Preventing Ovarian Hyperstimulation Syndrome (OHSS)

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Abstract

Ovarian Hyperstimulation Syndrome (OHSS) is a significant complication that can occur during fertility treatments, particularly in the context of assisted reproduction technologies (ART) such as In-vitro fertilization (IVF). It is characterized by enlarged ovaries and the accumulation of fluid in the abdomen and sometimes the chest, which can lead to various degrees of discomfort and, in severe cases, life-threatening complications. The incidence of clinically significant OHSS is 2-3%, however, milder forms of OHSS might develop in up to 20-30% of all IVF patients.

Introduction

Ovarian Hyperstimulation Syndrome (OHSS) is a significant complication that can occur during fertility treatments, particularly in the context of assisted reproduction technologies (ART) such as In-vitro fertilization (IVF). It is characterized by enlarged ovaries and the accumulation of fluid in the abdomen and sometimes the chest, which can lead to various degrees of discomfort and, in severe cases, life-threatening complications. The incidence of clinically significant OHSS is 2-3%, however, milder forms of OHSS might develop in up to 20-30% of all IVF patients (1).

The pathophysiology of OHSS is still not fully elucidated. Development of OHSS involves a complex interplay of hormonal, vascular, and inflammatory factors. It typically occurs when ovarian follicular development is excessively stimulated by exogenous gonadotropin. This leads to the production of multiple follicles, which are associated with increased vascular permeability and secretion of vasoactive substances, including vascular endothelial growth factor (VEGF) and other inflammatory mediators such as interleukins (e.g., IL-6, IL-8) and tumor necrosis factor-alpha (TNF-α) (2) (3).

These cytokines contribute to the inflammatory response in the ovaries and peritoneal cavity leading to increase in the vascular permeability and fluid accumulation in the third space. This causes ascites and pleural effusions. The major risk factor involved in the development of OHSS is human chorionic gonadotropin (HCG) hormone which is used to trigger final oocyte maturation. HCG has higher affinity for its receptors and relatively prolonged half life, which ultimately leads to cascade of events that results in OHSS (4).

Short Communication

Open Access &

Peer-Reviewed Article

DOI: 10.14302/issn.3070-5657.je-24-5272

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Keywords:

Ovarian Hyperstimulation, Reproduction, Pathophysiology, Gonadotropin.

Received: August 28, 2024

Accepted: November 17, 2025

Published: November 20, 2025

Citation:

Shruti Passan (2025). Preventing Ovarian Hyperstimulation Syndrome (OHSS). Journal of Embryology–1(2):1-12. https://doi.org/10.14302/issn.3070-5657.je-24-5272

Prevention of OHSS is crucial for the well-being of patients undergoing fertility treatments and to optimize their success rate. With this article we tend to explore the various strategies involved in the prevention of OHSS.

The preventive strategies begin right from the identification of risk factors and many other measures that can be taken to decrease the risk of OHSS.

Identifying women at risk of OHSS

OHSS can theoretically occur in any women undergoing ovarian hyperstimulation. Although, there are certain risk factors for its development, identifying such women can actually lower the incidence of OHSS.

Pre stimulation Risk Factors

- Young Age: Younger women undergoing ovarian stimulation for assisted reproduction technologies (ART) are at higher risk of developing OHSS due to increased ovarian sensitivity to gonadotropins (5).
- Polycystic Ovary Syndrome (PCOS): Women with PCOS are more likely to experience an exaggerated response to exogenous gonadotropin stimulation, leading to an increased risk of OHSS (6).
- High Ovarian Reserve Markers: Elevated levels of anti-müllerian hormone (AMH) and high antral follicle count (AFC) are indicators of a high ovarian reserve. Women with these characteristics are more prone to developing OHSS as they have a larger number of recruitable follicles (7).In terms of ovarian reserve markers, serum anti-Müllerian hormone (AMH) levels above 3.36ng/ml can predict the occurrence of OHSS with over 90% sensitivity (7). Similarly, a total antral follicle count (AFC) of 24 or higher are also associated with an increased risk of moderate-to severe OHSS (8)
- Previous History of OHSS: Women with previous history of OHSS are at increased risk of experiencing it again in the subsequent cycles (9).
- Low Body Mass Index (BMI): Women with a low BMI may have a higher risk of developing severe OHSS due to a potentially exaggerated response to gonadotropin stimulation relative to their body weight (10).

