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An update on the prevention of ovarian hyperstimulation syndrome

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Abstract

Ovarian hyperstimulation syndrome is a potentially life-threatening, but preventable iatrogenic complication of in vitro fertilisation treatment. In recent years, new strategies have been developed to minimise the risk of ovarian hyperstimulation syndrome after in vitro fertilisation, including better at-risk patient identification prior to starting treatment, the use of a lower human chorionic gonadotrophin dose or alternative medication instead of human chorionic gonadotrophin to induce final oocyte maturation such as gonadotrophin-releasing hormone agonist and kisspeptin in antagonist cycles, cryopreservation of all embryos and delayed embryo transfer, and the use of oral dopamine agonists after oocyte retrieval. In this article, the advantages and limitations of those new developments are discussed and future directions towards establishment of an ovarian hyperstimulation syndrome–free in vitro fertilisation clinic are explored.

Keywords

dopamine agonists, gonadotrophin-releasing hormone agonist, in vitro fertilisation, intra-cytoplasmic sperm injection, kisspeptin, luteal phase, oocyte retrieval, ovarian hyperstimulation syndrome, prevention

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening iatrogenic complication of controlled ovarian stimulation (COS) during assisted reproductive therapy (ART). It can occur during either the luteal phase (early-onset OHSS) or early pregnancy (late-onset OHSS).

COS is aimed at producing multiple ovarian follicles to increase the number of oocytes available for collection and fertilised oocytes available for transfer in order to enhance the success rate of ART.[1] The syndrome is classified according to the severity of its signs and symptoms. Increasingly aggressive treatment protocols have led to an increased risk of OHSS.[2] Data suggest that the incidence of mild OHSS is 20%–33% within all in vitro fertilisation (IVF) cycles, an incidence of 3%–6% for moderate OHSS and severe OHSS occurring in 0.1%–2% of cycles.[3]

Pathophysiology of OHSS

The clinical manifestations of moderate, severe and life-threatening OHSS occur as a result of the increased capillary membrane permeability due to production of ovarian vasoactive substances such as angiotensin and vascular endothelial growth factor (VEGF). These angiogenic factors mediate third-space fluid accumulation and subsequent intravascular volume depletion.[4] It is this fluid shift from the intravascular to the interstitial spaces which results in ascites, pleural effusion, hypotension, oliguria secondary to acute renal failure, thromboembolism, and in cases of severe intravascular volume depletion, multiple organ failure. An increase in ovarian size and the presence of numerous luteal cysts can lead to adnexal torsion during the early stages of OHSS.[2]

There is now substantial evidence to suggest that human chorionic gonadotrophin (hCG) plays a central role in triggering OHSS.[5] Agrawal et al.[6] demonstrated a serum rise in VEGF to be a marker of subsequent OHSS, with a greater sensitivity and specificity for OHSS prediction compared to oestradiol concentration and number of follicles developed and oocytes retrieved during IVF cycles.

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Furthermore, serum VEGF levels correlate with the clinical severity of OHSS,[7] suggesting that VEGF is integral in the development of OHSS. Although there is no unified theory regarding the aetiology of OHSS, it is likely that hCG induces the release of VEGF, which, together with other contributing cytokines, is responsible for the signs and symptoms of OHSS.

Conventional methods of prevention

A viable method of preventing OHSS involves withholding the hCG trigger entirely, a process known as cycle cancellation.[8] This is in line with the theory that hCG is required for the development of OHSS. In addition, withholding daily gonadotrophins prior to administration of hCG medication in IVF cycles, a technique called coasting, has also been used to reduce this risk of OHSS. However, results of a systematic review revealed that there was no difference in the incidence of moderate and severe OHSS between patients who underwent this technique, termed coasting, compared to patients where coasting was not performed.[9] Furthermore, monitoring of ovarian hyperstimulation using transvaginal ultrasonography (TVUS) and measurement of serum oestradiol levels have been shown to reduce the incidence of severe OHSS. Although safe and reliable methods of reducing OHSS, a systematic review[10] found no evidence of an increased efficacy when both are combined. These traditional methods of OHSS prevention are now being superseded by more recent, evidence-based approaches.

