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Prevention of Ovarian Hyperstimulation Syndrome

Harpreet Kaur

MD, FNB (Rep. Med.), Assistant Professor (fertility specialist), Gian Sagar Medical College & Hospital.

Abstract

Ovarian hyperstimulation syndrome (OHSS) is rare but most serious complication of ovarian stimulation. Symptoms are mainly related to increased capillary permeability leading to extravasation of fluid into extravascular compartment. Disease pathophysiology is linked to hCG (human chorionic gonadotropin) which acts through angiogenic molecule vascular endothelial growth factor (VEGF). There is recent development of interest in use of dopamine agonist for prevention of OHSS, which act through blockage of VEGF by preventing phosphorylation of VEGF-2 receptor. Once there is full blown OHSS, treatment is mainly symptomatic. By careful selection of stimulation protocols & recognisition of high risk cases at an early stage, early OHSS can be prevented to a major extent. Use of GnRH antagonist protocols & GnRH agonist as final trigger leads to marked reduction in incidence of OHSS without compromising pregnancy rates. So, prevention has been mainstay of treatment for this rare but life-threatening iatrogenic complication of ovarian stimulation.

Keywords: Prevention of OHSS, HCG, VEGF, risk factors.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is one of the most serious iatrogenic complications of ovulation induction (OI) and ovarian stimulation for assisted reproductive technology (ART). It is characterized by extravascular fluid accumulation due to increased vascular permeability (1). Due to increased vascular permeability there is leakage of fluid from the vascular compartment, with third space fluid accumulation and intravascular dehydration (2,3). It is a potentially life-threatening condition in its severe form, resulting in hospitalization in 1.9% of cases (2), and hCG, either exogenous or endogenous, is the triggering factor of the syndrome. The incidence of OHSS varies from patient to patient. This depends upon number of patient factors & type of stimulation regimen being used (2). Mild forms of OHSS are common, can be seen in upto 1/3rd of in-vitro fertilization (IVF) cycles. Moderate-severe OHSS is seen less frequently, approximately in 3-8% of IVF cycles (2).

*Corresponding Address: Dr. Harpreet Kaur, MD, FNB (Rep. Med.). Assistant Professor. H. No. 26-B, sector 38-A, Chandigarh, India,160036. Ph. 09872221818, Email:drharpreet_sidhu@hotmail.com.

OHSS is a self-limiting disorder. As hCG is the main culprit for OHSS, symptoms of OHSS may be more severe & it might persist for longer duration in the presence of endogenous HCG seen in pregnant women. The syndrome has a broad spectrum of clinical manifestations, from mild illness needing only careful observation which can be managed on outpatient basis to severe disease requiring hospitalization and intensive care (4).

Pathogenesis of OHSS: The main culprit for OHSS is hCG which acts through VEGF by increasing vascular permeability (1,2,3). The relationship between hCG and OHSS is thought to be mediated via the production of the angiogenic molecule vascular endothelial growth factor, VEGF. (1). Physiologically VEGF plays important role for angiogenesis & neovascularisation which is an integral part of folliculogenesis, corpus luteum formation and embryo implantation. Due to markedly increased mass of granulose cells in hyperstimulated ovaries there is increased production of VEGF. HCG increases VEGF expression in granulose cells that leads to increased serum VEGF levels. There is enough evidence to support the role of VEGF in

pathogenesis of OHSS as VEGF levels have been found to be high after HCG administration in superovulated women and severity of OHSS correlates with the serum VEGF levels (1,3). This has been the basis for recent development of dopamine agonists for the prevention & decreasing the severity of OHSS in hyper-responders. Dopamine agonists basically act by blocking VEGF receptor-2 phosphorylation. Many of the other factors like platlet derived growth factor (PDGF), insulin like growth factor-1, epidermal growth factor (EGF) may be involved for increased permeability either directly or indirectly through VEGF (3).

Classification of OHSS: Over the years several classification systems have been suggested depending upon the severity of condition. Most recently followed classification of OHSS (3) is given below (Cited from Gardener's textbook of assisted reproductive technologies, Third edition.

