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REVIEW ARTICLE

Time, time, time: see what governs the luteal phase endocrinology

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ABSTRACT

Two modes of ovulation trigger are used in IVF: hCG, acting on ovarian LH receptors, and GnRH agonist, eliciting pituitary LH and FSH surges. These two modes are evaluated herein, focusing on how they serve specific time-sensitive events crucial for achieving embryo implantation and pregnancy. hCG trigger is associated with significant timing deviation from physiology. Peak progesterone is not synchronized with implantation window; progesterone level does not rise continuously to a mid-luteal peak, but rather drops from a too early peak. The luteal phase endocrinology post GnRH agonist trigger is characterized by a quick and irreversible luteolysis. Therefore, freeze all strategy is advised, if there is a risk of ovarian hyperstimulation syndrome. If fresh transfer is desired, numerous approaches for luteal phase support have been suggested. However, a thorough understanding of time-sensitive events suggests that a single 1,500 IU hCG dose, administered 48 h post oocyte retrieval, is all that is needed to fully support the luteal phase and secure best chances of achieving pregnancy.

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Introduction

The male reproductive endocrinology is characterized by a stable, constant activity of the hypothalamus-pituitary-gonadal axis. In contrast, the female reproductive system is characterized by multiple time-sensitive events that must be precisely coordinated to achieve its ultimate goal: live birth.

Indeed, this adds considerable complication to the study of the female reproductive system; however, all hormonal events must be viewed with an eye focused on change over time. This concept was described previously [1]. The purpose of the current paper is to delineate crucial time-sensitive events in the luteal phase endocrinology post oocyte retrieval for IVF.

Ovarian stimulation for IVF is all but normal physiology. The aim is to achieve 10–12 oocytes, which means 10–12 estradiol (E_2)-producing follicles in the follicular phase, and progesterone (P) (and E_2)-producing corpora lutea (CL) in the luteal phase, with the associated significant deviation from the levels seen in a natural ovulatory cycle. Therefore, in order to secure embryo implantation, mid-luteal P must correlate with peak E_2 in the late follicular phase [2]. As a rule of thumb, if adequate P levels cannot be achieved without high risk of ovarian hyperstimulation syndrome (OHSS), freeze all embryos strategy is advised.

Currently, two modes of ovulation trigger are used in IVF: hCG, acting on ovarian LH receptors, and GnRH agonist, eliciting pituitary LH and FSH surges. These two modes are completely different from the time-dependent endocrine perspective, and deserve separate discussions.

hCG trigger

Currently, the most frequently used product is a pen-like injection device containing 250 µg human recombinant hCG (6,500 IU). The trigger shot is given 36 h before oocyte retrieval. The early luteal endocrinology post hCG trigger was described in details by Vuong et al. [3]. Peak P concentration occurred four days after oocyte retrieval, with an average of a 35% fall from day four to day six (start of implantation window). Goldrat et al. [4] reported similar results. This is a significant deviation from physiology in two important time-sensitive aspects:

- Excess early P might hasten endometrial receptivity, creating a time gap between endometrium and embryo age.
- In the natural ovulatory luteal phase, P rises continuously to a peak in the mid-luteal phase, which coincides with the implantation window. Post hCG trigger, peak P occurs 2–3 days before implantation window.

P-based luteal support dose not correct this anomaly [5].

Does high early luteal P have an effect on cycle outcome? Probably yes, and probably a negative effect. In a prospective study of 602 IVF/ICSI cycles, Thomsen et al. [6] showed that high early luteal P is associated with a reduced chance of a live birth.

In the ESHRE 36th annual meeting abstract, Uyanik et al. [7] reported that a drop in P, on the day of blastocyst transfer, is associated with significantly lower ongoing pregnancy rates. A drop in P level from day 3 to day 5 post oocyte retrieval was seen in 35% of patients, and was associated with significantly lower ongoing pregnancy rate.

In summary: hCG trigger is associated with significant deviation of time-sensitive endocrine events from physiology. Peak P is not synchronized with implantation window, P level does not rise continuously to a mid-luteal peak, but rather drops from a too early peak, undermining pregnancy rate. This drop does not happen in a natural ovulatory cycle.

GnRH agonist trigger

The use of GnRH agonist as trigger has gained popularity for two main reasons: its ability to almost completely prevent OHSS,

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and its ability to elicit a more physiological surge event (compared with hCG) comprised of LH and FSH surges.

The luteal phase endocrinology post GnRH agonist trigger is characterized by a quick and irreversible luteolysis [8,9].

Timing and mechanism of luteolysis post GnRH agonist trigger

In most patients, luteolysis starts 48 h post oocyte retrieval [10]. Importantly, based on Figure 1, peak P post GnRH agonist trigger in the early luteal phase is in the range of 40–100 nmol/l, which is comparable to the favorable levels described by Thomsen et al. [6] (60–100 nmol/l). Previous experiments [11,12] showed that natural cycle luteal physiology is based on pulsatile LH secretion. In the context of ovarian stimulation for IVF and GnRHa trigger, corpora lutea function reflects endogenous LH secretion only, as is the case in a natural cycle. We therefore hypothesized that GnRH agonist-induced luteolysis may reflect altered LH secretion. Since the luteolytic process is complete during the first half of the luteal phase after GnRH agonist trigger, we explored LH secretion pattern in two time points in early luteal phase post GnRH agonist trigger in IVF-ET cycles. The study [13] showed that although pulsatile LH secretion continues post GnRH agonist trigger, mean LH concentration and LH pulse amplitude are lower than those described for a natural cycle. Furthermore, the process of luteolysis starts very early in the luteal phase, as indicated by falling progesterone and estradiol levels two days after oocyte retrieval.

