Update

Principles of Diagnosis and Management in the Ovarian Hyperstimulation Syndrome

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ABSTRACT Ovarian hyperstimulation syndrome (OHSS) is the most serious consequence of ovulation induction and in vitro fertilisation (IVF), potentially resulting in death in its extreme manifestation. How best to manage this condition has been the subject of considerable study, with primary emphasis on risk recognition before commencing the IVF stimulation sequence. The exact etiology of OHSS remains unknown. The aim of this guideline is to provide clinicians with up-to-date information about the diagnosis and treatment of OHSS, based upon the best available evidence. This guideline covers outpatient management, criteria for hospital admission and basic inpatient management. Intensive care management of OHSS is not covered in detail. OHSS is an exaggerated response to ovulation induction with FSH and HCG. OHSS is a self-limiting disorder with a broad spectrum of clinical manifestations related to increased capillary permeability and fluid retention mediated by many inflammatory mediators including vascular endothelium growth factor. OHSS is a systemic disease resulting from vasoactive products released by hyperstimulated ovaries. The pathophysiology of OHSS is characterized by increased capillary permeability, leading to leakage of fluid from the vascular compartment, with third space fluid accumulation and intravascular dehydration. Severe manifestations include a tendency to develop thrombosis, renal and liver dysfunction and acute respiratory distress syndrome (ARDS), causing serious morbidity. The role of this guideline is to outline the risk factors, clinical features and appropriate management of severe OHSS. The guidelines also aim at assisting the determination of the appropriate site of care.

KEY WORDS *Ovarian hyperstimulation, risk factors, polycystic ovaries syndrome*

Introduction

All ovarian stimulation protocols result in some degree of hyperstimulation, usually with no adverse consequences to the patient. In contrast, ovarian hyperstimulation syndrome (OHSS) is a iatrogenic complication of ovulation induction (OI) and ovarian stimulation for assisted reproductive technology (ART) and is characterized by cystic enlargement of the ovaries and rapid fluid shifts from the intravascular compartment to the third space. It is a potentially life-threatening condition in its severe form, resulting in hospitalization in 1.9% of cases, and hCG, either exogenous or endogenous, is the triggering factor of the syndrome. Ovarian hyperstimulation syndrome (OHSS) is an exaggerated response to ovulation induction with FSH and hCG. OHSS is a self-limiting disorder with a broad spectrum of clinical manifestations related to increased capillary permeability and fluid retention mediated by many inflammatory mediators including VEGF. Patients need to be informed that mild stages of OHSS are frequent and affect about 33% of the IVF cycles and 3-8% of the cycles become more complicated due to moderate or severe forms of OHSS.

Risk factors

The exaggerate response to fertility stimulation medicine has unknown etiology, yet a high occurrence risk is found in:

1. Women with polycystic ovaries syndrome. Women with PCOS have a higher incidence of OHSS after gonadotropin therapy than women with other causes of anovulatory infertility owing to the high number of follicles recruited. The association between increased ovarian response and elevated OHSS risk means that prior warning regarding the level of response to ovarian stimulation could predict the likelihood of OHSS. Hormonal markers are, therefore, being investigated as potential predictors of ovarian response, with anti-Mullerian hormone (AMH) being a promising candidate. AMH is expressed in granulosa cells from preantral and small antral follicles and is a measure of ovarian reserve. Initial studies suggest that AMH is a reliable predictor of ovarian response, able to differentiate normal (more than 4 oocytes) responders (using a cut-off level of 1.26 ng/mL AMH) to ovarian stimulation with a success rate of 98% (1).

Data also suggest that AMH is a more accurate predictor of normal ovarian response than age,

FSH, or inhibin-B alone or in combination. One study noted that all cycle cancellations due to OHSS risk were in patients in the highest AMH quartile (>7 ng/mL), suggesting that AMH levels might be a predictor of direct risk of OHSS. These findings were substantiated by a recent cohort study of 262 IVF cycles with 21 cases (8%) of moderate or severe OHSS in which baseline serum AMH levels 3 days before ovarian stimulation were found to be significantly correlated with subsequent development of OHSS (2).

AMH predicted OHSS better than age and body mass index, and an AMH cut-off value of 3.36 ng/mL gave a sensitivity of 90.5% and a specificity of 81.3%.

