

Ovarian hyperstimulation syndrome

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Received: 01.06.11
Review completed: 01.06.11
Accepted: 04.06.11

ABSTRACT

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of assisted reproduction technology. The syndrome is characterized by cystic enlargement of the ovaries and a fluid shift from the intravascular to the third space due to increased capillary permeability and ovarian neoangiogenesis. Its occurrence is dependent on the administration of human chorionic gonadotrophin (hCG). β -hCG and its analogs, estrogen, estradiol, prolactin, histamine and prostaglandins have all been implicated in OHSS but now it is increasingly better understood that the vasoactive substances such as interleukins, tumor necrosis factor- α , endothelin-1, and vascular endothelial growth factor (VEGF) secreted by the ovaries have been implicated in increasing vascular permeability. Enlargement of the ovaries causes abdominal pain, nausea and vomiting. Leakage of fluid from follicles, increased capillary permeability leading to third spacing (due to the release of vasoactive substances), or frank rupture of follicles can all cause ascites. Due to leakage of fluid through the impaired blood vessels both within and outside the ovary there is massive fluid-shift from the intra-vesicular bed to the third compartment results in intravascular hypovolemia with concomitant development of edema, ascites, hydrothorax and/or hydropericardium. Low-dose gonadotrophin protocols have been implemented to reduce the risks of fertility treatment in polycystic ovary syndrome patients. Prophylactic albumin administration may interrupt the development of OHSS by increasing the plasma oncotic pressure and binding mediators of ovarian origin. OHSS is significantly lower in an antagonist protocol than in an agonist protocol. Cabergoline inhibits partially the VEGF receptor 2 phosphorylation levels and associated vascular permeability without affecting luteal angiogenesis reduces the 'early' (within the first 9 days after hCG) onset of OHSS. To prevent thrombosis, subcutaneous heparin 5000-7500 U/d is begun on the first day of admission. These patients need a hospital ward where the clinical picture is well understood and the personnel have expertise in its treatment and follow-up. Admission to an intensive care unit is necessary when critical OHSS develops.

KEY WORDS: Human chorionic gonadotrophin, ovarian hyperstimulation, intravascular depletion

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of assisted reproduction technology. The syndrome is characterized by cystic enlargement of the ovaries and a fluid shift from the intravascular to the third space due to increased capillary permeability and ovarian neoangiogenesis. Its occurrence is dependent on the administration of human chorionic gonadotrophin (hCG). OHSS is extremely rare without hCG administration. Its impact on the general health of the patient can be very deleterious and fatal cases have occasionally been reported. The relationship between hCG and OHSS is thought to be mediated via the production of the angiogenic molecule VEGF. The incidence of moderate OHSS is estimated to be between

3 and 6%, while the severe form may occur in 0.1-3% of all cycles. OHSS has been recognized in two forms: The early form of OHSS, (within days after the ovulation triggering injection of hCG) although elicited by hCG, is related to an exaggerated ovarian response to gonadotrophin stimulation, whereas the late form (10 days after hCG)^[1] is mainly related to the secretion of placental hCG. Those cases which constitute an early form followed by pregnancy are serious and long lasting.^[2]

PATHOPHYSIOLOGY

The pathophysiology of OHSS is unknown, but the process is related to increased vascular permeability in the region surrounding the

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10.4103/0974-1208.86080

ovaries and their vasculature.^[3] The crux is an equilibrium between proangiogenic and antiangiogenic factors present in follicular fluid. β -hCG and its analogs, estrogen, estradiol, prolactin, histamine and prostaglandins have all been implicated in OHSS but now it is increasingly better understood that the vasoactive substances such as interleukins, tumor necrosis factor (TNF)- α , endothelin-1 and VEGF secreted by the ovaries have been implicated in increasing vascular permeability.^[4]

PREDICTING OVARIAN HYPERSTIMULATION SYNDROME

Primary risk factors

Existing factors likely to amplify the response to ovarian stimulation include young age, a history of elevated response to gonadotrophins, previous OHSS, polycystic ovary syndrome (PCOS).^[5]

Secondary risk factors

A number of ovarian response parameters have been evaluated for their ability to predict the development of OHSS,^[6] including absolute levels or rate of increase of serum E2, follicular size and number, and number of oocytes collected. None of these measures have been shown to be independently predictive of OHSS.

CLINICAL FEATURES

Abdominal pain, nausea and vomiting

Enlargement of the ovaries causes abdominal pain, nausea and vomiting. The enlargement is sometimes as much as 25 cm. Another consequence is discomfort resulting from increased intra-abdominal pressure due to ascites.^[7]

Ascites and tense distention

Leakage of fluid from follicles, increased capillary permeability leading to third spacing (due to the release of vasoactive substances), or frank rupture of follicles can all cause ascites.^[7]

Localized or generalized peritonitis

Localized or generalized peritonitis is caused by peritoneal irritation secondary to blood from ruptured cysts, protein rich fluid, and inflammatory mediators.