In summary: Post GnRH agonist trigger, P rises continuously to a peak 48 h post oocyte retrieval, after which it declines as luteolysis takes over.

When and how to boost CL activity?

If a fresh embryo transfer is desired, P level must be boosted either exogenously (intensive E_2+P luteal support), or by boosting CL activity.

Engmann et al. [14] described intensive E_2 + P luteal support (the 'American approach'). It involves daily intramuscular administration of P in oil for weeks, which is not very convenient for the patient, to say the least.

Several approaches to boost CL activity were described so far. Humaidan et al. [15] suggested administering a single bolus of 1,500 IU hCG on the day of oocyte retrieval followed by standard luteal phase support (oral E_2 and vaginal P). This approach gave a mid-luteal P of 74 ± 52 nmol/l, too low according to Thomsen et al. [6].

Papanikolaou et al. [16] suggested to boost CL activity by six dosed of recombinant LH (300 IU each) given on alternate days from the day of oocyte retrieval, and standard luteal phase support.

Andersen et al. [17] Suggested to boost CL activity by daily administration of low dose hCG (125 IU) from the day of oocyte retrieval to the day of pregnancy test (14 days).

Bar-Hava et al. [18] suggested boosting CL activity by intranasal Buserlin (100 g) given three times daily from the day of oocyte retrieval for two weeks.

Wiser et al. [19] suggested boosting CL activity by Triptorelin (Decapeptyl) 0.1 mg every other day and vaginal P (Endometrin 100 mg, three times a day) from day 3 post oocyte retrieval to pregnancy test day.

With the knowledge we have so far on time-dependent events post GnRH agonist trigger, can we formulate an endocrine-based approach that will maximize pregnancy potential and serve patients convenience? Yes. Mainly because, fortunately, three time-dependent events coincide: The time point when luteolysis begins (48 h post oocyte retrieval), maximal P post hCG (5 days), and the time point when we need to reach maximal P level: mid-luteal phase (7 days post oocyte retrieval), i.e. implantation window.

Put all the above together, the solution is very simple. If we administer a single bolus of 1,500 IU hCG 48 h post oocyte retrieval we serve all three time-dependent events without the need for any additional support (Figure 2).

- hCG boost is given exactly when luteolysis begins.
- Early P level in the favorable range.
- Early luteal over stimulation is avoided (embryo-endometrium age well synchronized).
- Smooth continuous rise of P from oocyte retrieval to mid luteal peak.
- Mid luteal P peak correlates with late follicular E_2 since all CL are boosted.
- Patient convenience is well served, since a single hCG injection is all that is needed, avoiding multiple vaginal P applications for weeks.
- If pregnancy is achieved, endogenous hCG, secreted by the newly-formed placenta will take over CL maintenance.

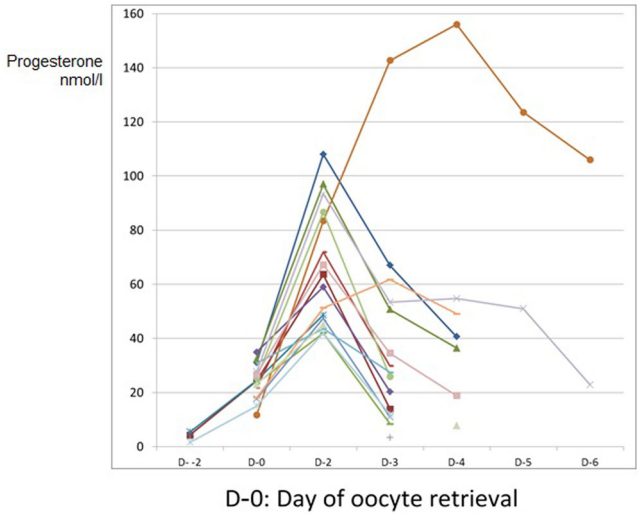

Figure 1. Serum Progesterone in the luteal phase post GnRH agonist trigger. Each colored line represents a single patient. No exogenous progesterone supplementation was given. In most patients, progesterone reached a peak 48 h post oocyte retrieval, and then decreased as luteolysis ensues. (Based on data from Kol et al. [10]).

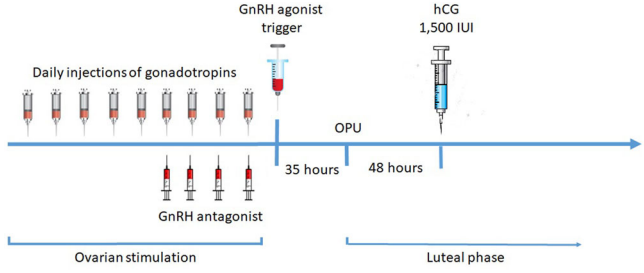

Figure 2. Schematic presentation of luteal support post GnRH agonist trigger based on 1500 IU of hCG administered 48 h post oocyte retrieval. No additional luteal support is needed.

So far, this approach was tested in a proof-of-concept study [20], and a subsequent larger retrospective study [21]. The results of these studies confirm that CL activity is well maintained with this approach.

In summary: If OHSS is a concern, freeze all strategy is advised post GnRH agonist trigger. If fresh transfer is desired, a thorough understanding of time-sensitive events suggests that a single 1500 IU hCG dose, administered 48 h post oocyte retrieval, fully supports the luteal phase and secures best chances of achieving pregnancy.

Disclosure statement

The author reports no conflicts of interest. The author alone is responsible for the content and writing of this article.

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