Major drawbacks and additional benefits of agonist trigger—not ovarian hyperstimulation syndrome related

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The GnRH agonist trigger alters traditional IVF paradigms when compared with hCG-only triggers. The agonist trigger induces rapid luteolysis and therefore separates the oocyte maturation aspect of LH from the luteal support previously afforded by lingering hCG. This might allow customized and more optimal luteal support. The agonist trigger option also allows continued stimulation and subsequent trigger of high responders with reasonable safety, potentially leading to retrievals of larger cohorts of mature oocytes. It may also reduce the number of retrievals needed to achieve a large family. The agonist trigger might alter other paradigms as well, such as making oocyte donation more efficient per stimulation by virtually eliminating follicular-phase cycle cancellation, coasting, and premature triggering. There are both corresponding potential benefits and drawbacks of using the agonist trigger and the shifting paradigms it allows. (Fertil Steril® 2015;103:874–8. ©2015 by American Society for Reproductive Medicine.)

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A large bolus of hCG has been routinely used for final follicular maturation and has for many years been considered the gold standard for cycles of IVF. However, because the hCG trigger was associated with excessive risk of ovarian hyperstimulation syndrome (OHSS) (1) in high responders, an alternative trigger agent was needed to safely induce oocyte maturation in such patients. The GnRH agonist (GnRHa) trigger was not effective in ovarian stimulation protocols that used daily GnRHa for pituitary down-regulation, and therefore the practical use of GnRHa trigger awaited the availability and wider use of GnRH antagonists. Today, the agonist trigger eliminates most, but not all, of the previous risk of OHSS.

Protocols can therefore be practically implemented to optimize oocyte yield, triggering based on when the cohort is optimally developed rather than on when OHSS threatens. This changes some historical paradigms but may also involve increased costs and potentially new medical risks.

PHYSIOLOGY

The hCG bolus induces oocyte maturation and follicular luteinization and also stimulates endogenous P production to promote implantation. Under the influence of hCG, the corpora lutea (CL) are still capable of producing sufficient P to promote uterine changes that support implantation, despite a large proportion of granulosa cells being removed during oocyte collection. Furthermore, irrespective of which stimulation protocol is used in the follicular phase, the supraphysiological concentrations of sex steroids seen in both the follicular and the luteal phase cause a pituitary down-regulation of gonadotropin secretion, necessitating CL stimulation from hCG to secure a sufficient P output. Thus, the hCG bolus trigger has proved an efficient and easy method in clinical practice for autologous IVF cycles using fresh ET.

The use of GnRHa as an alternative to hCG has now completely changed this traditional concept. The GnRHa trigger induces final maturation of follicles through an endogenous surge of LH and FSH resembling the natural midcycle surge. However, in contrast to hCG, the GnRHa trigger has no

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stimulatory effect on the early luteal phase. On the contrary, the GnRHa trigger causes a direct pituitary down-regulation, eventually resulting in reduced levels of LH insufficient to sustain adequate CL activity.

It is well known that the CL will not survive without sufficient LH stimulation. Hence the use of the GnRHa trigger without enhanced luteal support yields lower pregnancy rates (2, 3) because the GnRHa trigger alone results in decreased CL activity and therefore a reduced luteal phase P level that is too low for optimal implantation (4). Thus it is important to realize that the GnRHa trigger separates the two events traditionally undertaken by hCG, namely, induction of final follicular maturation and the maintenance of the CL for early luteal phase support.

The GnRHa trigger therefore allows more direct manipulation and potential optimization of the luteal phase, which was previously not possible in autologous patients undergoing fresh ET because the hCG from the hCG bolus trigger was present in circulation until shortly before the midluteal phase (4). Secondarily, this potential control of the luteal phase without the presence of hCG allows separate investigations of the distinct effects of E_2 and P in the early luteal phase of stimulated cycles.

