Ovarian Hyperstimulation Syndrome: Can We Eliminate It as a Complication of ART?

37

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Abstract

With the explosive increase in in vitro fertilization (IVF) cycles worldwide, the morbidity and mortality associated with ovarian hyperstimulation syndrome (OHSS) cannot be ignored. Researchers and clinicians all over the world are moving toward newer modifications to achieve the goal of OHSS-free clinic and eliminating it as a complication [1]. Segmentation of the IVF cycle with a combination of GnRH-antagonist protocol with GnRH-agonist (GnRHa) trigger followed by embryo/oocyte freezing with subsequent embryo transfer can probably eliminate the risk of OHSS after controlled ovarian stimulation (COS). In case of embryo transfer in COS cycle, combined use of a GnRH-antagonist protocol with GnRHa trigger followed by single embryo transfer (SET), preferably blastocyst, favors reduction in the incidence of OHSS. But due to luteolytic action of agonist trigger, intensive luteal phase support (LPS) should be considered with adequate monitoring for signs of OHSS. Decision making based on patient characteristics, monitoring techniques, clinical experience, laboratory outcomes, and recent evidence is the key to maintain a balance between incidence and severity of OHSS and IVF cycle outcomes in terms of successful healthy pregnancy.

Keywords

GnRH agonist • GnRH antagonist • Frozen-thawed embryo replacement cycle • Agonist triggering • In vitro fertilization (IVF) • Ovarian hyperstimulation syndrome (OHSS)

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37.1 Introduction

OHSS is the most serious iatrogenic complication of assisted reproductive technology (ART). Though use of exogenous gonadotropins for COS/IVF is the main cause, other agents such as clomiphene and gonadotropin-releasing hormone analogs are also responsible in occasional cases. Mild OHSS accounts for up to 33 % of IVF cycles, with the reported incidence of 3 to 6 % for moderate and 0.1 % and 2 % for severe OHSS [2].

Severe OHSS may be complicated by thromboembolism, pleural and pericardial effusion, adult respiratory distress syndrome (ARDS), renal failure, liver dysfunction, or even multiorgan failure. Very few cases of OHSS-related mortality have been reported in the literature [3–5]. In a survey on maternal deaths related to IVF in the Netherlands, 3 deaths per 100,000 IVF cycles were reported [6].

37.2 Pathophysiology of OHSS

OHSS involves marked ovarian enlargement, theca lutein cysts, and increased vascular permeability leading to acute fluid shift from intravascular to extravascular space and its sequelae (Fig. 37.1). Vascular endothelial growth factor (VEGF), a vasoactive cytokine, plays a pivotal role in pathophysiology of OHSS [7, 8].

Numerous factors acting directly or indirectly via VEGF, including interleukins, cytokines, angiotensin II, insulin-like growth factor 1 (IGF-1), etc. may be involved [9–11]. Some studies showed a direct correlation between plasma renin activity and the severity of OHSS [12], but it could probably be the effect and not the cause of OHSS [13]. Mutation of FSH receptor gene may also predispose to OHSS because of abnormally high sensitivity to hCG [14].

The classification of OHSS is beyond the scope of this chapter, but can be found in other sources [15, 16].

37.3 OHSS Prevention: A Stepwise Strategy

37.3.1 Identification of High-Risk Cases

Prediction of high-risk cases prior to COS and individualized approach is the first step in the prevention of OHSS (Tables 37.1 and 37.2) [17–25].

37.3.2 Adjustment of FSH Starting Dose

Starting with the lowest possible dose of gonadotropins and close monitoring during COS with ultrasound and serum estradiol levels reduces the risk of OHSS.

