Ovarian hyperstimulation syndrome: pathophysiology, prevention and management

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Abstract
Ovarian hyperstimulation syndrome (OHSS) is the most important short-term complication of fertility treatment involving ovarian stimulation. The pathophysiology is mediated by vasoactive mediators released by hyperstimulated ovaries under the influence of human chorionic gonadotrophin (hCG) and is characterised by ovarian enlargement, increased vascular permeability, intravascular dehydration and their sequelae. A number of pre-treatment patient characteristics and ovarian response parameters are used in practice to predict the risk of OHSS but current methods have a poor predictive value. In women with risk factors, a lower dose of gonadotrophin, the use of gonadotrophin-releasing hormone antagonist and metformin (for women with polycystic ovaries) may reduce the risk of OHSS. Overstimulated cycles may be managed by withholding gonadotrophin until the ovarian response settles to safe levels, or by cryopreservation of all embryos, avoiding luteal hCG. Cancellation of the treatment cycle (avoiding hCG completely) prevents OHSS but is often not acceptable to patients. Cabergoline shows promise as a preventative method, specifically targeting the increased vascular permeability seen in OHSS. All patients undergoing ovarian stimulation should be counselled about the symptoms of OHSS and advised to report them. Mild cases may be managed as outpatients, while severe cases need hospital admission for close monitoring of fluid balance, analgesia and, in some cases, paracentesis. Thromboprophylaxis should be provided for all inpatients with OHSS.

Keywords in-vitro fertilisation; ovarian hyperstimulation syndrome; polycystic ovarian syndrome; vascular endothelial growth factor

Introduction
Ovarian hyperstimulation syndrome (OHSS) is perhaps the most important short-term complication fertility treatment involving ovarian stimulation. It is an iatrogenic condition with the potential to cause severe morbidity and, in rare cases, may even lead to death. This review focuses on the clinical presentation of OHSS, measures to prevent it and aspects of managing OHSS according to its severity.

OHSS has a characteristic pathophysiology of ovarian enlargement, increased vascular permeability and their sequelae. The increase in vascular permeability is mediated by ovary-derived vasoactive substances and leads to the loss of fluid into the third space, causing effusions and intravascular dehydration. A number of inflammatory mediators are activated in the course of severe OHSS, but a pivotal role has been ascribed to vascular endothelial growth factor (VEGF) derived from ovarian granulosa cells (Figure 1). VEGF is a member of the heparin-binding protein that is a potent stimulator of vascular endothelium and appears to play an integral role in follicular growth, corpus luteum function and ovarian angiogenesis. Various studies confirm the role of VEGF in the development of OHSS and correlation has been seen in VEGF concentration in the peritoneal fluid and the development and severity of the syndrome. Peritoneal fluid from women with severe OHSS has vascular permeability-enhancing properties, which are neutralised by the addition of anti-VEGF antibodies. In-vitro studies show that granulosa cell VEGF production is stimulated by human chorionic gonadotrophin (hCG) in a time- and dose-dependent fashion. This may explain the clinically observed link with hCG exposure: cycles where pregnancy occurs or hCG is used for luteal support are more likely to be complicated by significant OHSS than cycles without exposure to endogenous or exogenous luteal hCG. The occurrence of multiple pregnancies — with higher hCG levels than singleton pregnancy — is a further risk factor for developing OHSS.

Other mediators activated in the course of the disease process include the pro-inflammatory cytokines, interleukin 6 (IL-6) and the ovarian renin–angiotensin system. Increased levels of renin and prorenin have been found in follicular fluid in women undergoing ovarian stimulation. IL-6 has been found to be significantly elevated in serum and ascitic fluid of women with OHSS. IL-6 mediates acute phase response to injury, which is characterised by leucocytosis, increased vascular permeability and increased production of acute phase proteins by the liver. All of the above may initiate or worsen the pathophysiology of OHSS. Other factors that have been implicated in OHSS are oestrogens, prostaglandins, tumour necrosis factor, histamines and prolactin. However, studies so far are inconclusive with regards to their exact role in OHSS.

