CHAPTER 20

Does ovulation triggering influence the risk for ovarian hyperstimulation syndrome?

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is the price patients pay for our attempt to override nature's delicate balances that were created to assure a single oocyte ovulation. Spontaneous OHSS does occur, as we delineate later. It is, however, very rare. Indeed, natural-cycle-based assisted reproductive technologies (ART) were responsible for the birth of the first IVF baby; however, this method was abandoned because it is cumbersome and, more important, yields poor results in terms of pregnancy rate. Therefore, human menopausal gonadotropin (hMG) has been used for decades in ovulation induction cycles, particularly in the context of *in vitro* fertilization (IVF). In recent years, recombinant follicle stimulating hormone (FSH) preparations have replaced hMG in most centers. Typically, in these cycles, human chorionic gonadotropin (hCG) is used as a surrogate to luteinizing hormone (LH) for the purpose of oocyte maturation and induction and ovulation. Given its significantly longer half-life (> 24 h versus 60 min for LH[1,2]), hCG administration results in a prolonged luteotrophic effect, characterized by the development of multiple corpora lutea and supraphysiological levels of estradiol (E_2) and progesterone (P). This sustained luteotrophic effect may result in the development of OHSS, still the most frequent and severe complication of ovarian stimulation treatments as described in other chapters of this volume. Although hCG (recombinant or urinary-derived in different doses) is used routinely, other modes of ovulation trigger are also available, namely, recombinant LH, native gonadotropin-releasing hormone (GnRH) and GnRH agonists. The aim of this chapter is to explore the association between the mode of trigger and the risk of OHSS. This association culminates in an OHSS risk-free clinical protocol that is available at the end of the chapter.

THE SPONTANEOUS LH/FSH SURGE: NATURAL-CYCLE OHSS

The mid-cycle spontaneous LH surge is characterized by three phases: a rapidly ascending limb of 14-h duration, a plateau of 14 h and a descending phase of 20 h[3]. The parallel FSH surge is of lower amplitude. Serum E_2 levels reach a peak at the time of onset of the LH surge and then decline rapidly. Serum levels of P begin to rise 12 h before the LH surge, continue to rise for an additional 12 h and then plateau until follicular rupture (36 h after the LH surge onset). Follicular rupture is associated with a

second rise in P and a fall in E_2, as the luteal pattern of ovarian steroidogenesis is attained.

The human natural cycle is designed to allow the recruitment of a single dominant follicle, from which a fertilizable oocyte emerges. Antral follicles that failed to reach dominance are destined to atresia, which occurs before the mid-cycle LH surge. This mechanism assures that only a single corpus luteum is formed in each cycle, explaining the rarity of spontaneous OHSS.

Spontaneous OHSS is typically associated with high hCG levels, i.e. multiple pregnancy or hydatidiform mole. Recurrent OHSS suggests a genetic predisposition. Indeed, an FSH receptor gene mutation was identified in a woman who developed spontaneous OHSS during each of her four pregnancies[3].

The corpus luteum originating from the dominant follicle is not 'responsible' for the development of spontaneous OHSS, but rather secondary corpora lutea that emerge while pregnancy is established.

OVULATION TRIGGERING WITH HCG

hCG is routinely used to trigger ovulation in ovarian stimulation cycles. Given its long half-life and luteotrophic activity, it is blamed for the initiation of the OHSS process. If pregnancy is achieved, the endogenous hCG production replaces and augments the trigger dose, leading to enhancement of the OHSS pathology. In the non-IVF patient, a low-dose stimulation protocol, resulting in monofollicular ovulation, will completely prevent OHSS[4] regardless of the hCG dose used. When multifolliculogenesis is required for ART, the risk of OHSS is a concern. Although there appears to be some degree of correlation with the degree of ovarian response, individual cases tend to be unpredictable. Withholding the hCG trigger (e.g. aborting the cycle) completely prevents OHSS, if measures are taken to prevent spontaneous ovulation. For the purpose of inducing ovulation and minimizing OHSS risk, reducing the hCG dose seems to be a logical step to take. While a dose of 10 000 IU is routinely used, reducing the trigger dose may be beneficial in terms of reducing OHSS risk. The comparison of single intramuscular doses of 2000, 5000 and 10 000 IU of hCG resulted in poor oocyte yield with the lowest dose[5]. Indeed, most clinicians administer the lower effective dose of hCG (5000 IU) in an effort to reduce OHSS risk. A retrospective review of IVF clinical data regarding high responders (defined as $E_2 \geq 2500$ but < 4000 pg/ml on the day of hCG trigger) tried to confirm that hCG in a dose of 3300 IU is sufficient to provide adequate oocyte maturation and fertilization. While the above was indeed confirmed, as the lower dose resulted in a similar proportion of mature eggs, similar fertilization rate and similar pregnancy rate compared with 5000 IU, reducing the dose did not eliminate the risk of OHSS[6]. Although a randomized controlled study that compares the two hCG doses has not been carried out, available data suggest that the practice of relying on the minimal hCG dose as a safeguard against OHSS should be discouraged.

Recombinant hCG (rhCG) has largely replaced the urinary product. Subcutaneous rhCG (250 μg) is superior to urinary hCG (5000 IU) in terms of luteal phase progesterone and serum hCG levels post-administration (Figures 1 and 2)[7]. However, in the context of OHSS it seems that there is no advantage. Although recombinant hCG (250 μg = 6500 IU) is as effective as 10 000 IU urinary hCG in terms of triggering, the rate of OHSS is similar[8,9].

