



IVF and the exogenous progesterone-free luteal phase

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Purpose of review

In a conventional IVF cycle, final oocyte maturation and ovulation is triggered with a bolus of hCG, followed by progesterone-based luteal support that spans several weeks if pregnancy is achieved. This article summarizes several approaches of the exogenous progesterone-free luteal support in IVF.

Recent findings

Triggering ovulation with GnRH agonist may serve as an alternative to hCG, with well established advantages. In addition, the luteal phase can be individualized in order to achieve a more physiologic hormonal milieu, and a more patient friendly treatment, alleviating the burden of a lengthy exogenous progesterone therapy.

Summary

GnRH agonist trigger followed by a 'freeze all' policy is undoubtedly the best approach towards the 'OHSS-free clinic'. If fresh embryo transfer is considered well tolerated after GnRH agonist trigger, rescue of the corpora lutea by LH activity supplementation is mandatory. Herein we discuss the different approaches of corpus luteum rescue.

Keywords

GnRH agonist trigger, human chorionic gonadotropin, IVF, luteal phase support, progesterone

INTRODUCTION

Follicular phase stimulation during IVF treatment, aiming at achieving multiple follicles and subsequently oocytes, results in a significant luteal phase deficiency of circulating endogenous LH, caused by supraphysiological luteal levels of progesterone (P4) and estradiol (E₂), which exert a negative feedback on the pituitary [1,2]. Importantly, LH plays a crucial role for the function of the corpus luteum, being totally responsible for its steroidogenic activity in terms of P4 and E₂ production [3,4]. In this aspect, the gold standard human chorionic gonadotropin (hCG) trigger functions not only as a trigger of final oocyte maturation, but the hCG bolus also – because of its long half-life via a gradually declining serum level-covers the early luteal phase LH activity deficiency for up to 5 days following oocyte retrieval (oocyte retrieval); importantly, P4 levels start declining already from oocyte retrieval + 4 because of this gradual decline in serum hCG (Fig. 1) [5^{***}]. As the embryo implants around days 8–10 after ovulation in the natural cycle [6], and the implantation period during IVF treatment could be considered the same, exogenous luteal phase support (LPS) is needed to bridge the LH (and P4) gap until implantation occurs.

In the following, we hypothesize that despite its universal usage, the gold standard hCG trigger protocol, followed by exogenous P4 administration might fall short of inducing the most optimal endometrial and peri-implantation conditions. On the basis of this hypothesis, we wish to discuss and possibly introduce a paradigm shift in ovulation trigger policy for IVF, optimally resulting in improved endometrial receptivity and a reduced treatment burden for the patient.

THE LUTEAL PHASE OF THE NATURAL CYCLE

P4, the key regulator of the 'window of implantation' during the natural cycle, starts to rise after the

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KEY POINTS

- Disadvantages of hCG as an ovulatory trigger: no FSH surge, early luteal phase supraphysiological stimulation, premature P4 peak, OHSS risk.
- Advantages of GnRHa as an ovulatory trigger: LH + FSH surge, more MII oocytes, more embryos, OHSS risk reduction.
- Post GnRHa trigger corpus luteum rescue can be performed by supplementing LH activity in different ways, without the need for any exogenous progesterone support.

mid-cycle gonadotropins surge. After ovulation, P4 rises continuously during the early luteal phase, reaching a peak 6 days after ovulation of about 10 ng/ml [7]. Following this rise, the P4 level plateaus for about 3 days (8–10 days post ovulation), defining the window of implantation [6]. If an embryo implants, the trophoblast will gradually start secreting hCG, which supports the corpus luteum function for about 6 weeks [8]. Following this period, the luteoplacental shift occurs, during

which the corpus luteum function is gradually compensated for by the newly formed placenta. In contrast, if an embryo does not implant, the corpus luteum regresses, resulting in declining endogenous levels of P4 and E₂ – and subsequently menses.

