



Commentary

GnRHa trigger and luteal coasting: a new approach for the ovarian hyperstimulation syndrome high-risk patient?

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ABSTRACT

Final oocyte maturation using gonadotrophin-releasing hormone agonist (GnRHa) is increasingly common as it almost eliminates the risk of developing ovarian hyperstimulation syndrome (OHSS) in high-responder patients. The first studies using this approach showed a poor reproductive outcome when only vaginal progesterone was used as luteal phase support, due to the luteolysis that will develop as a result of LH withdrawal. Timely luteal administration of human chorionic gonadotrophin (HCG) will counterbalance the low LH concentrations and therefore maintain progesterone production from the corpora lutea, however, some patients with a high number of follicles will develop OHSS using this approach. The concept of 'luteal coasting' transfers the experience from follicular phase coasting for OHSS prevention to the early luteal phase for patients having fresh transfers. Daily monitoring of progesterone concentrations is required and a rescue HCG bolus can be administered, once progesterone concentrations drop below 30 nmol/l. This approach reduces the risk of OHSS development in high-responder patients undergoing fresh embryo transfer, without negatively impacting the reproductive outcome.

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Final oocyte maturation is the crucial step in ovarian stimulation cycles for IVF in order to retrieve mature oocytes for further processing in the IVF laboratory. In gonadotrophin-releasing hormone (GnRH) antagonist cycles, human chorionic gonadotrophin (HCG) as well as GnRH agonist can be administered for final oocyte maturation.

HCG binds to and activates the same receptor as LH and is, therefore, capable of inducing final oocyte maturation. GnRH agonist, on the other hand, acts by dislocating the GnRH antagonist from the GnRH

receptors in the pituitary and its administration results in a surge of LH and FSH (so-called 'flare-up'). This surge is sufficient to induce final oocyte maturation and ovulation (Gonen et al., 1990). The most important difference between LH and HCG is the difference in half-life, which is six to eight times longer for HCG compared with LH. The longer half-life of HCG is the crucial factor for the higher risk of ovarian hyperstimulation syndrome (OHSS), especially in the high-responder patient.

In recent years, the use of GnRH agonist for final oocyte maturation has become increasingly common, primarily because this approach significantly reduces the incidence of OHSS (Devroey et al., 2011) by rapid luteolysis after administration.

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As has been established in primates as well as in humans, the duration of the LH/FSH surge is critical for a normal luteal function. An LH increment of too short a duration prevents the granulosa cells from completing luteinization, leading to a corpus luteum with impaired secretory function and a shortened lifespan. Due to the short duration of the induced LH/FSH peak after GnRH agonist administration, the luteal phase is characterized by severe luteolysis and luteal phase insufficiency (Fatemi et al., 2013). At the same time, the supra-physiological concentrations of oestradiol and progesterone after ovarian stimulation inhibit LH secretion from the pituitary via negative feedback mechanisms. Despite the continued pulsatile LH secretion, the mean LH concentration and LH pulse amplitude are lower compared with the natural cycle. Hence, the process of luteolysis starts very early in the luteal phase, which is demonstrated by the decline of progesterone and oestradiol concentrations 2 days after ovulation (Tannus et al., 2017).

After the introduction of GnRH agonist triggers, the first studies reported a very poor reproductive outcome using this approach with a standard luteal phase support (Humaidan et al., 2005) and it was clear that a standard luteal phase with application of vaginal progesterone only could not counterbalance the severe luteal phase insufficiency. However, a more 'aggressive' luteal phase support with the use of daily 50 mg i.m. progesterone and oestradiol supplementation leads to implantation, clinical and ongoing pregnancy rates which are comparable with the rates after HCG trigger (Engmann et al., 2008). Higher serum progesterone concentrations are achieved by i.m. progesterone than by vaginal progesterone administration and these might be able to compensate for the abnormal luteal phase after GnRH agonist trigger.