Any discussion about triggering ovulation should include the type of protocol used for ovarian stimulation. Currently, ovarian stimulation for ART relies on GnRH analogs to prevent a premature LH surge. Long GnRH agonist-based protocols are associated with an increased incidence of OHSS, reflecting the recruitment of a large number of follicles[10]. GnRH antagonist-based protocols may reduce the incidence of

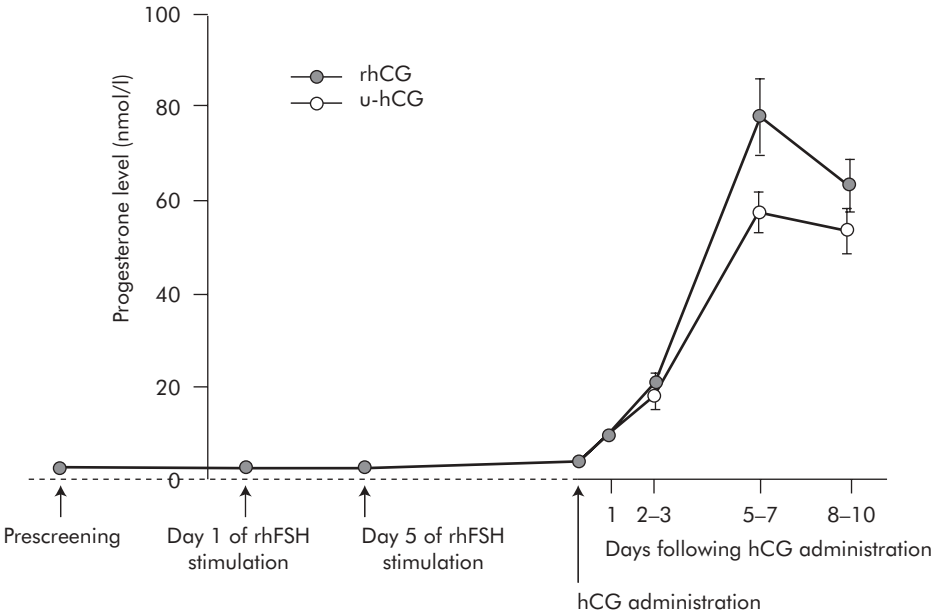

Figure 1 Mean progesterone levels (± SEM) before and during recombinant human follicle stimulating hormone (rhFSH) stimulation and after human chorionic gonadotropin (hCG) administration. Closed circles represent mean values in the group receiving recombinant (r)hCG 250 μg ($n = 85$); open boxes represent mean values in the group receiving urinary (u)hCG 5000 IU ($n = 92$). The difference in values at days 5–7 after hCG administration is statistically significant ($p = 0.0361$; analysis of variance (ANOVA), ranked data). From reference 7, by permission of the American Society for Reproductive Medicine

OHSS[11]. However, conflicting publications[12] suggest that the difference, if it exists, is minimal. The significant advantage of GnRH antagonist-based protocols, as discussed herein, lies in the ability to trigger ovulation with a GnRH agonist, and prevent OHSS altogether.

In summary, triggering ovulation with hCG is always associated with some risk of OHSS, depending primarily on the magnitude of the ovarian response. When the prolonged luteotrophic effect of hCG merges with endogenous hCG (if pregnancy is achieved), the continuous overstimulation of the corpora lutea may give rise to OHSS.

OVULATION TRIGGERING WITH LH

The availability of recombinant LH was met with hopes to replace hCG as trigger. After all, it makes sense to imitate nature. A prospective, comparative, dose-finding study was conducted to determine the minimal effective dose of recombinant LH[13]. In a long agonist protocol, recombinant LH was used in doses of 5000, 15 000 or 30 000 IU, or two doses of 15 000 and 10 000 IU 3 days apart. A control group was triggered with hCG 5000 IU. Moderate OHSS was reported in 12.4% of patients who received hCG and in 12% of patients who received the recom-

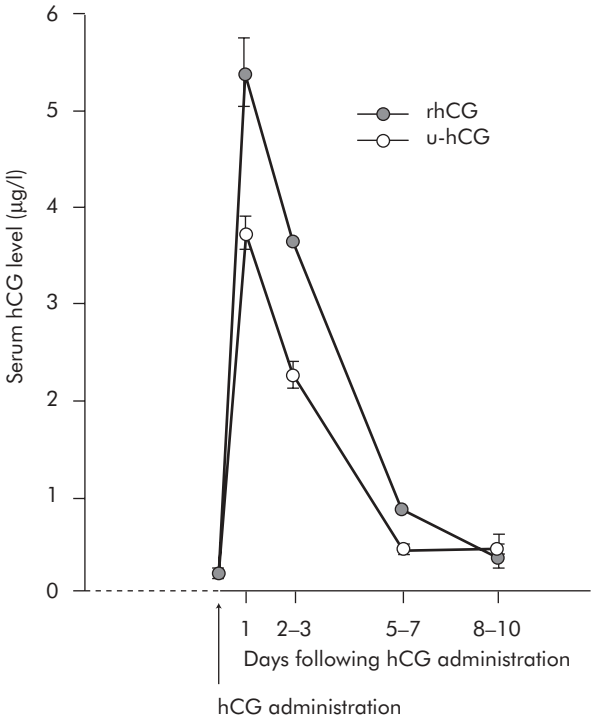

Figure 2 Mean human chorionic gonadotropin (hCG) levels (± SEM) at and after hCG administration. Closed circles represent mean values in the group receiving recombinant (r)hCG 250 µg ($n = 85$); open boxes represent mean values in the group receiving urinary (u)hCG 5000 IU ($n = 92$). Serum hCG levels on days 1, 2–3 and 5–7 after hCG administration were significantly higher in the rhCG group ($p = 0.0001$ for all time points; ANOVA, ranked data). From reference 7, by permission of the American Society for Reproductive Medicine

binant LH double dose. However, no OHSS was reported in patients who received a single dose of recombinant LH (up to 30 000 IU). The conclusion of this study was that a single dose of recombinant LH results in a significant reduction in OHSS compared with hCG. Unfortunately, the sponsoring company, Serono International, chose not to pursue this project further, and hence recombinant LH is not commercially available for ovulation triggering.