Clinical features and classification
OHSS most often occurs in women undergoing assisted conception treatments that require ovarian stimulation. Rare cases of OHSS occurring spontaneously in association with pregnancy have been reported and may relate to follicle-stimulating hormone (FSH) receptor mutations. The changes predisposing to OHSS occur during the phase of ovarian stimulation with FSH but the full manifestation requires exposure to luteinising hormone (LH) or its commonly used surrogate, hCG. The timing of OHSS reflects the effects of hCG exposure at different stages of treatment, resulting, in effect, in two distinct entities with different predisposing factors and potential for severity. Early OHSS occurs within 9 days of hCG administration for final follicular maturation and reflects the effect of exogenous hCG on...
a background of excessive ovarian response to FSH. Late OHSS occurs 10 or more days after the ovulatory dose of hCG and, in the absence of luteal hCG administration, reflects the effect of endogenous hCG from early pregnancy. Late OHSS is significantly more likely to be severe than early OHSS.

The symptoms and signs of OHSS can largely be explained by the pathophysiological changes described above, and worsening pathophysiology manifests in increased clinical severity of the condition, as described in the classification of Mathur et al (Table 1). Early clinical features include abdominal distension and discomfort, probably reflecting ovarian enlargement and the beginning of fluid accumulation in the peritoneal cavity. Severe pain is not a common feature of uncomplicated OHSS and its presence should lead to a suspicion of a co-incident complication, such as ovarian torsion or ectopic pregnancy.

As the severity of the condition rises, increasing distension and discomfort and gastrointestinal symptoms occur. Clinically detectable ascites is a sign of severe OHSS. The increased vascular permeability is most marked on mesothelial surfaces close to the ovaries but as the syndrome worsens, pleural and pericardial effusions can also develop. Dyspnoea may occur as a result of abdominal distension stenting the diaphragm or pleural effusions.

Intravascular dehydration and the specific effect of cytokines such as VEGF increase the risk of thrombosis. In patients with OHSS, thrombosis commonly affects the upper body and the arterial system and may not manifest clinically until after apparent resolution of the condition. Other causes of severe morbidity in patients with OHSS are pulmonary oedema and renal dysfunction. Hepatic dysfunction is common but as a rule resolves over time. In rare cases, serious complications of OHSS have lead to the death of the patient. The reported causes of death include: acute respiratory distress syndrome (two cases); cerebral infarction (two cases); and hepatorenal failure in a patient with pre-existing hepatitis C (one case).

The incidence of OHSS in various reports varies significantly owing to ascertainment bias and the different classification schemes proposed for the condition. Controlled ovarian hyperstimulation for in-vitro fertilisation (IVF) intentionally aims to hyperstimulate the ovaries, thus mild OHSS maybe almost ‘normal’ in conventional IVF cycles. Moderate or severe OHSS has been reported in 3.1—8% of IVF cycles. A Finnish study described the incidence of OHSS following different methods of ovarian stimulation using data from the social insurance reimbursement records and hospital discharge records between 1996 and 1998. The rates of hospitalisation for OHSS following ovulation induction were 0.04% per cycle whereas following IVF it was 0.9%.

**Risk factors and prediction**

A major difficulty with measures to prevent OHSS lies in the difficulty of predicting OHSS in individual treatment cycles. A number of pre-treatment patient characteristics and ovarian response parameters have been studied in attempts to improve the ability to predict the occurrence of OHSS. Younger age, presence of polycystic ovaries (PCO) and a past history of OHSS...
all increase the risk of OHSS. This information is available prior to the start of a treatment cycle and should be taken into account when deciding the choice of treatment and stimulation regimen for the cycle. Basal serum anti-Mullerian hormone level is an indicator of ovarian reserve and has been suggested as a measure of OHSS risk, although its precise predictive value is unclear at present.

In the course of a treatment cycle, high serum oestradiol concentrations, a rapid rise in serum oestradiol, high follicle numbers and increased egg numbers have been correlated with an increased risk of developing OHSS. However, there is no clear agreement in the literature on the cut-offs used to determine increased risk. In practice, many clinics define their own levels and it is accepted that reliance on these parameters will miss several cases of OHSS, while defining as high risk several other cycles where OHSS does not develop. In a study from Belgium, it was noted that around one-third of cases of severe OHSS occurred in cycles that were not considered high risk by the use of standard parameters. This emphasises the importance of considering all cycles of ovarian stimulation with gonadotrophins as being at some risk of developing OHSS and of counselling patients adequately with regard to the symptoms of OHSS.