37.3.3 Ovarian Stimulation Protocols Preferably GnRH-Antagonist Protocol

Unlike GnRHa, the GnRH antagonists directly and rapidly inhibit gonadotropin release within several hours through competitive binding to the

Table 37.1 Predictors of OHSS

Pretreatment characteristics	
Young age	<33 y
Lean body weight	Insufficient evidence
Polycystic ovaries on ultrasound/PCOS	
High basal antral follicle count (AFC)	≥12–14
Previous episodes of OHSS or hyperresponse	
High anti-Mullerian hormone (AMH)	Cutoff level of 3.36 ng/ml

From Humaiden et al. [17]

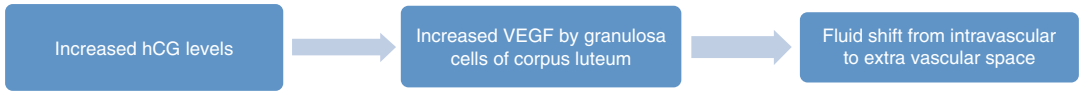

Fig. 37.1 Pathogenesis of OHSS

Table 37.2 Ovarian response parameters

High doses of exogenous gonadotropins in early follicular phase	
High number of growing follicles	>14 follicles with diameter of 11 mm >11 follicles with diameter of 10 mm
High serum estradiol (E2) levels	3500–6,000 pg/ml (better applicable in combination of growing follicles)
Rapidly rising serum E2 levels	
VEGF levels – in follicular fluid	
Number of oocytes retrieved	>15–20
Higher and/or repeated dose of exogenous hCG administration	
Follicular fluid IL-6 and IL-8 levels on the day of embryo transfer	
Pregnancy in fresh cycle	
Multifetal pregnancy	

From Humaiden et al. [17]

pituitary GnRH receptors [26]. GnRH-antagonist treatment protocols are effective and easy to use, allow flexibility of treatment with fewer side effects, and appear to offer a promising alternative to the long-established GnRHa regimens for prevention of a premature LH surge during COS. Flexibility of use of GnRHa as trigger for oocyte maturation is beneficial in reducing OHSS [27]. A Cochrane review in forty-five RCTs comparing the antagonist to the long agonist protocols showed significant lower incidence of OHSS in the antagonist group (29 RCTs; OR 0.43, 95 % CI 0.33–0.57) without any statistically significant difference in rates of live births (9 RCTs; OR 0.86, 95 % CI 0.69–1.08) [28].

37.3.4 Coasting

Coasting involves withholding the gonadotropins and postponing hCG administration until the patient's E2 levels drop to a "safer" level [29]. Prior to the use of GnRH antagonist during COS, it had been widely used in the prevention of severe OHSS. Lower gonadotropin levels increase granulosa cell inhibition and apoptosis leading to lower levels of VEGF and other vasoactive substances involved in the pathogenesis of OHSS [30]. Daily serum E2 levels are monitored in conjunction with follicle tracking until E2 levels decrease to a safe level usually below 3000 pg/ml. A recent Cochrane review showed no evidence of difference in the incidence of moderate and severe OHSS and significantly fewer oocytes retrieved in coasting groups compared with GnRHa (OR −2.44, 95 % CI −4.30 to −0.58; $P=0.01$) or no coasting (OR −3.92, 95 % CI −4.47 to −3.37; $P<0.0001$. But the problem with this review was that four studies which met the inclusion criteria were different as two studies compared coasting with unilateral follicular aspiration, one compared coasting vs. no coasting, and the last study compared coasting with replacement of GnRHa with GnRH antagonist [31]. There is a high risk of cycle cancelation with coasting especially if it is more than 3–4 days or there is >30 % fall in E2 levels [32, 33].

37.3.5 Minimize Use of hCG

Both exogenous and endogenous hCG due to its long half-life and leutrotrophic activity play a key role in the pathophysiology of OHSS [34]. Therefore, decreasing dose of hCG for triggering oocyte maturation, replacing GnRHa for hCG trigger, and avoiding hCG in luteal phase support (LPS) are various methods to prevent delayed-onset OHSS [17].

37.3.5.1 Lowering Dose of hCG Especially in GnRHa Protocol

In high-risk cases, the lowest effective dose of hCG has been proposed, ranging from 5,000 to 2,500 IU [35]. A low dose of hCG appears to reduce the incidence of OHSS but cannot eliminate it.