HUMAN CHORIONIC GONADOTROPIN AND FINAL OOCYTE MATURATION FOR IVF

Until now hCG has been the gold standard trigger in IVF, used for its LH-like activity. Presently, the most popular hCG-containing product comes in a 25-click, pen-like injection device containing 250 µg (6500 IU) of recombinant hCG. This dose is usually highly effective in securing optimal oocyte maturation, moreover the device is simple to use, and is relatively inexpensive. However, from an endocrine point of view, hCG trigger has some disadvantages. Although the natural mid-cycle surge of gonadotropins (LH and FSH) has a duration of approximately 48 h, hCG, because of its long half-life, remains in circulation for several days, resulting in supra-physiological corpus luteum stimulation, and excessive P4 and E₂ production during the early luteal phase. Moreover, the hCG trigger, apart from introducing

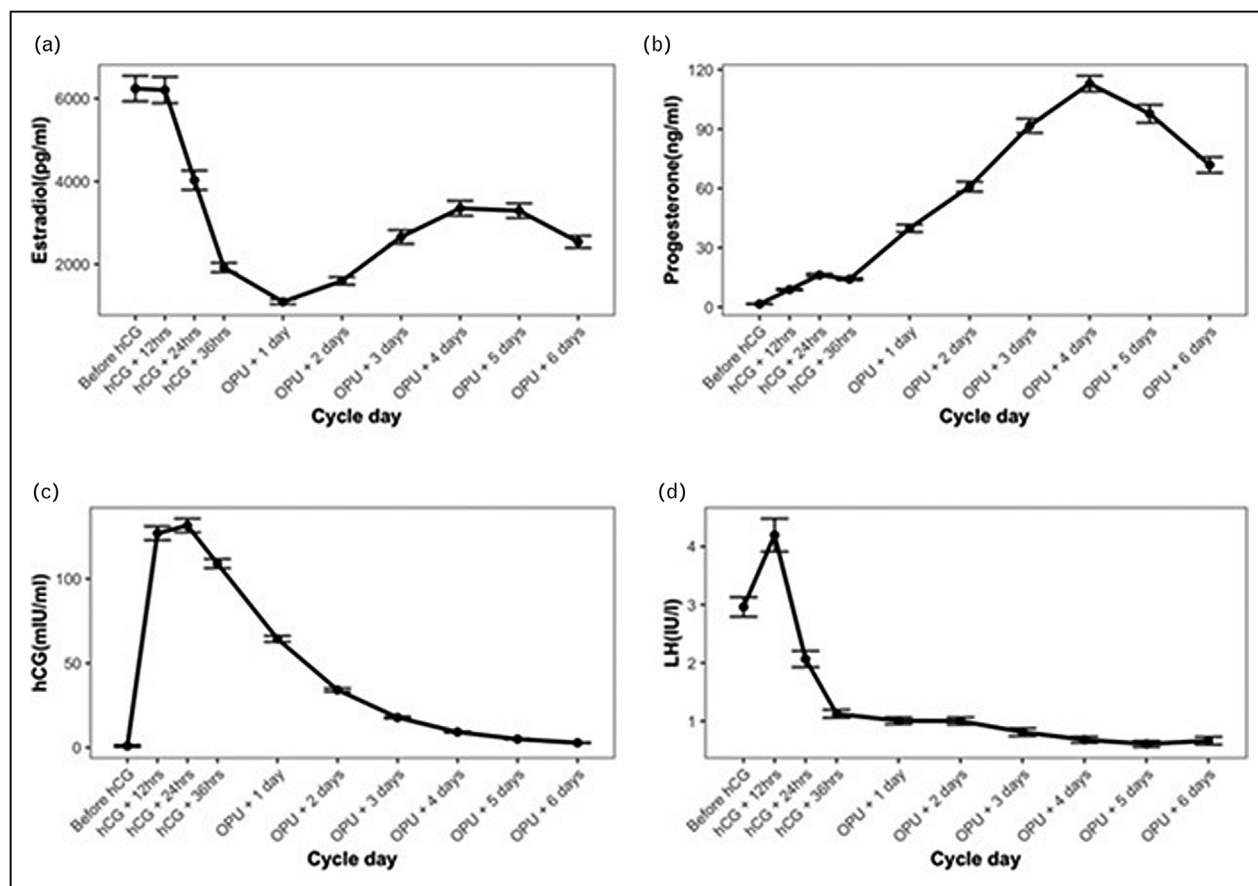


FIGURE 1. Early luteal phase profile in 161 patients triggered with 6,500 IU hCG, Reproduced with permission from [5**].

risk of ovarian hyperstimulation syndrome (OHSS), also advances the window of implantation, because of the supraphysiological steroid level, which may cause asynchrony between the embryo and the endometrium, and result in implantation failure [9]. In support of this, recent data have shown that the live birth rate is reduced when the early luteal P4 (oocyte retrieval + 2 – 3) exceeds 100 nmol/l [10[•]].

