Review Article

Prevention of ovarian hyperstimulation syndrome

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ABSTRACT

Ovarian hyperstimulation syndrome (OHSS) is a potentially serious complication of ovarian stimulation for fertility treatment. Risk factors include polycystic ovaries, high ovarian reserve, and excessive ovarian response to stimulation. It is important to be aware of the risk of OHSS, even in so called "low-risk" situations. An understanding of the pathophysiology of OHSS may help clinicians to target preventative measures in women who are at risk. Ovarian stimulation regimes based on an individualized reserve assessment may help reduce the incidence of OHSS. Gonadotropin-releasing hormone (GnRH) antagonist regimes are associated with a lower risk than GnRH agonist regimes and the risk may be further reduced if a GnRH agonist trigger is used in place of human chorionic gonadotropin (hCG). Other methods of reducing hCG exposure include avoiding hCG luteal support, cryopreservation of all embryos, and avoidance of multiple pregnancy. However, the only method that guarantees avoidance of OHSS in high-response cycles is cycle cancellation. Clinicians should be aware of the potential value of coasting and dopamine agonists, as measures to reduce risk in the presence of an excessive ovarian response.

Keywords: Complications, gonadotropin-releasing hormone (GnRH) antagonist, *in vitro* fertilization (IVF), ovarian hyperstimulation syndrome (OHSS)

INTRODUCTION

It is unfortunate that in modern fertility practice, more powerful interventions often carry an increased risk of complications. Women undergoing ovarian stimulation with gonadotropins are at risk of developing ovarian hyperstimulation syndrome (OHSS). This is a specific clinical condition with specific pathophysiological derangements and should be distinguished from "excessive ovarian response." While there is no agreed definition of excessive ovarian response, it can broadly be considered to be a condition where the ovaries exhibit growth of more ovarian follicles than what is aimed for. This in itself does not cause a problem but it often forms the background in which the woman develops the clinical features of OHSS.

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Not all women with an excessive ovarian response go on to develop OHSS, and not all women who suffer from OHSS do so in the background of excessive response. Further, the available tests are not very good at predicting when OHSS will develop and what the severity will be. As a result, it is sensible to always keep the risk of OHSS in mind, whenever gonadotropin therapy is used.

The incidence of significant OHSS has been reported to lie between 3.1% and 8% of *in vitro* fertilization (IVF) cycles in the literature (Delvigne *et al*.).[10] OHSS may also develop following ovulation induction with gonadotropins or clomifene, but is much less common. A Finnish study found that 0.04% of ovulation induction cycles and 0.9% of IVF cycles were associated with hospital admissions for OHSS (Klemetti *et al*.).[21]

This review addresses the evidence base underlying measures that can be taken to reduce the risk of OHSS. This subject has also been covered by recent guidelines from the British Fertility

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Society (Mathur and Tan)[28] and the Society of Obstetricians and Gynaecologists of Canada (Corbett *et al*.).[7]

PATHOPHYSIOLOGY OF OHSS

Women with OHSS demonstrate ovarian enlargement with multiple follicles and increased capillary permeability. Increased vascular permeability leads to loss of fluid from the circulation into the third space, causing ascites and in some cases pleural and pericardial effusions. Depletion of intravascular volume predisposes to renal dysfunction and may contribute to an increased risk of thrombosis and embolism.

The underlying cause of OHSS is unknown, but is most likely related to vasoactive mediators released by hyperstimulated ovaries. Several inflammatory mediators have been studied as the instigators of OHSS, chiefly vascular endothelial growth factor (VEGF)-A, interleukin (IL)-6, IL-8, IL-1α, IL-1ß, tumor necrosis factor-α, and basic fibroblast growth factor (Chen *et al*.).[6] A pivotal role is believed to be played by VEGF, a potent vasoactive peptide produced in ovarian granulosa cells. An elegant experiment by McClure *et al*.[29] showed that ascites from an OHSS patient enhanced vascular permeability, but not in the presence of antibodies to VEGF.