37.3.5.2 GnRHa Trigger

The role of GnRHa trigger (0.2 mg triptorelin, 0.5 mg buserelin, or 1 mg leuprolide) in elimination

of OHSS in high-risk patients was first suggested in 1988 [36]. GnRHa-induced surge of gonadotropins consists of 24–36 h span with resemblance to physiological mid-cycle LH surge [37]. This is in contrast to hCG-mediated LH surge which spans several days because of its long half-life leading to prolonged levels in circulation. GnRHa can replace hCG trigger in antagonist- or gonadotropin-only stimulated cycles but not in previous downregulation cycles with long-term agonist treatment [38]. In the oocyte donation model studies, avoidance of hCG exposure has been associated with complete elimination of OHSS, while recipient pregnancy rates are equivalent to those observed with hCG triggering [39, 40]. GnRHa trigger is the method of choice in oocyte donors and patients for fertility preservation. A recent Cochrane review of 11 RCTs reported no OHSS events in the GnRHa arm of the study and also concluded that GnRHa should not be routinely used to trigger oocyte maturation due to lower live birth rates and ongoing pregnancy rates, but makes an exception for women at high risk of OHSS, after appropriate counseling. It also concluded that combining GnRHa with embryo vitrification has the potential to provide a good clinical outcome [41]. In an analysis by Humaidan et al. comparing nine RCTs with fresh IVF cycles, no OHSS was reported after GnRHa triggering. Additionally, the delivery rate improved significantly after modified luteal support [6 % risk difference in favor of the hCG group (95 % CI: 20.14–0.2)] when compared with initial studies with conventional luteal phase support (LPS) [18 % risk difference (95 % CI: 20.36–0.01)]. They also reported 0 % incidence of OHSS in oocyte donation cycles (four RCTs). They concluded that GnRHa triggering with modified LPS is a valid alternative to hCG triggering, resulting in an elimination of OHSS [27]. Regarding the LPS after GnRHa triggering in fresh transfers, the majority of studies support supplementation with LH activity in addition to standard LPS with estradiol and progesterone [42]. Some studies showed beneficial effect of intensive LPS with intramuscular progesterone and estradiol patches as well as oral estradiol, but others showed lower pregnancy rates with similar LPS [43–45]. With the dual trigger – agonist followed by hCG (1000–2500 IU) and standard LPS – comparable reproductive outcome with no increased risk of OHSS is reported [44, 46]. Recombinant LH after GnRHa trigger for LPS has also been tried with similar implantation rates as compared to standard luteal progesterone protocol and no cases of OHSS [47].

37.3.6 Deciding Fate of the Stimulation Cycle

37.3.6.1 Cycle Cancelation

Termination of cycle by canceling further stimulation and trigger helps in the prevention of OHSS and associated morbidity. But due to the financial burden and psychological impact on dropout patients, it should only be reserved as a last resort for severe OHSS cases or in cases of total loss of cycle control.

37.3.6.2 Cryopreservation of Oocytes and Embryos

Embryo implantation and positive pregnancy can lead to late-onset OHSS or exacerbation of early OHSS. Therefore, cryopreservation of embryos or oocyte can be an option in the prevention of OHSS. Due to improvement in freezing techniques and culture media, pregnancy rates in the frozen cycles are comparable to the fresh cycles [48].

37.3.6.3 Fresh Cycle with Single Embryo Transfer (SET)

In case of decision of fresh embryo transfer, SET is preferred to decrease chance of multiple pregnancy and associated OHSS especially in younger patient. Adoption of strategies such as blastocyst transfer may permit more time for evaluation and decision regarding cryopreservation in case of aggravation of symptoms.

37.3.7 Other Preventive Regimens for OHSS

37.3.7.1 Intravenous Fluid at the Time of Oocyte Retrieval

Albumin is known to increase the plasma oncotic pressure and decrease the capillary permeability by binding to molecules like VEGF. The role of intravenous human albumin infusion at the time of oocyte retrieval for the prevention of OHSS is

controversial [49, 50]. A recent Cochrane meta-analysis showed a borderline statistically significant decrease in the incidence of severe OHSS with administration of human albumin (eight RCTs, OR 0.67, 95 % CI 0.45–0.99). But with administration of hydroxyethyl starch, a plasma expander, there was a significant decrease in the incidence of severe OHSS (three RCTs, OR 0.12, 95 % CI 0.04–0.40), without any effect on the pregnancy rates [51].