During the natural mid-cycle ovulatory surge, as mentioned, two surges are elicited: a prominent LH surge with an amplitude of greater than 100 IU/l and a smaller FSH surge with an amplitude of about 30 IU/l. When hCG is used for trigger, only LH activity is supplemented, thus, the impact of the natural cycle FSH surge is absent. Interestingly, the natural cycle FSH surge has several important functions in terms of LH receptor formation on luteinizing granulosa cells, nuclear maturation (i.e. resumption of meiosis) and cumulus expansion [11–15]. Despite these important actions of the FSH surge during final follicular maturation, the vast majority of patients respond well to an hCG trigger only, although adding high-dose FSH (450 IU) to the hCG trigger was shown to result in more oocytes and a higher fertilization rate [16].

LUTEAL SERUM PROGESTERONE AFTER HUMAN CHORIONIC GONADOTROPIN TRIGGER

After an hCG trigger, the peak P4 level occurs approximately 4 days after oocyte retrieval, significantly earlier than during the natural cycle (days 6–8 post ovulation, Fig. 1) [5^{••},17]. From this peak onwards, P4 decreases, resulting in a significant deviation from physiology and loss of synchronicity with the time course for implantation around day 8 [5^{••}]. A significant drop in serum P4 from day 3 to day 5 after oocyte retrieval has been reported in as many as 35% of patients, and the P4 drop was associated with significantly lower ongoing pregnancy rates [18]. Moreover, when IVF patients are triggered with hCG, the early luteal P4 may peak to more than 100 nmol/l [5^{••}], which, as mentioned is associated with compromised pregnancy rates [10[•]].

THE IMPORTANCE OF MID-LUTEAL SERUM PROGESTERONE

To imitate physiology, luteal P4 must increase gradually to a mid-luteal peak. However, the natural mid-luteal P4 of about 10 ng/ml (32 nmol/l) is not high enough during IVF because of the fact that high late follicular phase circulating E₂ induces endometrial P4 receptor ‘resistance’ [19,20]. In fact, in order to obtain the most optimal live birth rate

(LBR) in IVF, the mid-luteal P4 level at oocyte retrieval + 5 should be between 150 and 250 nmol/l, that is, five-fold higher than during the natural cycle [10[•]]. Hence, it is imperative that each corpus luteum obtained during IVF should fully express its P4 production potential. Indeed, the hCG trigger accomplishes this, as peak P4 was reported to be more than 10 times higher than during the natural cycle correlating with the number of follicles, exceeding 14 mm in diameter [5^{••}].

MIND THE GAP

The luteal phase defect (LPD) initially induced by ovarian stimulation with exogenous gonadotropins can be corrected using an exogenous P4-based LPS. However, as the level of hCG in circulation after the trigger reaches baseline at oocyte retrieval + 6 [5^{••}] (Fig. 1), the stimulation of the corpus luteum and subsequently the P4 production is suboptimal during the most crucial time of the IVF treatment: the peri-implantation period. In the majority of IVF patients, exogenous vaginal P4 supplementation is used to bridge this P4 gap; however, data show that this LPS might not be sufficient [10[•],21]. In the same line, Mitwally *et al.* [22] previously reported that the use of either vaginal or intramuscular P did not correct the luteal P4 gap. As recently shown in Vuong *et al.* [5^{••}], maximal P4 levels were achieved on day 4 after oocyte retrieval, followed by a sharp decrease from oocyte retrieval + 5 despite the use of vaginal or intramuscular P4 administration. To conclude, during the most crucial phase of the IVF treatment, that is, the peri-implantation period, control of the endocrine environment is lost with an important clinical impact on success rates [10[•]].

