Discordant ovarian reserve testing: what matters most?

When counseling patients planning in vitro fertilization (IVF), predictors of both potential oocyte yield and likelihood of live birth are invaluable. Reproductive endocrinologists have used antral follicle counts, basal follicle-stimulating hormone (FSH) levels, and antimüllerian hormone (AMH) values to predict diminished ovarian reserve (DOR), a poor response to ovarian stimulation (1). DOR is associated with increased risks of IVF cycle cancellation, lower oocyte yield, and less embryos available for transfer and cryopreservation. While predictive of increased gonadotropin requirements and poor oocyte yield, DOR's association with live birth remains less clear and more controversial, particularly when adjusted for female age. Elevated follicular phase FSH (>10 mIU/mL) has previously been shown to have a low sensitivity, but high specificity in predicting ovarian response to stimulation; many women with DOR have a normal FSH value (1). AMH has been shown to be a better predictor than FSH of ovarian response to stimulation (1), but is generally found to be poorly predictive of pregnancy rates, especially in younger women (2).

When counseling women before an initial attempt at IVF, physicians generally use a combination of antral follicle counts, FSH, and AMH to select an appropriate gonadotropin dose for stimulation and anticipate potential oocyte yield. Counseling is straightforward when testing is concordant (e.g. low FSH and high AMH or high FSH and low AMH), but it becomes more complicated when ovarian reserve testing is discordant. Approximately 20% of women have discordant values, with either a normal AMH/elevated FSH or a low AMH/normal FSH (3). It can also be difficult to impart accurate live birth expectations in this setting.

In this month's issue of *Fertility and Sterility*, Ligon, et al. (4) used data from the Society for Assisted Reproductive Technology Clinical Outcomes Reporting System in a retrospective cohort study to further investigate this clinical question. They included 44,696 fresh autologous oocyte cycles from 2013 to 2015, careful to exclude repeat cycles from the same women to not over-represent women with repeat failed cycles (and presumably a worse prognosis). Importantly, cycles are not linked between clinics in Society for Assisted Reproductive Technology Clinical Outcomes Reporting System, so it is possible that a woman could be represented multiple times if she switched clinics. The authors found a significant difference in live birth rates per cycle between the four groups of interest: 44% in women with normal FSH and AMH, 39% in women with high FSH and normal AMH, 26% in women with normal FSH and low AMH, and 19% in women with high FSH and low AMH. Low AMH continued to be a better predictor than high FSH of live birth when stratified by age and in predicting cycle cancellation as well. Cycle characteristics differed among the 4 groups; women with low AMH were more likely to have used an antagonist or agonist flare protocol and to have required a higher total gonadotropin dose. After multivariable analysis that adjusted for both these factors and demographic characteristics, such as age and BMI, low AMH remained significantly associated with lower live birth rate (adjusted risk ratio 0.87, 95% confidence interval 0.83–0.91).

This data substantiates findings from a previous publication that assessed live birth rates with discordant ovarian reserve results (5), in that low AMH was a better predictor of decreased chance of live birth than FSH in a sample of approximately 14,000 women. Ligon et al. (4) were able to use a larger database and adjust for variables beyond age. The findings also support prior studies that show high FSH to have low sensitivity when predicting ovarian stimulation response.

There are a few potential unmentioned limitations to the analysis. Exclusion of "freeze-all" cycles and those using preimplantation genetic testing may limit generalizability, especially in women of advanced reproductive age who are more likely to have DOR. Additionally, reporting of additional intermediate outcomes (e.g. peak estradiol levels, number of cryopreserved embryos) and other pregnancy outcomes (e.g. miscarriage rate, ectopic pregnancy rate) may have further characterized the counseling implications of low AMH in the setting of normal FSH. The impact of DOR on miscarriage risk remains unclear and, admittedly, was not the focus of this paper. Lastly, embryo stage at transfer and number of embryos transferred were not included in the multivariable analysis, both of which could affect outcomes.

The conclusion that low AMH is a better predictor than elevated FSH of live birth is an important finding, although a woman's age remains the most important clinical factor. The study will improve patient counseling, particularly in situations in which a woman with discrepant ovarian reserve results wants to know whether to trust her FSH or AMH more.

Heather S. Hipp, M.D.
Jennifer F. Kawwass, M.D.
Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, Emory Reproductive Center, Atlanta, Georgia

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