Advances in prevention of OHSS

Identification of high-risk patients

A case–control study demonstrated day 3 serum anti-Mullerian hormone (AMH) levels to be significantly higher in women with OHSS compared to age-matched controls in patients undergoing IVF cycles when measured before COS,[11] suggesting a predictive role of serum AMH measurement in identifying women with a high risk of OHSS. With a growing body of evidence suggesting that an elevated basal level of AMH was positively correlated with an increased risk of OHSS,[8] recent studies have suggested levels of 3.52–3.9 ng/mL to be an appropriate cut off for predicting hyper response.[12,13] Lee et al.[14] suggested a serum AMH cut off level of 3.36 ng/mL to be a reliable predictor of OHSS. Taken together, sufficient evidence now exists to support the use of serum AMH levels to assess ovarian response potential, identify women at high risk of OHSS, and therefore guide ovarian stimulation to prevent its occurrence.

Ovarian stimulation protocol

During the traditional IVF long pituitary downregulation protocol, a gonadotrophin-releasing hormone (GnRH) agonist is administered from the mid-luteal phase of the preceding menstrual cycle to prevent premature luteinizing hormone (LH) surge and therefore avoid premature ovulation. Initially, peripheral administration of a GnRH agonist would cause an increase in LH and follicle stimulating hormone (FSH) secretion from pituitary gonadotrophs, a phenomenon known as the 'flare effect'. However, continuous administration over a number of days leads to GnRH receptor desensitisation and subsequent receptor internalisation, leading to a decrease in LH (and FSH) secretion and a lack of progression to ovulation. Unlike the GnRH analogues, GnRH antagonists bind competitively to pituitary GnRH receptors, blocking the release of LH and FSH, with no initial flare and without receptor downregulation. The use of GnRH antagonist therapy in IVF is termed the short protocol. Deploying this regimen over the long protocol has been shown to reduce the risk of OHSS. A recent systematic review of 29 randomised controlled trials (RCTs) comparing either protocol demonstrated a statistically significantly lower incidence of OHSS in the GnRH antagonist group.[15] Furthermore, current scientific trend suggests that this regimen is especially beneficial for women with either a very high or very low ovarian reserve (extremes of ovarian reserve), suggesting that individualised IVF therapy can allow for a safer and more effective clinical outcome.[16]

Triggering medication

Low-dose hCG

The efficacy of a reduced dose hCG trigger was recently explored in two small prospective studies involving 41 high responders undergoing IVF therapy.[17,18] Both studies demonstrated that administration of the equivalent of 2000–3250 IU of hCG resulted in elimination of severe OHSS, and one case of moderate OHSS which did not require hospitalisation. Both studies suggest that reducing the trigger dose of hCG in a high-risk patient population can be effective in triggering final oocyte maturation and reducing the risk of OHSS. Sufficiently powered studies comparing different doses of hCG are required to determine its optimal dose in IVF to prevent OHSS while maintaining adequate oocyte maturation and pregnancy rates.

GnRH agonist

A GnRH agonist trigger displaces the antagonist from GnRH receptors on pituitary gonadotrophs during a short protocol; hence, the initial flare effect seen with GnRH agonist therapy can be used to trigger follicular maturation in women with intact pituitary reserve.[8] An updated meta-analysis by Youssef et al.[19] showed a significantly lower incidence of all degrees OHSS with GnRH agonist administration compared to hCG use. It has been shown experimentally that the administration of a bolus of

GnRH agonist shortens the duration of the LH surge, resulting in abnormal corpora lutea formation and a consequent decrease in the release of VEGF and other vasoactive peptides,[20] suggesting a mechanism of OHSS prevention. Garcia-Velasco et al.[21] subsequently demonstrated less free pelvic fluid accumulation and a significantly reduced mid-luteal ovarian volume after GnRH agonist trigger compared with hCG trigger. Thus, the use of a GnRH agonist trigger is highly effective in prevention of OHSS.