2. Young patients

3. Increased levels of estrogens and a high number of follicles or eggs.

4. Administration of GnRh antagonists

5. hCG use for luteal phase support

6. Pregnancy

OHSS diagnosis

The doctor needs to be updated with the OHSS symptoms and signs as the diagnosis is given on clinical grounds. It is usually an easy diagnosis, given the record of ovarian stimulation with either gonadotropins or antiestrogens, followed by typical symptomatology: abdominal distension, abdominal pain, nausea, vomiting. The differential diagnosis with the complications of the cystic ovary (torsion, haemorrhage), pelvic infections, intra-abdominal haemorrhage, ectopic pregnancy, appendicitis should not be ignored.

OHSS classification

Mild OHSS	Abdominal bloating
	Abdominal discomfort
	Ovaries enlarged to ‹8 cm*
Moderate OHSS	Moderate abdominal pain
	Nausea ± Vomiting
	Ascites shown by ultrasonography
	Ovaries enlarged to 8–12 cm*
Severe OHSS	Clinical evidence of ascites (occasionally hydrothorax)
	Oliguria
	Hemoconcentration (Ht ›45%)
	Hypoproteinemia
	Ovaries enlarged to ›12 cm*
Critical OHSS	Tense ascites or important hydrothorax
	Hematocrit ›55%
	White globules ›25 000/mm3
	Oliguria/anuria
	Thrombo-embolism
	Adult respiratory distress syndrome

*The enlargement of ovaries may not be correlated with OHSS severity in assissted reproduction cases, due to the effect of follicular aspiration.

The key to preventing OHSS lies in the experience with ovulation-inducing agents and in recognition of risk factors for OHSS. Induction regimes should be highly individualized and monitored, using the minimum dose and duration of gonadotropin therapy necessary to achieve the therapeutic goal.

Primary Prevention

1. *Reducing Exposure to Gonadotropins*

A) Reducing the Dose—IUI Cycles - Intrauterine Insemination (IUI) Cycles. As PCOS is a known risk factor for OHSS, a number of low-dose gonadotropin protocols have been implemented to reduce the risks of fertility treatment in this population. The aim of these protocols is to stimulate the ovaries without exceeding the FSH threshold, thus facilitating the development of a single dominant follicle rather than multiple follicles. A variety of stepwise protocols have been used. These include chronic low-dose step-up protocols, whereby a low starting dose of FSH (usually 75 IU) is administered for 14 days, followed by small incremental increases (e.g., 37.5 IU) at intervals of ≥7 days until follicular development is initiated. This dose is then continued until the criteria for triggering ovulation are met. This approach is associated with a higher rate of monofollicular development, fewer cases of multifollicular development, fewer cycles cancelled owing to hyperstimulation, and a significantly lower incidence of OHSS and multiple pregnancies than conventional low-dose protocols or step-down protocols. Moreover, it has been shown that in women who received a starting dose of FSH 50 IU/day for 7 days, followed by weekly increments of either 25 or 50 IU, patients receiving the lower dose had a higher incidence of monofollicular ovulation and fewer cycle cancellations.

B) Reducing Duration of FSH Exposure—IVF/intracytoplasmic sperm injection (ICSI) Cycles. Little consensus exists on the appropriate duration of FSH treatment, partly because of the wide variation in individual responses to gonadotropin therapy. However, there is also great variability in the criteria used to determine when to stop gonadotropin therapy and trigger final oocyte maturation. Investigators have used different follicle sizes, with or without predetermined serum E2 level.

2. GnRH Antagonist Protocols. The differential action of GnRH antagonists at both pituitary and ovarian receptors suggests that antagonist-suppressed cycles might result in a lower incidence of OHSS compared with agonist cycles, and this hypothesis has been supported by two recent meta-analyses. A Cochrane review demonstrated that the incidence of severe OHSS was significantly lower in an antagonist protocol than in an agonist protocol and that secondary

intervention methods such as coasting and cycle cancellation were administered more frequently in agonist-suppressed cycles. A second meta-analysis found that the incidence of hospital admissions for OHSS was significantly lower in antagonist cycles than in agonist cycles (4,5).

3. Avoidance of hCG for luteal phase support.

4. In Vitro Maturation. In patients with PCOS and in normoovulatory patients at high risk of developing OHSS, in vitro maturation (IVM) of oocytes offers great potential for OHSS prevention.

5. Insulin-Sensitizing Agents. Insulin resistance with compensatory hyperinsulinemia is thought to play a pathophysiological role in the ovarian dysfunction and hyperandrogenism associated with PCOS. There is evidence that, in metformin administration during the induction of ovulation, in patients with PCOS under treatment for IVF, there is a lower risk of OHSS (6).

