In search of a new biomarker to predict poor ovarian response

Optimizing outcomes for poor ovarian responders remains a challenge in the field of assisted reproductive technologies. A variety of stimulation protocols and adjunct medications have been developed and studied, with no clear advantage in this population (1). The administration of estradiol in the luteal phase preceding stimulation is a widely used and low-cost technique. Data are mixed, but there may be benefit in improving outcomes in this population; however, the resulting stimulation tends to be longer and requires more gonadotropins.

In the current issue of *Fertility and Sterility*, a study by Man et al. (2) investigates whether serum levels of insulin-like growth factor 1 (IGF-1) are predictive of ovarian response and whether estradiol pretreatment has an impact on IGF-1 levels. By analyzing stored frozen serum from 184 cycles in early 2013 to early 2015, the authors found that day 2 IGF-1 levels were significantly higher in poor responders ($\leq$4 oocytes or canceled prior to retrieval) than in normal or high responders. Levels were highest in those who were canceled for lack of response. In a limited analysis of 16 patients, it appeared that the difference in IGF-1 levels between poor and normal responders was no longer present by the time of trigger for final oocyte maturation. Although definite conclusions are limited due to the retrospective nature of this study, the authors concluded that an IGF-1 level >72 ng/mL was highly predictive of a negative cycle outcome.

Given that estradiol is known to antagonize the GH receptor and to suppress IGF-1 levels, the authors sought to evaluate the effect of estradiol pretreatment. In a matched control group prescribed estradiol pretreatment, usually transdermally at this center, cycle day 2 serum IGF-1 levels were lower and not different from those of the normal responder group. A subgroup of 21 of the 67 poor responders underwent a subsequent estradiol pretreated cycle. Cycle day 2 IGF-1 levels were lower in the subsequent cycles, which on averaged yielded more oocytes and embryos. The authors suggest that IGF-1 may be a biomarker that can be measured at the start of stimulation and can guide management, perhaps delaying stimulation if the level is above a certain threshold.

Although these data are intriguing, it is difficult to draw conclusions regarding the improved subsequent cycle outcomes. The authors attempted to correct for the "regression toward the mean" phenomenon, but the outcomes still may be confounded. Nevertheless, this biomarker merits further study.

Rather than checking at the start of stimulation, as suggested, perhaps IGF-1 could be checked with early follicular estradiol and follicle-stimulating hormone during routine diagnostic evaluation. Those with high IGF-1 levels might benefit most from an estradiol priming protocol.

It would also be useful to know whether the baseline serum IGF-1 level has any predictive value in women with normal markers of ovarian reserve (antral follicle count and anti-Müllerian hormone). Do high day 2 IGF-1 levels in these patients predict a poorer response than expected based on traditional ovarian reserve markers? If so, this marker could be used to guide the starting dose and protocol selected for these patients.

The concept of starting stimulation in the luteal phase may be another option for women with high IGF-1 levels. It would be interesting to determine whether their mid-luteal IGF-1 levels normalize and whether they have a better response to stimulation with a luteal start. Of course, this would necessitate a freeze-all approach, which has become standard at many clinics and has been shown to be beneficial in different clinical settings (3, 4).

IVF stimulation protocols still remain more of an art than a science. Investigating biomarkers may help us finally move to a more evidence-based approach to stimulation.

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