Unexpected poor oocyte retrieval: the phenomenon of the borderline response to the gonadotropin-releasing hormone (GnRH) agonist trigger

Few innovations in ovarian stimulation have changed the practice of in vitro fertilization as much as the triggering of ovulation with a gonadotropin-releasing hormone (GnRH) agonist (1). Prior to its introduction, ovulation was always triggered with human chorionic gonadotropin (hCG). This type of trigger resulted in a predictable ovulatory response in the ovary, but also in the predictable side-effect of ovarian hyperstimulation syndrome (OHSS). The probability and severity of OHSS were primarily driven by patient factors, but also the degree of ovarian stimulation preceding the hCG trigger. Controlled ovarian stimulation was a constant balance of maintaining adequate follicular stimulation while avoiding overstimulation, thus minimizing the risk of OHSS. (When I see some of the unbridled stimulations used by more recent fellowship graduates, with estradiol (E_2) levels exceeding 10,000 pg/mL, I shudder to think what the incidence of OHSS would have been if hCG trigger were the only option!) When cryopreservation methods reached a level of efficiency that allowed for freeze-all cycles, (thus avoiding pregnancy-associated hCG levels further stimulating already hyperstimulated ovaries), severe OHSS decreased dramatically, but it did not disappear. Patients still experienced abdominal pain, intravenous dehydration, and abdominal distention. Paracenteses were still performed for the relief of pain and difficulties with breathing, all caused by the long half-life of hCG, which continued to stimulate the corpora lutea, long after the oocytes had been removed from the follicles. However, OHSS is almost never seen anymore, and the reason is the agonist trigger.

The GnRH agonist trigger, in a patient with intact pituitary function and adequate GnRH receptors, results in a large increase in luteinizing hormone (LH) secretion. This induced LH "surge" is, in the vast majority of cases, sufficient to lead to the successful retrieval of mature oocytes. Peak LH levels after agonist trigger are similar to those of a natural LH surge, but the agonist-induced LH response is considerably shorter: 12–18 hours vs. 36 hours for the naturally occurring LH surge. The short duration of LH stimulation appears adequate for ovulation triggering, but the short half-life of LH does not allow for continued stimulation of the corpora lutea and the resulting OHSS. It is actually intriguing that the short LH stimulation afforded by the agonist trigger works at all. Why would nature make the LH surge 36 hours if 12–18 hours was all that was needed?

It is worth noting that the follicular response to the midcycle gonadotropin surge consists of several components: the oocyte must undergo nuclear maturation with a release of the first polar body, the oocyte must be released from its attachment to the inside of the follicle, and hormonal secretion must be converted from E_2 to progesterone (P), with neovascularization of the corpus luteum. When the only goal is egg retrieval, all that is required is oocyte maturation and its release from the inside of the follicle. The hormonal changes are not necessary. In fact, these changes likely bring with them the vascular changes associated with the development of OHSS. This is the magic of the agonist trigger: it only produces the changes we need, not the ones that cause the side effects.

The problem with the agonist trigger is that it doesn't always work. Patients with inadequate GnRH receptors or those whose pituitary has not been stimulated by GnRH in a long time (as in cases of hypogonadotropic hypogonadism) may not respond with adequate LH stimulation. This results in a disastrous egg retrieval procedure, in which no eggs are found in the follicular aspirates. The "empty follicle syndrome" is also a phenomenon that is observed if the hCG trigger is administered at the wrong time (2). It is possible to try and predict who will and who will not fail to respond to the agonist trigger (3), but these predictions are not perfect. Additionally, a more subtle problem is now being encountered: the borderline response to agonist trigger. Our practice has experienced a few of them, and other clinicians have confirmed this phenomenon. The common link is a good responder, a GnRH agonist trigger, an apparently normal hormonal response to the trigger, and then an unexpectedly poor egg retrieval. This may be manifested by a surprisingly low egg yield, unexpectedly low egg maturity, or both. Some of these cases may be associated with a borderline hormonal response, but most have normal LH and P levels on the morning after trigger, at levels which are expected to yield a normal ovulatory response.

The concept of an inadequate ovulatory stimulus was first introduced by Georgeanna Seegar Jones in 1949, when she introduced the concept of the luteal phase defect (4). In her discussion of endocrine causes of infertility, she described ovulatory defects, follicular phase defects, and luteal phase defects. Luteal phase defects, she postulated, could be caused by an inadequate stimulation by LH in the late follicular phase or during the midcycle surge. One may wonder what Dr. Jones would have thought of the GnRH agonist trigger. It certainly makes sense that the pituitary must have the capacity for a spectrum of gonadotropin responses to GnRH, ranging from complete failure to a full gonadotropin surge. It may also be that the different components of the follicular response to the ovulatory trigger (oocyte maturity, release of the egg, hormonal reprogramming of the corpus luteum) may react differently to borderline stimulation. Therefore, with the large volume of stimulation cycles that we now manage, we should not be surprised to be experiencing a borderline response.

The one thing that we can be sure of is that we do not yet know everything there is to be known about ovarian function and stimulation. Avoiding OHSS is a major accomplishment, and the agonist trigger deserves the credit. The price that is being paid may well be the unexpected poor oocyte retrieval caused by an unexpected borderline response to the agonist

trigger. What is the solution? Using hCG together with the agonist (5) would likely avoid this phenomenon, but that would take us back to OHSS. Perhaps a second agonist trigger administered 12 hours after the first dose was not such a bad idea. Perhaps we will get better at predicting the borderline response so that we can avoid it. However, the first step has to be the recognition of this phenomenon so that we can look for it and study it.

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Richard J. Paulson: Conceptualization, Writing – original draft, Writing – review & editing.

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REFERENCES

1. Humaidan P, Haahr T. GnRHa trigger – the story of the ugly duckling. Fertil Steril Rep 2023;4:15–9.
2. Sauer MV, Paulson RJ. Mishaps and misfortunes: complications that occur in oocyte donation. Fertil Steril 1994;61:963–5.
3. Ganer Herman H, Horowitz E, Mizrachi Y, Farhi J, Raziel A, Weissman A. Prediction, assessment, and management of suboptimal GnRH agonist trigger: a systematic review. J Assist Reprod Genet 2022;39:291–303.
4. Jones GE. Some newer aspects of the management of infertility. J Am Med Assoc 1949;141:1123–9.
5. Haas J, Bassil R, Samara N, Zilberberg E, Mehta C, Orvieto R, et al. GnRH agonist and hCG (dual trigger) versus hCG trigger for final follicular maturation: a double-blinded, randomized controlled study. Hum Reprod 2020;35:1648–54.