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COMMENTARY

Time-sensitive assessment of luteal phase progesterone after HCG ovulation triggering: another brick off the wall?

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ABSTRACT

In recent years, there has been growing interest in understanding the dynamics of progesterone levels during the luteal phase after HCG-triggered ovulation. Recent studies have provided data showing a deviation from the natural ovulatory cycle, with peak progesterone concentrations occurring earlier and declining steadily thereafter, demonstrating that a fall in progesterone concentration early in the luteal phase was associated with lower rates of ongoing pregnancy. These findings highlight the importance of changes in progesterone concentration, rather than absolute concentrations, in determining optimal endometrial conditions. The disadvantages of HCG triggering, including the lack of a natural FSH surge and asynchronization between embryo age and endometrium receptivity, can be addressed by using gonadotrophin-releasing hormone agonist (GnRHa) triggering. GnRHa triggering induces both LH and FSH surges, ensures appropriate progesterone concentrations and offers flexibility in manipulating the luteal phase. Transitioning to GnRHa triggering could improve infertility treatment.

INTRODUCTION

In recent years, there has been growing interest in the precise dynamics of progesterone concentrations during the luteal phase following HCG-triggered ovulation. Although HCG has been widely used for ovulation triggering, only recently have we seen a detailed, time-sensitive account of luteal phase progesterone concentrations. The importance of changes in luteal phase progesterone concentrations over time was previously postulated by *Kol and Homburg (2008)*.

HCG OVULATION TRIGGERING

Vuong and colleagues (*Vuong et al., 2020*) provided data on early luteal phase progesterone concentrations after HCG (6500 IU) triggering in 161 patients who did not receive any exogenous luteal phase support. Repeated blood sampling was used to follow changes in progesterone concentration following oocyte retrieval. Although there was marked interpersonal variation, serum progesterone peaked at oocyte retrieval + 4 days in 38.8% of the whole patient population (median 106.53 ng/ml with a range of 24.79–253.05 ng/ml). A total of 65% of patients had a fall in progesterone concentration from oocyte retrieval + 4 days to oocyte retrieval + 6 days. About 40% of patients had a significant (>50%) decrease in progesterone concentration from oocyte retrieval + 4 days to oocyte retrieval + 6 days. Such findings clearly deviate from the physiological pattern seen in a natural ovulatory cycle, where progesterone concentrations typically increase continuously from the day of ovulation, reaching a peak that coincides with the implantation window.

Do we pay a price for this deviation from physiology? A positive answer to this question came recently with a study of 340 patients by Uyanik and colleagues (*Uyanik et al., 2023*). These patients were stimulated with a long agonist or antagonist protocol, and were triggered with HCG (6500 IU). Standard luteal support was given starting a day after oocyte retrieval. Repeated progesterone measurements demonstrated a lower (about two-fold decrease) ongoing pregnancy rate in women with a fall in circulating progesterone concentration from 3 days after oocyte retrieval to 5 days after oocyte retrieval, which occurred in one-third of the participants. Moreover, the study showed that the larger the fall in progesterone, the lower the ongoing pregnancy rate.

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KEY WORDS
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These two studies clearly demonstrate that the crucial impact of changes in progesterone concentration during the early luteal phase (following the HCG trigger) on cycle outcome is primarily influenced by the change in progesterone (a sharp drop), rather than the concentration itself, which ultimately determines optimal endometrial conditions.

This disadvantage of using HCG for ovulation triggering adds to those previously described: the absence of a natural HCG surge, excessive stimulation of the corpora lutea during the early luteal phase resulting in elevated concentrations of oestradiol and progesterone leading to negative feedback at the pituitary level, suppression of pituitary LH secretion, the need to support luteal phase with exogenous progesterone, and the risk of asynchronization between the age of the embryo and the receptivity of the endometrium due to the implantation window occurring too early (*Fauser and Devroey, 2003*; *Tesarik et al., 2020*; *Yding Andersen and Vilbour Andersen, 2014*).

GONADOTROPHIN-RELEASING HORMONE AGONIST OVULATION TRIGGERING

All these issues can be circumvented by using gonadotrophin-releasing hormone agonist (GnRHa) for ovulation triggering, which elicits surges in both LH and FSH. In most patients peak progesterone is reached 2 days after oocyte retrieval (range 40–100 nmol/l), and decreases thereafter (*Kol et al., 2015*). This finding was confirmed later by Vuong and colleagues (*Vuong et al., 2016*). This progesterone range is comparable to the optimum window for the early luteal phase demonstrated by Thomsen and co-workers (*Thomsen et al., 2018*).

Moreover, GnRHa triggering gives the practitioner the flexibility to use the 'freeze-all' approach if ovarian hyperstimulation syndrome risk is imminent, or to manipulate the luteal phase at will. For example, a single bolus of 1500 IU HCG given 48 hours after oocyte retrieval will secure a continuous rise of progesterone all the way to the implantation window (*Kol and Segal, 2020*), without the need for any additional luteal phase support. Moreover, this approach guarantees that each retrieved follicle develops into a functional corpus luteum, overcoming the diminished capacity of progesterone receptors induced by high oestradiol concentrations.

CONCLUSIONS

The assessment of female reproductive endocrinology must consider changes in hormonal concentrations over time, as they convey vital biological messages. Recent comprehensive studies shed more light on the luteal phase after ovulation triggering, emphasizing changes in hormonal concentration, rather than a fixed point measurement. These studies further establish the need to replace the 'time-honoured' HCG triggering approach with GnRHa triggering as previously suggested (*Humaidan et al., 2011*).

DATA AVAILABILITY

No data was used for the research described in the article.

DECLARATION

The authors report no financial or commercial conflicts of interest.

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