*** Classification of OHSS**

Mild	Moderate	Severe	Critical
Bloating	Vomiting	Massive ascites	Tense ascites
Nausea	Abdominal pain	Hydrothorax	Hypoxemia
Abdominal distension	USG evidence of ascites	Haematocrit >45%	Pericardial effusion
Ovaries ≤ 5 cm	Haematocrit> 41%	WBC>15000/ mm^3	Haematocrit >55%
	WBC >10,000/mm^3	Oliguria	WBC >25000/ mm^3
	Ovaries>5 cm	Creatinine 1-1.5mg/dl	Oliguria or anuria
		Creatinine clearance ≥50ml/min	Creatinine >1.5mg/dl
		Hepatic dysfunction	Creatinine clearance<50ml/min
		Anasarca	Renal failure
		Ovaries variably enlarged	Thromboembolic phenomena
			ARDS
			Ovaries variably enlarged

Mild OHSS is quite common and may be seen in almost one-third of patients during ovarian stimulation. So patients should counseled about this & explained about the signs & symptoms of more severe forms of OHSS so as to prevent serious morbidity & mortality related to this dreaded complication.

A division of OHSS into 'early' and 'late', depending on the time of onset, may be useful in determining the prognosis. OHSS presenting within 9 days after the ovulatory dose of human chorionic gonadotrophin (hCG) is likely to reflect excessive ovarian response and the precipitating effect of exogenous hCG administered for final follicular maturation. OHSS presenting after this period reflects endogenous hCG stimulation from an early pregnancy. Late OHSS is more likely to be severe and to last longer than early OHSS (2).

Identification of patients at risk of OHSS: It is important to identify patients who are at high risk of developing OHSS so that changes can be made in stimulation regimen & other preventive steps can be taken at appropriate stage (3). High risk patients for OHSS include: young women, polycystic ovaries, thin built, previous history of OHSS, multiple stimulated follicles (>20 in ART and >6 in ovulation induction cycles), high serum estradiol levels (ART >4000pg/ml, OI >1700 pg/ml), when HCG is used as luteal phase support, use of GnRH long down regulation protocol.

Patients in low risk category include :- non-PCOS, elderly, poor response to gonadotropins, few antral follicles, elevated baseline FSH levels use of antagonist protocol.

One of the important parameters which have been recently used for predicting OHSS is serum anti-mullerian hormone (AMH) levels. As AMH is

secreted by pre-antral & small antral follicles, AMH can be measured on any day of menstrual cycle. Various studies have shown a correlation of high AMH levels with the development of OHSS, though the cut-off values vary depending on the assay used (6).

Prevention of OHSS: The first step in prevention of OHSS is to identify patients at high risk of developing the syndrome. Though complete prevention of OHSS is still not possible, but with early identification of potential risk factors and careful clinical management of all patients undergoing ovarian stimulation regimens, the incidence of OHSS can be significantly reduced (7).
The stimulation protocol should be individualized to suit the patient. Based on the risk factors & AMH levels, patient can be categorized as poor, normal, or high responders. Secondarily, if there is excessive response to stimulation,changes should be made in the stimulation protocol (1).

Preventive steps before OHSS has developed: These are the measures taken in patients considered to be at high risk of developing OHSS. This is a kind of primary prevention to prevent OHSS.

1. Reducing the starting dose of gonadotropins: Patients with PCOS and history of severe OHSS in previous IVF cycle should be started on low dose of gonadotropins & dose increments should be slow. (7)Various protocols proposed for such patients include chronic low dose step-up protocol (8), limited ovarian stimulation (9); mild stimulation protocol (IVF); no FSH on day of hCG (1,3). Patients should be closely monitored using ultrasonography & serial serum estradiol levels.

2. Reducing Duration of FSH Exposure: This can be achieved via the use of ‘‘mild stimulation’’ protocols, where administration of FSH is delayed until the mid to late follicular phase (1).

3. Type of GnRH analogue used for controlled ovarian stimulation: In two recent meta-analysis comparing the outcome of GnRH agonist versus antagonist, both showed that the incidence of OHSS was significantly reduced in the antagonist protocol without compromising the pregnancy rates. (10,11) It seems logical that the patients with a history of OHSS & who are considered at high risk of developing OHSS should be treated by GnRH antagonist protocol. Recent Cochrane review has shown 50% reduction in the incidence of OHSS in antagonist group compared to long agonist protocol (12).