Acute abdominal pain

It may be due to ovarian torsion, intraperitoneal hemorrhage or rupture of cysts.

Hypotension and/or hypovolemia

Due to leakage of fluid through the impaired blood vessels both within and outside the ovary there is massive fluid-shift from the intravesicular bed to the third compartment results in intravascular hypovolemia with concomitant

development of edema, ascites, hydrothorax and/or hydropericardium.^[8]

Dyspnea

Pulmonary function may be compromised as enlarged ovaries and ascites restrict diaphragmatic movement. Other possible causes of dyspnea are the relatively rare manifestations of OHSS, such as pleural effusion, pulmonary edema, atelectasis, pulmonary embolism, acute respiratory distress syndrome (ARDS) and pericardial effusion.^[9]

Hypercoagulable state

It is likely due to hemoconcentration and hypovolemia resulting from fluid to third space shift. Patients have an increased risk of developing deep venous thromboses and pulmonary embolism. Both venous (65.7%) and arterial localizations have been described and 83% of these occur in the veins of neck, arm or head (60%). Thrombosis also occurs in arteries and veins of the lower body.^[10] Pulmonary embolism occurs in 4-12%.^[11]

Electrolyte imbalance

Extravasation of fluid and resultant renal dysfunction resulting from decreased perfusion leads to oliguria. Increased reabsorption of sodium and water which occurs in the proximal tubule, leads to low urinary sodium excretion. The exchange of hydrogen and potassium for sodium in the distal tubule is reduced causing, hyperkalemia and a tendency to develop acidosis.^[12]

Acute renal failure

The hypovolemia of OHSS leads to hemoconcentration and creates a hypercoagulable state. Microthrombi tubules lead to decreased renal perfusion. Acute renal failure may result.

Classification

To understand OHSS and its management, one must first be aware of its classifications of severity. Grades of OHSS are as follows^[2]:

Mild OHSS

- Grade 1 - Abdominal distention and discomfort
- Grade 2 - Grade 1 disease plus nausea, vomiting and/or diarrhea plus ovarian enlargement from 5 to 12 cm

Moderate OHSS

- Grade 3 - Features of mild OHSS plus ultrasonographic evidence of ascites

Severe OHSS

- Grade 4 - Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax and breathing difficulties
- Grade 5 - All of the above plus a change in the blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities and diminished renal perfusion and function

PREVENTIVE MEASURES: PRIMARY PREVENTION

Reducing exposure to gonadotrophins

Low-dose gonadotrophin protocols have been implemented to reduce the risks of fertility treatment in PCOS patients. The aim of these protocols is to stimulate the ovaries without exceeding the follicle stimulating hormone (FSH) threshold, thus facilitating the development of a few dominant follicle rather than multiple follicles.

a) Cycle cancellation: In ovulation induction, withholding hCG prevents the early form of OHSS. Avoiding hCG prevents both the early and late form. This decision is often psychologically difficult, especially in *in vitro* fertilization (IVF), because it may entail the loss of considerable financial efforts in countries with no reimbursement. In very severe cases with poor follow-up possibilities, however, it may be the only method to avoid disaster.

b) Coasting (“Soft landing”): When high risk patients rapidly have high (>3000 pg/mL) serum estradiol levels with a large number (>20 per ovary) of follicles during stimulation, gonadotrophin administration can be decreased or stopped while continuing GnRH agonist administration. This allows larger follicles to continue to grow, while intermediary and small follicles enter atresia.^[13] Regarding the duration of coasting, withholding gonadotrophin administration for, at most, 3 days may decrease the risk of OHSS without modifying the pregnancy rate. However, withholding for four or more days is associated with a lower implantation rate, probably because of the effect on endometrial receptivity.^[14]

c) Modification of the ovulation triggering agent: Although good data are lacking, it is not impossible that doses of hCG lower than 5000 or 10,000 IU usually utilized may cause sufficient oocyte maturation while reducing the risk for OHSS. Replacement of hCG by exogenous or endogenous LH as ovulation trigger could have a considerable impact on the incidence of early form of OHSS. An endogenous LH surge can be provoked by the administration of a short-acting GnRH agonist. This is only possible in cycles without pituitary desensitization by a GnRH agonist. Combination with an antagonist remains a possibility.