It is important to recognize the crucial role of human chorionic gonadotropin (hCG) in the development of OHSS in the majority of cases. In clinical practice, hCG is used as a "surrogate" for luteinizing hormone (LH) to induce final follicular maturation. However, hCG has a significantly longer half-life than native LH and binds the LH receptor more avidly. As a result, use of hCG is more often associated with precipitating OHSS than the use of endogenous LH. In treatment cycles with an excessive ovarian response to follicle-stimulating hormone (FSH), OHSS can be avoided if hCG is not administered and an endogenous LH rise is blocked by the use of a GnRH agonist. It is significant that it has been shown that hCG stimulates VEGF production in human granulosa cells *in vitro* in a dose-dependent manner and increases serum VEGF levels *in vivo* (Neulen *et al*.).[33] The link between hCG and VEGF may explain the association of increased hCG exposure and the risk of developing OHSS. OHSS is more common in cycles where conception occurs compared to non-conception cycles and more common in cycles with multiple pregnancy compared to cycles with singleton pregnancy (Mathur *et al*.).[27]

PREDICTION OF OHSS

Pretreatment patient characteristics

Studies have identified a number of patient characteristics that are associated with an increased risk of OHSS, including young age, previous history of OHSS, and the presence of polycystic ovary (PCO) or polycystic ovarian syndrome (PCOS) (Delvigne *et al*.).[10] High serum anti-Müllerian hormone (AMH) levels are predictive of the risk of over-response and OHSS (Nardo *et al*., Lee *et al*.).[30,23] As a result of these studies AMH-based tailored ovarian stimulation protocols have gained popularity, aiming to optimize and "individualize" ovarian stimulation. One claimed benefit of individualized ovarian stimulation is a possible reduction in the risk of OHSS, supported by nonrandomized studies. Yates *et al*.[47] and Nelson *et al*.[32] used serum AMH to select women with a high risk of developing OHSS for GnRH antagonist protocols and a starting dose of 150 iμ FSH daily. Nelson *et al*.[32] carried out a prospective cohort study between two centers, one of which used GnRH agonist and the other GnRH antagonist to control LH during ovarian stimulation with high AMH concentrations. Hospitalization for OHSS was required in 20 out of 148 women receiving GnRH agonist (13.9%) compared to 0 out of 34 women receiving GnRH antagonist. In the study by Yates *et al*.[47] AMH-guided ovarian stimulation was associated with a reduced incidence of cycle cancellation or "freeze-all" due to a perceived risk of OHSS, although the incidence of hospital admission due to severe OHSS did not differ significantly between the two groups.

A high antral follicle count (AFC) is associated with an increased risk of developing OHSS. Jayaprakasan *et al*.[19] found that the incidence of OHSS was 2.2% in women with an AFC <24 and 8.6% in women with AFC ≥ 24. Kwee *et al*.[22] found that AFC was predictive of excessive ovarian response (defined as the collection of 20 or more oocytes). An AFC of 14 provided the best combination of sensitivity (82%) and sensitivity (89%) with a positive predictive value of 58. As a result, AFC has been proposed as a marker that may be used, similar to AMH, to individualize ovarian stimulation.

Ovarian response parameters

In general terms, an excessive ovarian response is associated with a higher risk of developing OHSS. High serum estradiol (E_2) large numbers of follicles and a large number of oocytes retrieved have all been studied as markers of risk (Delvigne *et al*.).[10] However, ovarian response parameters have only modest predictive value for OHSS. A significant proportion of cases of severe OHSS occurs in cycles where no risk factor was identified in the treatment cycle or patient characteristics (Delvigne *et al*.),[10] while the incidence of severe OHSS in cycles considered "high-risk" by commonly used predictive variables is around 20% (Orvieto).[34]

A further problem with using ovarian response parameters to predict the risk of OHSS is the lack of a clear cut-off that can reliably differentiate "high" from "low" risk cycles. It is useful to think of the risk of developing OHSS as lying on a continuum. For instance, there is a certain risk of developing OHSS in a cycle where 20 eggs are collected but with the collection of fewer eggs, there is still a risk of OHSS (although lower than 20 eggs). Hence, any treatment cycle in which gonadotropin ovarian stimulation is used should be considered at risk of OHSS. When using ovarian response to judge whether or not to take preventative measures, clinicians should bear in mind the limitations discussed above.

PREVENTION OF OHSS

Alternatives to gonadotropins

All too often, gonadotropin stimulation and IVF are seen as the default option for couples with fertility problems. However, in several scenarios, there are alternatives that do not carry the same risk of OHSS. For instance, it is appropriate to advise women with ovulatory dysfunction about lifestyle modification

as the first step. In women with PCOS, clomifene, metformin, aromatase inhibitors, and laparoscopic ovarian diathermy should be considered before IVF. An additional option for some women with PCOS, who are at especially high risk of OHSS is *in vitro* maturation (IVM) of oocytes obtained from unstimulated ovarian follicles. Although IVM has a lower live birth rate than stimulated IVF (Gremeau *et al*.),[17] it is to be expected that success rates will improve with advances in technique.