37.3.7.2 Dopamine Agonist

Cabergoline, a dopamine agonist, binds to VEGF receptor-2 and inhibits its phosphorylation leading to decrease in capillary permeability [52, 53]. Oral cabergoline 0.5 mg/day can be administered for at least 8 days in high-risk patients to prevent early OHSS. Cabergoline may reduce the risk of OHSS in high-risk women, especially moderate OHSS. It is unlikely to have a clinically relevant negative impact on clinical pregnancy or on the number of retrieved oocytes [54]. However, impact on live birth, miscarriage, and congenital abnormalities is still uncertain [55]. More recently, quinagolide has been shown to reduce the incidence and severity of OHSS [56].

37.3.7.3 Insulin-Sensitizing Agents: Metformin

Insulin is known to stimulate VEGF protein expression and secretion. Metformin improves insulin sensitivity and reduction of hyperinsulinemia and decreases OHSS. In a Cochrane review on efficacy of metformin treatment in women with PCOS undergoing IVF or ICSI cycles, there was a significant reduction in the risk of OHSS (5.7 % vs. 21.2 %) [57, 58].

37.3.8 Additional Preventive Measures with Limited Evidence

37.3.8.1 In Vitro Maturation of Oocytes (IVM)

In patients with PCOS and in normoovulatory patients at high risk of developing OHSS, IVM of oocytes offers great potential for OHSS prevention. Due to technical difficulties in oocyte retrieval, lower success rate, and reports of high rates of meiotic spindle and chromosomal abnormalities, its practice is limited to very few centers [59, 60].

37.3.8.2 Glucocorticoids

Glucocorticoids are a vasodilator, are an anti-inflammatory, and have inhibitory effect on VEGF gene expression [61, 62]. But sparse evidence and side effects limit its use in the prevention of OHSS.

37.3.8.3 Follicular Aspiration

Timed aspiration of granulosa cells from one ovary prior to hCG administration reduces the production of OHSS mediators while allowing continued contralateral ovarian development [63]. It is not recommended because of cost, invasive procedure, and limited evidence.

37.3.8.4 Aromatase Inhibitors

Luteal phase estradiol suppression by letrozole is suggested with very limited evidence [64, 65].

37.3.8.5 Nonsteroidal Anti-inflammatory Drugs

Low-dose aspirin beginning on the first day of COS has shown to decrease OHSS incidence (0.25 % vs.8.4 %) in a high-risk group [66]. Meloxicam was capable of reducing the OHSS-associated ovarian weight and expression of VEGF in an animal model [67].

37.3.8.6 GnRH-Antagonist Salvage

Luteal phase GnRH-antagonist administration in patients with established severe early OHSS appears to prevent patient hospitalization and results in quick regression of the syndrome [68]. Decision of concomitant administration with embryo transfer requires more studies [69].

37.4 Segmentation for OHSS-Free Clinic by Freeze-All Policy

As stated by Devroey, the strategy to obtain an OHSS-free clinic is closely related to the segmentation concept (Fig. 37.2) [1]. With the advent of vitrification techniques, there has been a major improvement in the embryo survival and subsequent pregnancy rates [70, 71]. For couples

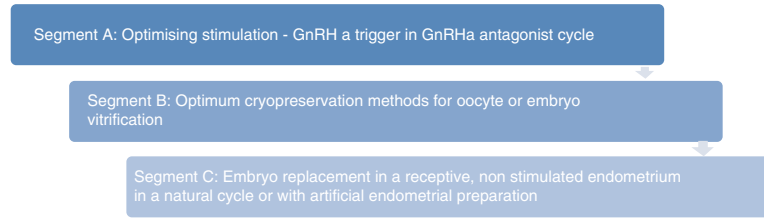

Fig. 37.2 Segmentation of IVF

who do not desire embryo cryopreservation, oocyte vitrification is another option. In a proof-of-concept study by Greisinger et al., 20 high-risk patients (≥20 follicles of ≥10 mm or estradiol ≥4000 pg/ml on trigger day) with GnRHa trigger and cryopreservation of all two pronucleate oocytes reported no case of OHSS and 29.2 % ongoing pregnancy rate in subsequent thaw cycle [38, 72]. Excellent embryo or oocyte survival rates after vitrification support the use of cryopreservation as a routine approach [70]