WHEN SHOULD EXOGENOUS LUTEAL PROGESTERONE SUPPLEMENTATION BE STARTED?

No consensus exists regarding the starting point of LPS in IVF. As discussed above, peak P4 levels are achieved 4 days after oocyte retrieval when hCG is used for trigger, and a total of 80% of clinicians start LPS on the day of oocyte retrieval [5^{••},23] at a time point when the exogenous LPS plays a very minor role as compared with the contribution from the corpus luteum. From a physiological point of view, the LPS could be postponed until day 4 after oocyte retrieval following hCG trigger, further supported by the fact that excessive early luteal P4 exposure seems to be detrimental to the reproductive outcome [10[•]]. In short, it makes little physiological sense to start exogenous LPS before day 4 after oocyte retrieval when hCG is used for trigger.

WHEN SHOULD EXOGENOUS LUTEAL PROGESTERONE SUPPLEMENTATION BE STOPPED?

Although, the luteoplacental shift occurs around 6 weeks of gestation, most clinicians (72%) extend the LPS beyond gestational week 8 in fresh embryo transfer cycles (IVF worldwide). However, if hCG, P4, and E₂ levels at the time of pregnancy testing approximately 2 weeks after oocyte retrieval reveal a robust corpus luteum activity, further LPS is not needed from a physiological and clinical point of view, as the endogenous hCG will secure the LH activity needed to maintain corpus luteum function until the luteoplacental shift occurs [24,25].

THE HUMAN CHORIONIC GONADOTROPIN TRIGGER CONCEPT IN SUMMARY

Despite the fact that hCG is the gold standard trigger agent, some important disadvantages are involved in its use:

- (1) Early luteal phase supra-physiological stimulation of the corpus luteum
- (2) No FSH surge
- (3) Peak P4 levels do not occur during the window of implantation
- (4) Negative feedback from high P4 on the pituitary increases the need for exogenous LPS
- (5) Risk of embryo-endometrium asynchrony
- (6) Risk of OHSS development

Which qualities should an alternative trigger concept possess?

- (1) Reduction in early luteal phase supraphysiological stimulation
- (2) Induction of an FSH surge
- (3) Peak mid-luteal P4 level corresponding to peak late follicular E₂ levels
- (4) Continuous P4 increase from oocyte retrieval to the mid-luteal peak
- (5) Peak luteal P4 coinciding with the window of implantation
- (6) Reduced treatment burden for the patient
- (7) Reduced risk of OHSS development

GnRH AGONIST TRIGGER AS AN ALTERNATIVE TO HUMAN CHORIONIC GONADOTROPIN TRIGGER

The use of gonadotropin releasing hormone agonist (GnRHa) for final oocyte maturation trigger in IVF has previously been extensively reviewed and studied [26,27]. This trigger elicits LH and FSH surges

comparable with the physiological surges in amplitudes, however, of a significantly shorter duration. Moreover, GnRHa trigger without any 'rescue' attempt induces luteolysis [28] with almost complete OHSS elimination [29[■],30,31]. However, if corpus luteum rescue is performed after a GnRHa trigger, the luteal phase can be personalized to the needs of the patient. Thus, in patients at risk of OHSS development a 'freeze all' strategy must be implemented; in contrast, in non-OHSS-risk patients, fresh transfer can be performed safely with excellent reproductive outcomes after corpus luteum rescue [32–34]. As an added bonus, the use of a GnRHa trigger was previously reported to result in more MII oocytes, higher fertilization rates, and more embryos [4,35–38].

GnRH AGONIST TRIGGER AND LUTEOLYSIS

To the best of our knowledge, only a few studies documented in details the endocrine events of the early luteal phase after GnRHa trigger [39,40]. These studies show that the early luteal P4 increases continuously to a peak around 24 h after GnRHa trigger, followed by a plateau phase until oocyte retrieval + 2, after which P4 declines rapidly (Fig. 2). In addition, after GnRHa trigger, the early luteal endogenous LH level is significantly lower than that documented during the natural cycle [39–41]. Importantly, the characteristic LH pulsatile pattern, seen during the natural cycle [42], is eliminated post-GnRHa trigger, which, at least in part, activates the luteolysis mechanism. As mentioned, the peak P4 level is obtained approximately 24 h after oocyte retrieval, resulting in an early luteal phase P4 level of 40–100 nmol/l [39,43], which fits nicely with a clinically favorable early P4 level of 60–100 nmol/l, previously suggested by Thomsen *et al.* [10[■]].