Limitations of a GnRH agonist trigger

Although GnRH agonist triggering can significantly reduce or even eliminate OHSS,[22] it has been shown to be associated with luteal phase insufficiency. GnRH agonist triggering shortens the duration of the endogenous LH surge and decreases the efficacy of the LH receptor, thus reducing LH activity during the luteal phase leading to premature luteolysis and implantation failure.[23] GnRH agonist treatment was disappointingly also associated with a higher early miscarriage rate (odds ratio (OR): 1.74, 95% confidence interval (CI): 1.10–2.75) and a lower live birth rate (LBR) than was seen with hCG (OR: 0.47, 95% CI: 0.31–0.70).[21] Thus, it became necessary to optimise luteal phase support (LPS) in order to improve reproductive outcome seen with GnRH agonist triggering.

A dual trigger of luteal support

A prospective RCT in normoovulatory women undergoing IVF showed no difference in early pregnancy loss rates in those given an hCG trigger compared to those given GnRH agonist triggering with an additional bolus of hCG supplemented with progesterone and oestradiol support,[24] suggesting that this protocol could rescue the luteal phase. This study also demonstrated an elimination of OHSS in the GnRH agonist group. Subsequent trials were conducted to investigate whether an hCG bolus following a GnRH agonist trigger reduces the incidence of OHSS in an at-risk patient population, compared to an hCG trigger. A recent multicentre retrospective study[25] reported a clinical pregnancy rate of 42% in a cohort of 275 women at high risk of OHSS who received a 'dual trigger' of GnRH agonist and hCG, with only two cases of severe OHSS (0.72%). These results were supported by three further retrospective analyses,[26–28] all indicating that this so-called dual trigger can correct the luteal phase without causing OHSS in a high-risk patient population. Research is ongoing regarding the optimal dose of hCG administered, and promising results are anticipated. Regardless of the chosen protocol, substantial efforts should be made to tailor the concentration of hCG according to the ovarian response to stimulation to reduce the likelihood of OHSS.[23]

Intensive luteal phase steroid support

The usefulness of high-dose oestradiol and progesterone luteal support has been advocated to avoid the abnormal corpora luteal function observed following administration of a GnRH agonist trigger. The first prospective RCT conducted by Engmann et al.[29] randomised 66 patients at high risk of OHSS to an ovarian stimulation protocol consisting of either GnRH agonist trigger in a GnRH antagonist protocol, or hCG trigger after pituitary suppression with a GnRH agonist. Both groups received intramuscular (IM) progesterone, with the first group additionally receiving oestradiol patches as luteal phase supplementation. No significant differences were observed in clinical pregnancy and implantation rates, but an encouraging elimination of OHSS was reported in the GnRH agonist trigger group. Since this seminal study was published, several studies have also demonstrated that intensive steroidal support during the luteal phase and early pregnancy have similar LBRs compared with the hCG trigger.[25,30,31]

However, despite intensive luteal phase steroid support, a prospective RCT[32] of 28 IVF patients diagnosed with polycystic ovary syndrome (PCOS), and therefore considered as patients at a high risk of OHSS, reported an overall LBR of only 6% and early pregnancy loss of 80% in a group of patients who received GnRH agonist triggering. A subsequent study[33] in 2011 also reported no difference in reproductive outcome in a cohort of 67 women with a high risk of OHSS when their LPS protocol was modified by increasing the oestradiol and progesterone doses. Taken together, these data suggest that although the risk of OHSS is significantly reduced with this protocol, further modifications should be made to improve conception rates. Therefore, with such contrasting available evidence, larger trials to explore the efficacy of the intensive steroid support protocol among patients at risk of OHSS are still necessary.

Kisspeptin

Discovered exactly 20 years ago, kisspeptins are a family of neuropeptides of varying length encoded by the *KISS1* gene. The most abundant isoform of kisspeptin in the human circulation is kisspeptin-54.[34] Evidence accumulating in humans has identified kisspeptin as a critical regulator of the reproductive axis by stimulating endogenous GnRH secretion from hypothalamic neurones.[35] A randomised, double-blind crossover study in healthy women demonstrated that peripheral administration of kisspeptin-54 led to a maximal LH response during the preovulatory phase of the menstrual cycle,[36] suggesting that kisspeptin is responsible for the mid-cyclical LH surge, providing a novel method for manipulating the female reproductive axis. It was therefore hypothesised that kisspeptin could be used as a trigger of oocyte maturation in a GnRH antagonist protocol instead of hCG during an IVF cycle.