OVULATION TRIGGERING WITH NATIVE GNRH

In an effort to mimic the endogenous LH/FSH surges, native GnRH was used as trigger[14] in OHSS high-risk patients with polycystic ovaries undergoing hMG ovulation induction. Late-follicular E_2 of > 6000 pmol/l was chosen as high-risk cut-off. Ten patients became pregnant, of whom two experienced OHSS. Evidently, native

GnRH lacks the luteolytic effect of GnRH agonist as trigger, and hence its failure to prevent OHSS. Native GnRH trigger in the context of OHSS prevention was not pursued further to the above-cited study, therefore, there is no evidence to recommend its use.

OVULATION TRIGGERING WITH GNRH AGONIST

The GnRH agonist-induced LH/FSH surge

A GnRH agonist (GnRH-a) elicits pituitary secretion of gonadotropins, which can be utilized for triggering oocyte maturation and ovulation, if given at the right time of the cycle. Numerous compounds, administered in different regimens, have been successfully used for that purpose[15–22]. Based on these studies, it appears that the single administration of a GnRH-a in a dose of 200–500 μg effectively and reliably triggers the required gonadotropin surge[21,22]. However, the minimal effective dose of GnRH-a required to trigger an endogenous mid-cycle LH surge sufficient to induce oocyte maturation and ovulation remains to be established. Preliminary experience[23] suggests that a single dose of 50 μg intranasal buserelin is the minimal effective dose to trigger ovulation.

The pituitary and ovarian responses to mid-cycle GnRH-a injections in stimulated cycles have been described previously[18]. The injection of GnRH-a results in an acute release of LH and FSH. Serum LH and FSH levels rise during 4 and 12 h, respectively, and are elevated for 24–36 h. The amplitude of the surge is similar to that seen in the normal menstrual cycle, but in contrast with the natural cycle, the surge consists of only two phases: a short ascending limb (> 4 h) and a long descending limb (> 20 h). This has no bearing on the ovarian hormone secretion pattern, which is qualitatively similar to the pattern observed in a natural cycle. The LH surge is associated with a rapid rise of P and the attainment of peak E_2 levels during the first 12 h after GnRH-a administration. This is followed by a transient suppression of P biosynthesis and a gradual decline in E_2 levels during the 24 h preceding follicle aspiration. After oocyte retrieval, a second rapid rise in P and a continuous fall in E_2 are observed, reflecting normal transition from the follicular to the luteal phase in ovarian steroidogenesis.

The luteal phase

While the endogenous LH surge triggered by GnRH-a is associated with a normal early follicular–luteal shift in ovarian steroidogenesis, serum levels of E_2 and P during the luteal phase are lower compared with those achieved after hCG administration[18]. This may be related to the longer duration of plasma hCG activity compared with the shorter GnRH-a-induced LH elevation. Normal function of the corpus luteum is dependent on pituitary pulsatile LH[24]. It is possible, therefore, that the presumed down-regulation of pituitary GnRH receptors after a mid-cycle injection of GnRH-a results in reduced LH support for the developing corpora lutea, reduced steroidogenesis and early luteolysis. Based on these considerations, it is prudent to support the luteal phase with P (and possibly E_2) in patients treated with mid-cycle GnRH-a. Continued support during early pregnancy (until the luteal–placental shift) is probably required.

Prevention of OHSS

The most important benefit emerging from the use of GnRH-a, rather than hCG, for ovulation induction, is the ability of this regimen to eliminate completely the threat of clinically significant OHSS. It should be emphasized that the clinical findings attributable to mild[25] OHSS (e.g. ovarian enlargement, abdominal discomfort and excessive steroid production) are an integral part of most cases of ovulation induction in IVF,

and hence are meaningless in this context. As mentioned above, clinical experience with mid-cycle administration of GnRH-a in the context of OHSS prevention is very encouraging. Effective ovulation is triggered with no risk of OHSS even in patients with extremely high E_2 levels during the late follicular phase[20].

Previous reports described cases in which OHSS developed despite the use of GnRH-a to induce ovulation. Three cases were reported by van der Meer *et al*[26]. The clinical details of these cases are in line with mild to moderate OHSS. Severe ascites, hypovolemia or electrolyte imbalance did not occur, nor were the patients hospitalized. Of note, the three patients received nasal GnRH-a preparations (buserelin, Suprefact®, Hoechst, Germany). In one of them, a very weak response to GnRH-a was noted, with an LH-surge peak of 15.9 mIU/ml, suggesting that the dose used or the route of administration was less than optimal. The possibility of incomplete absorption using nasal administration cannot be ignored. In addition, the three patients were stimulated in preparation for intrauterine insemination (IU). Gerris *et al*.[27] have also reported OHSS following this approach; however, in this case, use was made of *native* GnRH (and not *GnRH-a*), resulting in successful ovulation triggering, but without the critical gonadotropin suppression, which is the key element in preventing OHSS. Shoham *et al*.[28] reported a personal communication of two OHSS cases. However, the complete details of the treatment protocols, symptoms and signs leading to the diagnosis of OHSS, severity of the syndrome and clinical outcome were not available. Last, a group from Saudi Arabia has presented its large and impressive experience with this strategy[29]. Of 708 polycystic ovarian syndrome (PCOS); high-responder IVF patients (mean E_2 on the day of ovulation triggering 7817 pg/ml!) ovulation was effectively triggered with GnRH-a in 682 (96%). One patient (0.1%) developed severe OHSS. Significantly, this patient was treated with hCG-based luteal support, probably by mistake, as the protocol dictated progesterone-only luteal support. Also of note is that in 26 patients a GnRH-a-induced LH surge was judged as 'inadequate'. In 18 of these patients, hCG was used, resulting in 11 (61%) cases of severe OHSS. This last figure may reflect the large number of severe OHSS cases in this series that were prevented by this strategy. The reason(s) for an inadequate LH surge may have to do with the dose (too low) or route (intranasal) of GnRH-a administration. A key point in this strategy is the ability of an adequate single dose of GnRH-a to bring about an effective LH surge, and subsequently to induce early luteal-phase relative pituitary down-regulation. Luteolysis could be induced by diminished early luteal-phase LH pulsatility, leading to the prevention of OHSS. Our protocol calls for a single subcutaneous. injection of 0.2 mg triptorelin (Decapeptyl®; Ferring, Malmö, Sweden). We recorded no LH surge failures with this protocol, and of course, no clinically significant OHSS thus far (thousands of patients, some of which have been published).

