

Short Review:

A rationale for timing of luteal support post GnRH agonist trigger

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## Abstract

GnRH antagonist-based ovarian stimulation protocol is gaining popularity. This protocol allows for the use of GnRH agonist as a trigger of final oocyte maturation, instead of the "gold standard" hCG trigger. GnRH agonist trigger causes quick luteolysis, hence its widespread use in the context of ovarian hyperstimulation syndrome (OHSS) prevention. To secure pregnancy post GnRH agonist trigger, the luteal phase must be supplemented to counteract the luteolysis. Several luteal phase protocols post GnRH agonist trigger have been suggested, most notably based on increasing luteal LH activity (by adding LH or hCG). The current review aims at delineating a rationale for timing luteal support with a single hCG bolus post GnRH agonist trigger. The review also suggest a set of simple rules that must be followed when designing luteal phase support post GnRH agonist trigger.

Running title: Day 2 1,500 IU hCG provides excellent luteal support post GnRH agonist trigger

Key words: GnRH antagonist; GnRH agonist; human chorionic gonadotropin; luteal phase support.

## Introduction

As GnRH antagonist protocol for ovarian stimulation gains popularity, it is time to fine-tune the luteal phase that follows. The "gold standard" trigger in this protocol is hCG followed by progesterone (in most cases by vaginal application). However, as GnRH agonist trigger becomes increasingly popular [1], it is time to revisit luteal phase support in an effort to maximize its effectiveness while keeping close attention to patients' convenience. The purpose of the current paper is to suggest a set of simple rules that must be followed when designing luteal phase support post GnRH agonist trigger, and to formulate a rationale for timing luteal support post GnRH agonist trigger

## hCG as trigger

As stated above, hCG is the "gold standard" to trigger ovulation and final oocyte maturation in IVF cycles (either in agonist or antagonist protocols). The hCG dose required for effective trigger is derived from the physiologic mid-cycle LH surge (>100 IU/L). However, while the physiologic surge is of short duration, given LH short half-life, hCG remains in the system for about 1 week. This long activity is the source for significant deviations from physiology:

- Lack of FSH surge, which seems to be of importance [2, 3]
- Supra physiologic stimulation of corpora lutea (CL) in early luteal phase
- Supra physiologic levels of E<sub>2</sub> and P
- Negative feedback at the pituitary level
- Low endogenous LH secretion
- Luteal phase defect
- Need of luteal phase supplementation
- Abnormal P production (peak P not with implantation)
- Out-of-phase endometrium given high early luteal P

Serum hCG reaches a peak of 100-150 IU/L about 1 -2 days post trigger dose, followed by a slow decline. On day 5 - 6 after oocyte retrieval, hCG concentration is too low to sustain P production by the CL. Hence, following the "gold standard" paradigm (hCG for trigger, and luteal P supplementation) there is a mid-luteal reduction in LH activity, leaving the CL devoid of sufficient stimulation [4]. If the decay of exogenous hCG (derived from the hCG trigger) overlaps with the endogenous hCG (derived from the newly implanted embryo), continuous CL stimulation is secured and high P production is maintained. However, if the exogenous hCG terminates before the endogenous one is produced, than we have a "luteal hole" which is supposedly covered by the supplemented P. However, in order to maintain receptive endometrium we need extremely high mid-luteal progesterone that cannot be supplied by the added P [5].

This is an awkward situation in "controlled ovarian stimulation", when we actually lose control of the endocrine environment in the most crucial step of the whole process: The implantation window.

#### Luteal phase P post ovarian stimulation

In the physiologic cycle, luteal P of 30 nmol/l seems to be enough to secure receptive endometrium. However, this does not hold for stimulation cycles. Apparently, in order to secure receptive endometrium we need ten times more P [6]. Physiologic levels (30 nmol/l) are associated with poor reproductive outcome and very high miscarriage rate [5]. The reason for that observation is not known, but there seems to be a direct correlation between the follicular  $E_2$  levels that the endometrium is exposed to, and the P levels needed to sustain receptive endometrium. This is probably the reason for a detrimental effect on uterine receptivity of high serum estradiol concentrations in high responder patients [7].

