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;■:■–■. ©2015 by American Society for Reproductive Medicine.)

Key Words: Ovarian stimulation, in vitro fertilization, GnRH agonist, human chorionic gonadotropin

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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.

This permits retrieval of larger oocyte cohorts than is safe or practical with hCG trigger.

The ability to retrieve more eggs produced the additional benefit of supernumerary eggs and embryos in autologous and oocyte donation cycles. One result is a greater chance of having supernumerary embryos for cryopreservation, affording a greater opportunity for pregnancy in subsequent FET cycles if the initial (fresh or frozen) transfer does not succeed. With modern cryopreservation techniques, collection of a large, mature oocyte cohort should reduce the chance of the patient ever needing another cycle of ovarian stimulation, even if a large family is desired. Large cohorts also increase the opportunity for embryo donation after the biological parents have had their desired number of children, greatly reducing treatment costs for the recipients.

Furthermore, the ability to more reliably obtain sufficient numbers of eggs for egg-sharing cycles and egg-banking cycles has been enhanced by the ability to produce large numbers of eggs in GnRHa-triggered cycles. In donor egg banking, the GnRHa trigger combined with the short GnRH antagonist protocol allows ovarian stimulation and oocyte collection in consecutive menstrual cycles, making more efficient use of oocyte donors' time.

In shared oocyte donation cycles or donor oocyte banking, a large cohort can increase the number of recipients and therefore reduce costs per recipient and per intended parent. A large cohort might also increase the chance of having at least one embryo with normal chromosome number or other desired characteristics, such as with matching human leukocyte antigen. A major cost benefit of GnRHa triggers in autologous high responders and oocyte donors is that there is virtually never a need to cancel oocyte collection due to OHSS risk, avoiding one potential wasted expense.

However, the development of very large follicular cohorts and the concomitant high E_2 levels have both theoretical concerns and unknown risks associated with these extremes that may elicit mechanical, physiologic, and hormonally initiated complications rarely, if ever, seen before. For example, the puncture of extremely large follicular cohorts might result in bleeding with significant blood loss more frequently than the relatively rare cases encountered previously. Extremely high levels of E_2 might overwhelm normal hemostatic mechanisms and result in a higher incidence of thrombosis or have other unforeseen consequences. Sustained ovarian enlargement after retrieval in these high responders might result in more frequent ovarian torsion. The published reports on GnRHa trigger have addressed OHSS risk in high responders, while other potential risks remain to be adequately studied.

Oocyte maturation after GnRHa trigger results from the secondary effect of pituitary LH release instead of the direct effect of hCG on the ovary. Final oocyte maturation therefore requires a sufficient LH response. Some reports have suggested that the GnRHa trigger is insufficient for optimal final oocyte maturation in a small proportion of cases and have suggested combining it with a low dose of hCG, the so-called dual trigger concept (25, 26). This approach provides a stronger ovulatory signal and has been suggested to improve oocyte maturity, blastulation rates, and pregnancy rates (27–31). With the use of GnRHa, post-trigger monitoring is critical, and, if inadequate LH response is detected, this can be ameliorated with a booster of hCG in a rescue protocol with subsequent delayed follicular puncture (32). Minimal efficacious serum LH levels 12 hours after trigger seem to be in the 12–15 IU/L range, while optimal efficacy might be achieved when serum levels exceed about 50 IU/L (26, 33).

The dual trigger concept may be expanded to include a new intriguing possibility of using a combined collective effect of hCG for follicular stimulation in the follicular phase, for final maturation of follicles, and for early luteal phase support. It is well known that LH-like activity (i.e., hCG) is capable of replacing FSH and stimulating follicular growth in the second part of the follicular phase when LH receptor expression has increased the granulosa cell responsiveness (34). Studies have shown that it is possible to exchange FSH stimulation from day 6 of the menstrual cycle with hCG (for instance, 200 IU daily) for the remaining 3–4 days of follicular stimulation with equally good reproductive outcomes while reducing the cost of medications (35, 36). Depending on the number of days in which hCG is administered, the concentration of hCG may reach levels of around 6–10 IU/L at the time of ovulation induction (37). In addition to stimulating follicular growth in the follicular phase, this residual hCG may augment a GnRHa trigger, although this has yet to be demonstrated. This could potentially further improve the final maturation of follicles obtained in connection with the GnRHa trigger, without affecting the OHSS rate. Furthermore, the hCG administered in the follicular phase may sustain the CL. Immediately after termination of the surge released by the GnRHa trigger, the concentration of hCG may afford LH-like activity that may be similar to that observed in luteal phase of the natural menstrual cycle (around 4–8 IU LH/L).

Agonist-triggered cycles frequently result in cryopreservation of the entire embryo or oocyte cohort (38–40), and this increased use of cryopreservation will incur added clinical costs for cryopreservation and storage and might result in added costs to patients, depending on clinical pricing models and insurance coverage. However, recent findings suggest cycles using cryopreserved embryos have reduced risks, including reduced risks of low birth weight and prematurity (41), potentially reducing perinatal and postnatal costs.

However, if a fresh ET is used after agonist-only trigger, then intensive luteal support should be employed (31, 42–44), which may potentially incur increased costs for associated medications. If enhanced luteal support or a dual trigger are not used, the resulting decreased birth rates after fresh transfer may increase the number of ETs required to achieve live birth, with a corresponding potential increase in cost. Hence, a low dose of hCG can be administered with the agonist (25–31) as a "dual trigger" or follow 36 hours later (after retrieval) as "luteal rescue" (45). Concomitant dosing of hCG and agonist might be superior to either trigger alone in terms of oocyte maturity, blastocyst development, and IVF outcome (27–31).

GnRHa trigger is ineffective in cycles using daily GnRHa for pituitary down-regulation, and GnRHa trigger is therefore used mainly in GnRH antagonist protocols. Unfortunately,

GnRH antagonists are currently more expensive than GnRH agonists. Furthermore, the choice of trigger might become clear only at the completion of ovarian stimulation, so that potential high responders might need to purchase both hCG and GnRHa, and the purchase of two trigger medications will cost more than one alone. Also, patients with extremely high E_2 and follicular numbers have a potential for disaster should they accidentally take their hCG.

SUMMARY

The GnRHa trigger has recently become common for the safer trigger of high responders after ovarian stimulation with gonadotropins when compared with the previous standard of hCG trigger. This practice allows greater E_2 levels and follicle numbers associated with increased yields of mature oocytes and viable embryos. This approach might be used to increase the cumulative probability of live birth for one patient undergoing one oocyte retrieval, increase the number of recipients who may be practically supported by one oocyte donor, or to decrease the average number of retrievals in patients seeking large families. The option for making oocyte donation cycles less costly per recipient is particularly appealing, as donor cycles are typically more expensive than autologous cycles and usually not covered by health insurance. However, these new vistas may incur corresponding new or unknown risks.

Through rapid luteolysis, the GnRHa trigger also allows more direct and complete control of the hormonal milieu in the luteal phase of fresh transfer cycles.

Future research should elucidate optimal luteal E_2 and P levels, explore the potential risks of continued stimulation of high responders, and determine appropriate safe upper limits of follicular phase E_2 levels and follicle numbers.

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