Identifying the risk factors during stimulation

Multi follicular development, elevated estradiol levels, and numerous recruited oocytes are established risk factors of OHSS development. Specifically, the presence of over 20 follicles during ovarian stimulation and retrieval of more than 24(11) or 30 (12), oocytes, and estradiol levels exceeding 3,500 pg/mL (13) have been associated with an increased risk of OHSS

Changing the stimulation protocols

Starting Low-Dose Stimulation Protocols

Low-dose stimulation protocols aim to achieve controlled ovarian response with reduced gonadotropin doses, thereby minimizing the number of developing follicles and decreasing the risk of OHSS. Here comes the role of mild stimulation which is defined as the stimulation of ovaries with the intention to retrieve 7 or less follicles (14). Milder stimulation protocols aim to achieve a more gradual and controlled follicular development. Characteristically, starting doses are adjusted according to the patient's age, ovarian reserve, and risk of OHSS.

Till now many studies have demonstrated that low-dose stimulation protocols effectively reduce the incidence and severity of OHSS as compared to conventional high-dose protocols (15) .In fact, as per Cochrane review published in 2018, the authors found that a gonadotropin dosage equal to 150 IU daily or lower reduces the likelihood of moderate to severe OHSS in high-risk patients (16) without any difference in the clinical pregnancy rate. Similar are the findings in a recent review published by Dutta et al., where mild stimulation with doses of 150 IU or less resulted in lower incidence of OHSS without any adverse effect on live birth rates (17).

So mild stimulation strategies could be an effective option as despite using lower gonadotropin doses, low-dose stimulation protocols maintain comparable pregnancy rates to conventional protocols, ensuring that treatment efficacy is not compromised.

Decreasing the gonadotropin dose

In patients with an unexpected hyper-response to FSH, decreasing the FSH dose during treatment may reduce the occurrence of OHSS. Concerning the FSH dose decrease strategy, a systematic review by (18) including 18 studies published from 2007 to 2017 for 6630 IVF cycles concluded that decreasing the r-FSH dose during the mid-follicular phase of the ovarian stimulation may reduce the occurrence of OHSS compared to a fixed FSH dosage. Decreasing the FSH dose not only reduces the risk of OHSS but it also reduces the related risk for cycle cancellation.

Type of Gonadotropin

Gonadotropins over the time have emerged from the most primitive urinary preparations to purified FSH, Hp FSH ,recombinant FSH. The newest preparations are corifollitropin alpha and follitropin delta.

Various studies have looked into the types of gonadotropins and the risk of OHSS. Practically, no difference in the risk of OHSS development was found while comparing urinary vs. recombinant gonadotropins (19). Another, systematic review with meta-analysis was done comparing the risk of OHSS with corifollitropin alfa vs. traditional gonadotropins. However, no significant difference between total risk of OHSS development between corifollitropin alfa vs. traditional gonadotropin could be found (20).

The next generation molecule is follitropin delta

Evolution of Follitropin delta signifies the latest advancement in the field of ART. Folliotropin delta offers a more precise and controlled approach to the ovarian stimulation. Clinical trials have demonstrated that follitropin delta is effective in achieving comparable or even improved pregnancy rates as compared to conventional FSH preparations. Also, it potentially reduces the incidence of OHSS due to its optimized pharmacokinetic profile (21,22). Although, statistical data is less but it could be a promising molecule to prevent OHSS.

Using the antagonist protocol

The antagonist protocol is another effective strategy utilized in assisted reproduction to prevent OHSS. The antagonist protocol involves the administration of GnRH antagonists, such as cetrorelix or ganirelix, during the late follicular phase of ovarian stimulation to prevent premature LH surge. A large number of Clinical studies have demonstrated that the antagonist protocol significantly reduces the incidence of severe OHSS compared to long GnRH agonist protocols.