Prevention

Choice of treatment

The risk of OHSS can be reduced by choosing lower-risk treatments as alternatives to ovarian stimulation for treating subfertility where clinically appropriate. For instance, weight optimisation intervention in women who are obese or underweight should form first-line treatment, rather than recourse to ovarian stimulation. In women with polycystic ovarian syndrome (PCOS) who fail to ovulate on clomifene, laparoscopic ovarian diathermy provides an alternative to gonadotrophin stimulation without the risk of ovarian over-response.

Ovulation induction

In anovulatory women undergoing monofollicular ovulation induction, the use of a chronic low-dose step-up regimen carries a lower risk of overstimulation and cycle cancellation than a step-down regimen. The aim with the step-up protocol is to safely reach the FSH threshold for stimulation of ovarian activity. In one commonly used regimen, treatment is initiated with a low dose of FSH (75 IU) for 14 days. The dose is increased by 37.5 IU every 7 days if there is no ovarian response (no follicle >10 mm diameter). The dose that initiates follicular development is continued until the criteria for giving hCG are attained. In the step-down protocol, the starting dose is 150 IU, decreased by 75 IU once ovarian response is initiated. Randomised trials show a lower risk of overstimulation with the step-up as compared with the step-down protocol.

IVF regimens

Gonadotrophin-releasing hormone antagonist Ovarian stimulation regimens for IVF include gonadotrophin-releasing hormone (GnRH) analogues to prevent spontaneous LH surges, which can lead to premature ovulation and a poor cycle outcome. Commonly, the analogues used are GnRH agonists, which act by causing pituitary desensitisation due to down-regulation of GnRH receptors on gonadotrophs. While the use of GnRH agonists has been associated with an improvement in livebirth rates, the incidence of OHSS has increased, probably because the loss of an endogenous LH surge allows ovarian stimulation to proceed to a greater degree than otherwise. More recently, pure GnRH antagonists have been widely used to achieve suppression of endogenous LH without impairing pituitary sensitivity to GnRH. Regimens using GnRH antagonists yield fewer oocytes and lower oestradiol levels as compared with agonist regimens and there is evidence from meta-analysis that the risk of severe OHSS is also lower with GnRH antagonists. However, this improvement in safety needs to be balanced against an apparent reduction in pregnancy rates with antagonists compared with agonist regimens. There may be a specific role for GnRH antagonist regimens in women thought to be at high risk of OHSS, for instance due to PCOS or a previous history of OHSS.

Coasting IVF cycles where the ovarian response is judged to be excessive can be managed by stopping gonadotrophin injections while continuing pituitary suppression, a process referred to as ‘coasting’. This leads to atresia of small and intermediate-sized follicles, while larger follicles with a degree of FSH independence continue to grow. Serum oestradiol concentrations continue to rise for 24–48 hours before falling. When the oestradiol reaches a ‘safe’ level, ovulation is induced and the cycle resumed. A number of observational studies show a reduced incidence of OHSS in high-risk cycles managed by coasting, but evidence from randomised trials is lacking. The proposed mechanism for the protective effect of coasting is through a reduction in the granulosa cell production of vasoactive mediators, such as VEGF.

Coasting is a widely-used method to prevent OHSS in cycles with ovarian over-response but criteria for initiating and stopping coasting vary significantly between clinics. In one commonly used protocol, coasting is started if the number of ovarian follicles is >20, with serum oestradiol >3000 pg/ml (11,000 pmol/l). Further gonadotrophin is withheld until the oestradiol drops below 3000 pg/ml. A sharp fall in oestradiol or a concentration below 1000 pg/ml may be associated with a poor likelihood of pregnancy. Some studies indicate a detrimental effect on pregnancy rates if coasting is continued for more than 4 days. Hence, if the ovarian response has not settled to safe levels in 4 days of coasting, consideration should be given to cancellation of the treatment cycle. The oestradiol drop with coasting may be quicker if GnRH antagonist is used in place of agonist during coasting. This measure has the potential to reduce the duration of coasting and thereby mitigate any reduction in pregnancy rates from prolonged coasting. Follicle size should also be taken into account in deciding whether to use coasting in any given cycle: starting coasting before follicles reach 14–15 mm in diameter may compromise follicle development, while the presence of follicles ≥17 mm may make it preferable to proceed with hCG and consider freezing of all embryos.
Triggering oocyte maturation