4. In-vitro maturation: In patients with PCOS & those at high risk of developing OHSS, in vitro maturation (IVM) of oocytes offers benefit of OHSS prevention. Though IVM is not used routinely in ART practice due to low live- birth rates but there has been much improvement in pregnancy rates in recent years with reported pregnancy rates being as high as 20-50% (1).

5. Avoidance of hCG for luteal phase support (LPS): Due to supra-physiological steroid (estradiol & progesterone) levels in IVF, LPS is required. As HCG has been shown to markedly increase the risk of OHSS without any significant increase in pregnancy rates, it is recommended that LPS be given the form of progesterone, with or without supplemental estradiol , rather than in the form of hCG (1).

6. Use of Metformin: Though metformin coadministration during gonadotropin-stimulated OI or IVF in women with PCOS show little benefit of metformin treatment in terms of improved ovulation or clinical outcome but it has significant positive effect on the incidence of OHSS. A systematic review compared whether metformin co-administration with gonadotropins for IVF improves outcome in women with PCOS. Metformin co-administration to IVF treatment does not improve pregnancy rate (OR 1.29; 95% CI 0.84-1.98) or live-birth rates (OR2.02; CI 0.98-4.14), but significantly reduces the risk of OHSS (OR 0.21;CI0.11-0.41, $p<0.00001$) (13).

Strategies to prevent OHSS during stimulation: During ovarian stimulation, patients are considered at high risk if a large number of follicles are visualized in both the ovaries as well as increasing E_2 levels above 3000 pg/ml (7).

1. Coasting: Coasting involves withholding further gonadotropin stimulation and delaying hCG administration until estradiol levels plateau or decrease significantly. Though there is insufficient evidence to determine whether coasting is an effective strategy for preventing OHSS, still coasting has been widely adopted as the first-line intervention of choice for reducing the risk and severity of OHSS in patients with excessive follicular response to ovarian stimulation (1,7).

2. Reduced Dose of hCG: As hCG is known to be a risk factor for OHSS, a number of investigators have assessed the value of using lower doses for triggering

ovulation. Compared with the standard dose of 10,000 IU, doses of 5,000 IU have been used successfully to trigger ovulation without impairing clinical outcome (1,7).

3.Alternative Agents for Triggering Ovulation: HCG has been used successfully to trigger ovulation for over 60 years. However, the relatively long serum half-life of hCG results in a prolonged luteotropic effect, multiple corpus luteum development, and raised serum levels of estrogen and progesterone throughout the luteal phase which increases the risk of OHSS. To prevent OHSS, alternative agents for triggering final oocyte maturation and ovulation have been investigated.

a. GnRH-agonist: In antagonist-stimulated cycles, administration of a bolus of GnRHa results in a surge (flare) of gonadotropins (LH and FSH) released by the pituitary, mimicking the natural midcycle surge of gonadotropins and effectively stimulating ovulation and final oocyte maturation. This approach significantly reduces or eliminates the OHSS (1). But, the likelihood of clinical pregnancy after GnRH agonist triggering has been shown to be significantly lower as compared with standard hCG protocol (7). When a GnRHa is used to trigger ovulation, additional LPS is particularly important.

b: Recombinant LH. It has been suggested that triggering ovulation via administration of recombinant LH would more closely mimic the natural LH surge than is achieved with hCG administration. Despite the safety advantages of recombinant human LH in terms of OHSS reduction, however, reduced pregnancy rates and a poor cost/benefit ratio reduce its applicability in the clinical situation (1).

4. Cryopreservation of All Embryos: Another alternative is the normal progression of IVF until oocyte pickup (OPU), followed by cryopreservation of embryos to be thawed and transferred at a later date when the patient's serum hormone levels are not elevated. Although early OHSS associated with hCG administration may still occur, it is the increase in endogenous hCG associated with pregnancy that is responsible for secondary exacerbation of early OHSS or the development of late OHSS, and these more serious forms of the condition can thus be avoided. Whereas OHSS does occur after cryopreservation, the severity and duration of the condition appear to be reduced (1).