Laparoscopic ovarian diathermy prior to IVF

Two studies in women with ultrasound evidence of PCO found a lower risk of cancellation due to over-response, but no difference in the incidence of OHSS with the use of laparoscopic ovarian diathermy carried out 1 week prior to the start of gonadotropin stimulation in GnRH agonist cycles (Rimington *et al*., Tozer *et al*.).[37,42] This is an extra invasive procedure and the evidence is not sufficient to recommend routine use for this indication.

Ovarian stimulation regimes

Starting dose of FSH

The rationale for using AMH- or AFC-based ovarian stimulation regimes has been discussed above. In women who are considered to be at high risk for OHSS, clinicians will often apply a lower starting dose of FSH. Although there are no randomized trials on this subject, one study (Macri *et al*.)[25] found a significant reduction in cycle cancellation rate with a starting dose of 75 iu recombinant FSH (rFSH) in 61 women who had previously responded excessively to a starting dose of 150-225 iμ human menopausal gonadotropin (hMG).

Choice of FSH

The type of FSH used (urinary vs. recombinant) does not affect the risk of OHSS (van Wely *et al*.).[45]

GNRH AGONIST VERSUS GNRH ANTAGONIST

A meta-analysis of randomized trials comparing GnRH antagonist with long protocol GnRH agonist treatment cycles (Al-Inany *et al*.)[1] showed that the incidence of OHSS is significantly lower in cycles using GnRH antagonist compared to cycles using GnRH agonist. Information on the incidence of severe OHSS was available in 29 studies with a total of 5,417 subjects. The incidence of severe OHSS was significantly lower in GnRH antagonist cycles compared to GnRH agonist cycles [2.65% vs. 6.61%; 95% confidence interval (CI) = −0.05 to −0.02; $P < 0.00001$]. In the overall study population, the risk of OHSS was 60% lower in women receiving GnRH antagonist with an absolute risk reduction of 4% and the corresponding number needed to harm was 25 (that is, for every 25 women receiving the long protocol GnRH agonist regime, there would be one extra case of severe OHSS). The protective effect of GnRH antagonist was even more marked when women with PCOS were considered separately: The incidence of severe OHSS among women with PCOS was significantly lower with the use of GnRH antagonist (3.44% vs. 15.02%; 95% CI = −0.14 to −0.07; $P < 0.00001$). The incidence of coasting or cycle cancellation due to a perceived risk of OHSS was also significantly lower in GnRH antagonist cycles, lending further plausibility to the findings.

MODIFYING THE "TRIGGER"

GnRH agonist for final follicular maturation in GnRH antagonist cycles

The risk of OHSS in GnRH antagonist cycles may be further reduced by using GnRH agonist for final follicular maturation in place of hCG. This exploits a specific property of GnRH antagonist, namely, the retention of pituitary gonadotroph cells' sensitivity to GnRH. Hence, GnRH agonist administration to a woman receiving GnRH antagonist leads to an initial "flare" effect, characterized by the release of LH and FSH. The resulting LH surge is sufficient to cause follicular maturation. LH has a shorter half-life than hCG and is less likely to precipitate OHSS than hCG (Humaidan *et al*.).[18]

The evidence shows that GnRH agonist trigger in GnRH antagonist cycles significantly reduce the risk of developing OHSS compared to an hCG trigger in GnRH antagonist cycles. A meta-analysis of five randomized controlled trials found a significantly lower risk of OHSS with a GnRH agonist trigger compared with hCG trigger (OR 0.10, 95% CI 0.01 to 0.82), suggesting that for a population with an OHSS incidence of 3% using hCG trigger, the incidence using GnRH agonist trigger would be 0-2.6%. The incidence of OHSS in egg donation cycles (3 trials and 342 cycles) was also significantly lower with GnRH agonist trigger compared to hCG trigger (OR 0.06, 95% CI 0.01 to 0.31) (Youssef *et al*.).[49]

