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REVIEW

Improving the luteal phase after ovarian stimulation: reviewing new options

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Abstract The human chorionic gonadotrophin (HCG) trigger used for final follicular maturation in connection with assisted reproduction treatment combines ovulation induction and early luteal-phase stimulation of the corpora lutea. The use of a gonadotrophin-releasing hormone agonist (GnRHa) for final follicular maturation has, however, for the first time allowed a separation of the ovulatory signal from the early luteal-phase support. This has generated new information that may improve the currently employed luteal-phase support. Thus, combined results from a number of randomized controlled trials using the GnRHa trigger suggest an association between the reproductive outcome after IVF treatment and the mid-luteal-phase serum progesterone concentration. It appears that a minimum mid-luteal progesterone threshold of approximately 80–100 nmol/l exists, which, when surpassed, results in reduced early pregnancy loss and an increased live birth rate. Further, the trade off between the HCG bolus and the subsequent risk of ovarian hyperstimulation syndrome has resulted in a trend to reduce the HCG bolus from 10,000 IU to 6500–5000 IU, which augments the HCG/LH deficiency during the early/mid-luteal phase. The mid-luteal HCG/LH shortage results in an altered progesterone profile, showing the highest concentration during the early luteal phase, contrasting with the mid-luteal peak seen in the natural menstrual cycle.

KEYWORDS: corpus luteum function, early pregnancy loss, GnRH agonist trigger, low dose hCG, luteal phase, progesterone

Introduction

Ovarian stimulation protocols for patients who receive fertility treatment have undergone numerous refinements during the last two to three decades. Efforts to optimize ovarian stimulation protocols during the follicular phase have been the focus of many clinical trials and studies in which the whole armamentarium of drugs affecting

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follicular development has been tested in different combinations. In parallel, a huge effort has been made to optimize treatment outcomes by introducing the highest standards of embryo culture and laboratory techniques. The two remaining essential parts for a successful assisted reproduction treatment — the type of stimulation used for final follicular maturation and the luteal-phase support — have received less interest. Thus, final follicular maturation and rescue of the disrupted luteal phase seen after ovarian stimulation has almost exclusively been performed by the use of a large bolus of human chorionic gonadotrophin (HCG; i.e. 5000–10,000 IU), which, apart from the induction of the ovulatory processes, also directly stimulates the endogenous progesterone production by the multiple corpora lutea during the early luteal phase. The two combined effects of the HCG bolus trigger merge the period of events leading to final maturation of oocytes and appropriate luteal-phase stimulation prior to implantation.

However, the use of an HCG bolus for final follicular maturation as the golden standard has recently been challenged by the use of a GnRH agonist (GnRHa) trigger in patients cotreated with a GnRH antagonist. The GnRHa trigger concept utilizes a different mechanism to induce final follicular maturation than that of HCG, resulting in the release of an endogenous surge of both LH and FSH from the pituitary. The GnRHa trigger was originally developed in the early 1990s (Andersen et al., 1993; Gonen et al., 1990; Itskovitz et al., 1991), but cannot be used in connection with the use of GnRHa for pituitary down-regulation, as in the long agonist protocol, and has only received renewed interest in parallel to the introduction of the antagonist protocol in the early part of the 21st century (Felberbaum et al., 2000).

Although the GnRHa-elicited surge is sufficient to induce final maturation of oocytes with a similar efficacy as HCG (Acevedo et al., 2006; Bodri et al., 2009; Griesinger et al., 2007), it is short lived and does not provide the continuous prolonged stimulation of the early corpus luteum that HCG does. The separation of the ovulatory signal from the stimulation of the early corpus luteum by the use of the GnRHa trigger for the first time allowed studies that directly addressed either one of these two events separately. Indeed, despite good oocyte and embryo quality, an initial substantial effort was required to develop support for the luteal phase after GnRHa trigger in order to obtain results similar to the use of the HCG trigger (Humaidan et al., 2005, 2006, 2010, 2013; Kolibianakis et al., 2005).

Importantly, these direct studies of the luteal-phase support have offered new insights as to how the current luteal-phase support may be improved. The aim of the present review is to discuss these issues and to suggest modes of possibly optimizing the luteal phase after ovarian stimulation.

Hormone concentrations during the normal luteal phase and after ovarian stimulation: the functions of progesterone

In response to the mid-cycle surge of gonadotrophins or to an exogenous HCG bolus administration, the corpus luteum is created by the transformation of granulosa and theca cells into luteal cells. The most important function of the corpus luteum is progesterone secretion, as progesterone is necessary to obtain a secretory transformation of the endometrium, crucial for successful implantation. Further and equally important, progesterone is indispensable for the maintenance of early pregnancy. Thus, an insufficient progesterone concentration at the time of implantation or during early pregnancy may cause early pregnancy loss (EPL) or lack of implantation. The incidence of luteal-phase deficiency has been reported to be in the range of 3.5–20% of infertile patients (Balasch et al., 1995).

In addition to supporting endometrial development, progesterone is thought to facilitate implantation by promoting the immune system to produce noninflammatory T-helper-2 cytokines (Druckmann and Druckmann, 2005; Szekeres-Bartho et al., 2008). Moreover, improvement of blood flow and oxygen to the endometrium is also accomplished through progesterone actions by increasing nitric oxide production (Simoncini et al., 2006; Sladek et al., 1997). Finally, progesterone reduces the contractility of the myometrium at the time of implantation, which is believed to promote implantation (Hill et al., 1990).

Throughout the luteal phase of the normal menstrual cycle, LH concentration is confined to a relatively narrow range of about 4–10 IU/l. This concentration is sufficient to induce a peak of progesterone during the mid-luteal phase, normally occurring approximately 7 or 8 days after the mid-cycle surge (unless pregnancy occurs). A progesterone concentration of 25 nmol/l during the mid-luteal phase of the natural cycle is considered to reflect ovulation and a normally functioning corpus luteum. However, progesterone concentration often varies and rises to considerably more than this, even after monofollicular ovulation. Moreover, peripheral progesterone concentration starts to increase in connection with ovulation, exceeding 20 nmol/l about 3 or 4 days after the mid-cycle surge (Groome et al., 1996).

Ovarian stimulation typically involves pituitary desensitization either in the form of GnRHa or GnRH antagonist administration. In the early luteal phase, this often results in reduced endogenous release of gonadotrophins (Messinis, 2006), and the HCG activity from the HCG bolus is necessary to maintain functional corpus luteum. Furthermore, due to the multiple corpora lutea, supraphysiological concentrations of oestradiol and progesterone are observed during the luteal phase following ovarian stimulation, which, by negative feedback, reduce the amount of LH released from the pituitary. Therefore, the continuous release of progesterone from the corpora lutea is dependent on exogenous LH-like activity (or HCG produced by an implanting embryo). Due to the multiple corpora lutea and the use of a large bolus of HCG for final follicular maturation, progesterone concentration during the mid-luteal phase often rises to 100–250 nmol/l or more, and its concentration is positively associated with the dose of HCG used for luteal-phase support (Humaidan et al., 2010, 2013).

Luteal-phase support after GnRHa trigger

This study group has performed three randomized controlled trials in which a GnRHa trigger was compared with