5. Cycle Cancellation: Cycle cancellation and withholding of hCG is the only guaranteed method for prevention of early OHSS. This creates a frustrating condition for both the physician & patient. In ovulation induction cycles without GnRH-analog use, a natural LH surge may still result in ovulation and natural conception in some cases, resulting in the possibility of late OHSS. Thus, suitable contraceptive methods should be used to avoid this in high-risk cases (1,7).

6. Dopamine agonists: The dopamine agonist cabergoline can reverse the VEGFR-2 mediated increase in vascular permeability which is the main culprit for OHSS. Dopamine agonists act by blocking the phosphorylation of VEGF-2 receptor, thereby targeting the pathophysiology of syndrome. Though the mainstay of treatment for OHSS is symptomatic, the use of dopamine agonists is one of the approaches acting through pathophysiology of disease (15). A systematic review and meta-analysis of randomized trials comparing the prophylactic effect of the dopamine agonist, cabergoline, versus no treatment in IVF/ICSI cycle has been conducted. Four randomized trials entailing 570 women were included. There was evidence of a statistically significant reduction in the incidence of OHSS in the cabergoline group (OR 0.41, 95% CI 0.25–0.66) with an absolute risk reduction of 12% (95% CI 6.1–18.2%), but there was no statistically significant evidence of a reduction in severe OHSS (OR 0.50, 95% CI 0.20–1.26). There was no evidence for a difference in clinical pregnancy rate (OR 1.07, 95% CI 0.70–1.62) and miscarriage rate (OR 0.31, 95% CI 0.03–3.07) (14,16).

7. Intravenous Albumin and Hydroxyethyl Starch.: Though albumin has been used in past for prevention & treatment of OHSS, but recent Cochrane review has shown no significant benefit with use of albumin. Hydroxyethyl starch (HES) solution has been suggested as an alternative to albumin. Only a small number of studies evaluating the benefits of HES in the prevention of OHSS have been reported; however, it is thought that, as a cheaper, potentially safer alternative to albumin, HES should be the first-line treatment (1,2).

Management of OHSS

Outpatient Management: Patients with mild manifestations of OHSS can be managed on an outpatient basis. Treatment usually requires only oral analgesics and counseling regarding the signs and symptoms of progressing illness. Intercourse is best avoided as it may be painful and may increase the

risk of ovarian rupture. Treatment of worsening OHSS typically requires antiemetics and more potent analgesics. Most patients still can be effectively managed and monitored on an outpatient basis, but they require more careful evaluation including frequent physical and ultrasound examinations (to detect increasing ascites), daily weight measurements, and serial laboratory determinations of hematocrit, electrolytes, and serum creatinine. Careful monitoring is essential and should include at least daily communication, if not examination, to ensure that progression to more severe disease is promptly recognized.

Hospitalization: Serious illness requiring hospitalization is relatively uncommon but by no means rare. No one symptom or sign is an absolute indication, but hospitalization should be considered when one or more of the following are present:

- Severe abdominal pain or peritoneal signs.
- Intractable nausea and vomiting that prevents ingestion of food and adequate fluids.
- Severe oliguria or anuria.
- Tense ascites.
- Dyspnea or tachypnea.
- Hypotension (relative to baseline), dizziness, or syncope.
- Severe electrolyte imbalance (hyponatremia, hyperkalemia).
- Hemoconcentration.
- Abnormal liver function tests.

Careful and frequent re-evaluation of the hospitalized patient with severe OHSS is essential. Serial clinical and laboratory evaluations provide the means to monitor progression of illness, to judge the response to treatment, and to recognize evidence of resolution.

Conclusion

OHSS is one of the most serious complications of ovarian stimulation which can be life-threatening in its severest form. And it is an iatrogenic condition which can prove fatal in otherwise young, healthy infertile women. Currently available treatment for OHSS is mainly supportive, so prevention remains the most important step in its management. There is evidence to support use of dopamine agonists for prevention & management of OHSS. With early identification of potential risk factors and careful clinical management of all patients undergoing ovarian stimulation regimens, the incidence of OHSS can be significantly reduced.

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