Human chorionic gonadotropin vs. gonadotropin-releasing hormone agonist trigger in assisted reproductive technology—"The king is dead, long live the king!"

"The king is dead" is the traditional announcement after a monarch has just died. "Long live the king!" refers to the heir who immediately upon the death of the preceding monarch succeeds them to the throne. The original phrase was translated from the French *Le roi est mort, vive le roi!*, which was first declared upon the accession to the French throne of Charles VII after the death of his father Charles VI in 1422.

Similar to the old king, human chorionic gonadotropin (hCG) has been used for decades to trigger final oocyte maturation in assisted reproductive technology (ART), closely mimicking the actions of the midcycle surge of luteinizing hormone (LH). With this long-standing trigger concept, excellent results have been obtained; however, these come at the expense of an increased risk of ovarian hyperstimulation syndrome (OHSS), ranging from 3% in the normal-responder patient to more than 30% in the high-responder patient. This increase in OHSS risk is caused by the long half-life of hCG, which promotes a prolonged luteotropic effect, the formation of multiple active corpora lutea (CL-a), and production of vascular endothelial growth factor (VEGF).

In the early 1990s, this fact prompted clinical researchers to explore the use of a bolus of gonadotropin-releasing hormone agonist (GnRH-a) to trigger final oocyte maturation instead of hCG in OHSS risk patients, and results were promising. Thus, mature oocytes were retrieved, and OHSS seemed to be prevented. However, after the long GnRH-a down-regulation protocol was introduced in controlled ovarian stimulation, the GnRH-a trigger concept was more or less forgotten, as use of a GnRH-a trigger is not possible during GnRH-a down-regulation. Once the GnRH antagonist protocol was introduced, it became feasible to use the GnRH-a trigger in controlled ovarian stimulation again, as a bolus of GnRH-a will dislocate the GnRH antagonist from the receptors in the pituitary, eliciting a surge of LH and follicle-stimulating hormone (FSH; flare-up), similar to that of the natural cycle.

Quite unexpectedly, the first randomized controlled studies using the GnRH-a trigger concept had to be prematurely discontinued owing to unacceptably high early-pregnancy loss rates, caused by a severe CL-a dysfunction, which could not be solved by standard luteal phase support (LPS) policies. Following these early studies, efforts were made to overcome the luteal phase insufficiency. These efforts resulted in the development of two concepts: the modified LPS, which uses a small bolus of 1.500 IU hCG administered on the day of oocyte retrieval, in combination with a standard LPS to overcome the luteal phase insufficiency (1); and the intensive LPS, using supplementation with exogenous steroids (progesterone and estradiol) (2). Thus, whereas the modified LPS concept adds LH activity and thus boosts endogenous progesterone production, partly rescuing some CL-a function after the GnRH-a trigger, the intensive LPS with steroids disregards the CL-a and relies on only exogenous support with progesterone and estradiol.

Over the years, these two concepts have proven equally effective in significantly reducing OHSS in the OHSS risk patient and, notably, allowing fresh transfer with excellent reproductive outcomes. However, until now, the GnRH-a trigger is being used in daily in vitro fertilization (IVF) practice mainly for patients at risk of OHSS. Although many clinicians currently prefer GnRH-a to be used as the ovulation trigger for patients at high risk of OHSS, the question is whether scientific evidence also supports the use of GnRH-a and fresh transfer for the normal-responder patient?

GnRH-a TRIGGER AND MODIFIED LPS IN NORMAL-RESPONDER PATIENTS

This question was explored in two randomized controlled trials (RCTs). The first study included a total of 302 patients randomized to either hCG trigger or GnRH-a trigger, followed by a modified LPS. The modified LPS consisted of one bolus of 1.500 IU hCG administered on the day of oocyte retrieval, as well as a standard LPS including daily vaginal progesterone and oral estradiol. Two thirds of patients in both study groups were normal-responder patients (defined as having <13 follicles ≥ 11 mm on the day of trigger), whereas one third were at risk of OHSS development (≥ 13 follicles ≥ 11 mm). No OHSS case was seen in the collective group of patients who had GnRH-a trigger, compared with 2% in the hCG trigger group. The delivery rate was 31% after the hCG trigger, compared with 24% after the GnRH-a trigger; this difference was nonsignificant, so the reproductive outcome results still favor the hCG trigger (1).

