a unifying mechanism responsible for both qualitative and quantitative decline would be the likely culprit. However, if the blastulation rate, aneuploidy rate, and pregnancy outcomes remain consistent with those of age-matched controls who have a normal OS response, then the mechanisms governing follicular depletion and quality parameters would appear to be divergent (2).

When oocyte quantity is impaired due to an age-independent factor—such as endometriosis, past surgery for endometriosis, or other ovarian pathologies—the evidence has indicated that oocyte quality is not decreased. A retrospective cohort analysis showed that endometriosis is not associated with decreased oocyte quality. We also found this to be evident when we observed similar aneuploidy rates in women with endometriosis and age-matched controls (3).

In the context of DOR/PR, several prior studies have reported that pretreatment markers of DOR or posttreatment evidence of PR are associated with evidence of reduced oocyte quality. However, more recent reports focusing on the characteristics of DOR patients have failed to determine whether poor outcomes are solely due to quantitative penalty or whether there is also a qualitative issue. Nonetheless, a poor response to OS is known to significantly limit the success of ART (4). These findings have underscored the quantitative factor for lower pregnancy rates in patients with DOR/PR.

ANEUPLOIDY RATE IN DOR/PR

The aneuploidy rate in DOR/PR patients compared with age-matched controls sheds some light on the biological processes that mediate the age-related increase in meiotic errors in oocytes. Indeed, there is still disagreement regarding whether segregation errors in oocytes are a reflection of the size of the remaining follicular pool or a function of cumulative, temporal exposure to oxidative damage and other stressors that predispose to aneuploidy (5).

The study by Hu et al. (1) focused on the quantity/quality oocyte issue by enrolling only patients younger than 35 years old, thus circumventing the age-related diminution in oocyte quality. They found that young patients with DOR/PR still had acceptable pregnancy outcomes and had a similar risk of biochemical pregnancy, pregnancy loss, multiple live births, and abnormal perinatal outcomes when compared with young patients who had a normal ovarian reserve. This follows the prior literature that implied that more embryos were required for obtaining a live birth in these patients while suggesting that ovarian reserve and response do not impact the anticipated competence of a given embryo. Also, it reiterates the hypothesis that a fertilized oocyte retrieved from a young patient with DOR/PR is no less likely to form a euploid blastocyst and produce a live birth.

CONCLUSION

The work of Hu et al. (1) on DOR/PR is important and could represent valuable information for counseling patients. Even though fewer oocytes may be retrieved from DOR/PR patients, they have the same capacity to develop into competent embryos. These data are derived from substantial experience with pregnancy outcomes of DOR/PR patients compared with normal responders, but the limitations include the retrospective nature of the analysis, the inclusion of only the first fresh embryo transfer, and the exclusion of patients with endometriosis. Also, no information is provided on potential confounders that could bias pregnancy outcomes, such as smoking, a family history of type 2 diabetes or hypertension, abnormal pregnancy history, or gestational weight gain. Further work in this area should be pursued, and more studies should be conducted to elucidate the effect of frozen embryo transfer on these outcomes.

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https://doi.org/10.1016/j.fertnstert.2020.03.040

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