Advantages of segmentation:

(a) Minimizes late-onset OHSS.
(b) No need of intensive LPS.
(c) No embryo transfer in out-of-phase endometrium, which is common in high responder patients.
(d) Allows embryo transfer in a natural cycle where applicable. With effective cryopreservation that results in little or no damage to embryos, cumulative birth rates per retrieval should, in theory, be highest when embryos are transferred individually [73].
(e) Decrease in multiple pregnancy rate and perinatal and maternal morbidity and mortality associated with it.

37.5 Various Proposals for Decision Making Between Fresh Embryo Transfer or Freeze-All Policy

Although the use of a GnRH-agonist trigger can dramatically reduce the risk of OHSS in high-risk patients, for some patients segmentation of the cycle would still be better option. At present, the optimal threshold for performing a freeze-all after a GnRH-agonist trigger is not clear. Following are the various proposals by different studies (Fig. 37.3):

1. Griffin et al. stratified patients according to their estradiol concentration on the day of triggering final oocyte maturation to add 1000 IU of hCG and GnRHa for patients with peak estradiol <4000 pg/ml and GnRHa alone if peak estradiol is ≥4000 pg/ml [74].
2. In a protocol by Orvieto et al., in patients in whom <20 oocytes were retrieved in the first IVF cycle attempt, and in low responders or patients >40 years old, the COH protocol is individually tailored. In the latter groups, if the tailored COH protocols yield 20 oocytes, or 10 embryos develop, the patient is followed for 5 days after oocyte retrieval for signs of early OHSS (ultrasonographic signs of ascites, hematocrit levels for the degree of hemoconcentration). If early signs develop, ET is withheld and all resulting embryos cryopreserved. If it does not appear, they transferred one blastocyst, with 1500 IU of hCG with the consequent decrease in the risk of multiple pregnancy to almost zero, thereby eliminating the risk of late OHSS [75, 76].
3. According to Kol and Humaidan, ≤25 follicles is a safe threshold for 1500 IU hCG, but above 25 follicles, either a freeze-all policy or intensive luteal phase support with estradiol and progesterone is suggested [77, 78].

Fig. 37.3 Stepwise approach to be individualized and combined to reach the goal of eliminating OHSS

37.6 Investigation and Monitoring of an OHSS Patient

37.6.1 General Condition

General condition is monitored by regular charting of vital signs, weight charts, abdominal girth measurement, and a strict fluid balance record.

37.6.2 Biochemical Tests

A complete biochemical assessment includes hematocrit, electrolytes, liver function tests, kidney function tests, and coagulation profile. Blood gases and acid-base balance are required if there is a respiratory or renal compromise. Serum β-hCG is done to rule out pregnancy. Serum and urinary osmolarity and urinary electrolytes may be needed in more severe forms of the disease. The frequency of these tests is guided by the severity of the disease.

37.6.3 Ultrasonographic Examination

Ultrasound gives important information on ovarian size, amount of ascites, presence of hydrothorax

or pericardial effusion, and detection of pregnancy, whether single or multiple.

37.6.4 Chest X-Ray

A chest X-ray can rule out pleural effusion.

37.6.5 Serum ß-hCG

It is done to confirm pregnancy making the women at a high risk for developing severe disease.

37.6.6 Invasive Hemodynamic Monitoring

When OHSS becomes critical, monitoring of pulmonary artery pressure and central venous pressure may be required.

37.7 Treatment

The condition usually resolves within 10–14 days. Treatment is based on severity of the disease.

37.7.1 Mild OHSS

In mild cases, the treatment is usually conservative and is done at outpatient level with close follow-up. Plenty of fluids is advised. She is advised to avoid exertion and counseled on the warning signs like nausea, vomiting, abdominal pain or distension, and decreased urinary output. Serum electrolytes, hematocrit, and ultrasonography should be done. Analgesics and antiemetics may be used if required. Intake-output monitoring is important.

