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REVIEW

The luteal phase after GnRH-agonist triggering of ovulation: present and future perspectives

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Abstract In stimulated IVF/intracytoplasmic sperm injection cycles, the luteal phase is disrupted, necessitating luteal-phase supplementation. The most plausible reason behind this is the ovarian multifollicular development obtained after ovarian stimulation, resulting in supraphysiological steroid concentrations and consecutive inhibition of LH secretion by the pituitary via negative feedback at the level of the hypothalamic–pituitary axis. With the introduction of the gonadotrophin-releasing hormone-(GnRH) antagonist, an alternative to human chorionic gonadotrophin triggering of final oocyte maturation is the use of GnRH agonist (GnRHa) which reduces or even prevents ovarian hyperstimulation syndrome (OHSS). Interestingly, the current regimens of luteal support after HCG triggering are not sufficient to secure the early implanting embryo after GnRHa triggering. This review discusses the luteal-phase insufficiency seen after GnRHa triggering and the various trials that have been performed to assess the most optimal luteal support in relation to GnRHa triggering. Although more research is needed, GnRHa triggering is now an alternative to HCG triggering, combining a significant reduction in OHSS with high ongoing pregnancy rates.

KEYWORDS: GnRH agonist, GnRH antagonist, HCG, IVF, luteal phase, ovulation induction

Introduction

With the introduction of gonadotrophins for ovarian stimulation in patients undergoing IVF treatment, it became obvious that the luteal phase of all stimulated IVF cycles was abnormal (Edwards et al., 1980) as compared with 8% of natural cycles (Rosenberg et al., 1980).

The aetiology of the luteal-phase defect in stimulated IVF cycles has been debated for more than three decades.

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Initially, it was argued that the removal of large quantities of granulosa cells during oocyte retrieval might negatively impact the function of the corpora lutea, leading to a luteal-phase insufficiency. However, this hypothesis was rejected when it was established that the aspiration of pre-ovulatory oocytes in a natural cycle neither diminished the luteal-phase steroid secretion nor shortened the length of the luteal phase (Kerin et al., 1981).

As steroid-hormone production by the corpus luteum is totally dependent on the pulsatile secretion of LH by the pituitary (Devoto et al., 2000), it was suggested that the prolonged pituitary desensitization following a long gonadotrophin-releasing hormone-(GnRH) agonist (GnRHa) down-regulation to prevent a premature LH rise might result in circulating LH concentrations too low to support the corpora lutea, causing a luteal-phase defect (Smitz et al., 1992a,b). Thus, with the introduction of GnRH antagonists in IVF protocols it was anticipated that luteal-phase supplementation would be unnecessary due to the rapid recovery of the pituitary (within 2 days) after GnRH-antagonist discontinuation (Oberyé et al., 1999). However, subsequent IVF/intracytoplasmic sperm injection (ICSI) studies using GnRH antagonist co-treatment did not confirm this expectation. On the contrary, luteolysis was also induced prematurely after GnRH-antagonist co-treatment, resulting in a significant reduction in the luteal-phase length and a compromised reproductive outcome (Albano et al., 1998; Beckers et al., 2003). Thus, despite the rapid recovery of the pituitary in GnRH-antagonist protocols, luteal-phase supplementation was necessary (Dal Prato and Borini, 2005; Tarlatzis et al., 2006).

Finally, it was proposed that the triggering bolus of human chorionic gonadotrophin (HCG) administered for final oocyte maturation in stimulated cycles could potentially cause a luteal-phase defect by suppressing the LH secretion of the pituitary via a short-loop feedback mechanism (Miyake et al., 1979). However, this theory was questioned after the results of a cohort study, showing that the administration of HCG did not decrease luteal-phase LH concentrations in the natural cycle of normogonadotrophic women (Tavaniotou and Devroey, 2003).

Presently, according to recent research, the most plausible reason for the luteal-phase insufficiency seen after ovarian stimulation is the multifollicular development achieved during the follicular phase, resulting in luteal supraphysiological concentrations of progesterone and oestradiol which directly inhibit the LH secretion by the pituitary via negative feedback actions at the level of the hypothalamic–pituitary axis (Fatemi, 2009; Fauser and Devroey, 2003; Tavaniotou and Devroey, 2003; Tavaniotou et al., 2001). This has been shown to have a dramatic effect on the reproductive outcome (Humaidan et al., 2005, 2010) as LH plays a crucial role during the luteal phase not only for the steroidogenic activity of the corpus luteum (Casper and Yen, 1979), but also for the up-regulation of growth factors (Sugino et al., 2000; Wang et al., 2002) and cytokines (Licht et al., 2001a,b), which are important for implantation. Apart from this, the activation of extragonadal LH receptors, expressed in human endometrium, is thought to enhance and support implantation (Rao, 2001; Tesarik et al., 2003).

Ovarian stimulation and the endometrium

During ovarian stimulation, an endometrial histological advancement has been observed on the day of oocyte retrieval when comparing with the endometrium from the ovulation day in natural cycles (Bourgain et al., 2002; Kolibianakis et al., 2002). The endometrial advancement has mainly been considered to be the result of the exposure of the endometrium to supraphysiological steroid hormones throughout the IVF treatment, independent of the type of GnRH analogue administered during the follicular phase (Bourgain et al., 2002). Importantly, an endometrial advancement exceeding 3 days has been shown to negatively impact the reproductive outcome (Kolibianakis et al., 2002; Ubaldi et al., 1997).

HCG triggering of final oocyte maturation

In the natural cycle, ovulation is induced by the mid-cycle surge of LH (and FSH) from the pituitary, elicited by an increasing late follicular concentration of oestradiol. More than 50 years ago, exogenous HCG (5000–10,000 IU) was successfully introduced as a substitute for the endogenous LH surge to induce final oocyte maturation. Sharing the same α subunit and 81% of the amino-acid residues of the β subunit, LH and HCG bind to the same receptor, the LH/HCG receptor (Kessler et al., 1979). However, due to the significantly longer half-life of HCG, the ovulatory dose will support the corpora lutea for 7–10 days, after which HCG is cleared from circulation (Damewood et al., 1989; Mannaerts et al., 1998); from now on, the corpora lutea will be totally dependent on the endogenous LH secretion by the pituitary or by the HCG production from an implanting embryo. Importantly, the significantly longer half-life of HCG, as compared with LH, leads to a prolonged luteotrophic effect, development of multiple corpora lutea and raised serum concentrations of oestradiol and progesterone throughout the luteal phase (Itskovitz et al., 1991), increasing the risk of ovarian hyperstimulation syndrome (OHSS) (Haning et al., 1985). Not only because of the increased risk of OHSS by triggering final oocyte maturation with HCG but also because of reports on a negative impact of HCG on endometrial receptivity and embryo implantation (Fanchin et al., 2001; Fatemi et al., 2010; Forman et al., 1988; Valbuena et al., 2001), alternative triggering methods have been investigated.

GnRHa triggering of final oocyte maturation

Previously, GnRHa was shown to effectively stimulate ovulation and final oocyte maturation, inducing an initial secretion of LH and FSH (flare-up), similar to that of the natural cycle, prior to down-regulation of the receptor (Gonen et al., 1990; Itskovitz et al., 1991). The GnRHa trigger concept gained some interest in the late 1980s and early 1990s. However, with the introduction of GnRHa for pituitary down-regulation prior to IVF/ICSI treatment (Porter et al., 1984), this concept was clearly not applicable, as the simultaneous use of GnRHa for down-regulation and triggering of final oocyte maturation is not possible.