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ARTICLE

‘Luteal coasting’ after GnRH agonist trigger – individualized, HCG-based, progesterone-free luteal support in ‘high responders’: a case series

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Abstract This study reports 21 IVF cases with excessive ovarian response, who received gonadotrophin-releasing hormone agonist (GnRHa) triggering for final oocyte maturation, followed by a human chorionic gonadotrophin (HCG)-based, progesterone-free, luteal support, individually timed (‘luteal coasting’) according to endogenous luteal progesterone concentrations. One patient developed a brief early-onset moderate ovarian hyperstimulation syndrome (OHSS) condition. Six clinical pregnancies were achieved, two of which have resulted in live births thus far. To further individualize the luteal phase support post GnRHa trigger, the same principle that holds for follicular coasting, used in the context of OHSS prevention, may be valid. Monitoring luteal progesterone concentrations from the day of oocyte retrieval, and administering a bolus of HCG (1500 IU) when the concentration drops significantly, seems to facilitate fresh embryo transfer, even in patients with excessive ovarian responses.

KEYWORDS: GnRHa trigger, HCG, luteal coasting, luteal support, ovarian hyperstimulation syndrome

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Introduction

After the initial findings of poor reproductive outcome when a standard luteal phase support was used in relation to gonadotrophin-releasing hormone agonist (GnRHa) trigger (Humaidan et al., 2005; Kolibianakis et al., 2005), the subsequent development of modified luteal phase support policies – either human chorionic gonadotrophin (HCG) rescue, or intensive steroid rescue (reviewed in Humaidan and Alsbjerg, 2014) – resulted in a reproductive outcome comparable to that of HCG trigger and with the advantage of a reduction in, if not elimination of, ovarian hyperstimulation syndrome (OHSS). Thus, GnRHa trigger has become a viable alternative for the gold standard HCG trigger (Humaidan and Polyzos, 2014), which is also depicted in a survey indicating that as many as 36% of IVF GnRH antagonist cycles in Europe are triggered with GnRHa (IVF Worldwide, 2013).

GnRHa trigger causes a swift luteolysis if not counteracted by HCG, which is the reason why modifications of the standard luteal phase support are necessary to obtain a good reproductive outcome after fresh embryo transfer. In this line, the concept of 'tailored', ovarian response-based, luteal support was suggested. One bolus of HCG (1500 IU) on the day of oocyte retrieval, followed by a standard luteal phase support in normal responders (<14 follicles >11 mm), yielded good clinical outcomes (Humaidan and Alsbjerg, 2014; Humaidan et al., 2013). Furthermore, in patients with <12 follicles it has been shown that two boluses of 1500 HCG only (4 days apart), can successfully support the full luteal phase after GnRHa trigger, introducing for the first time the exogenous progesterone-free luteal phase in IVF (Kol et al., 2011). Finally, in OHSS-risk patients (15–25 follicles > 11 mm), a single bolus of 1500 HCG at the time of oocyte retrieval will result in excellent clinical outcomes and no OHSS development (Humaidan and Alsbjerg, 2014; Humaidan et al., 2013).

In contrast, for patients with a very high ovarian response (>25 follicles >11 mm), the options after GnRHa trigger so far have been either a segmentation of the cycle, i.e. 'freeze all' followed by subsequent frozen–thawed embryo transfer (Devroey et al., 2011), or intensive luteal steroid support; however, not even these policies preclude severe OHSS (Fatemi et al., 2014; Gurbuz et al., 2014).

The above strategies after GnRHa trigger take into account the cycle-specific, follicular ovarian responses as the only factor on which to base the 'tailoring', i.e. either fresh transfer and modified luteal phase support, or segmentation. In addition, fixed time points are pre-set for the administration of HCG, i.e. either on the day of GnRHa trigger ('dual trigger', Griffin et al., 2012; Shapiro et al., 2011), on the day of oocyte retrieval (Humaidan and Alsbjerg, 2014), or 3 days after oocyte retrieval (Haas et al., 2014). The present publication introduces the concept of cycle-specific luteal response as the key factor in determining luteal rescue timing.