Secondary Prevention Strategies

1. Coasting involves withholding further gonadotropin stimulation and delaying hCG administration until E2 levels plateau or decrease significantly. The majority of the reports on coasting in the literature are retrospective analyses, and there is a need for large prospective, randomized controlled trials to identify optimal coasting guidelines and to evaluate the safety and efficacy of coasting compared with other prevention methods (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 (8).

Promising results have also been reported from the Cornell low dose protocol, which determines hCG dosage according to serum E2 levels on the day of hCG administration. A sliding scale is used, with between 5,000 and 3,300 IU of hCG administered to women with E2 levels of 2,000–3,000 pg/mL

3. 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 reimplanted 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. Where OHSS does occur after cryopreservation, the severity and duration of the condition appear to be reduced (9).

4. Cycle Cancellation and withholding of hCG is the only guaranteed method for prevention of early OHSS. It should be noted that, in OI 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. Despite the success of cycle cancellation in the prevention of OHSS, most physicians are reluctant to use this method, particularly in IVF, where the financial burden of treatment and the patient's psychological distress may be significant.

5. Alternative Agents for Triggering Ovulation.

a. GnRHa. Continual application of a GnRHa results in receptor down-regulation and desensitization. However, in gonadotropinonly or 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. However, the total amount of gonadotropins secreted by the pituitary after a bolus of GnRHa is significantly reduced compared with the midcycle surge of gonadotropins, owing to differences in the duration and profile of the surge. Evidence from small-scale trials in OHSS high-risk patient populations suggests that this approach significantly reduces, or even eliminates, the incidence of OHSS (10).

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 (11).

6. Other Possible Strategies for Preventing OHSS

a. GnRH Antagonist Salvage. An initial decrease or plateau in serum E2 levels has been reported in some women in the 24–48 hours after the initial administration of a GnRH antagonist in IVF cycles, with no apparent impact on treatment outcome. Thus, it is possible that administration of

an antagonist to patients with elevated serum E2 at risk of developing OHSS may provide a means of interrupting the development or progression of the condition while salvaging the current treatment cycle.

b. Intravenous Albumin. Albumin is a major plasma-binding protein that may bind to the vasoactive agents responsible for the development of OHSS and facilitate their removal from the circulation. Additionally, albumin administration could increase plasma osmotic pressure, helping to maintain the intravascular volume and attenuate the effects of hypovolemia, hemoconcentration, and ascites. Together with potential side effects, the potential for worsening OHSS, and the risk of pulmonary edema in patients with diminished cardiac reserve, this intervention cannot be recommended (12).

c. Dopamine Agonists. Evidence exists for a dopaminergic component in the control of LH release in PCOS patients, and pretreatment with the dopamine agonist cabergoline before OI reduces ovarian response to FSH, making this a potential primary OHSS prevention measure in this population. Cabergoline also acts at the VEGF receptor implicated in vascular hyperpermeability during OHSS, and studies have suggested a role for cabergoline in secondary prevention after ovarian stimulation (13).

d. Glucocorticoids and their synthetic derivatives have an inhibitory effect on the VEGF gene expression in vascular smooth muscle cells. By inhibiting vasodilation and preventing increases in vascular permeability, these agents can dampen the inflammatory response and prevent edema formation, thus offering a potential therapeutic intervention in the case of early signs of developing OHSS (14).

7. Nonrecommended Strategies

a. Follicular Aspiration.

b. Aromatase Inhibitors. The aromatase enzyme catalyzes the rate-limiting step in the production of estrogen. Aromatase inhibitors may therefore help to reduce excessive E2 synthesis during ovarian stimulation and thereby reduce the risk of OHSS (15).

Treatment and ambulatory management

Medical units with an activity which may generate OHSS need to have management protocols including both initial conduct and inpatient management. The doctors involved and gynecology and emergency units should have easy access to them. Mild forms of OHSS and many of the moderate forms may be treated ambulatory.

Paracetamol and opiates (codeine) may be used for analgesia. AINS is not recommended.

Water hydration recommended is the one dictated by thirst, and not exceeding liquids.

Intense physical efforts and sexual contact should be avoided to prevent injury/ torsion of hyperstimulated ovaries.

Luteal support with progesterone needs to be continued but hCG support is not recommended.

