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COMMENTARY

LH (as HCG) and FSH surges for final oocyte maturation: sometimes it takes two to tango?

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Abstract Until now, clinicians have been relying solely on LH activity-dependent triggering of final oocyte maturation and thus taken it for granted that the natural midcycle FSH surge is biologically redundant. However, it is time to question this paradigm. Evidence from clinical studies hint that in a yet-to-be-defined subset of patients, dual LH and FSH surge is advantageous compared with LH-only surge in the form of human chorionic gonadotrophin (HCG) trigger. Dual surge can be triggered by a bolus of gonadotrophin-releasing hormone agonist causing a flare-up of both endogenous LH and FSH, resembling the natural midcycle surge of gonadotrophins. HCG given in parallel secures adequate exposure to LH activity. Further research is needed to characterize the patients in whom FSH surge is needed for proper resumption of the oocyte meiotic process. 

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In assisted reproduction treatment, human chorionic gonadotrophin (HCG) has been used as a surrogate for the midcycle luteinizing hormone (LH) surge for several decades, ensuring excellent exposure of the growing follicle to LH activity. Due to its structural and biological similarities with LH, HCG binds to and activates the same receptor as LH, the LH/HCG receptor (Ascoli et al., 2002). However, as the half-life of HCG is considerably longer than that of LH (Damewood et al., 1989), the LH like activity induced by a bolus of HCG, is significantly different from that of the natural midcycle LH surge. Moreover, there is a complete lack of the FSH surge seen during the natural midcycle surge of gonadotrophins (Hoff et al., 1983). Although, the role of the FSH midcycle surge is not fully explored, it is known to promote LH receptor formation in luteinizing granulosa cells, nuclear maturation (i.e. resumption of meiosis) and cumulus expansion (Eppig, 1979; Stickland and Beers, 1976; Yding Andersen, 2002; Yding Andersen et al., 1999; Zelinski-Wooten et al., 1995).

Until now, clinicians have been relying solely on LH activity-dependent triggering of final oocyte maturation and thus taken it for granted that the natural midcycle FSH surge is biologically redundant. However, this paradigm should be questioned. How can an FSH surge be induced? To give a very large bolus of recombinant FSH at the time of triggering ovulation with HCG is one option, although not very practical, and as far as is known is not described in a randomized trial. However, with the introduction of the gonadotrophin-releasing hormone (GnRH) antagonist protocols for the prevention of a premature LH surge it has become possible to reintroduce the FSH surge in assisted reproduction treatment, as a bolus of GnRH agonist will displace the GnRH antagonist from the GnRH receptor and induce a flare-up of both endogenous LH and FSH, resembling the natural midcycle surge of gonadotrophins, prior to down-regulation of the receptor. Although the surge of gonadotrophins elicited by a bolus of GnRH agonist differs significantly from the natural midcycle of gonadotrophins in duration and profile, it has previously been shown to

effectively stimulate final oocyte maturation and ovulation (Gonen et al., 1990; Hoff et al., 1983; Itskovitz et al., 1991). However, the reduced LH secretion in the early to midluteal phase seen after GnRH agonist triggering has been shown to induce corpus luteum deficiency and a defective luteal phase (Balasch et al., 1995; Segal and Casper, 1992), leading to a poor reproductive outcome in IVF/intracytoplasmic sperm injection (ICSI) cycles (Humaidan et al., 2005; Kolibianakis et al., 2005).

During a series of trials Humaidan (2009) and Humaidan et al. (2006, 2009) have developed a protocol employing GnRH agonist for ovulation induction and securing the luteal phase function with a small bolus of 1500 IU HCG administered after the oocyte retrieval just before the patient leaves the clinic in order not to interfere with the ovulatory signal induced by GnRH agonist. This results in live birth rates comparable to those seen after HCG triggering. Importantly, more metaphase II oocytes have repeatedly been retrieved following GnRH agonist triggering as compared with HCG triggering (Humaidan et al., 2005, 2009; Imoedemhe et al., 1991; Oktay et al., 2009). The underlying mechanism for this finding is not determined, but could be a result of LH and FSH activity closer to the conditions of the natural midcycle surge of gonadotrophins.

Another option is using a dual trigger. This way of triggering final oocyte maturation was reported by Schachter et al. (2008) who conducted a randomized prospective controlled study in 200 IVF/ICSI patients undergoing a GnRH antagonist protocol. The study group consisted of 97 patients who were triggered with a combination of HCG (5000 IU) and GnRH agonist (triptorelin 0.2 mg) while the control group consisted of 103 patients who were triggered with HCG (5000 IU), only. A significantly higher serum FSH and LH concentrations on the day of oocyte retrieval and a significantly higher ongoing pregnancy rate in completed cycles was seen in the study group.

Furthermore, Shapiro et al. (2008) employed the dual-trigger concept in 45 IVF/ICSI patients at risk of developing ovarian hyperstimulation syndrome (OHSS). The bolus of GnRH agonist was fixed (leuprolide acetate, 4 mg), while the HCG bolus varied between 1000 to 2500 IU according to weight. A mean of 20 oocytes were retrieved, and an ongoing pregnancy rate of 53% and a low early pregnancy loss rate was reported, while no OHSS was seen.

Some of the studies mentioned (Humaidan, 2009; Humaidan et al., 2006, 2009; Shapiro et al., 2008) employed a minimal bolus of HCG to rescue the function of the corpus luteum/luteal phase in relation to triggering with GnRH agonist; either GnRH agonist trigger followed by a small bolus of 1500 IU HCG at 35 h, or dual-trigger including a combination of GnRH agonist and 1000–2500 IU HCG. Apart from rescuing the luteal phase, the reduction in HCG could have an impact on the growth of medium-sized follicles in the late follicular phase (Sullivan et al., 1999). Moreover, it should be recalled that the commonly used bolus of 10,000 IU HCG induces a significant histological advancement and reduced mitotic activity of the endometrium, which might negatively affect the endometrial receptivity (Fanchin et al., 2001).

Finally, a standard bolus of 10,000 IU HCG will induce supraphysiological steroid concentrations (progesterone and oestradiol) during the luteal phase whereas GnRH ago-

nist triggering including a small bolus of HCG will induce steroid concentrations closer to those of the natural cycle which positively affects the secretion of LH from the pituitary (Fatemi, 2009; Tavaniotou and Devroey, 2003; Tavaniotou et al., 2001).

In conclusion, the exact role of the midcycle FSH surge is still far from being unraveled and more data is needed to prove that the FSH surge induced by GnRH agonist triggering is an efficacious component. However, with GnRH agonist triggering, the negative impact of high-dose HCG administration both in terms of endometrial receptivity, luteal phase steroid concentrations and OHSS can be significantly reduced. Finally, for the time being, it cannot be ruled out that in some patients, the FSH surge is needed for proper resumption of the meiotic processes of the oocyte.

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