Benefits and limitations

As discussed above, GnRH-a is an effective alternative to hCG in ART, particularly when the threat of OHSS is imminent. In addition, it offers a more physiological stimulus for ovulation, combining both LH and FSH surges. Apparently, the presence of a mid-cycle FSH is not obligatory for successful ovulation, given the widespread use of hCG, and hence it is not known whether the FSH surge associated with GnRH-a is of any advantage.

Although a large body of evidence supports the role of this approach in OHSS prevention, none of the published papers reports the results of a bone fide prospective, randomized, study comparing GnRH-a and hCG in terms of OHSS occurrence. Admittedly, without such a study, rapid dissemination of this approach cannot be anticipated. The applicability of such a study at

this time is questionable owing to ethical considerations ('Catch 22' situation).

A practical, major, limitation of GnRH-a-induced ovulation is that it would not be effective in women with a low gonadotropin reserve. Therefore, it is not applicable in IVF stimulation cycles during which pituitary down-regulation with a GnRH agonist is used. This protocol renders the pituitary unresponsive for induction of an endogenous LH surge. Since GnRH agonist-based protocols have been used routinely by most IVF programs until the year 2000, GnRH-a-induced ovulation for OHSS prevention has not gained much popularity.

GnRH antagonists: new opportunities

The introduction of GnRH antagonists in controlled ovarian hyperstimulation (COH) protocols[22,23], has opened up opportunities for novel stimulation protocols. A large (730 subjects) prospective randomized study[30] was carried out to compare long GnRH-a (buserelin) and GnRH antagonist (ganirelix, Orgalutran®) protocols. The results suggest that ganirelix introduces a new treatment option for patients undergoing ovarian stimulation for IVF or intracytoplasmic sperm injection (ICSI) which is safe, short and simple. The clinical outcome was good, and the ongoing pregnancy rate was acceptable. This novel protocol also introduces new opportunities in the context of OHSS prevention. One possibility is to prevent spontaneous LH surges in high-risk patients safely with a high-dose GnRH antagonist, waiting for follicular demise and ovarian quiescence[31]. In order to prevent OHSS effectively, and to rescue the cycle at the same time, the quick reversibility of antagonist-induced pituitary suppression can be of advantage by allowing the use of GnRH-a for the purpose of ovulation triggering. This possibility was assessed in a randomized prospective multicenter study[32]. Two different GnRH agonists (0.2 mg triptorelin and 0.5 mg leuprorelin) were compared with hCG for triggering ovulation in a GnRH antagonist-based (Orgalutran® or Antagon®) protocol for IVF. High responders (> 25 follicles beyond 11 mm) were considered drop-outs from the study; hence, agonist trigger in the context of OHSS prevention was not assessed. Luteal support was given by daily progesterone administration. Both agonists kick-started a successful LH surge (peak LH 4 h post-trigger). Interestingly, LH dynamics post-trigger was similar to that reported without GnRH antagonist pretreatment[18]. In other words, the routine daily dose of a GnRH antagonist (ganirelix 0.25 mg) does not blunt the effect of an agonist (given about 12 h apart) at the pituitary level. The three treatment groups (two agonists and hCG) had comparable numbers of oocytes retrieved, percentages of mature oocytes, fertilization rates and implantation rates. The authors summarized the results stating, 'corpus luteum formation is induced by GnRH agonists with luteal phase steroid level closer to the physiological range compared with hCG'. This statement merits a deeper look. Since progesterone was given as luteal support, the estradiol level may represent endogenous luteal activity. Mid-luteal levels of estradiol were 46 pg/ml and 45 pg/ml in the agonist trigger groups vs. 490 pg/ml in the hCG group. These levels reflect the sum of E_2 production by all the corpora lutea, the number of which can be drawn from the number of oocytes retrieved (8.3 in the hCG group, 8.7 and 9.8 in the agonist groups). When the estradiol levels are plotted against the natural cycle (Figure 3), it becomes apparent that the agonist triggers resulted in extremely low mid-luteal E_2 levels that cannot be considered as 'physiological'. In fact, the natural-cycle mid-luteal estradiol levels from a single corpus luteum (around 600 pmol/l, or 160 pg/ml[33]) is > 3-fold higher than the mid-luteal estradiol levels produced by 8–9 corpora lutea post agonist triggers. These low levels can only be interpreted as a result of complete luteolysis, far from the 'physiological range'.