#### Peak P timing

The physiologic P level rises gradually from ovulation to a peak in the mid luteal phase. Peak P coincides with the implantation window (6-8 days post ovulation). Post hCG trigger, peak P is achieved 5-7 days post trigger, or 3.5-5.5 days after oocyte retrieval [8, 9]. This is a significant time shift of 2-3 days before the embryo implants. This significant deviation from physiology may hamper implantation by a perfectly normal embryo, simply for the lack of adequate mid-luteal LH activity.

#### The advantages of GnRH agonist trigger

GnRH agonist elicits both LH and FSH surges, exposing the growing ovarian follicles to a more physiologic stimulus of final oocyte maturation compared with hCG trigger. Its potential advantages led researchers to wonder if it is time for a change of practice (for review see [10]). GnRH agonist also causes a quick and irreversible luteolysis, by which OHSS is prevented, even after excessive ovarian stimulation [11]. Complete luteolysis is attained about 5 days after the trigger [12]. In OHSS high-risk cases, a freeze all strategy is recommended. Another significant advantage of GnRH agonist trigger is the fact that we can manipulate the endocrine environment in luteal phase that follows to serve our patients' needs.

#### Luteolysis timing following GnRH agonist trigger

GnRH agonist trigger causes an early physiologic shift from follicular to luteal endocrine status. During the first 48 hours after oocyte retrieval there is a gradual increase in P levels [13, 14, figure 1]. In fact, in most patients, peak P level is reached 48 hours after oocyte retrieval, following a decline to complete luteolysis 3 days later (five days after oocyte retrieval). If we wish to maintain continuous rise in P, this is exactly the time to intervene.

#### Luteal support based on repeated LH/hCG dosing

Post GnRH agonist trigger luteolysis may be prevented by repeated doses of LH or hCG. Papanikolaou et al., [15] showed that six doses (every other day) of 300 IU recombinant LH, starting on the day of oocyte retrieval up to day 10 after oocyte retrieval result in good clinical outcome. In addition, standard luteal P (600 mg micronized P vaginally) was administered from the day after oocyte retrieval and maintained until 7 weeks of gestation.

Andersen et al., [16, 17] showed that a daily dose of hCG (125 IU) starting on the day of oocyte retrieval (without exogenous P) results in very high mid luteal P. Daily hCG was stopped 12 days after embryo transfer.

#### Luteal support based on repeated GnRH agonist dosing

Repeated GnRH agonist dosing may prevent luteolysis post GnRH agonist trigger as shown by Pirard [18] and Bar Hava [19].

#### Luteal support based on a single hCG dose

A single hCG dose in addition to E<sub>2</sub> +P luteal support was reported as follows:

"Double trigger": Griffin et al., [20] added 1,000 IU of hCG with the GnRH agonist trigger dose, followed by intensive E<sub>2</sub>+P support.

hCG on the day of oocyte retrieval: Humaidan et al., [21] added 1,500 IU of hCG on the day of oocyte retrieval followed by standard luteal phase support.

hCG 3 days post oocyte retrieval: Haas et al., [22] added 1,500 IU of hCG 3 days after oocyte retrieval followed by intensive E<sub>2</sub>+ P support.

Any use of early luteal hCG support may lead to significant OHSS [23].

#### How to time a single hCG dose?

Three factors must be considered:

- Maximal P is reached 5 days after hCG administration.

- Post GnRH agonist trigger luteolysis starts 48 hours post oocyte retrieval.
- Peak P should coincide with implantation window, 7 days after oocyte retrieval.

Based on these three factors we may analyze the above approaches:

1. hCG bolus with trigger results in early luteal P peak, with the risk of endometrial receptivity shift.
2. hCG bolus on the day of oocyte retrieval results in peak P two days before implantation day. By implantation day, P may decrease from its peak, which is a significant deviation from physiology.
3. hCG bolus three days after oocyte retrieval may be too late, since by that time luteolysis is well established in most patients, resulting in decreasing P. Physiology dictates continuous P rise to mid-luteal period. Breaching this dictum is a significant deviation from physiology, possibly eroding implantation potential.

Based on the above considerations, the optimum single hCG dose timing is two days after oocyte retrieval, which results in the following:

1. hCG is given just before luteolysis begins, allowing for a smooth P rise until its peak.
2. Peak P is attained 7 days after oocyte retrieval, exactly when we need it.
3. If pregnancy is established, endogenous hCG will take over the role of CL stimulation, therefore, any additional exogenous support ( $E_2+P$ ) is not needed.