Administration of macromolecules

i) Albumin administration

Prophylactic albumin administration may interrupt the development of OHSS by increasing the plasma oncotic pressure and binding mediators of ovarian origin. This effect could be counteracted by increased capillary permeability. Prospective randomized trials and one retrospective study with a control group show 39 cases of OHSS in 468 treated risk cycles (8.3%) vs 89 OHSS cases in 611 untreated risk

cycles (14.6%). The Cochrane review also shows that intravenous albumin administration at the time of oocyte collection has a preventive effect in cycles with a severe risk for OHSS.^[15] However, a recent prospective randomized trial of 488 cases in each arm of the study seems, to prove the inefficiency of human albumin.^[16] Albumin administration also has side effects like viral transmission, nausea, vomiting, and febrile and allergic reactions. Besides albumin is expensive too.

ii) Hydroxyethyl starch solution

Because of the risk of viral transmission with human albumin, some authors have tested the effect of this safer nonbiological substitute with comparable physiological properties. Three studies suggest a useful effect but the cohorts are too small to draw definite conclusions^[10] Further clinical research seems warranted.

d) Cryopreservation of all embryos: Instead of canceling the cycle, it is also possible to administer hCG to retrieve the oocytes and to freeze all embryos. This does not exclude the risk for the early form of OHSS. The removal of a large number of granulosa cells from the follicles probably also decreases the risk. The Cochrane Review concludes that the present evidence is insufficient to consider this approach as the standard of treatment.^[17]

GnRH antagonist protocols

GnRH agonists (GnRHa) are associated with an increase in the incidence of OHSS.^[18] One possible explanation is that pretreatment blockade of endogenous gonadotrophins necessitates an increased dose of exogenous FSH for adequate ovarian stimulation. In contrast to the extended pretreatment phase with GnRHa, the rapid competitive blockade of pituitary GnRH receptors by antagonists can be given usually at a follicle size of 12-14 mm. 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. A Cochrane review^[19] demonstrated that the incidence of severe OHSS was significantly lower in an antagonist protocol than in an agonist protocol.^[19]

Avoidance of hCG for luteal phase support

The use of hCG in luteal phase support (LPS) has been shown to confer significant benefits over placebo in agonist suppressed cycles; however, hCG is also known to increase the risk of OHSS. The use of Progestogens (P) appears to halve this risk, while demonstrating similar improvements in pregnancy and miscarriage rates.^[20]

In vitro maturation

In patients at high risk of developing OHSS, *in vitro* maturation

(IVM) of oocytes offers great potential for OHSS prevention. Despite safety advantages, IVM is not yet widely used owing to a reduced live-birth rate in comparison with standard IVF. However, clinical outcomes have improved in recent years, and pregnancy rates of between 20% and 54% have been reported.^[21]

Insulin-sensitizing agents

Insulin resistance with compensatory hyperinsulinemia is thought to play a pathophysiological role in the ovarian dysfunction^[22] and hyperandrogenism^[23] associated with PCOS. Metformin is a cheap, effective insulin-sensitizing agent with a good safety profile that has been widely used in ovulation induction (OI) as monotherapy or in combination with other OI drugs and also as pretreatment before intrauterine insemination (IUI) or *in-vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) in women with PCOS. A 2006 meta-analysis of eight randomized controlled trials of metformin co-administration during gonadotrophin-stimulated OI or IVF in women with PCOS found little benefit of metformin treatment in terms of improved ovulation or clinical outcome in this population but did note a significant positive effect on the incidence of OHSS.^[24]

Dopamine agonist administration

Cabergoline inhibits partially the VEGF receptor 2 phosphorylation levels and associated vascular permeability without affecting luteal angiogenesis reduces the 'early' (within the first 9 days after hCG) onset of OHSS.^[25] Even using cabergoline, the OHSS incidence may be as high as 10.8%^[25]

Nonsteroidal anti-inflammatory administration

A large RCT demonstrated that low-dose aspirin was associated with reduction in the OHSS incidence (0.25% vs.8.4%) in a high-risk group with similar pregnancy rates.^[26] Meloxicam was capable of reducing the OHSS associated ovarian weight and expression of VEGF in an animal model.^[27]

Treatment based on degree of hyperstimulation

Mild hyperstimulation

Treatment for OHSS is supportive, as needed. Mild ovarian hyperstimulation can develop into moderate or severe disease, especially if conception ensues. Therefore, women with mild disease should be observed for enlarging abdominal girth, acute weight gain, and abdominal discomfort on an ambulatory basis for at least 2 weeks or until menstrual bleeding occurs.

Moderate hyperstimulation

Treatment of moderate OHSS consists of observation, bed rest, provision of adequate fluids and sonographic monitoring of the size of cysts. Serum electrolyte

concentrations, hematocrits and creatinine levels should also be evaluated.