Previously, follicular phase coasting in the 'long' GnRHa down-regulation protocol has been suggested as a strategy for OHSS prevention (Delvigne and Rozenberg, 2002). Coasting seeks to induce partial atresia of the developing follicles by withholding gonadotrophin stimulation, while monitoring oestradiol concentrations, considered to reflect theca- and granulosa-cell function. Using this strategy, HCG trigger is administered when oestradiol concentrations drop below a certain cut-off point (Abdallah et al., 2010), reflecting partial demise of the developing follicles, decreasing the burden of multiple corpura lutea formation that follows.

The luteolysis pattern after GnRHa trigger has been described, showing that on day 1 after trigger circulating progesterone concentrations are comparable, regardless of whether HCG or GnRHa was used for trigger. In contrast, progesterone concentrations return to baseline 5 days after GnRHa trigger, reflecting complete luteolysis by this day (Fatemi et al., 2013).

To further individualize the luteal phase support in OHSS high-risk patients, having a fresh transfer after GnRHa trigger, the same principle that holds for follicular phase coasting might be valid during the luteal phase. In other words, monitoring progesterone concentrations, and administering the HCG luteal phase rescue bolus when progesterone concentrations drop significantly.

The following case series explore, for the first time, the above-mentioned novel approach.

Materials and methods

Patients

The files of 21 consecutive patients treated at the Rambam IVF unit from April 2014 to April 2015 were summarized. Ovarian stimulation was performed using highly purified gonadotropin (Menopur, Ferring) with a starting dose of 150 IU daily, followed by daily injections of a GnRH antagonist 0.25 mg (Cetrotide, Merck Serono) once the leading follicle reached a size of ≥14 mm in diameter. Patients were considered at high risk of developing severe OHSS having either an oestradiol > 12,000 pmol/l or ≥15 follicles of more than 12 mm in diameter on the trigger day (day −2) (Humaidan et al., 2013). All patients were triggered with a bolus of 0.2 mg triptorelin (Decapeptyl, Ferring) when ≥3 follicles were ≥17 mm in diameter. Oocyte retrieval was performed 36 h later (day 0). Daily measurement of oestradiol, progesterone and LH was initiated 48 h post oocyte retrieval (day +2) until it was decided to administer the HCG bolus. In most patients, no more blood tests were taken after the HCG bolus, in four patients mid-luteal progesterone was measured to ascertain that the 1500 HCG bolus maintained adequate progesterone during the window of implantation.

Embryo transfer was performed on day +2 or +3 post oocyte retrieval.

Luteal support

Since it is assumed that decreasing luteal progesterone concentrations reflect luteolysis, luteal support with a single bolus of HCG (1500 IU) was given when progesterone concentration decreased below 30 nmol/l. No further luteal support was given. A pregnancy test was performed 14 days post oocyte retrieval (day +14), including oestradiol and progesterone measurements; vaginal ultrasound 1 month after embryo transfer ascertained a viable pregnancy. Data are given as mean ± SD.

The study was approved by the Rambam Health Care Centre Institutional Review Board on 11 June 2015.

Table 1 Main demographic parameters of the study population.

Age (years)	26.4 ± 4.9
Indication	
Unexplained	4
Male	14
Mechanical	2
PCO	1
BMI	23.9 ± 3.8

BMI = body mass index; PCO = polycystic ovaries.

Table 2 Stimulation characteristics and embryology data.

Stimulation (days)	9.8 ± 2.3
FSH (units)	1570 ± 633
Follicles >12 mm	18.0 ± 4.8
Oestradiol trigger day (pmol/l)	16,839 ± 3919
Oocytes retrieved	16.9 ± 5.4
Fertilizations	8.5 ± 3.7
Embryos transferred	1.86 ± 0.48
Embryos frozen	3.1 ± 2.6
Day 1500 IU HCG administered	3.7 ± 1.4

HCG = human chorionic gonadotrophin.

Results

Patients' demographics are given in **Table 1**. Stimulation details are given in **Table 2**.