The first proof of concept study was performed by Jayasena et al.[37] in 2014 in which 53 women with normal ovarian reserve undergoing IVF therapy were randomised to increasing doses of a single subcutaneous kisspeptin-54 injection to act as a trigger in a GnRH antagonist protocol following superovulation with FSH. It was found that kisspeptin-54 dose-dependently increased the number of mature oocytes per patient, with the transfer of resulting embryos leading to clinical pregnancy. A subsequent phase 2 clinical trial investigating the safety and efficacy of a kisspeptin trigger in women at high risk of OHSS, with either a serum AMH level of >40 pmol/L or an antral follicle count of >23, demonstrated oocyte maturation occurring in 95% of women with 90% of these women having at least one embryo available for transfer. Crucially, none of the women developed moderate, severe or critical OHSS following embryo transfer.[38] Such promising results need further clarification from larger RCTs of women at risk of developing OHSS comparing kisspeptin with existing therapies for egg maturation during IVF or intra-cytoplasmic sperm injection (ICSI) to form an evidence base for this novel treatment. Early trials have produced encouraging results, but this area of research is still very much in its infancy.

Recombinant LH

Another possible prevention strategy in high-risk women involves the use of recombinant human luteinizing hormone (rhLH) as a way of increasing the LH activity to trigger final oocyte maturation. A prospective multicentre double-blind study performed by the European Recombinant LH Study Group substantiated the results seen above, demonstrating no difference in the efficacy of a single dose of rhLH in inducing follicular maturation in IVF and embryo transfer patients compared with urinary human chorionic gonadotrophin (uhCG) administration.[39] Moreover, this study revealed a highly significant reduction in the incidence of OHSS in the rhLH group. A total of 259 women were enrolled in this study, increasing the statistical power of its results. All women underwent pituitary desensitisation with administration of a GnRH agonist. A systematic review[40] assessing the safety and efficacy of an rhLH trigger compared with uhCG demonstrated no significant difference in the LBR between two groups of patients undergoing IVF randomised to each treatment arm. It remains to be seen whether a small dose of rhLH could be administered after GnRH agonist triggering to improve reproductive outcome by supplementing the insufficient luteal phase observed in patients on this treatment protocol, without increasing the risk of OHSS.

The first proof of concept study investigating this innovative technique was performed by Papanikolaou et al.,[41] in which 17 patients were randomised to a standard treatment arm consisting of recombinant hCG triggering and luteal progesterone, whereas 18 patients were randomised to GnRH agonist triggering, progesterone luteal support and an additional six doses of 300 IU rhLH starting on the day of oocyte retrieval and ending up to 10 days later. Implantation rates and OHSS incidence were determined in both groups. Implantation rates were comparable between the two groups (31.2% in the novel regimen versus 26.7% in the standard regimen, $p=0.91$), and no cases of OHSS were reported in either treatment arm. Although appealing, further studies are needed to validate these findings, particularly in patients undergoing IVF/ICSI with a high risk of developing OHSS. It is unlikely that such a low dose of rhLH will trigger OHSS, particularly as a repeated dose of 10,000 IU rhLH after an initial 15,000 IU triggering dose resulted in no difference in moderate OHSS incidence compared to uhCG in the study by the European group discussed above.[39] Larger RCTs should focus on refining this approach, to find the minimal dose of rhLH that ensures implantation, while also eliminating the risk of OHSS.