A randomised controlled trial comparing agonist vs antagonist protocol with aim to detect the risk of OHSS found that the risk of OHSS was lower with the antagonist protocol without any difference in the live birth rates (23).

Similar are the findings of the Cochrane review which concludes a lower incidence of OHSS in the antagonist protocol as compared to agonist protocol without any significant difference in live birth, ongoing pregnancy rates, clinical pregnancy rates and miscarriage rates (24)

Cycle Cancellation

In patients who are at the a high risk of OHSS, cancellation of the cycles could be one option (25). Cycle cancellation involves withholding HCG in GnRH agonist cycles to as to stop the stimulus for OHSS. But cycle cancellation involves a huge financial and psychological burden for the couples undergoing treatment

Coasting

Coasting is the practice of withholding gonadotropins at the end of controlled ovarian stimulation for up to 4 days. This, leads to a significant reduction in serum estradiol levels thereby decreasing OHSS risk (26). Studies on the outcomes of coasting are variable with variable results. However, as per the Cochrane review, coasting effectively reduces OHSS risk (24). Although, there was insufficient evidence to assess the procedure's efficacy in terms of live birth, clinical pregnancy, and miscarriage rate (27).It should be noted that coasting for more than 4 days can have a negative impact on the cycle outcomes

Changing the trigger

Agonist Trigger

In high-risk patients, triggering final oocyte maturation with a GnRH agonist instead of hCG reduces the risk of OHSS. GnRH agonist when used as trigger, induces a surge in LH and FSH that mimics the natural LH surge but with a shorter duration and lower amplitude compared to hCG. This LH surge is sufficient to induce final oocyte maturation and subsequent luteinization of the follicles without causing overstimulation (28).

Clinical studies have demonstrated that the GnRH agonist trigger significantly reduces the incidence of moderate to severe OHSS compared to traditional hCG triggers (29).

Youssef et al., in their systematic review and meta-analysis reported that the incidence of OHSS was lower when GnRH agonist was used as a trigger as compared to standard HCG (30). However, there was a reduction in live birth and ongoing pregnancy rates, and an increase in early miscarriage rates in fresh autologous transfer cycles after GnRH-a triggering (without hCG rescue) as compared to the standard hCG trigger. This is because of the luteolysis and luteal phase defect that is seen with GnRH agonist trigger. So, to combat this luteal phase defect intensive luteal phase support with both estrogen and progesterone or low dose HCG supplementation has been suggested for those undergoing fresh transfers after the agonist trigger

Low dose HCG protocol

OHSS is primarily triggered by the administration of high doses of hCG to induce final oocyte maturation. This leads to cascade of events eventually leading to increased vascular permeability and fluid shift into third spaces. Clinical studies have indicated that using low-dose hCG significantly reduces the incidence and severity of OHSS compared to traditional high-dose hCG trigger.

Minimizing the intensity of the LH surge, it mitigates the adverse effects associated with fluid extravasation and vascular permeability (28).

Single dose of 5000 IU uhCG used for triggering ovulation was found to be as effective as 10000 IU on the outcome of ICSI cycles with the added advantage of reduced incidence of OHSS (31). A RCT was conducted by kolibianakis [32] in a selected high-risk population of 80 PCOS patients who underwent ovarian stimulation in GnRH-ant IVF cycles. They compared the administration of different hCG doses for triggering, i.e., 10,000 IU vs. 5000 IU vs. 2500 IU. It was found that the dose decrease in u-hCG to trigger final oocyte maturation did not affect the ongoing pregnancy rate, the early pregnancy loss, and the oocyte retrieved, although cycle cancellation rates were higher in those receiving 2500 IU of HCG. An observational study that compared the different doses of recombinant HCG also reported a good reproductive outcome with lower incidence of OHSS in a cohort of high-responder IVF patients who received 125 mcg r-hCG (33). ESHRE in its guidelines on ovarian stimulation for IVF/ICSI also recommends low dose HCG in view of added safety (25).