Luteolysis kinetics and luteal support timing

The majority of patients (12) received the 1500 IU HCG bolus on day +3. In one patient a 'quick' luteolysis resulted in day +2 bolus. Five patients received the 1500 IU HCG bolus on day +4. In three patients 'slow' luteolysis was observed, leading to the rescue bolus of HCG being administered on either day +5, +7, or +8.

While progesterone concentrations (nmol/l) decreased from day +2 to day +3 (63.2 ± 31.3 and 38.3 ± 35.7, respectively), oestradiol concentrations (pmol/l) did not change (3794 ± 1770 and 3,738 ± 2,454, respectively). Progesterone and oestradiol concentrations on the day of the HCG bolus were reduced to 38% ± 19 and 87% ± 46, respectively, of the concentrations on day +2.

Importantly, LH secretion (IU/l) was not eliminated by a single 0.2 mg GnRHa bolus. In fact, its concentrations remained fairly constant in the early luteal phase (1.56 ± 0.9 and 2.4 ± 1.3 for day +2 and day +3, respectively).

Another patient intended to be included in the current cases series was monitored per the protocol; however, progesterone concentrations remained >190 nmol/l during the luteal phase, and so no rescue HCG bolus was given. Therefore this patient was excluded from this report. Interestingly, an ongoing pregnancy was achieved.

HCG-driven luteal rescue

Mid-luteal phase (7–8 days post oocyte retrieval, implantation window) progesterone was 140 ± 42 nmol/l (n = 4).

Table 3 Reproductive outcome.

Positive HCG n, (%)	9/21 (43)
Clinical pregnancy n, (%)	6/21 (29)
Early pregnancy loss n, (%)	3/9 (33)

HCG = human chorionic gonadotrophin.

In ongoing pregnancies, day +14 progesterone concentrations were >190 nmol/l in all cases, oestradiol = 10,304 ± 5048 pmol/l.

OHSS

One patient who received the HCG bolus on day +2 developed a brief early onset moderate OHSS condition, characterized by large ovaries, abdominal discomfort and moderate amounts of free pelvic fluid.

Reproductive outcome

So far two pregnancies resulted in live births, while another four pregnancies are presently ongoing. **Table 3** summarizes the reproductive outcome so far. Of the six clinical pregnancies, 1, 3 and 2 were achieved after HCG boluses on day +2, +3 and +4, respectively. Three 'biochemical' pregnancies were observed (defined as rising serum HCG concentrations from day +14 onwards, followed by decreasing concentrations after HCG boluses on day +5, +7 and +8).

Discussion

To the best of the present authors' knowledge, the herein described case series is the first attempt to further tailor, or individualize, an HCG-based luteal phase support after GnRHa trigger and fresh transfer in OHSS high-risk patients. None of the patients developed any OHSS in need of hospitalization – importantly, no late-onset OHSS was seen.

The basic principle of this new concept – 'luteal coasting' – is to closely monitor the individual luteolytic process after GnRHa trigger in terms of circulating progesterone concentrations, and to intervene with an HCG rescue bolus when the process is firmly underway, but well before total and irreversible luteolysis has occurred.

While segmentation is certainly an option in cases of high ovarian response (Devroey et al., 2011), luteal coasting as suggested herein may be more acceptable for both patients and clinicians. Importantly, there may be regional, legal, economical and ethical considerations that do not facilitate cryopreservation. Moreover, although the success rate after cryopreservation has increased significantly worldwide, still not all IVF units have successful cryopreservation programmes at their disposal. Finally, not even the segmentation protocol will eliminate severe OHSS in the OHSS high-risk patient (Fatemi et al., 2014).