Post-retrieval methods

Segmentation

An alternative strategy to overcome luteal phase insufficiency is to segment the IVF cycle; this involves the use of a GnRH antagonist protocol, a GnRH agonist trigger, cryopreservation of all embryos and frozen-thawed embryo transfer in a subsequent unstimulated cycle, where the woman's ovarian response has normalised.[42] With the advent of modern oocyte cryopreservation laboratory techniques such as vitrification, there is now evidence to suggest that frozen embryo transfer results in comparable clinical pregnancy rates compared to fresh embryo transfer.[43] In a randomised trial of normal responders by Shapiro et al.,[44] it was suggested that this discrepancy in reproductive outcome was due to impaired endometrial receptivity in the fresh embryo transfer group, that is, improved synchronisation between the endometrium and embryo development achieved in the cryopreservation group.

Encouragingly, this technique also seems to erase the risk of OHSS. A subsequent study by Shapiro et al.[45] in high responders controlled for differences in embryo quality demonstrated a significantly greater clinical pregnancy rate with frozen embryos when compared with fresh, suggesting the efficacy of this approach in patients with a high risk of OHSS. Furthermore, oocyte vitrification tested in an observational trial was found to not only decrease the incidence of OHSS in patients at risk, but also significantly increase pregnancy rates compared to coasting.[46] Taken together, these conclusions suggest that oocyte and embryo cryopreservation may now be the best treatment options for patients at high risk of OHSS, particularly with the advent of vitrification which has resulted in a significantly

higher clinical pregnancy rate compared to older methods of slow and ultra-rapid freezing.[47]

Several case studies have recently emerged demonstrating incidence of severe OHSS after GnRH agonist triggering and a freeze-all approach in a GnRH antagonist protocol.[48] Three women undergoing treatment for infertility presented with abdominal pain and distension, with ultrasonographic examination showing enlarged ovaries and severe ascites. With a previous study reporting fatal complications occurring in the worst cases,[49] it is clear that the burden of OHSS is still a major concern of fertility clinicians. Such case reports highlight that it may still be too early to safely shift ART to a freeze-all approach in high responders. Confirmation of a clinical benefit that remains safe is needed from sufficiently powered studies to justify cryopreservation as a routine approach in ART.

Dopamine agonists

Several studies have evaluated the role of dopamine receptor 2 (D2R) agonists, as a preventative strategy for OHSS in women undergoing IVF/ICSI treatment. Accumulation of evidence suggests that D2R agonists inhibit VEGF secretion in luteinised granulosa cells at the post-transcriptional level in vivo,[50] suggesting a mechanism for OHSS prevention. Combination of a D2R agonist with a GnRH agonist trigger, which inhibits VEGF transcription, could prove efficacious in the delivery of an OHSS-free ART clinic. A systematic review and meta-analysis of eight RCTs assessing the efficacy and safety of cabergoline, a D2R agonist, reported a significant reduction in the incidence of moderate–severe OHSS and no deleterious impact on clinical pregnancy or the number of retrieved oocytes, in comparison to placebo or no treatment.[51] Subsequent research comparing the effect of cabergoline in comparison to several pharmacologic interventions for OHSS prevention identified a superiority of aspirin and intravenous (IV) calcium to cabergoline as OHSS prophylactic agents.[52] This study provides a relative standard for choosing an agent, but it remains crucial that treatment is tailored based on a patient's clinical need. The proposition of exogenous cabergoline use during ART remains attractive, particularly if patient subfertility is secondary to hyperprolactinaemia. However, cabergoline has a known dose-related side effect of cardiac valvular fibrosis;[8] therefore, further studies should focus on whether the efficacy of cabergoline to prevent OHSS justifies its administration with such a significant side-effect profile. In addition, the foetal safety of D2R agonists has not been defined. A prospective study reporting on the outcomes of 380 pregnancies in women treated with cabergoline demonstrated neonatal abnormalities in 9% of infants delivered with no pattern in type or severity, although no specific increase in miscarriage risk was reported.[53] RCTs using different D2R agonists in pregnant women at risk of OHSS should be performed to determine their foetal safety, particularly as cabergoline in OHSS prevention is administered at doses exceeding those used in the treatment of hyperprolactinaemia. Results of these trials will allow a more informed decision before wider D2R agonist use.