Urine-derived hCG is commonly used as a very effective surrogate for LH to induce final follicular maturation but the longer half-life and more sustained luteotrophic action of hCG leads to an increased risk of OHSS. Recombinant LH has been studied as a means of inducing oocyte maturation and luteinisation with similar results in terms of number of oocytes, embryos and pregnancy rates when compared with hCG. However, a meta-analysis of two trials comparing recombinant LH with urinary hCG did not show any difference in the risk of severe OHSS. An alternative approach, using endogenous LH can be applied in cycles where GnRH antagonists have been used. In such cycles, the pre-ovulatory hCG can be replaced by a dose of GnRH agonist. The ‘flare’ effect resulting from this mimics an LH surge but carries a lower risk of inducing OHSS than hCG because of the shorter half-life of LH compared with hCG. The risk of OHSS appears to increase with increasing exposure to hCG in the luteal phase and it makes sense to use the lowest effective dose for follicular maturation. Pregnancy rates in IVF treatment appear not to be different for doses of hCG ≥5000 IU. A dose of 5000 IU hCG for final follicular maturation would, therefore, be reasonable, particularly in high-risk patients. In a recent study, OHSS incidence could be reduced in high-risk patients by reducing the dosage of hCG to 2500 IU. The incidence of OHSS with the use of recombinant hCG does not differ from that with urinary hCG.

Metformin

In women with PCOS, metformin co-administration from the time of down-regulation has been reported to reduce the risk of OHSS. The mechanism of action may be through improved insulin sensitivity and reduction of hyperinsulinaemia. Insulin is known to stimulate VEGF protein expression and secretion. A systematic review using data from five randomised controlled trials showed a significant reduction in the incidence of OHSS in women with PCOS undergoing IVF with the use of metformin (12/216 vs 44/210; odds ratio (OR) 0.21, 95% confidence interval (CI) = 0.11–0.41).

Intravenous albumin around the time of oocyte collection

Administration of intravenous albumin around the time of oocyte retrieval has been proposed as a measure to prevent OHSS, possibly by binding to vasoactive mediators. A Cochrane meta-analysis of five controlled trials with a total of 378 subjects showed a significant reduction in the incidence of severe OHSS in women receiving albumin (OR 0.28, 95% CI 0.11–0.73). However, a subsequent randomised controlled single-centre trial on 976 women who had 20 or more oocytes collected showed no protective effect of 40 g intravenous albumin administered immediately after oocyte retrieval. The incidence of moderate and severe OHSS or severe OHSS alone did not differ significantly between the two groups (7.1% moderate or severe OHSS in the albumin group vs 6.7% in the control group). Hence, the current evidence does not support a benefit for albumin administered around the time of oocyte retrieval in preventing OHSS. Albumin is a blood-derived product with a significant cost and potential for side effects. Given these factors, it appears that the use of albumin for the purpose of prevention of OHSS is not justified.

The synthetic plasma volume expander hydroxyethyl starch (HES) has shown promise as a preventative measure for OHSS in high-risk cycles. However, the small numbers of subjects in the trials and the lack of effect of albumin suggest that further studies are required before HES is recommended for this purpose.

Blastocyst transfer and elective cryopreservation

Adoption of strategies such as blastocyst transfer may permit more time for evaluation and decision regarding OHSS. Cryopreservation of all embryos avoids exposure to endogenous hCG of pregnancy thereby avoiding the possibility of late OHSS. Early OHSS can of course still occur.

Single embryo transfer

The increased risk of OHSS in multiple pregnancies encourages adopting a policy of single embryo transfer in younger, more fertile women, who are at increased risk of OHSS.

Luteal phase support

Luteal support is required for early pregnancy maintenance in cycles where pituitary gonadotrophin production has been therapeutically suppressed. Progesterone is equally effective as hCG for luteal support with reduced OHSS risk.