Drug therapy may be started in an established case.

GnRH antagonists: If given on day 6 after oocyte retrieval in women with OHSS for 4 days, combined with luteal phase support using exogenous estradiol and progesterone, OHSS regressed [69]. In women on antagonist regime, antagonist administration was re-initiated if OHSS developed and continued daily for a week, while all embryos were cryopreserved.

Role of GnRH agonists: This resolved the OHSS. A marked decrease of hematocrit, white blood cell count, ovarian volume, and ascitic fluid has been observed during one week of follow-up [68].

Cabergoline: Cabergoline is given as 0.5 mg/day. It reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction [79].

37.7.1.1 Reassessment

Reassessment is required if there is increase in weight more than 2 kg or worsening of symptoms.

37.7.1.2 Indication of Hospitalization

Hospitalization should be considered in all severe and critical cases of the disease or if condition worsens. In cases of mild to moderate OHSS, admission is required if a woman is not responding to treatment and if there is intolerable nausea and vomiting, hypotension, signs of pleural effusion or ascites, a hematocrit of more than 48 %, potassium level more than 5.0 mg/l, and serum creatinine more than 1.2 mg.

37.7.2 Severe OHSS

The aim of therapy is correction of circulatory volume, electrolyte imbalance, maintenance of renal function, and prevention of thrombosis.

37.7.2.1 Maintenance of Intravascular Volume and Electrolyte Imbalance

The aim must be to restore normal intravascular volume and preserve adequate renal function. Colloid expander may be used for this purpose, but they have the disadvantage that after a short while, they redistribute into the extravascular space worsening the ascites. Low-salt albumin is the expander of choice and is given in a dose of 50–100 g every 2–12 h. It reverses hematocrit changes, improves renal function, and is safe

from viral contamination. Other options tried are mannitol, dextran, and fresh frozen plasma. Dextran can cause ARDS. Only if there is hyponatremia, normal saline with or without glucose is the crystalloid used for replacement. Up to 1.5–3 l may be needed. Other electrolyte imbalances like hyperkalemia are corrected.

37.7.2.2 Prevention of Thrombosis

Low-dose heparin should be given, as prophylaxis, in cases where there is an altered coagulation profile.

37.7.2.3 Dopamine

Dopamine may help to avoid fluid and salt retention by improving the renal blood flow in oliguric patient.

37.7.2.4 Management of Ascites and Hydrothorax

Paracentesis under ultrasound guidance is done where there is severe discomfort and compromise of venous return leading to a decreased cardiac output and hypotension, renal compromise, respiratory distress, or hemoconcentration unresponsive to medical therapy. Repeat aspiration may be required. This should be done if dyspnea is present because of severe pleural effusion.

37.7.3 Critical OHSS

Critical OHSS causes multisystem failure and requires multidisciplinary intensive care. Renal failure may need to be treated with dopamine, central venous pressure line, and hemodialysis. In case of pulmonary complications, arterial blood gas monitoring, thoracocentesis, or assisted ventilation is required if they do not respond to basic treatment. Patients with thromboembolic episodes require therapeutic anticoagulation with heparin. Laparotomy is required if the cysts undergo torsion, hemorrhage, or rupture. Laparoscopic unwinding can be done in cases of torsion.

Termination of pregnancy: If critical condition does not improve, one may consider termination of pregnancy.

Conclusions

GnRH-agonist trigger with antagonist cycle and freeze-all or fresh transfer with intensive LPS will help in achieving the goal toward elimination of OHSS without compromising pregnancy outcome. The optimal LPS, mode of administration, and length after COH still need to be determined. Currently, the ideal strategy that will eliminate OHSS without compromising ART outcome seems to be cycle segmentation and freezing of all embryos. Continuation of GnRH antagonists for a few days will rapidly regress the ovarian size, and transfer of embryos in subsequent natural cycles will give the best pregnancy outcomes. OHSS-related morbidity and mortality can be reduced by appropriate preventive measures, timely detection of OHSS, and management based on the severity of OHSS.

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