There is paucity of studies relating to the use of other dopamine agonists in the prevention of OHSS; however, one study reported a reduction in the incidence of clinically significant OHSS from 40.9% to 17.5% when comparing a control group to a patient group administered bromocriptine, with no difference in clinical pregnancy rates detected.[54] Currently, there is insufficient evidence to recommend the use of bromocriptine for OHSS prevention, but trials comparing different dopamine agonists to determine the most effective drug and dosage should be performed in women at risk of OHSS undergoing fertility treatment.

Future perspective

Emerging molecular technologies have advanced our understanding of OHSS pathogenesis, leading to the development of treatment strategies to aid in its prevention. GnRH agonist or kisspeptin triggers of follicular maturation, as a substitute for an hCG trigger, have shown promising results. Cryopreservation of all embryos has been effective in reducing progression to OHSS, and recent evidence suggests that dopamine agonists have increased efficacy in the prevention of OHSS, in comparison to traditional techniques in ART such as coasting (withholding gonadotrophins prior to initiating ovulation) or cycle cancellation.

For many years, an hCG trigger has been the gold standard for final follicular maturation in ART due to its long half-life and ready availability. Once it had emerged that it is responsible for causing OHSS in women undergoing fertility treatment, GnRH antagonist co-treatment with a GnRH agonist trigger became a useful tool to eliminate severe OHSS.[55] Several evidence-based strategies have been developed to rescue the luteal phase insufficiency reported with GnRH agonist triggering to try to improve reproductive outcome in women at high risk of OHSS. Administration of a dual GnRH agonist and hCG trigger 35–37 h prior to oocyte retrieval,[55] the use of rhLH, or intensive monitored luteal steroid support have demonstrated promising results compared to GnRH agonist trigger alone without increasing the risk of OHSS. Until the most optimal luteal support protocol has been defined, a freeze-all strategy and frozen embryo transfer combined with a GnRH agonist trigger remains as the best alternative option in making an OHSS-free clinic a reality.[23] A multicentre prospective RCT is currently underway investigating the clinical and cost-effectiveness of frozen compared to fresh embryo transfer (ISRCTN61225414). If this study, scheduled to run until February 2019,

demonstrates comparable LBRs in the two groups, then this would provide further evidence for a move towards the freeze-all approach. Additionally, intensive research in the efficacy of a kisspeptin trigger or the concomitant use of a dopamine receptor 2 agonist might shed further light on the best method of preventing OHSS in its entirety. The transition to an OHSS-free ART era now appears to be within sight.

Executive summary

- OHSS is a serious iatrogenic condition that has arisen due to increasingly aggressive treatment protocols for ovarian stimulation during ART.
- Experimental evidence suggests that the signs and symptoms of OHSS are due to the role of hCG in stimulating the release of ovarian vasoactive cytokines such as VEGF.
- Identification of patients at high risk of OHSS using serum AMH levels can be used to individualise IVF therapy to prevent its occurrence.
- Several recent studies have demonstrated efficacy of a GnRH agonist trigger in a GnRH antagonist protocol in preventing OHSS; however, this technique can cause luteal phase insufficiency.
- The so-called 'dual trigger' of luteal support has been shown to correct the luteal phase without causing OHSS in a high-risk patient population.
- An oestrogen and progesterone luteal phase rescue protocol with intensive monitoring eliminates OHSS; however, some studies have shown this method to hinder live birth rates.
- Preliminary studies have demonstrated the safety and efficacy of a kisspeptin trigger of oocyte maturation during IVF therapy, without incidence of OHSS.
- Early trials investigating the administration of cabergoline, a dopamine agonist, post oocyte retrieval have reported a significant reduction in the incidence of moderate–severe OHSS in a high-risk patient group.
- Accumulation of evidence suggests that segmentation with the new vitrification method significantly reduces the incidence of OHSS and results in a higher clinical pregnancy rate compared to fresh embryo transfer in patients undergoing IVF treatment.
- A freeze-all strategy and frozen embryo transfer combined with GnRH agonist triggering remains as the best option in eliminating OHSS entirely.
- We propose that future studies should focus on the efficacy of a freeze-all approach, as well as providing more evidence to support the use of a kisspeptin trigger or a dopamine agonist to make an OHSS-free ART clinic a reality.

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