Interestingly, luteolysis after GnRH agonist trigger is not always complete and may vary, indicating individual differences among patients (Lawrenz et al., 2017). Luteolysis will be induced if LH support is withdrawn from the corpus luteum for ≥ 3 days, hence, corpus luteum function can be rescued if LH activity is reinitiated within approximately 72 h (Hutchison and Zeleznik, 1985) and in the appropriate dosage (HCG ≥ 1500 IU) (Dubourdieu et al., 1991).

Thus, according to physiology, luteolysis can be prevented by LH activity administration and it was shown that administration of 1500 IU of HCG 35 h after GnRH agonist trigger results in ongoing pregnancy rates similar to those of HCG trigger. Unfortunately, with this dosage, OHSS may still occur in the high-responder-group (Humaidan, 2009).

One could argue that GnRH agonist trigger followed by a 'freeze-all' approach (cycle segmentation) would result in the 'OHSS-free clinic'; however, even with this approach, OHSS cannot be completely avoided (Fatemi et al., 2014). Cycle segmentation may not be acceptable for all parties due to legal, ethical or economic reasons. Moreover, cryopreservation may produce molecular alterations in key genes and transcripts which are undetectable by traditional assays, and such modifications might have long-term consequences for the child conceived after frozen-thawed embryo transfer (Kopeika et al., 2015). Until now there is still a lack of long-term safety – and children – follow-up studies.

A relatively new concept is so-called 'luteal coasting'. To avoid premature HCG application with the risk of OHSS development, Kol et al. (2015) introduced the principle of luteal coasting into the luteal phase support after final oocyte maturation using GnRH agonist, by transferring the experience from follicular phase coasting for OHSS prevention to the early luteal phase. This approach requires daily monitoring of serum progesterone concentrations and the administration

of a rescue bolus of HCG once progesterone concentrations drop below 30 nmol/l (Kol et al., 2015). As was recently shown, the range of progesterone concentrations 48 h after GnRH agonist trigger differs widely between patients (Lawrenz et al., 2017); thus, this approach requires individualization of luteal phase support according to the patient-specific luteolysis.

The lower limit of progesterone to achieve a pregnancy is unknown and different concentrations have been described in the literature, one defining mid-luteal progesterone concentrations below 10 ng/ml (31.8 nmol/L) or a sum of three random serum P measurements < 30 ng/ml (95.4 nmol/l) as sufficient to define luteal phase deficiency in the natural cycle (Jordan et al., 1994). Kol et al. (2015) suggested that the cut-off level for corpus luteum rescue, using a bolus of HCG, should be chosen according to the progesterone threshold in the natural cycle, which was described at a level of 30 nmol/l ($= 9.43$ ng/ml), whereas others reported that patients undergoing IVF treatment with progesterone concentrations of more than 30 ng/ml and oestradiol concentrations of more than 100 pg/ml on the day of implantation are more likely to have a viable and ongoing pregnancy compared with patients with hormone concentrations below those thresholds.

Administration of HCG can reverse luteolysis when administered within 72 h after withdrawal of the LH support, however, the amount of HCG needed is still a matter for discussion and might require individualization. Besides the administration of 1500 IU HCG 35 h after GnRH agonist, approaches with lower amounts of HCG were evaluated and showed a normalization of the reproductive outcome. Interestingly, some patients may not require any HCG for corpus luteum rescue at all due to a lack of luteolysis (Kol and Breyzman, 2016).

In summary, 'luteal coasting' seems to reduce the risk of OHSS development in high-responder patients undergoing fresh embryo transfer, without negatively impacting the reproductive outcome. The key to this approach is daily monitoring of the progesterone level and, depending on the patient's individual degree of luteolysis, the application of a rescue HCG bolus. In order to fine-tune this concept, future studies should investigate its efficacy, the predictive parameters of luteolysis, the lowest progesterone level consistent with ongoing pregnancy and the minimum amount of HCG needed to rescue the luteal phase.

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