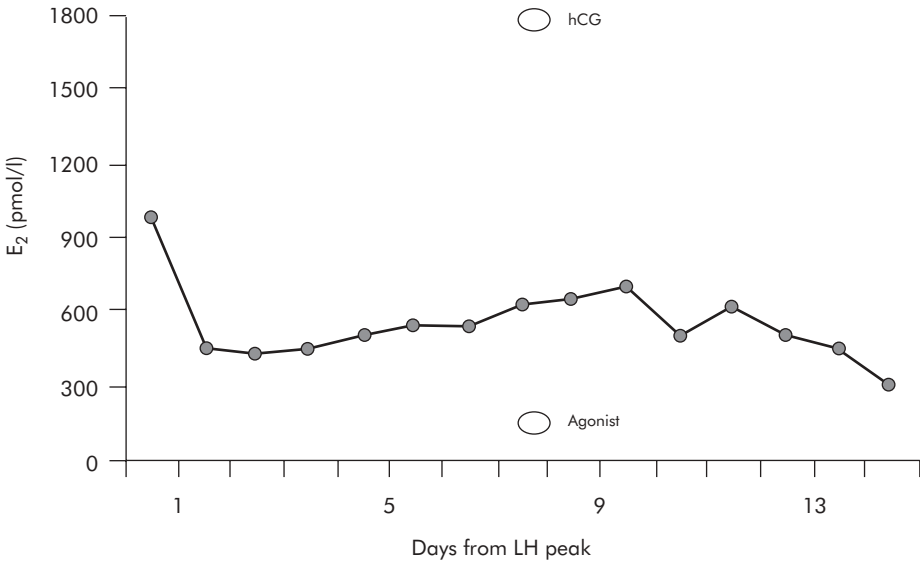

Figure 3 Luteal phase estradiol (E_2) (reflecting total luteolysis) after triggering ovulation with gonadotropin-releasing hormone (GnRH) agonist. Natural-cycle luteal phase estradiol is depicted by grey circles (based on reference 33). Mean mid-luteal serum concentrations of E_2 after triggering of final oocyte maturation with GnRH agonist or human chorionic gonadotropin (hCG) after ovarian stimulation for *in vitro* fertilization (IVF) (based on reference 32) are plotted against the natural-cycle levels. In agonist- and hCG-triggered cycles, 9 and 8 (mean) oocytes were retrieved, respectively (reference 32). LH, luteinizing hormone

Another randomized controlled study was performed to compare unsupplemented luteal phase characteristics after three different triggers: recombinant hCG, recombinant LH and GnRH agonist[34]. This approach allows assessment of progesterone levels to reflect luteal activity. Indeed, the 'area under the curve' progesterone secretion post-agonist trigger was practically zero. This remarkable phenomenon again attests for complete luteolysis post-agonist trigger. The concept of luteolysis post agonist was first put forward by Casper and Yen[35], in 1979. They gave mid-luteal agonist to five normal volunteers. Luteolysis occurred as indicated by a fall in E_2 and P levels, followed by a shortened luteal phase.

To characterize further the presumed luteolytic process induced by mid-cycle injection of GnRH-a, and to avoid confusion between endogenous biosynthesis and exogenous luteal support, we have measured non-steroidal luteal function markers, inhibin A and pro-αC[36]. Agonist trigger caused a sharp decrease in these markers compared with patients who were treated with hCG (Figure 4). Pregnancy was not associated with a rise in the levels of luteal markers. This is the most important message arising from this chapter: GnRH-agonist trigger results in complete and dramatic luteolysis. By the time endogenous hCG appears (if pregnancy is achieved), the corpora lutea are beyond the point of 'resuscitation', therefore, endogenous