HOW CAN THE CORPUS LUTEUM RESCUE BE PERFORMED AFTER GNRH AGONIST TRIGGER?

As mentioned above, if fresh embryo transfer is planned after GnRHa trigger, the peak mid-luteal P4 should correspond to the peak late follicular E₂. This can be accomplished by rescuing the corpus luteum before luteolysis occurs. The rescue strategy should fulfill the following:

- (1) A continuous P4 increase from oocyte retrieval to the window of implantation
- (2) Avoid early luteal phase supraphysiological LH activity-induced stimulation
- (3) Peak P4 should coincide with the window of implantation

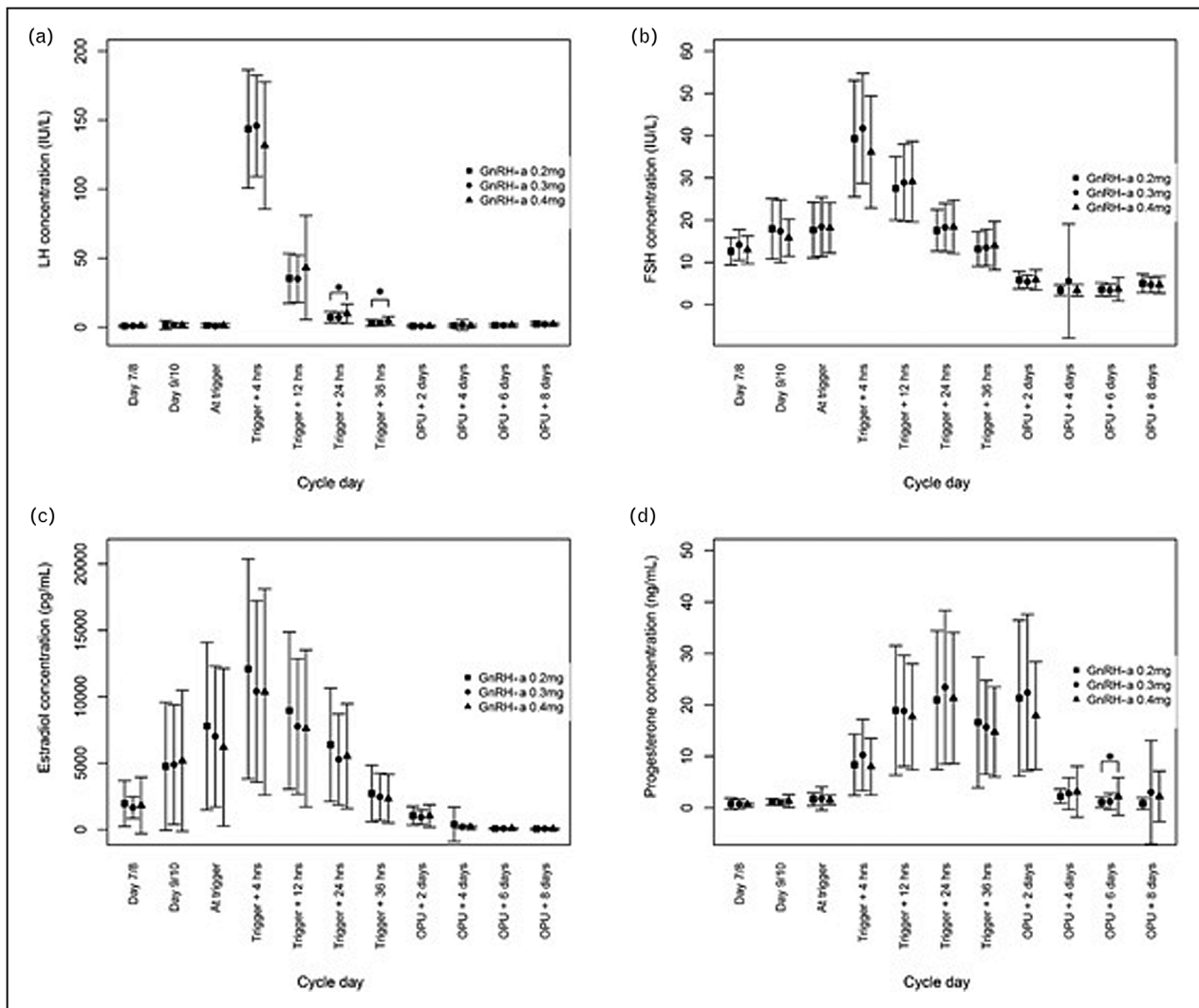


FIGURE 2. Early luteal phase profile in 165 patients triggered with either 0.2, 0.3, or 0.4 mg Triptorelin. Reproduced with permission from [39].

- (4) Should be as patient-friendly as possible
- (5) Should reduce the risk of OHSS development

CORPUS LUTEUM RESCUE: THE EXOGENOUS PROGESTERONE-FREE CONCEPT

The idea behind the exogenous progesterone-free (EPF) luteal phase concept in IVF is based on the premise that if the corpus luteum are rescued after the initial GnRHa trigger, securing full endocrine output at the time of implantation, further luteal support is redundant, as the newly formed trophoblast will produce sufficient amounts of hCG to support the corpus luteum function until the luteoplacental shift.

The first attempt to explore this novel concept was performed in a group of 15 normal responder

IVF patients, and we called it the hCG-based EPF-LPS concept [44]. In that study, 15 normal responder IVF patients underwent GnRHa trigger, followed by a total of two boluses of 1,500 IU hCG, administered on the day of oocyte retrieval and 4 days later (Fig. 3). Neither progesterone nor estradiol was administered for LPS, and a high ongoing clinical pregnancy rate was reported (47%).

Later, the EPF-LPS concept was further explored in a three-arm proof-of-concept RCT in 93 normal responder IVF patients, using daily boluses of 125 IU hCG from the day of oocyte retrieval until the day of the pregnancy test [45] (Fig. 4). Again, neither progesterone nor estradiol were administered for LPS, resulting in an ongoing clinical pregnancy rate of 38% in the two GnRHa-triggered EPF-LPS groups, as compared with 41% in the hCG-triggered, standard LPS group. It was concluded that, the EPF-LPS concept secured physiological E₂ and P₄ levels during

