Ovarian hyperstimulation syndrome

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Key content
- Ovarian hyperstimulation syndrome (OHSS) is characterised by ovarian enlargement, increased vascular permeability and fluid shift.
- Patients with polycystic ovary syndrome (PCOS) or previous history of OHSS are at increased risk.
- A reduced risk of OHSS is seen with use of gonadotrophin-releasing hormone antagonist instead of agonist, coasting of overstimulated cycles, metformin in women with PCOS and dopamine agonists.
- OHSS is likely to be more severe and prolonged in cycles where conception occurs.
- Patients of severe OHSS require close monitoring of fluid balance, thromboprophylaxis and attention to effusions.

Learning objectives
- To identify patients and cycles at high risk of OHSS and apply preventative measures.
- To assess and classify the severity of OHSS.
- To manage cases of severe OHSS.

Ethical issues
- How do we counsel patients about the risk of an uncommon serious complication of fertility treatment in the face of an overwhelming desire to have a family?
- Should the risk of OHSS be considered a reason to restrict funding for assisted conception treatment?

Keywords: coasting / in vitro fertilisation / ovarian hyperstimulation syndrome / polycystic ovary syndrome


Introduction

Assisted conception is an integral part of mainstream medical practice, with over 44 000 cycles of in vitro fertilisation (IVF) carried out annually in the UK, leading to over 10 000 births.1 Ovarian stimulation, designed to increase the number of eggs and embryos available, is used in the vast majority of these cycles. The most significant short-term complication associated with ovarian stimulation is ovarian hyperstimulation syndrome (OHSS), with moderate or severe OHSS reported in 3–8% of IVF cycles.2 In this review, the authors highlight the clinical presentation, prevention and management of OHSS. The iatrogenic nature and potential severity of OHSS emphasises the importance of ethical considerations in modern reproductive medicine practice. The purpose of fertility treatment is to create new life rather than save lives, making it especially important that clinicians remember the principle of ‘first do no harm’ and seek to minimise the risk of serious complications occurring as a result of treatment. This is a specially marked responsibility when looking after women who only undergo ovarian stimulation in order to donate eggs for the treatment of others.

The characteristic feature of the pathophysiology of OHSS is increased vascular permeability. This is mediated by vasoactive substances derived from the hyperstimulated ovary following the action of human chorionic gonadotrophin (hCG) or lutetiumising hormone (LH). Vascular endothelial growth factor (VEGF) appears to play a critical role in the development of OHSS.3 In vitro studies have shown hCG to be a potent stimulator for granulosa cell VEGF production, which may explain the clinically observed link between hCG exposure and the development of OHSS. Increased vascular permeability is most marked in the peritoneal surfaces nearest the ovary, leading to ascites, but may also affect pleural and pericardial cavities and the systemic circulation. Loss of fluid into the third space causes hypovolaemia and effusions.

Clinical features and classification

OHSS occurs in two distinct time frames, reflecting the effects of hCG exposure at different stages of treatment. Early and late OHSS are distinct entities with different predisposing factors and differ in their potential for severity. Early OHSS occurs soon after oocyte retrieval and reflects the effect of exogenous hCG administered for final follicular maturation 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, is precipitated by the effect of endogenous hCG from an early pregnancy. Late OHSS...
tends to be more severe than early OHSS and is poorly predictable from the antecedent ovarian response to stimulation. There is no consensus on the most appropriate classification of OHSS severity. The scheme put forward by Mathur et al. represents an evolution of previous classifications and aims to identify patients most in need of close monitoring and treatment (Box 1). Furthermore, it is important to realise that OHSS is a dynamic condition and the level of severity may change over time and hence all patients should be counselled regarding warning symptoms. The risk of OHSS is one of the reasons why alternative treatments that do not require ovarian stimulation should be considered where clinically appropriate. Weight optimisation intervention for women who are obese or underweight should form first-line treatment. Anti-estrogens, dopamine agonists and gonadotrophin-releasing hormone (GnRH) pump may have a role in certain cases and are all associated with a lower risk of OHSS than ovarian stimulation. Laparoscopic ovarian diathermy may be an effective alternative to gonadotrophin ovulation induction in women with PCOS who do not conceive with clomifene.