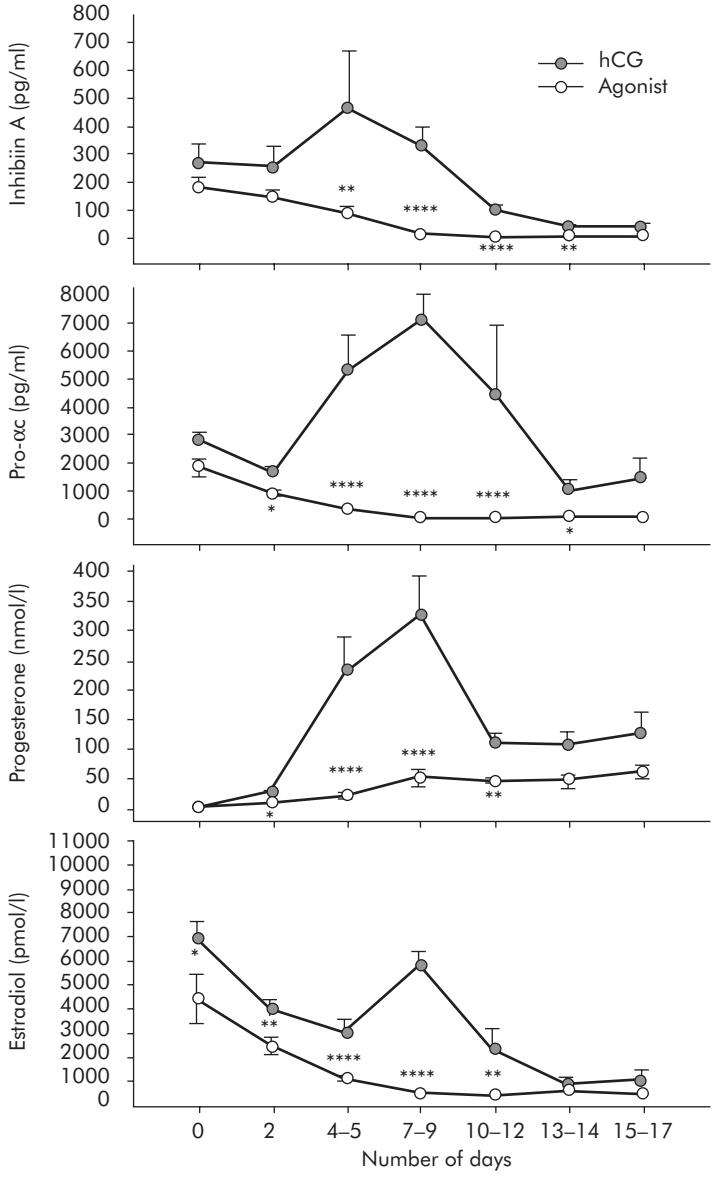

Figure 4 Luteal phase serum concentrations (mean ± SE) of inhibin A (a), pro-αC (b), progesterone (c) and estradiol (d) in two *in vitro* fertilization (IVF) protocols: GnRH antagonist for ovulation prevention and hCG (hCG group) or GnRH-a (agonist group) for oocyte maturation triggering. Time is represented as days relative to oocyte maturation triggering day (day 0). Changes in levels of all four hormones in both groups were significant over time ($p < 0.0001$) (Friedman test). $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$. From reference 36, by permission of the American Society for Reproductive Medicine

sex steroid production does not resume, together with the long list of mediators responsible for OHSS. Although covered in another chapter in this volume, it must be emphasized here that OHSS is a serious and protracted disease especially if pregnancy is achieved. Therefore, it is of utmost importance to secure a trigger that will 'kill' the corpora lutea before endogenous hCG appears on the scene. This is exactly what an agonist trigger does.

GNRH-a OVULATION TRIGGERING IN GNRH ANTAGONIST STIMULATION PROTOCOLS PREVENTS OHSS

The tremendous strength of the proposed approach is also its weakness in terms of 'evidence-based medicine'. It is very difficult to conduct a randomized controlled study comparing hCG and agonist trigger in high responders. Ethics committees might find it problematic to administer hCG to extremely high responders. One can compare the situation with a study on the merit of using a parachute when jumping from an airplane[37]. Indeed, agonist trigger can be looked on as a parachute to bring high responders safely down to the ground without an OHSS crash. Consequently, such studies are not available, although an unpublished research effort is currently ongoing in the USA, the results of which will probably be available by the time this volume is published. A preliminary report[38] describes the use of 0.2 mg triptorelin (Decapeptyl®) to trigger ovulation in eight patients who underwent controlled ovarian hyperstimulation with recombinant FSH (Puregon®) and concomitant treatment with the GnRH antagonist ganirelix (Orgalutran®) for the prevention of a premature LH surge. All patients were considered to have an increased risk for developing OHSS (at least 20 follicles ≥ 11 mm and/or serum estradiol at least 3000 pg/ml). On the day of triggering the LH surge, the mean number of follicles ≥ 11 mm was 25.1 ± 4.5, and the median serum estradiol concentration was 3675 (range 2980–7670) pg/ml. After GnRH agonist injection, endogenous serum LH and FSH surges were observed with median peak values of 219 and 19 IU/l, respectively, measured 4 h after injection. The mean number of oocytes obtained was 23.4 ± 15.4, of which 83% were mature (metaphase II). None of the patients developed any signs or symptoms of OHSS. So far, four clinical pregnancies have been achieved from the embryos obtained during these cycles, including the first birth following this approach. These preliminary results underlined the effectiveness of this approach in OHSS prevention.

THE QUESTION OF PREGNANCY RATE FOLLOWING AGONIST TRIGGER

Although not yet established as a tool to prevent OHSS, criticism of agonist trigger arose around the question of the pregnancy rate. In normal responders the pregnancy rate following agonist trigger is comparable to that following hCG[19,21,39]. The question of pregnancy rate in high responders was addressed in cycles during which hCG was used as trigger. Pellicer *et al.*[40] found that the implantation rate was significantly higher in normal (18.5%) as compared with high (0%) responders. These researchers concluded that a different endocrine milieu between normal and high responders is detected by daily steroid measurements up to the preimplantation period, suggesting that this difference could be responsible for an impaired implantation in high-responder patients undergoing IVF. An increase in serum E_2 levels seems to be the cause of this difference. Simon *et al.*[41] reached similar conclusions, stating that their clinical results demonstrate that high serum estradiol concentrations on the day of hCG injection in high- and normal-responder patients, regardless of the number of oocytes retrieved and the serum progesterone concentration, are detrimental to uterine receptivity without affecting

embryo quality. These results led to an effort to increase uterine receptivity by decreasing estradiol levels in high responders with the use of a follicle stimulating hormone step-down regimen. Simon *et al*.[42] were successful in that regard, although the step-down regimen resulted in a 17% cancellation rate, i.e. patients in whom FSH support to the growing follicles was too low, leading to a sharp decrease in estradiol level. At the 2004 annual European Society of Human Reproduction and Embryology (ESHRE) meeting in Berlin, Bankowski *et al*.[43] presented their experience with agonist trigger in high responders. Apparently, they have adopted a routine to trigger high responders (E_2 > 3000 pg/ml) with an agonist. From May 2000 to July 2003 a total of 317 patients were triggered with hCG (normal responders) while 97 patients were triggered with an agonist (high responders). Peak E_2 levels were 2050 vs. 4800 pg/ml, number of oocytes 10 vs. 21 and number of embryos 5.6 vs. 12.5, respectively. The pregnancy rate was 21.5% in the normal responders vs. 11.3% in the high responders. Importantly, they had three cases of severe OHSS, all in the hCG group. These results demonstrate again the tremendous efficacy of agonist trigger in terms of OHSS prevention. In addition, given the large number of oocytes and embryos obtained (with no risk of OHSS), the clinical rate per oocyte retrieval (fresh and thaw cycles combined) is more relevant to the patient. It may be argued that a decrease in fresh-cycle pregnancy rate is a reasonable price to pay for total OHSS prevention (patient safety) and a large number of embryos obtained (subsequent thaw cycles).