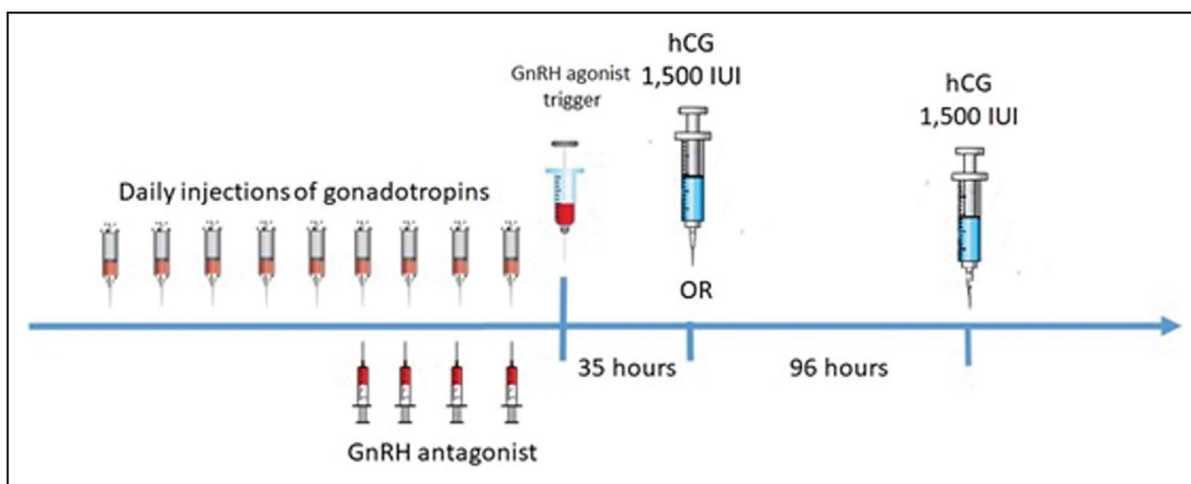


FIGURE 3. Following a GnRH antagonist-based stimulation, ovulation is triggered by a GnRH agonist. Luteal phase is supported by two boluses of hCG 1500 IU: on day of OR and 96 h later. OR, oocyte retrieval.

the early and mid-luteal phases as well as a nonsignificant difference in reproductive outcomes; moreover, patient satisfaction was higher in the EPF-LPS groups as patients did not experience any vaginal discomfort from exogenous progesterone supplementation.

Another protocol for LH activity supplementation after GnRHa trigger was previously introduced in terms of daily intranasal doses of GnRHa, securing flares of endogenous LH. The concept was initially explored in a proof-of-concept study, including a total of 17 IVF patients [46]. Later, the same group explored the same concept in 40 patients randomized to either GnRHa trigger and GnRHa-only for LPS compared with hCG trigger and vaginal progesterone for LPS. Similar ongoing pregnancy rates were seen between the 2 groups [47]. More recently,

the daily luteal GnRHa LPS concept was tested in a retrospective study, including 46 OHSS high-risk patients, using daily intranasal doses of GnRHa (200 µg twice daily) commencing 2 days after the trigger in GnRHa-triggered cycles. Again, no exogenous steroids were used for LPS and an ongoing pregnancy rate of 52% was reported [48]. Interestingly, the same group reported the use of daily nasal GnRHa for LPS in natural cycle frozen embryo transfer. A total of 51 regular cycling patients had their ovulation induced with a bolus of 0.2 mg triptorelin followed by LPS in the form of intranasal GnRHa (200 µg twice daily), commencing 2 days after the trigger in the evening of the oocyte retrieval day. An ongoing pregnancy rate of 39% was reported alongside luteal steroid levels similar to those of the natural cycle [49].

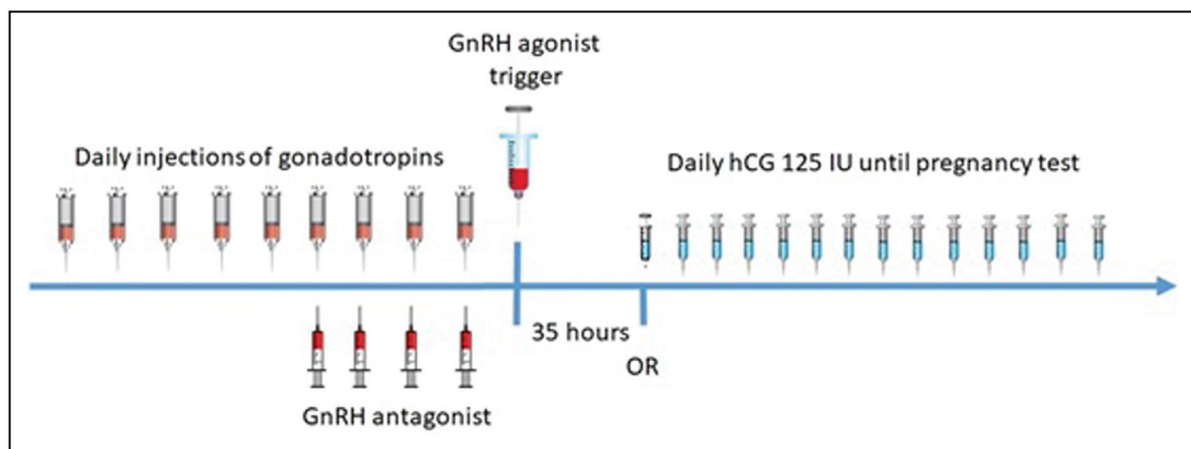


FIGURE 4. Following a GnRH antagonist-based stimulation, ovulation is triggered by a GnRH agonist. Luteal phase is supported by daily injections of hCG 125 IU until pregnancy test.

