Challenges and Considerations in Optimizing Stimulation Protocols

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Ovarian stimulation is frequently misunderstood by patients. The name "stimulation" implies we are stimulating follicles (oocytes) to a greater degree than would otherwise be possible. It also implies, to the patient, there is no limit to this potential. In fact, we do not "stimulate" follicles – we "rescue" follicles (oocytes) that would otherwise undergo atresia. However, all follicles come from the individual patient's recruitable pool. So the most important factor in determining the expected number of oocytes retrieved is that individual patient's capacity. And while oocyte/follicle number declines with aging, < 30% of this variation is determined by age. So the first part of stimulation is assessment of the ovarian reserve. The two best predictors are antral follicle count (AFC) and anti-Müllerian hormone (AMH). This number allows us to counsel individuals, in the context of the female age, regarding expectations for eggs retrieved and potential treatment success. For AFC, the expected response is +/- 2 of the AFC.

The second principle in stimulation, atresia, is due to declining FSH levels. Therefore, an increase in FSH is required to "rescue" oocytes to stimulate to maturity. FSH is most often administered as exogenous gonadotropins (FSH and/or hMG), but can also be stimulated endogenously with GnRH agonist, clomiphene citrate or letrozole. Selection of the "best" protocol is driven by these two factors: ovarian reserve and options for increasing FSH.

There are a number of potential stimulation variations: pre-treatment medications – typically to increase synchronization; stimulation protocol type; varied dosing; and alternative triggers. As we increasingly are better able to characterize our patients, it may be the most important thing is to "do no harm". Individualized dosing, and stimulation selection, seem most beneficial to prevent ovarian hyperstimulation syndrome: lowered dosing with use of GnRH antagonist protocol with agonist trigger in those with high ovarian reserve. Unfortunately, individualization has not been as beneficial for the individual with low ovarian reserve. Optimizing recruitment of a limited number of oocytes seems to be less responsive to dose adjustments (increasing dosing) and may benefit more from stimulation protocol changes (moderate/mild stimulation protocols). Again, the "do no harm" principle may apply – where the harm may be higher cost of non-beneficial high dosing and conflicting information re: negative impact of high dosing on oocyte quality.

It is also important to understand the difference between poor response and intrinsic low ovarian reserve. While many classification systems combine both of these, counseling of patients requires we understand the difference. A low, but expected response (+/- 2 the AFC), is a good response in a low reserve patient (e.g. 4 lead follicles in a patient with AFC of 4-5). This is different from a response in an individual where the response is < 50% of expected from ovarian reserve testing (3 lead follicles with an AFC of 15). This later might actually respond to greater pre-cycle suppression and/or increased dosing. It is these subtleties that drive the art of ovarian stimulation.