Follicular versus luteal stimulation in suboptimal responders: Maybe timing isn't everything?

Arguably, the two most important factors for in vitro fertilization (IVF) success are patient age and the number of oocytes retrieved. Unfortunately, up to 43% of all IVF patients may be expected to have a suboptimal response to ovarian stimulation based on age, ovarian reserve markers, or the outcome of prior cycles (1). Although age is a fixed variable, the number of oocytes retrieved varies from cycle to cycle, and in patients for whom a low number of oocytes are expected, each additional oocyte retrieved may have a significant clinical and prognostic impact. Over the past three decades, protocol selection has been the major focus of research to optimize oocyte yield in poor responders, including microdose gonadotropin-releasing hormone agonist (GnRH-a) protocols, minimal stimulation, and adjuncts to stimulation such as clomiphene citrate. However, more recently, attention has turned also to the timing of stimulation as a factor that may also significantly affect oocyte yield.

Luteal phase stimulation (LPS) is based on a "wave-like" model of ovarian folliculogenesis in which multiple waves of antral follicles may emerge throughout the menstrual cycle, even in the luteal phase (2). Luteal phase stimulation was initially undertaken in the context of emergency fertility preservation in patients with cancer diagnoses to prevent delay in chemotherapy administration, either as an isolated LPS or as a double ovarian stimulation (DuoStim), in which a follicular phase stimulation (FPS) was followed by a LPS a few days later in the same menstrual cycle (3). In these patients, LPS led to the retrieval of competent mature oocytes and the development of viable embryos.

The DuoStim strategy was then naturally applied to poor responders, for whom time is also of the essence, although less critically, to maximize the number of oocytes retrieved in a cycle and hence increase the chances of embryo transfer. Initial non-randomized cohort studies reported promising results for DuoStim in poor responders, even suggesting increased oocyte yield with LPS compared with the first FPS (4). This has led to considerable interest in LPS as a strategy for patients anticipated to have a poor prognosis for IVF.

There are two big unanswered questions that remain regarding LPS in poor responders. First, and likely most central, is how does the yield of an isolated FPS compare with that of an isolated LPS? DuoStim is not the ideal setting to answer this question, as many DuoStim studies use GnRH-a triggers and start LPS 5 days after oocyte retrieval (4). Premature luteolysis would be expected after the GnRH-a trigger, begging the question whether this is an evaluation of a true LPS or rather a very late luteal, even near-follicular, second stimulation. Second, can improved outcomes be intrinsic to a second cycle regardless of whether it is started in the subsequent luteal phase or the next follicular phase? It could be that a recent stimulation or retrieval procedure alters sensitivity to gonadotropins regardless of the cycle phase at which the second stimulation is initiated.

Suñol et al. (5) help us answer the first of these two questions in their randomized clinical trial, "Conventional follicular phase ovarian stimulation versus luteal phase stimulation in suboptimal responders: a randomized controlled trial," comparing oocyte yield in conventional FPS with LPS in suboptimal responders. The key methodology employed was a crossover study design in which two stimulations were separated by 45 days to 6 months. They found that LPS itself did not increase the number of oocytes retrieved in the intention-to-treat or per-protocol analyses. In both analyses, FPS and LPS led to the retrieval of approximately seven total oocytes and five mature oocytes. In other words, oocyte yield was not significantly different between an isolated FPS and an isolated LPS. There were also no significant differences in any of the secondary outcomes analyzed between FPS and LPS, including duration of stimulation, gonadotropin dose, fertilization, estradiol levels at trigger, or cost of the cycle.

Their study thus answers the first big question, which is whether LPS is superior to FPS in terms of oocyte yield, which it does not appear to be. The other question, as to whether the ovary may respond better or worse in the immediate aftermath of prior stimulation, remains unanswered. Patients with cancer diagnoses arguably have no other choice, but in suboptimal responders, we await additional data to help decide how best to maximize the number of oocytes retrieved.

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https://doi.org/10.1016/j.xfre.2023.08.005

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