Based on limited previous data, complete functional luteolysis seems to be reached within 5 days after GnRHa

trigger (Fatemi et al., 2013). However, the present data clearly indicate that there is a wide variability between patients as to luteolysis kinetics. Although most patients received the HCG bolus between day +2 and +4, three patients had a relatively slow luteolytic process, receiving the bolus on day +5, +7 and +8. This finding reflects significant population variability in the context of the luteolytic process kinetics, and underlines the basic concept of careful individualized follow-up when deciding the timing of the HCG rescue bolus. Although more research is needed, according to our experience, so far, we suggest that as soon as the progesterone concentration drops below 30 nmol/l, an HCG bolus should be administered. This cut-off point was chosen based on previous research describing the luteal progesterone threshold concentration in a natural cycle (Hull et al., 1982; Yovich et al., 1986). However, further research is needed, since one cannot rule out the possibility of inadequate luteal support, using this concentration as the cut-off. Although the reported series is too small to draw meaningful conclusions regarding the reproductive outcome, the relatively high pregnancy loss (33%) noted in this small series could be related to inadequate luteal support. One of the limitations of this study is the lack of a control group. Therefore, we are not able to conclude if this novel approach is better than the fixed administration of 1500 IU of HCG on the morning of oocyte retrieval.

There is a notable difference between progesterone and oestradiol kinetics during the luteolytic process. Progesterone concentrations sharply decrease in the early luteal phase (day 2 to day 3), while oestradiol concentrations stay the same. Similarly, on the day of HCG bolus progesterone concentration is only 38% of its day 2 peak, while oestradiol concentration decreases only slightly (87%).

We speculate that genetic differences may explain wide variability in post GnRHa trigger luteolysis kinetics, as well as OHSS post agonist trigger (Fatemi et al., 2014; Gurbuz et al., 2014), or frequent severe early OHSS following GnRHa trigger with the addition of 1500 IU HCG on retrieval day (Seyhan et al., 2013). Therefore, we suggest that these differences might be best dealt with using an individualized post GnRHa trigger follow-up of the luteolytic process in order to facilitate a fresh transfer and minimize the OHSS risk.

The novel concept of 'luteal coasting' after GnRHa trigger offers two advantages. Firstly, it seems to allow fresh transfer in high-risk OHSS patients. Secondly, it paves the way for the exogenous progesterone-free luteal phase in IVF, a concept previously suggested (Humaidan and Alsbjerg, 2014; Kol et al., 2011), and which frees the patient of either leaky vaginal discharge caused by vaginal administration of progesterone, or painful daily intramuscular progesterone injections. Recently, a subcutaneous daily progesterone formulation (Baker et al., 2014) was brought to the market, to be used from the day of oocyte retrieval and up to 10 weeks if pregnancy is achieved. Although it is not the intention of this communication to conduct a cost-analysis, it seems reasonable to assume that an additional three to four progesterone measurements are more cost-effective and patient friendly compared with 70 subcutaneous progesterone injections.

Deferring the early luteal phase HCG rescue bolus from the day of trigger or retrieval to 2–4 days later, brings it closer to the day of implantation, which *per se* might increase the receptivity of the endometrium (Tesarik et al., 2003). Although the early luteal phase progesterone drops precipitously with this concept, it recovers quickly after the rescue bolus towards the mid-luteal phase, reflecting partial rescue of the corpora luteae. Importantly, in all ongoing clinical pregnancies high progesterone concentration on the day of pregnancy test (>190 nmol/l) clearly shows that any additional exogenous progesterone is redundant.

As mentioned a limitation of the current report is obviously that a control group was not part of the case series. Moreover, one might suggest that for this category of high-risk OHSS patients a freeze-all policy should be adopted. However, the primary intention was to perform an explorative case series, using a novel concept rather than a randomized controlled trial; furthermore, not even a freeze-all policy will eliminate OHSS development in the high-risk OHSS patient (Fatemi et al., 2014; Gurbuz et al., 2014), and as previously mentioned, there are regional, legal, economical and ethical considerations that do not support the use of cryopreservation.

In summary, a case series of HCG-based tailored luteal phase support in OHSS high-risk patients undergoing fresh transfer after GnRHa trigger is described. No further exogenous luteal support was administered, and the endogenous early luteal progesterone concentration was used to decide when to administer the HCG rescue bolus. Clearly, the present results need to be corroborated in a larger group of IVF patients at risk of OHSS development – if possible adding a control group of freeze-all patients. However, this novel luteal tailoring concept after GnRHa trigger and fresh transfer might help cover the full scope of ovarian responses.

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