Other agents

Dopamine agonist was initially found to inhibit VEGF-induced vascular permeability and animal model studies showed that low dose cabergoline reversed vascular permeability without affecting luteal angiogenesis. A pilot study on patients at risk of developing OHSS, who were given low dose cabergoline (0.5 mg/day) from the day of egg collection, reported a reduction in ascites, haemoconcentration and vascular permeability. However, further studies with larger numbers are required before such therapeutic interventions can be put to routine clinical practice.

Cycle cancellation

Cycle cancellation remains the most effective prevention of OHSS. However, due to the emotional and financial costs, there is a general reluctance on the part of patients to let the ovarian response go to waste. Patients need to be counselled with regard to their individual risk of developing OHSS, with its potential morbidity.

Management

All patients undergoing ovarian stimulation with gonadotrophins should receive information about the warning signs of OHSS and should be asked to report these. They should also have access to an emergency contact out of hours. In addition, all units that may potentially see patients with OHSS should put in place protocols and arrangements for access to specialised expertise in an emergency.

The management of OHSS depends on the severity of the condition in the individual case, although it is important to remember that severity may evolve over time. Patients presenting with abdominal distension or other suspicious symptoms following ovarian stimulation should, therefore, be assessed to determine if they have OHSS and to assess its severity (Table 1).

Most patients with mild OHSS can be managed on an outpatient basis, with symptomatic relief, monitoring, counselling...
and support. Resolution of symptoms usually occurs in 7–10 days and certainly by the time of the withdrawal bleed if treatment has not resulted in pregnancy. Where pregnancy occurs, the course may be more prolonged and there is a risk of increased severity due to endogenous hCG stimulation. Outpatient monitoring of mild OHSS is designed to detect any worsening of the condition. Patients should, therefore, be asked for, and asked to report, symptoms such as increasing abdominal distension and pain, vomiting, shortness of breath, a subjective impression of reduced urine output and weight gain. In the absence of worsening symptoms, a telephone follow-up every 2 or 3 days is adequate till the symptoms settle.

Patients of severe OHSS are best managed as inpatients, until their condition begins to improve. In addition, patients who have difficulty managing their pain with simple analgesia, or who have severe nausea and/or vomiting that prevents them from eating or drinking may also benefit from admission.

**Analgesia**

Analgesia is provided by paracetamol and codeine. Injectable opiates may be used for more severe pain. However, the occurrence of severe pain should prompt a search for a complication or co-incident problem such as ovarian torsion, cyst rupture or ectopic pregnancy. Non-steroidal anti-inflammatory medications should be avoided as they may compromise renal function.

**Fluid balance**

There is insufficient evidence in the literature to determine the optimum method of achieving fluid balance in women with severe OHSS. Intravenous fluid therapy in the presence of increased capillary permeability carries a risk of increasing ascites and effusions. Oral fluid intake, guided by the patients thirst, allows a more physiological approach to fluid replacement and is the preferred method of fluid management. Patients should be encouraged to drink to thirst rather than to an arbitrary volume. Pain relief and anti-emetic therapy may be required to help the patient achieve oral hydration. Intravenous fluid has a role where the patient is unable to drink, or for initial hydration when the patient presents with severe haemoconcentration. Initial replacement is with crystalloids such as normal saline. If elevated haematocrit and poor urine output persist despite crystalloid infusion, colloids such as human albumin or HES may have a role.

Strict input/output recording, daily weight and abdominal girth recording are important parts of the inpatient management of OHSS. Increasing weight and girth with output lagging behind intake are signs of worsening fluid retention. Conversely, an increased urine output and negative fluid balance is an early sign of recovery from OHSS.

Electrolyte imbalances affect around 50% of patients with severe OHSS. Characteristic problems include hyponatraemia and hyperkalaemia, which usually respond to correction of dehydration. Diuretics should generally be avoided as they may worsen hypovolaemia, although there may be a role for diuretic use if urine output remains poor despite adequate fluid replacement (as judged by invasive haemodynamic monitoring). Low-dose dopamine infusion has been used in such situations. Often these patients will be seriously ill and input should be sought from intensive care and/or renal colleagues.