Further evaluation of the data regarding numbers of follicles on the day of trigger showed that the normal-responder GnRH-a trigger patient group had a higher early-pregnancy loss rate compared with the patients at risk of OHSS, i.e., the group of patients with a high follicular count on the trigger day. This prompted us to perform a new RCT, in which normal-responder patients (≤ 14 follicles ≥ 11 mm) were randomized to either hCG trigger, followed by a standard LPS or GnRH-a trigger followed by the modified LPS described earlier. In this new study (3), however, an additional bolus of 1.500 IU hCG was added to the LPS regimen, on the day of oocyte retrieval $+5$.

At the time of randomization, patients in the GnRH-a group ($N = 125$) had developed a mean of 8.1 follicles, vs. 7.7 follicles in the hCG group ($N = 141$). Again, a nonsignificant difference in ongoing pregnancy rates between the GnRH-a and hCG trigger groups was seen. However, for the first time, results favored the GnRH-a trigger, 30% vs. 26% for the GnRH-a and hCG triggers, respectively. Thus, adding more LH activity around the time of implantation reduced the early-pregnancy loss rate in the GnRH-a trigger normal-responder group (3). However, the fact that two patients in the GnRH-a trigger group developed late-onset moderate OHSS shows that future studies are needed to explore the minimal hCG activity needed for luteal support without inducing late-onset OHSS.

Taken together, two large RCTs have proven the feasibility of the GnRH-a trigger and fresh transfer in the normal-responder patient. The potential future benefit of the GnRH-a trigger in the normal-responder patient, who is generally at low risk of OHSS development, is the possibility of introducing the exogenous progesterone–free LPS. This concept relies solely on endogenous progesterone production from the CL driven by small boluses of LH activity (hCG or recombinant LH) administered during the luteal phase. A further development of this concept would bring an end to unpleasant vaginal discharge and/or painful intramuscular injections, introducing a highly patient friendly protocol in IVF.

A GnRH-a TRIGGER AND A FREEZE-ALL-EMBRYO POLICY IN NORMAL-RESPONDER PATIENTS

In spite of the advantages linked to the GnRH-a trigger and modified LPS, late-onset OHSS may not be completely eliminated in a very small subgroup of normal-responder patients. This fact prompted researchers (4) to challenge the traditional concept of IVF treatment, which consists of ovarian stimulation, triggering of oocyte maturation, and embryo transfer (ET) during the same cycle. Instead, segmentation of the IVF cycle was suggested, separating the ovarian stimulation and trigger with a bolus of GnRH-a from the fresh transfer, and vitrifying all embryos for subsequent transfer in preferably stimulation-free frozen thawed cycles, as this could be the only way to completely eliminate OHSS.

However, the critical question is whether GnRH-a trigger with segmentation of the cycle is the optimal choice for women who are not at high risk of OHSS development. Considerable disadvantages do result from such a change in policy. First, the psychological burden for the patient, who would have to postpone ET, cannot be disregarded. Couples with 2 or more years of infertility are eager to proceed to treatment; thus, any delay of ET will increase the burden.

Second, such a shift in policy would increase the number of embryos that need to be frozen and the number of patients needed for follow-up for an additional treatment (frozen-thawed cycle). This shift would also undeniably increase the costs and the workload for fertility units; moreover, this increase could be quite high. For example, in a unit with a live-birth rate of 20%–30%, a freeze-all-embryo policy would mean an equal increase in the number of frozen-thawed cycles, and in blood testing and ultrasound scans. Finally, not all centers have good cryopreservation programs, so such a change of policy could be detrimental for cumulative pregnancy rates. Therefore, for many reasons, this concept may not be appropriate for the normal-responder patient.

On the other hand, proponents might claim that the GnRH-a trigger is more effective than the hCG trigger, given that some studies reported the retrieval of more mature oocytes after the former compared with the latter. This finding was attributed to the release of a more-physiological surge of gonadotropins, containing not only LH, but also FSH. However, this argument is not strong enough to justify implementation of a complete shift in clinical practice from the hCG to the GnRH-a trigger. We treat neither oocytes nor metaphase II oocytes; we treat infertile women and we care for a pregnancy and a live birth. In this context, recent data could indicate that a more effective approach is to use a GnRH-a trigger and a freeze-all strategy.