TAKE-HOME MESSAGES

A single mid-cycle dose of GnRH-a is able to trigger a preovulatory LH/FSH surge, leading to oocyte maturation in women undergoing ovarian stimulation for IVF, or induction of ovulation *in vivo*. The main advantage of this approach is the complete elimination of clinically significant OHSS. The application of this trigger in high responders requires a responsive pituitary. Therefore, it is not applicable in GnRH agonist-based cycles during which pituitary down-regulation is achieved. GnRH antagonist-induced competitive inhibition of the pituitary GnRH receptors is easily reversible with a GnRH agonist. In fact, a major reason to use GnRH antagonists in ovarian stimulation is to keep the option of agonist trigger if needed. A clinical protocol for the high responder is as follows:

(1) Start stimulation with 150–225 IU recombinant FSH.

(2) Start antagonist on day 6 of stimulation. Consider adding 1 ampoule of recombinant LH (75 IU) daily.

(3) Ignore E_2 levels! There is no need to step down! Give the growing follicles *full* FSH support!

(4) Trigger with 0.2 mg triptorelin or 0.5 mg leuprorelin (at least 12 h after the last antagonist injection).

(5) Start luteal support with E_2 and progesterone on the day of oocyte retrieval.

In our experience, this protocol will eliminate OHSS.

REFERENCES

1. Yen SSC, Lenera G, Little B, et al. Disappearance rate of endogenous luteinizing hormone and chorionic gonadotropin in man. J Clin Endocrinol Metab 1968; 28: 1763–7.

2. Damewood MD, Shen W, Zacur HA, et al. Disappearance of exogenously administered human chorionic gonadotropin. Fertil Steril 1989; 52: 398-400.

3. Smits G, Olatunbosun OA, Delbaere A, et al. Spontaneous ovarian hyperstimulation syn-

drome caused by a mutant follitropin receptor. N Engl J Med 2003; 349: 760–6.

4. Homburg R, Howles CM. Low dose FSH therapy for anovulatory infertility associated with polycystic ovary syndrome: rationale, reflections and refinements. Hum Reprod Update 1999; 5: 493–9.

5. Abdalla HI, Ah-Moye M, Brinsden P, et al. The effect of the dose of hCG and the type of gonadotropin stimulation on oocyte recovery rates in an IVF program. Fertil Steril 1987; 48: 958–63.

6. Schmidt DW, Maier DB, Nulsen JC, et al. Reducing the dose of human chorionic gonadotropin in high responders does not affect the outcomes of in vitro fertilization. Fertil Steril 2004; 82: 841–6.

7. Fertil Steril 2001; 75: 1115.

8. Driscoll GL, tyler JP, Hangan JT, et al. A prospective randomized controlled, double-blind, double-dummy comparison of recombinant and urinary HCG for inducing oocyte maturation and follicular luteinization in ovarian stimulation. Hum Reprod 2000; 15: 1305–10.

9. Chang P, Kenley S, Burns T, et al. Recombinant human chorionic gonadotropin (rhCG) in assisted reproductive technology: results of a clinical trial comparing two doses of rhCG (Ovidrel) to urinary hCG (Profasi) for induction of final follicular maturation in in vitro fertilization–embryo transfer. Fertil Steril 2001; 76: 67–74 .

10. Smitz J, Camus M, Devroey P, et al. Incidence of severe ovarian hyperstimulation syndrome after GnRH agonist/HMG superovulation for in-vitro fertilization. Hum Reprod 1990; 5: 933–7.

11. Ludwig M, Katalinic A, Diedrich K. Use of GnRH antagonists in ovarian stimulation for assisted reproductive technologies compared to the long protocol. Meta-analysis. Arch Gynecol Obstet 2001; 265: 175–82.

12. Al-Inany H, Aboulghar M. GnRH antagonist in assisted reproduction: a Cochrane review. Hum Reprod 2002; 17: 874–85.

13. European Recombinant LH Study Group. Human recombinant luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: results of a multicenter double-blind study. J Clin Endocrinol Metab 2001; 86: 2607–18.

14. Blumenfeld Z, Lang N, Amit A, et al. Native gonadotropin-releasing hormone for triggering follicular maturation in polycystic ovary syndrome patients undergoing human menopausal gonadotropin ovulation induction. Fertil Steril 1994; 62: 456–60.

15. Emperaire JC, Ruffie A. Triggering ovulation with endogenous luteinizing hormone may prevent the ovarian hyperstimulation syndrome. Hum Reprod 1991; 6: 506–10.

16. Imoedemhe DAG, Chan RCW. Sigue AB, et al. A new approach to the management of patients at risk of ovarian hyperstimulation in an in-vitro fertilization programme. Hum Reprod 1991; 6: 1088–91.

17. Itskovitz J, Boldes R, Barlev A, et al. The induction of LH surge and oocyte maturation by GnRH analogue (buserelin) in women undergoing ovarian stimulation for in vitro fertilization. Gynecol Endocrinol 1988; 2: 165.

18. Itskovitz J, Boldes R, Levron J, et al. Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyperstimulation syndrome by gonadotropin-releasing hormone agonist. Fertil Steril 1991; 56: 213–20.