**Thromboprophylaxis**

The reported incidence of thrombosis with OHSS ranges from 0.7–10%. Women with OHSS are at an increased risk of thrombosis, probably secondary to high oestrogen levels, dehydration, specific cytokine effect and the effects of ascites and enlarged ovaries on venous return. Thromboembolism is a life-threatening complication of severe OHSS and prophylactic measures are warranted despite the lack of clinical studies on the value of thromboprophylaxis. Signs and symptoms of thromboembolism demand prompt additional diagnostic measures (arterial blood gas measurements, ventilation/perfusion scan) and therapeutic anticoagulation when the diagnosis is confirmed or strongly suspected. Thrombosis in women with OHSS frequently affects upper body sites and the arterial system.

Thromboprophylaxis in the form of venous support stockings and prophylactic low molecular weight heparin should be used in all women admitted with OHSS, cases of severe OHSS and in individuals with pre-existing risk factors for thrombosis. It is unclear on how long to continue thromboprophylaxis. In women who conceive, there are several reports of thrombosis following apparent improvement of OHSS up to the 13th week of pregnancy. Current Royal College of Obstetricians and Gynaecologists guidelines recommend continuing prophylactic measures until the end of the first trimester of pregnancy. However, patients should be individualised and counselled depending on their risk factors and in some cases it may be reasonable to continue thromboprophylaxis for the duration of pregnancy. In women who do not conceive, thromboprophylaxis is discontinued at the time of the withdrawal bleed.

**Management of ascites/effusion**

Paracentesis of ascitic fluid is indicated in patients with severe discomfort or respiratory embarrassment due to abdominal distension and in those who remain oliguric despite adequate rehydration. Paracentesis should be carried out under ultrasound guidance to avoid injury to the enlarged ovaries. Hydrothorax often resolves when the ascites are drained but, on occasion, pleural effusions causing respiratory compromise may need tapping independently. There is some evidence that paracentesis shortens the course of the disease and reduces the number of days in hospital. Hence, it should also be considered for patients with a prolonged course of OHSS.

**Surgery**

Surgical intervention is not commonly indicated in patients with OHSS. Indications for surgery include ovarian torsion and ectopic pregnancy. Diagnosis or viability of twisted ovary can sometimes be assessed preoperatively by colour Doppler, which may give information about the blood flow to the ovary. Hyperstimulated ovaries are very friable and vascular; hence any surgery should be undertaken by an experienced surgeon.

**Intensive care**

Intensive care may be required in patients with critical OHSS, especially in the presence of complications such as adult respiratory distress syndrome, thromboembolic phenomena and renal failure.
Conclusion

OHSS is an iatrogenic condition affecting women undergoing ovarian stimulation for fertility treatment. None of the available methods guarantee complete avoidance of OHSS and there is little agreement on criteria for applying various preventative measures. Patients receiving ovarian stimulation should be counselled about the symptoms of OHSS and asked to report these. The management of mild OHSS is on an outpatient basis with monitoring and symptomatic relief. Women with severe OHSS and those in whom nausea and pain are significant should be admitted. Inpatient management of OHSS involves strict input/output monitoring, attention to fluid balance, analgesia and thromboprophylaxis. Oral fluid intake should be preferred to intravenous fluids. Paracentesis of ascites and effusions may occasionally be required.

Practice points

- OHSS is a potentially serious complication of ovarian stimulation, risk factors for which include young age, PCO and previous history of OHSS
- Measures to reduce the risk of OHSS include using GnRH antagonist instead of agonist, metformin in women with PCOS undergoing IVF and avoiding luteal support with hCG. Cycles with an excessive ovarian response may be managed by coasting or cryopreservation of all embryos or cabergoline to selectively counter increased vascular permeability
- Management of OHSS is essentially supportive, awaiting resolution, which may take longer if pregnancy occurs. Mild cases can be managed in an outpatient setting with regular monitoring
- Fluid balance, analgesia and thromboprophylaxis are important in inpatient management. Paracentesis may be required for severe distress due to abdominal distension or oliguria despite rehydration. Women with critical OHSS require multidisciplinary input and sometimes intensive care

FURTHER READING