However, there are significant drawbacks in the use of GnRH agonist trigger, in the form of a lower clinical pregnancy and live birth rate compared with hCG trigger. Meta-analysis shows significantly lower live birth rates (OR 0.44, 95% CI 0.29 to 0.68; 4 trials comprising 497 cycles) and increased risk of miscarriage (OR 1.89, 95% CI 1.11 to 3.21; 8 trials comprising 713 cycles) with GnRH agonist trigger compared to hCG trigger in autologous IVF cycles. It is thought that this is because the endogenous LH surge induced by the agonist trigger is of a shorter duration than a typical "natural" preovulatory LH surge. While this attenuated surge is sufficient for oocyte maturation, it is not adequate for normal corpus luteum formation, leading to a reduced implantation rate and a higher rate of early pregnancy loss. Clearly, this is not a drawback if fresh embryo transfer is not contemplated, e.g., in egg donation or fertility preservation cycles.

Various regimes have been suggested to address the luteal phase defect associated with GnRH agonist trigger treatment. A small dose of hCG may be administered, either at the time of the trigger or at egg collection. In a randomized controlled trial of 302 patients, Humaidan *et al*.[18] found that 1500 iu hCG administered 35 h after the GnRH agonist trigger was associated with no cases of OHSS and live birth rates comparable to the conventional hCG trigger. On the contrary, a retrospective study by Seyhan *et al*.[39] of 23 women at increased risk of OHSS found severe early OHSS in 6 (26%) patients with the use of GnRH agonist trigger and 1,500 iu hCG luteal rescue. This highlights the potential problems with the use of even small doses of hCG in situations of excessive ovarian response.

Other regimes that have been studied include intensive steroid replacement (intramuscular progesterone and transdermal or oral oestradiol) (Babayof *et al*., Engman *et al*.),[4,15] recombinant

LH injections during the luteal phase (Papanikolau *et al*.),[35] and daily intranasal GnRH agonist during the luteal phase (Pirard *et al*.).[36] At present there is insufficient evidence to say which, if any, regime is able to overcome the luteal phase defect; further research is clearly needed. It is interesting to speculate that as embryo vitrification techniques continue to improve and clinics become more comfortable with freezing embryos (or if ongoing clinical trials show a benefit from elective embryo cryopreservation as routine treatment), this issue may become less of a problem in the future.

Recombinant LH/hCG

Neither recombinant LH nor recombinant hCG offers any protection against OHSS in clinical trials (Youssef *et al*.)[50] when compared with urinary hCG.

Dose of hCG

It has been shown that a dose of 2,500 iu of urinary hCG may be sufficient in women with a high ovarian response (Nargund *et al*.).[31] A dose of 250 µg recombinant hCG is associated with a lower risk of OHSS than a dose of 500 µg (Chang *et al*.).[5]

COASTING

The term "coasting" refers to the practice of withholding gonadotropins while maintaining pituitary suppression. The theoretical basis is that this leads to atresia of smaller follicles, which are FSH-dependent, while larger follicles continue to grow (Dhont).[11] There is evidence that granulosa cell apoptosis may increase as FSH concentrations fall, accompanied by falling concentrations of vasoactive mediators produced by the ovaries (Tortoriello, Tozer *et al*.).[41,43] In practice, coasting is monitored by daily E_2 estimation and follicular tracking until E2 drops to a "safe" level, allowing the trigger to be administered.

There is no general agreement on the criteria for starting and ending coasting. In general, follicle diameters of at least 15 mm should be present. The E_2 level to initiate coasting varies in the literature from 2,500 pg/mL (Dhont *et al*.)[11] to 6,000 pg/mL (Egbase *et al*.).[13] It is not possible to be prescriptive about these criteria, and there is a role for the clinician to judge the risk of OHSS considering the overall picture of the treatment cycle. Similarly, it is not possible to be dogmatic about the E_2 level at which coasting can be stopped and trigger administered. However, the experience of Mansour *et al*.[24] is useful in this regard. In a large retrospective series of 1,223 cycles, they reported that 16 cases of severe OHSS occurred (1.3%), all in cycles where hCG was administered when E_2 was greater than 3,000 pg/mL. Hence, a level of 3,000 pg/mL would appear to be a reasonable cut-off.

Data on the duration of coasting and its effect on pregnancy rates are contradictory. It has been recommended by experts that coasting for longer than 3 days is associated with a reduction in clinical pregnancy rates, and cycle cancellation should be considered in this situation (Corbett *et al*.).[7] However, experience shows that even with prolonged coasting, clinical pregnancies do occur (Kailasam, personal correspondence). Hence, rather than setting an arbitrary duration for coasting, each case should be considered on its merits.