Oocyte vitrification techniques have changed the success rates of frozen-thawed cycles considerably. In addition, single-center randomized studies suggest a higher clinical pregnancy rate after frozen compared to fresh ET in normal-responder patients (5). Thus, GnRH-a trigger and a freeze-all policy could be a promising option to treat all IVF patients, regardless of their risk of developing OHSS. However, evidence is still lacking regarding the optimal protocol for priming of the endometrium in the oligo/amenorrhoic patient before frozen ET, and the optimal LPS. Moreover, possible epigenetic impacts, mainly related to birth weight, have been attributed to the freeze–thaw procedure, and large long-term follow-up studies are lacking in children conceived after frozen transfer.

In terms of total medical costs, the cost per live birth may be substantially lower, if a freeze-all strategy is universally adopted, given that clinical pregnancy rates appear to be higher after frozen ET (5). Additionally, data from recent registry analyses show that infants conceived from frozen embryos may have a significantly lower incidence of preterm birth compared to infants conceived from fresh embryos. Taken together, these finding further underscore the fact that a freeze-all policy may substantially reduce the costs for healthcare systems.

CONCLUSION

In this Conceptions piece, we set out to explore whether current scientific evidence supports the future use of a GnRH-a trigger in all IVF patients co-treated with a GnRH antagonist, regardless of ovarian response on the day of trigger. The studies examined, our own and those of others, provide evidence that this is a helpful approach. The GnRH-a trigger has offered an important insight into the early/mid luteal phase, which allows for a tailored approach to LPS, taking into account the ovarian response to stimulation of each individual patient. We predict that in near future the frequently used term "standard LPS" will be replaced by "tailored LPS," similar to the tailored approach to ovarian stimulation. The clear benefit of a GnRH-a trigger is that it leaves the clinician with several options for handling a patient's case. Thus, in patients with an extreme response to stimulation, a GnRH-a trigger followed by a "freeze-all" strategy is an optimal tool to eliminate OHSS.

In centers with good cryopreservation programs, this approach will secure a high live-birth rate during the subsequent frozen-ET cycles. In contrast, in patients with a high ovarian response (15–25 folicles $\geq$ 11 mm), a GnRH-a trigger followed by modifications of the LPS will still allow fresh transfer with an excellent reproductive outcome and a significantly reduced risk of OHSS. Finally, in patients with a normal ovarian response ($\leq$ 14 follicles), a GnRH-a trigger

with modified LPS can be an alternative to an hCG trigger, given the excellent pregnancy rates.

Segmentation of the IVF treatment appears to be an attractive option for women undergoing IVF treatment, and this approach has the potential to replace traditional IVF treatment. However, more evidence is needed to establish that the benefits of such a shift in clinical practice outnumber the disadvantages. Such evidence can only be achieved through well-conducted prospective trials, which are urgently needed.

However, we strongly believe that all the above-mentioned options will ensure that patients receive treatment that is safe, high quality, efficacious, and friendly. To answer the original question posed as to whether GnRH-a has the potential to become the gold standard for triggering ovulation in IVF, we say: "The king is dead—long live the king."

Peter Humaidan, M.D., D.M.Sc.[a]
Nikolaos P. Polyzos, M.D., Ph.D.[b]
[a] Faculty of Health, Aarhus University, and The Fertility Clinic, Skive Regional Hospital, Skive, Denmark; and
[b] Center for Reproductive Medicine, Universiteit Ziekenhuis Brussel, VUB, Brussels, Belgium

http://dx.doi.org/10.1016/j.fertnstert.2014.04.047

You can discuss this article with its authors and with other ASRM members at

http://fertstertforum.com/humaidanp-hcg-gnrha-trigger-art/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

REFERENCES

1. Humaidan P, Ejdrup BH, Westergaard LG, Yding AC. 1,500 IU human chorionic gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing hormone agonist is used for ovulation induction: a prospective, randomized, controlled study. Fertil Steril 2010;93:847–54.
2. Engmann L, DiLuigi A, Schmidt D, Benadiva C, Maier D, Nulsen J. The effect of luteal phase vaginal estradiol supplementation on the success of in vitro fertilization treatment: a prospective randomized study. Fertil Steril 2008; 89:554–61.
3. Humaidan P, Polyzos NP, Alsbjerg B, Erb K, Mikkelsen AL, Elbaek HO, et al. GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients. Hum Reprod 2013;28:2511–21.
4. Devroey P, Polyzos NP, Blockeel C. An OHSS-free clinic by segmentation of IVF treatment. Hum Reprod 2011;26:2593–7.
5. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. Fertil Steril 2011;96:344–8.