This approach was examined thus far in a retrospective manner. However, the endocrinology is supportive of the protocol, since robust luteal activity is maintained in early pregnancy [24].

#### Endocrine rules for luteal phase support post GnRH agonist trigger

Taken together, we can now formulate the rules for luteal phase support post GnRH agonist trigger.

- Receptive endometrium requires physiological P exposure
- Need to mimic luteal P profile pattern
- Maximal P to coincide with implantation window
- Maximal luteal P in relation to maximal follicular E<sub>2</sub>.
- If pregnancy is achieved, no further support is needed if the CL are functional.

Day two-post retrieval, single 1500 IU hCG bolus seems to perfectly obey the above rules, with the following benefits:

- Patient friendly: cheap, simple, short. No need for daily vaginal P for a long time.
- Effective: Peak P when needed: implantation window.
- No early luteal over-stimulation.

#### Summary

The advantages associated with GnRH agonist trigger are well documented: physiologic trigger (combined LH and FSH surges), and quick luteolysis that follows. These advantages paved the way to an "OHSS-free clinic" by applying the freeze all strategy in OHSS high-risk situations [25, 26]. OHSS risk can be estimated the by number of growing follicles [27], but other pertinent clinical aspects should be considered (patient's age, weight, history). If fresh transfer is deemed feasible, the luteal phase can be successfully supplemented with a single bolus of hCG (1,500 IU). Based on the endocrine considerations outlined above, hCG supplementation is best given 48 hours post oocyte retrieval. Apparently, no further supplementation is needed.

Although the suggested paradigm is well supported by endocrine evidence, formal RCT's are needed before it is used routinely for all patients worldwide.



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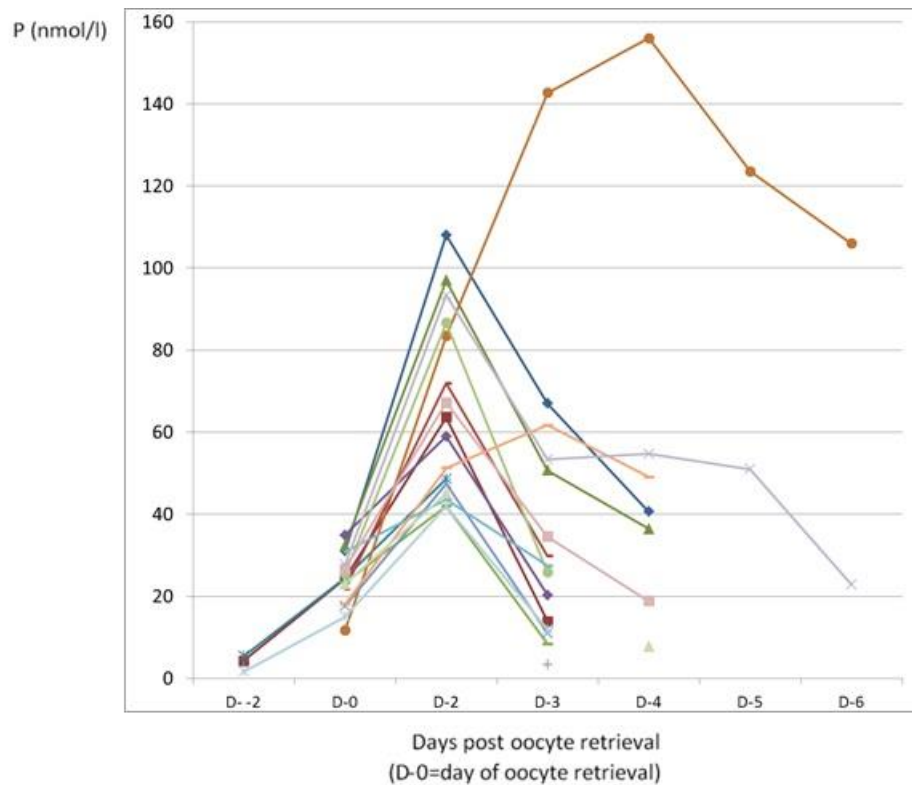
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Legend for Figure 1

Individual P profile post GnRH agonist trigger, without any supplementation. In most patients, P reaches a peak 48 hours after oocyte retrieval, and then declines (based on data from ref 14).