Dual Trigger Approach

In some cases, a dual trigger approach combining both GnRH agonist and a low dose of hCG has been proposed. This method aims to provide adequate luteal support while further minimizing the risk of OHSS. but caution needs to be there as cases of OHSS have been reported using dual trigger (34)

Kisspeptin

Kisspeptin stimulates GnRH secretion from the hypothalamus and induces gonadotropin secretion (35). At present kisspeptin is not a licensed medication, limiting its use in clinical practice. A phase 2 RCT in an IVF population of sixty women at high risk of OHSS explored the safety of kisspeptin-54 administration at different dosages (36). Kisspeptin-54 was shown to be effective in triggering oocyte maturation without any moderate, severe, or critical OHSS event. Further, research into the molecule may make it an alternative trigger option in ART cycles

Freeze-only Strategy

Elective Cryopreservation is another option in cases with high risk of OHSS. In elective cryopreservation of the embryos freeze-only strategy is followed instead of proceeding with fresh embryo transfer. This approach allows the avoidance of the hormonal changes associated with pregnancy, reducing the production of HCG. Theoretically this should decrease the risk of late onset OHSS.Segmentation of IVF cycles is one option routinely followed to prevent OHSS. This involves oocyte retrieval, elective cryopreservation of the embryos and subsequent transfer in a frozen thaw cycle (37).

One RCT of 125 patients showed that cryopreservation results in a lower incidence of OHSS than controls with fresh embryo transfers (0 events in the cryopreservation group vs. 4 events in the fresh transfer group) without any difference in pregnancy rates (38). Zaat et al., in their meta analysis also found lower risk of OHSS with the freeze all policy (39)

ASRM also recommends to consider a freeze-only cycle and subsequent frozen embryo transfer in patients at risk for OHSS (40)

Elective Single Embryo Transfer (e-SET)

The risk and severity of OHSS is closely related to luteal hCG levels and the luteal HCG levels seems to be correlated to the number of gestational sacs being significantly higher in multiple pregnancies. Therefore, this risk can be mitigated by opting for elective single embryo transfer where the incidence

of late onset OHSS may be reduced owing to lower HCG levels as compared to pregnancies with multiple gestational sacs.

Post Oocyte Pick Up Pharmacological Interventions

Cabergoline

Dopamine agonists like cabergoline have been used prophylactically to reduce the risk of OHSS. It has been postulated that treatment with a dopamine receptor agonist such as cabergoline may result in a reduction of vascular endothelial derived factors (VEGF) production and a subsequent reduction in OHSS. The drug acts primarily by stimulating dopamine receptors in the pituitary gland thereby inhibiting prolactin secretion .The reduction in prolactin levels helps modulate ovarian vascular permeability and fluid shifts, which are central mechanisms underlying the development of OHSS (41).

Cabergolin has been shown to significantly decrease the incidence of moderate to severe OHSS without compromising the success rates of ART cycles (42)

Similar are the findings of the most recent analysis by Tang et al., which concluded that dopaminergic agonists effectively prevent moderate-severe OHSS compared to no treatment and/or placebo (43). Although there is no fixed regime that can be recommended the dose in the studies incorporated varied from 0.25 to 5 mg per day, the day of administration varying from the day of OPU or after OPU for 3-8 days.

As per ASRM guidelines, patients at risk for moderate-to-severe OHSS, it is recommended to start a dopamine agonist such as cabergoline on the day of the hCG trigger or soon thereafter and continue for several days (40).

Metformin

Metformin, is a widely used medication for managing type 2 diabetes mellitus. This drug has also been explored for its potential role in preventing Ovarian Hyperstimulation Syndrome (OHSS). Administration of metformin in PCOS patients undergoing ovarian stimulation has been shown to reduce the incidence and severity of OHSS, possibly by modulating insulin sensitivity and ovarian response.

It has been observed that Metformin may reduce ovarian volume and the number of developing follicles during ovarian stimulation which may ultimately lead to a more controlled ovarian response, thereby reducing the risk of developing OHSS (44). Many studies have looked into the role of metformin for prevention of OHSS in Gn RH agonist cycles and found to have a positive effect of the drug in reducing the risk of developing OHSS but its use in GnRH antagonist cycles may not be beneficial.