Although coasting is widely used, it has been mainly studied retrospectively. While coasting does not abolish the risk of OHSS, there does appear to be a lower incidence of OHSS in coasted cycles than would be expected from the literature (Garcia Velasco *et al*.).[16] D'Angelo *et al*.[8] identified four randomized trials of coasting, but only one of these compared coasting with no coasting, showing a reduction in the risk of moderate or severe OHSS with coasting (OR 0.17, 95% CI 0.03-0.88; P = 0.03). Other trials compared coasting with other preventative measures (such as early follicular aspiration or GnRH antagonist) and no significant difference was found in the incidence of OHSS in these comparisons. Owing to the comparison with another method of prevention, these results may not correctly reflect the efficacy of coasting.

AVOIDANCE OF HCG

Cycle cancellation

If hCG is withheld in cycles at risk of OHSS and an endogenous LH surge is avoided, OHSS should not develop. Treatment can then restart using a modified regime with a lower risk of OHSS. Although patients and clinicians may be reluctant to "waste" a treatment cycle, in cases of extreme response this may be the safest option and should be kept in mind at all times.

Cryopreservation of all embryos

Avoiding fresh embryo transfer eliminates exposure to endogenous hCG and should thereby eliminate the possibility of pregnancy-associated "late" OHSS. Of course, early OHSS that is related to the preovulatory exogenous hCG can still occur. It is recognized that late OHSS is more likely to be severe than the early variant. An important consideration is whether to continue pituitary suppression after egg collection if all embryos are to be cryopreserved. There is evidence that the incidence of OHSS is reduced if GnRH agonist is continued for a week after the trigger injection (Endo *et al*.).[14]

ADJUVANT TREATMENTS

Metformin cotreatment during gonadotropin stimulation

A systematic review of randomized trials shows that metformin reduces the risk of OHSS in women with PCOS undergoing IVF (Tso *et al*.)[44] (13/227 vs. 47/222; OR 0.27, 95% CI = 0.16-0.47). A typical regime (Tang *et al*.)[40] would be to use metformin 850 mg twice daily from the first day of downregulation to the day of oocyte retrieval. It also appears to be effective in cycles where GnRH antagonist is used (Doldi *et al*.).[12]

Dopamine agonists

Dopamine agonists have a role as a preventative measure for OHSS, based on the action of dopamine in antagonizing the vascular permeability-enhancing effect of VEGF through the dopamine receptor type 2 (Chen *et al*.).[6] Initial studies in rats were followed by a trial in oocyte donors (Alvarez *et al*.),[2] which showed a reduced incidence of moderate, but not severe, OHSS in oocyte donors receiving 0.5 mg cabergoline daily from the day of hCG administration for 8 days. It appears that cabergoline is effective in preventing early, but not late, OHSS (Youssef *et al*.);[48] however, whether this can be overcome by altering the dose or duration of treatment remains to be seen. Implantation appears

to be unaffected by the use of cabergoline in the luteal phase (Alvarez *et al*.).[3]

Intravenous albumin

Administration of intravenous albumin around the time of oocyte retrieval has been proposed as a measure to prevent OHSS, but the rationale for this is unclear and the evidence of efficacy is poor. Two meta-analyses on this subject reached different conclusions (Youssef *et al*., Venetis *et al*.)[51,46] and there are significant limitations in the methodology and subject numbers in studies. The largest single-center trial on this subject (Bellver *et al*.,)[52] did not find a protective effect of albumin administration in preventing OHSS. Recent expert guidance does not support the use of albumin for the purpose of OHSS prevention (Corbett *et al*.).[7]

CHOICE OF LUTEAL SUPPORT

The role of hCG in precipitating OHSS is well-established. It is known that progesterone is as effective as hCG for luteal support and is associated with a lower risk of OHSS (Daya and Gunby).[9] It follows that hCG should not be used for luteal support. The association of multiple pregnancies with OHSS (Mathur *et al*.)[26] is another reason to adopt a policy of single embryo transfer in women at risk of OHSS (Corbett *et al*.).[7] Some investigators have recommended high-dose progesterone to prevent OHSS, but the study design is such that this effect could simply be due to the avoidance of hCG, rather than an effect of progesterone (Schwarzler *et al*.).[38]

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Conflicts of interest

There are no conflicts of interest.

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