The patient's evaluation involves physical examination (including measurement of daily weight, body mass and abdominal girth) and pelvic ultrasonography to assess the dimension of ovaries and presence of ascites. Laboratory samples useful in assessing the severity of the syndrome are Hb, Ht, serum creatinine, ionogram and liver function tests. Their dynamic follow-up may provide data on the evolution of the disease.

A 2-3 day reevaluation is enough. However, an emergency evaluation is required if the patient complains about more severe pain, abdominal distension, dyspnea and diminution of diuresis. If pregnancy occurs, prolonged monitoring is necessary.

Inpatient management

Hospitalization is recommended in the case of severe OHSS. Patients are to be monitored until symptomatology is resolved.

Patients with severe OHSS need to be admitted to hospital, along with patients with moderate OHSS in which oral medication cannot manage pain and nausea. Moreover, inpatient management needs to be considered in all cases that cannot be rightly monitored in ambulatory until action is taken to deal with the medical condition.

The management of OHSS patients has to be multidisciplinary in the case of patients with critical or severe manifestations of OHSS that present hemoconcentration or persistent dehydration. Signs of critical OHSS require inpatient management in Intensive Care Units.

An experienced doctor in OHSS management will coordinate patient care supplying information to the personnel less familiar with this pathology.

Symptomatic treatment

Analgesia will be ensured by paracetamol, and oral/ parenteral opiates, if necessary. AINS are not recommended as they could compromise liver function in severe OHSS.

Antiemetics will be used in the event of pregnancy (prochlorperazine, metoclopramide, cyclizine).

Monitoring hospitalized OHSS patients

Daily monitoring is required, even more frequent in critical forms.

Daily monitoring of hospitalized OHSS patients

Evaluation Measurements

Anamnesis and clinical examination	Pain Dyspnea Hydration Weight Cardiovascular system Pulse, TA Abdominal girth, distension, ascites Hydric balance
Investigations	Complete hemogram Hemoglobin, hematocrit, white globules Urea, ionogram Liver function tests Coagulation tests Pelvic ultrasonography (ascites, dimension of ovaries) Thoracic Rx or ultrasonography (in the presence of difficulty in breathing) ECG and echocardiography (if pericardial effusions are suspected)

Hydric balance management

The most physiological approach is that the volume of liquids drunk needs to be dictated by the sensation of thirst.

Patients with severe OHSS in which oliguria and hemoconcentration persist, despite the initial treatment of volemic expansion with macromolecular solutions may require invasive monitoring; the decision will be made according to the recommendations of the intensive care specialist.

Diuretics should be avoided as they deepen intravascular volume depletion. They may be used in careful hemodynamic monitoring if oliguria persists, despite of a correct volemic expansion and a normal intra-abdominal pressure.

Conduct on ascites and other serum effusions

Paracentesis should be considered in patients with significant discomfort due to abdominal distension or those in which oliguria persists despite adequate volemic expansion. Paracentesis will be conducted under ultrasonography to avoid accidental puncture of vascularised ovaries separated from corpus luteum cysts. In patients that had a large quantity of ascites evacuated, the need for volemic compensation with macromolecular solutions requires evaluation.

Thromboembolic disease prophylaxis

Trombophilia screening is not a routine check in patients with assisted reproduction but it can be useful in cases with a history of the disease or a family history of thrombosis.

Thromboprophylaxis may be administered in all patient hospitalized with OHSS. Prophylaxis will be continued at least until discharge or more, according to the patient's risk factors.

Any unusual neurological symptomatology occurred after ovary stimulation will be a sign to suspect a thrombotic episode with atypical localization requiring a speciality neurological exam for clarification.

Surgical treatment – is used in patients with ovarian torsion or concurrent pathology that requires surgical treatment which will be performed by an experienced surgeon after rigorous evaluation.

OHSS and pregnancy

Patients should be assured that an eventual pregnancy obtained may evolve normally despite OHSS and that there are no proofs on an increased risk for any congenital malformations.

Psychological problems

For the couples that already had to cope with infertility stress, OHSS as a treatment complication is an additional challenge that requires further counselling. The couple will be explained the generally favourable evolution of the syndrome. An optimist attitude will be adopted during treatment.

Conclusions

OHSS is the most severe complication of ovulation induction and IVF with vital risk in the most severe cases (16). Optimal conduct has been largely debated on, particular emphasis being given to risk acknowledgement before beginning of the simulation sequence for IVF (17). The exact etiology remains unknown. As pregnancy can aggravate OHSS, embryo transfer is sometimes deliberately postponed, and embryos are cryopreserved until the clinical condition ameliorates.

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