The luteal phase support provided by the traditional hCG bolus might not result in optimal P concentrations in the early luteal phase or optimal implantation rates. The hCG bolus exerts a potentially premature and massive stimulation of the CL in the early luteal phase. This early stimulation of numerous CL often results in supraphysiological levels of P in the early luteal phase, with P levels reaching maximal levels about 3 days after oocyte collection (4, 5). This is in contrast to the natural cycle in which P levels peak around the time of implantation in the midluteal phase. To what extent this early supraphysiological P release in the luteal phase affects the timing of endometrial development has yet to be elucidated. The recent superior results reported with the freeze-all strategy may reflect more receptive endometria during frozen ET (FET) cycles absent the early, massive P exposure characteristic of fresh autologous cycles (6). Furthermore, there is evidence that prolonged hCG exposure directly reduces the ability of endometrial epithelial cells to respond to hCG, potentially impairing blastocyst implantation (7).

The GnRHa trigger provides an opportunity to develop luteal phase strategies including the use of daily or intermittent low-dose hCG (4) that mimic the natural course of LH-like activity and result in a more natural P profile in the luteal phase. This may also be accomplished by individualization of E_2 and P support together as is done in donor egg recipient cycles and FET cycles. Either strategy may provide an opportunity to improve pregnancy rates and patient comfort.

The LH surge from the GnRHa trigger induces final oocyte maturation with similar or better efficacy when compared with hCG (8, 9), and several studies have reported that the GnRHa trigger resulted in increased proportions of metaphase II oocytes when compared with hCG (2,10–13). In contrast to the hCG bolus trigger, the GnRHa trigger also stimulates a surge of FSH. A number of specific effects of FSH during the midcycle surge have been described, including a specific effect on oocyte maturation (14), stimulation of cumulus expansion, and release of proteolytic enzymes involved in ovulation (15–17). Collectively, the GnRHa trigger may encompass some of these FSH effects in the process of final follicular maturation, leading to a more physiologic oocyte maturation. The greater oocyte maturity reported with GnRHa might be related to the more rapid increase in serum LH after agonist trigger when compared with the rise of serum hCG level after 10,000 IU IM injection of hCG (5), the concurrent FSH surge, or possibly both. The rate of hCG increase following SC injection of 250 μg recombinant hCG is even slower than with IM hCG (18), implying a rise of hCG levels that is much slower than the LH rise after GnRHa trigger.

CLINICAL ASPECTS

Although a few case reports of OHSS after agonist trigger have surfaced in the literature (19), the use of GnRHa has nearly eliminated OHSS as a complication of ovarian stimulation with gonadotropins, and such cases are much less common than when hCG trigger is used (20). The GnRHa trigger virtually eliminates OHSS incidence and therefore the costs associated with OHSS treatment and alternative prophylaxes. This has encouraged the practice of more aggressive IVF stimulation protocols that were unsafe with the traditional trigger of 10,000 IU hCG. This has resulted in unique opportunities for IVF treatments augmented by the concomitant development of other IVF strategies, such as vitrification.

Previously, one OHSS prophylaxis for patients with large follicular cohorts and high E_2 levels was to deprive them of FSH for a varying number of days, a practice referred to as coasting, before follicular maturity. Coasting was maintained until E_2 levels fell significantly in an effort to induce atresia in the smaller follicles and reduce the incidence of OHSS. Unfortunately, while having a modest impact on OHSS incidence, these protocols often resulted in smaller oocyte cohorts when compared with no coasting (21) or when compared with GnRHa trigger (22).

Coasting, which can compromise the oocyte cohort (22, 23), may be avoided with GnRHa trigger. Another alternative is to trigger early, while most follicles are still small. However, small follicles are associated with immature oocytes (24), therefore triggering while follicles are still small can be expected to increase the proportion of immature oocytes. However, the use of GnRHa trigger allows large cohorts of mature oocytes to be obtained from high responders with minimal OHSS risk. While such large cohorts may be medically advantageous (22), they also require increased lab work to inseminate, culture, and cryopreserve the resulting larger numbers of embryos. The continuation of stimulation, when compared with coasting or early triggering, will obviously increase costs for exogenous gonadotropins. Whether a large cohort is worth the added costs depends on many factors but should be assessed against comprehensive outcomes such as total live births, particularly in oocyte-sharing cycles.

With little risk of OHSS, patients with large follicular cohorts can be safely triggered on the basis of markers of follicular maturity rather than on markers of OHSS risk.