Intake or output less than 1000 mL/d or a discrepancy in fluid balance greater than 1000 mL/d is a cause for concern.^[28] The beginning of the resolution of OHSS is apparent when the cysts shrink, as seen on two consecutive ultrasonographic examinations, and when clinical symptoms recede. In contrast, early detection of progression to the severe form of the syndrome is marked by continuous weight gain (>2 lb/d), increased severity of existing symptoms, or appearance of new symptoms (eg, vomiting, diarrhea or dyspnea).^[29]

Severe hyperstimulation

One should transfer the patient to a different center if no one who is experienced in managing severe OHSS is available at the present location.

Severe OHSS is not common, but it is dangerous. Severe and critical forms of OHSS are potentially lethal disorders, and history taking and physical examination are paramount at the time of admission. In most clinical situations, patients require bed rest. Daily physical examination should consist of measuring the patient's weight and abdominal girth. Fluid balance must be assessed every 4 hours.

Medical treatment of severe hyperstimulation is directed at maintaining intravascular blood volume. Simultaneous goals are correcting the disturbed fluid and electrolyte balance, relieving secondary complications of ascites and hydrothorax and preventing thromboembolic phenomena.

The main interventions are fluid management and correction of hypovolemia. These measures consist of initial fast intravenous administration of normal saline. Dextrose 5% in normal saline or normal saline is infused at a rate of 125-150 mL/h with 4-hour tabulations of urine production. If urine production is restored or improved, a maintenance protocol is started. The patient should be closely monitored for clinical signs of overhydration. If urine output is unsatisfactory, hyperosmolar intravenous therapy is indicated with an infusion of 200 mL of 25% human albumin. The use of diuretics in patients with low urine production and hypovolemia is counterproductive and dangerous.^[29]

To prevent thrombosis, subcutaneous heparin 5000-7500 U/d is begun on the first day of admission. It is stopped after adequate mobilization is achieved.

To manage ascites, ultrasonographic-guided paracentesis is indicated if the patient has severe discomfort or pain or if she has pulmonary or renal compromise.

Critical hyperstimulation

Critical OHSS may include renal failure, hepatic damage,

thromboembolic phenomena, ARDS and multiorgan failure.^[30] Its management and treatment requires intensive care in a critical care unit.

Resolution

After several days, third-space fluid begins to re-enter the intravascular space, hemoconcentration reverses and natural diuresis ensues. Intravenous fluids may be tapered as the patient's oral intake increases. Complete resolution typically takes 10-14 days from the onset of initial symptoms.

Surgical care

OHSS is a self-limiting disease. Therefore, treatment should be conservative and directed at symptoms. Medical therapy suffices for most patients. Women with severe symptoms often require intensive medical care. Surgery is necessary only in extreme cases, such as in the case of a ruptured cyst, ovarian torsion or internal hemorrhage.

Medication

Anticoagulant

These agents inhibit key factors involved in thrombogenesis.

Heparin

Augments activity of antithrombin III and prevents conversion of fibrinogen to fibrin and does not actively lyse but can inhibit further thrombogenesis. It prevents reaccumulation of clot after spontaneous fibrinolysis.

Adult

5000 – 7500 units subcutaneously (SC) twice a day.

Prognosis

The prognosis is excellent if OHSS is mild or moderate. In severe OHSS, the prognosis is optimistic if good treatment is given.

RECOMMENDATIONS

- If gonadotrophin stimulation for ovulation induction is unavoidable, one should use "friendly" stimulation regimens aiming at (SOFT) single ovarian follicle viz., low-dose step-up regimen, step-down regimen, use of antagonists, and utilization of blood and sonographic control of ovarian response.
- hCG as an ovulation trigger should be replaced by safer methods like rLH and endogenous GnRH-surge by an agonist.
- In IVF/ICSI the principle of obtaining as many oocytes as possible should be replaced by softer stimulation regimens aiming at fewer oocytes of good quality.
- In risk situations the patient should be informed about possibilities such as cancelling, coasting and freezing

embryos for subsequent replacement.

- When signs of OHSS occur, the patient must be adequately informed and hospitalization should be proposed at the slightest deterioration.
- These patients need a hospital ward where the clinical picture is well understood and the personnel have expertise in its treatment and follow-up. Admission to an intensive care unit is necessary when critical OHSS develops.
- Registration of all cases of severe OHSS and their outcome should become compulsory in all ART programs and also after every ovulation induction.

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How to cite this article: Kumar P, Sait SF, Sharma A, Kumar M. Ovarian hyperstimulation syndrome. *J Hum Reprod Sci* 2011;4:70-5.

Source of Support: Nil, **Conflict of Interest:** None declared.

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