19. Lanzone A, Fulghesu AM, Villa P, et al. Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin as a trigger of ovulation in polycystic ovarian disease gonadotropin hyperstimulated cycles. Fertil Steril 1994; 62: 35–41.

20. Lewit N, Kol S, Manor D, et al. The use of GnRH analogs for induction of the preovulatory gonadotropin surge in assisted reproduction and prevention of the ovarian hyperstimulation syndrome. Gynecol Endocrinol 1995; 4: 13–17.

21. Segal S, Casper RF. Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin for triggering follicular maturation in in vitro fertilization. Fertil Steril 1992; 57: 1254–8.

22. Lewit N, Kol S, Manor D, et al. Comparison of GnRH analogs and hCG for the induction of ovulation and prevention of ovarian hyperstimulation syndrome (OHSS): a case–control study. Hum Reprod 1996; 11: 1399–402.

23. Buckett WM, Bentick B, Shaw RW. Induction of the endogenous gonadotrophin surge for oocyte maturation with intra-nasal gonadotrophin-releasing hormone analogue (buserelin): effective minimal dose. Hum Reprod 1998; 13: 811–14.

24. Mais V, Kazar RR, Cetel NS, et al. The dependency of folliculogenesis and corpus luteum function on pulsatile gonadotropin secretion in cycling women using a gonadotropin-releasing hormone antagonist as a probe. J Clin Endocrinol Metab 1986; 62: 1250–5.

25. Schenker JG, Weinstein D. Ovarian hyperstimulation syndrome: a current survey. Fertil Steril 1978; 30: 255–68.

26. van der Meer S, Gerris J, Joostens M, et al. Triggering of ovulation using a gonadotropin-releasing hormone agonist does not prevent ovarian hyperstimulation syndrome. Hum Reprod 1993; 8: 1628–31.

27. Gerris J, De Vits A, Joostens M, et al. Triggering of ovulation in human menopausal gonadotropin-stimulated cycles: comparison between intravenous administered gonadotrophin-releasing hormone (100 and 500 ?g), GnRH agonist (buserelin, 500 ?g) and human chorionic gonadotrophin (10,000 IU). Hum Reprod 1995; 10: 56–62.

28. Shoham Z, Schachter M, Loumaye E, et al. The luteinizing hormone surge – the final stage in ovulation induction: modern aspects of ovulation triggering. Fertil Steril 1995; 64: 237–51.

29. Imoedemhe D, Chan R, Pacpaco E, et al. Preventing OHSS in at-risk patients: evidence from a long-term prospective study. Hum Reprod 1999; 14: 102–3.

30. The European Orgalutran Study Group. Treatment with the gonadotrophin-releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: results of a controlled, randomized, multicentre trial. Hum Reprod 2000; 15: 1490–8.

31. de Jong D, Macklon NS, Mannaerts BMJL, et al. High dose gonadotrophin-releasing hormone antagonist (ganirelix) may prevent ovarian hyperstimulation syndrome caused by ovarian stimulation for in-vitro fertilization. Hum Reprod 1998; 13: 573–5.

32. Fauser BC, de Jong D, Olivennes F, et al. Endocrine profiles after triggering of final oocyte maturation with GnRH agonist after cotreatment with the GnRH antagonist ganirelix during ovarian hyperstimulation for in vitro fertilization. J Clin Endocrinol Metab. 2002; 87: 709–15.

33. Yen SSC. The human menstrual cycle: neuroendocrine regulation. In Yen SSC, Jaffe RB, eds. Reproductive Endocrinology 3rd edn. Philadelphia, PA: WB Saunders Co, 1991: 273–308.

34. Beckers NG, Macklon NS, Eijkemans MJ, et al. Nonsupplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. J Clin Endocrinol Metab 2003; 88: 4186–92.

35. Casper RF, Yen SSC. Induction of luteolysis in the human with a long acting analog of luteinizing hormone releasing factor. Science 1979; 205: 408–10.

36. Nevo O, Eldar-Geva T, Kol S, et al. Lower levels of inhibin A and pro-alphaC during the luteal phase after triggering oocyte maturation with a gonadotropin-releasing hormone agonist versus human chorionic gonadotropin. Fertil Steril 2003; 79: 1123–8.

37. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. Br Med J 2003; 327: 1459–61.

38. Itskovitz-Eldor J, Kol S, Mannaerts B. Use of a single bolus of GnRH agonist triptorelin to trigger ovulation after GnRH antagonist ganirelix treatment in women undergoing ovarian stimu-

lation for assisted reproduction, with special reference to the prevention of ovarian hyperstimulation syndrome: preliminary report: Short communication. Hum Reprod 2000; 15: 1965–8.

39. Gonen Y, Balakier H, Powell W, et al. Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for in vitro fertilization. J Clin Endocrinol Metab 1990; 71: 918–22.

40. Pellicer A, Valbuena D, Cano F, et al. Lower implantation rates in high responders: evidence for an altered endocrine milieu during the preimplantation period. Fertil Steril 1996; 65: 1190–5.

41. Simon C, Cano F, Valbuena D, et al. Clinical evidence for a detrimental effect on uterine receptivity of high serum oestradiol concentrations in high and normal responder patients. Hum Reprod 1995; 10: 2432–7.

42. Simon C, Garcia Velasco JJ, Valbuena D, et al. Increasing uterine receptivity by decreasing estradiol levels during the preimplantation period in high responders with the use of a follicle-stimulating hormone step-down regimen. Fertil Steril 1998; 70: 234–9.

43. Bankowski B, Bracero N, King J, et al Triggering ovulation with leuprolide acetate is associated with lower pregnancy rate. Hum Reprod 2004; 19 (Suppl 1): i103.