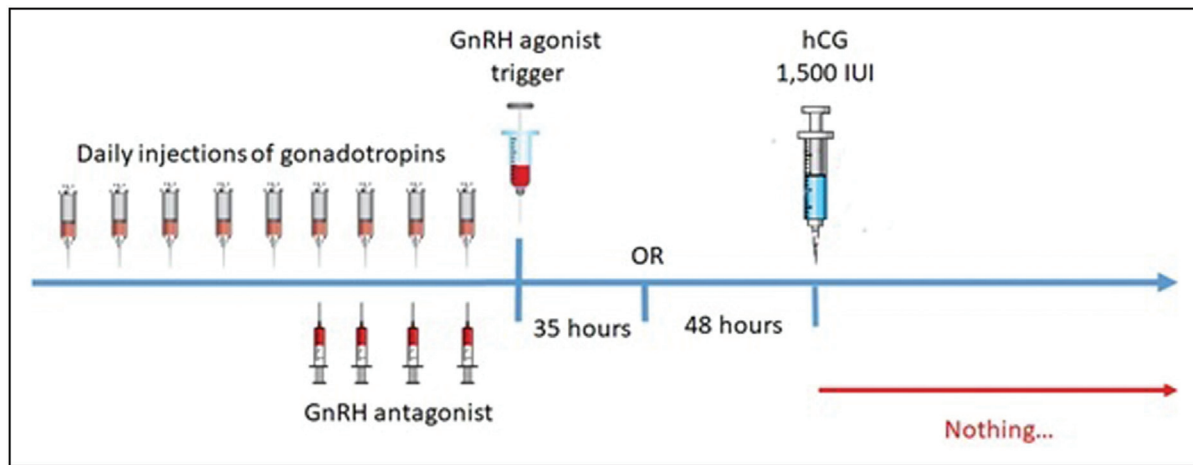


FIGURE 5. Following a GnRH antagonist-based stimulation, ovulation is triggered by a GnRH agonist. Luteal phase is supported by a single bolus of hCG 1500 IU, 48 h after oocyte retrieval.

THE EXOGENOUS PROGESTERONE-FREE LUTEAL PHASE SUPPORT IN DAILY PRACTICE

On the basis of the abovementioned studies, the question to ask is whether the EPF-LPS is an option for daily clinical practice. To answer this question, one has to consider three time points: luteolysis, which starts 48 h in a GnRHa-triggered cycle without corpus luteum rescue, the endogenous P4 level, which reaches a peak at oocyte retrieval + 4 after hCG trigger, and the window of implantation occurring 6–8 days after oocyte retrieval. Therefore, if in a GnRHa-triggered cycle, a single bolus of 1500 IU hCG is administered 48 h after oocyte retrieval (Fig. 5), all the above requirements are met. From a physiological point of view, no further support would be needed. So far, this approach was reported in a proof-of-concept study [50], and in a retrospective study [51], only. Both articles reported comparable clinical outcomes between the study group – GnRHa trigger and a single bolus of 1500 IU hCG 48 h after oocyte retrieval – and the control group of hCG trigger and vaginal progesterone for LPS. Obviously, further research is needed to confirm these preliminary reports.

CONCLUSION

We state that GnRHa trigger completely revolutionized modern IVF and opened research into the luteal phase. We hold in our hands a very effective weapon against OHSS, and GnRHa trigger followed by a ‘freeze all’ policy is undoubtedly the best approach towards the ‘OHSS free clinic’. However, fresh embryo transfer can also be performed after GnRHa trigger, in patients not considered at risk of OHSS

development, provided that the corpus luteum are rescued. Corpus luteum rescue can be performed by supplementing LH activity in different ways without the need for any exogenous progesterone support. GnRHa trigger followed by either a single bolus of 1500 IU hCG on oocyte retrieval + 2, or a total of two boluses on oocyte retrieval and oocyte retrieval + 4 without any further support might serve the best interest of the patient. Future studies should explore the most optimal dosing and type of LH activity to be used in the EPF-LPS protocol.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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