A meta-analysis by Tso Lo et al demonstrated that metformin supplementation in GnRH-agonist IVF cycles significantly reduces the risk of OHSS however, these results were not replicated in GnRH-antagonist IVF cycles(45).

As per ASRM it is not recommended to administer metformin for the sole purpose of reducing the incidence of OHSS in GnRH antagonist cycles because most studies do not report a significant reduction in rates of OHSS in women with PCOS who were given metformin. Metformin may, however, be considered for OHSS risk reduction among women with PCOS using a GnRH-agonist protocol.(40)

Luteal GnRH-Ant Administration

Luteal administration of GnRH-ant injections can be used as a potential strategy to prevent early OHSS and decrease the severity of OHSS (46). GnRH-ant injections act by enhancing luteolysis by suppressing the release of LH by the pituitary, and inducing a significant reduction in circulating VEGF. Zeng

et al., (2019) in their prospective cohort study in patients at high risk of OHSS concluded that GnRH-ant administration for three days could be an effective option in reducing the moderate-to-severe OHSS incidence and inducing a faster regression of OHSS symptoms (47). Due to scarcity of data many small or low-quality studies are conflicting regarding the effectiveness of GnRH antagonist administration in the luteal phase to reduce rates of OHSS.

Letrozole

The administration of 2.5 (48) mg or 5 mg (49) of letrozole during the luteal phase has an impact on corpus luteum (CL) function. Risk of development of OHSS is directly correlated to the estradiol levels, therefore letrozole administration during the luteal phase might help in reducing the risk of OHSS by reducing serum E2 levels.

Therefore it is proposed that administering 2.5 mg of letrozole once per day for 5 days, starting on the day of egg retrieval, is a simple, quick, and safe way to reduce E2 concentrations thereby leading to a quicker recovery as well as lower OHSS incidence. But the data is still controversial and there are studies where letrozole has not been shown to reduce the risk of OHSS.(50,51)

Calcium infusion

It has been seen that elevated serum calcium levels may inhibit the cyclic adenosine monophosphate (cAMP)-stimulated renin secretion which is involved in the pathogenesis of OHSS. This can eventually cause a decreased VEGF expression in human luteinized granulosa cells (52) .On this basis intravenous administration of calcium has been tried as a modality to prevent OHSS.

One randomised control trial concluded that 200 ml saline containing 10 ml of 10% calcium gluconate for 3 consecutive days after oocyte retrieval significantly prevented OHSS compared to the placebo group (53). In another randomised control trial, intravenous or oral calcium was significantly more effective than cabergoline in preventing OHSS (54).

Volume expanders

Various volume expanders, including albumin, hydroxyethylstarch (HES), mannitol and dextran, have been used to prevent OHSS but the results are still inconclusive

Youssef et al., reported a systematic review and meta-analysis of RCT's on the usage of volume expanders for preventing OHSS (55). This review that intravenous administration of human albumin at the time of oocyte retrieval reduced the incidence of moderate-to-severe OHSS compared to no treatment or placebo in high-risk patients But along with this, there was a reduction in pregnancy rate in those receiving albumin. HES administration similarly, reduced OHSS risk but it did not affect the pregnancy rate .

Till date there is weak evidence that the use of volume expanders such as albumin, HES, and mannitol can reduce rates of moderate-to-severe OHSS. Therefore it is not recommended to use volume expanders such as albumin, HES,or mannitol in patients who are at high risk of developing moderate or severe OHSS (40).

Summary

Ovarian hyper stimulation syndrome (OHSS) is an iatrogenic potentially life-threatening condition resulting from excessive ovarian stimulation. It is important to identify women at risk for this complication before stimulation, and stimulation protocols should be tailored so as to reduce the risk to minimum. The use of GnRH antagonist protocols with a GnRH agonistto trigger final oocyte maturation is

a particularly effective strategy and should be considered first-line for OHSS prevention. Elective cryo-preservation of embryos can be applied whenever feasible provided the clinic has a vitrification programme Other strategies that show some benefit include the use of cabergoline. other modalities in the form of letrozole ,Gn RH antagonists and calcium infusion are still suggested but data is highly controversial.

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