**Risk factors and prediction**

A number of pretreatment patient characteristics and ovarian response parameters have been studied as predictors of OHSS. Younger age, presence of polycystic ovaries (PCO) and a past history of OHSS all increase the risk of OHSS.

During ovarian stimulation, high serum estradiol (E2) concentrations, a rapid rise in serum E2, high follicle numbers and increased egg numbers have been correlated with increased risk of developing OHSS. However, there is no clear agreement in the literature on the cut-offs used to determine increased risk. The predictive value of these parameters is poor, especially for late OHSS. Around a third of cases of severe OHSS occur in cycles that would not be considered ‘high-risk’ on the basis of these parameters, whilst the majority of cycles identified as being ‘high-risk’ do not result in OHSS. In cycles where the ovarian response has exceeded limits thought to be safe, serum VEGF concentrations prior to the onset of OHSS do not distinguish between cycles that result in OHSS and cycles that do not. Prestimulation levels of anti-müllerian hormone may be useful predictors of OHSS risk. However, more work is required to determine cut off levels and ascertain predictive values. At present there is no single parameter, or combination of parameters, that offers reliable prediction of OHSS.

**Prevention (Box 2)**

The risk of OHSS is one of the reasons why alternative treatments that do not require ovarian stimulation should be considered where clinically appropriate. Weight optimisation intervention for women who are obese or underweight should form first-line treatment. Anti-estrogens, dopamine agonists and gonadotrophin-releasing hormone (GnRH) pump may have a role in certain cases and are all associated with a lower risk of OHSS than ovarian stimulation. Laparoscopic ovarian diathermy may be an effective alternative to gonadotrophin ovulation induction in women with PCOS who do not conceive with clomifene.

**Ovulation induction**

In anovulatory women, mono-follicular ovulation induction using gonadotrophins in a chronic low-dose step-up regimen carries a lower risk of over-stimulation and cycle cancellation than a step-down regimen.
Ovarian stimulation regimens for IVF

GnRH antagonists are able to provide suppression of endogenous gonadotrophin release without impairing pituitary sensitivity to GnRH during ovarian stimulation for IVF. Regimens using GnRH antagonists yield fewer oocytes and lower E2 levels compared with GnRH agonist regimens, and there is evidence from meta-analysis that the risk of severe OHSS is also lower with GnRH antagonists. 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. These groups are at particularly high risk for developing OHSS and a cautious regimen for ovarian stimulation, using a low starting dose of follicle-stimulating hormone (FSH), is appropriate for them. In women with PCOS who exhibit the highest sensitivity to FSH, is appropriate for them.

Coasting

During the course of IVF cycles, an excessive ovarian response 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. The proposed mechanism for the protective effect of coasting is through a reduction in the granulosa cell production of vasoactive mediators, such as VEGF. Serum E2 concentrations continue to rise for 24 to 48 hours, before falling. When the E2 reaches a ‘safe’ level, final follicular maturation is induced and the cycle resumed. Most studies quote E2 levels of 3000 pg/ml as the ‘safe’ level of E2 when they would proceed with triggering ovulation. 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. Coasting for periods of greater than 3 days may be associated with a reduction in pregnancy rate; hence, if the ovarian response has not settled sufficiently in such circumstances, cycle cancellation should be discussed with the patient.

Reducing hCG exposure

The pivotal role of hCG in precipitating OHSS is demonstrated by in vitro studies and epidemiological data showing a significantly higher risk of OHSS in IVF cycles with increased hCG exposure (cycles with conception, multiple pregnancy or hCG used for luteal support). Complete avoidance of both hCG and endogenous LH – achieved by stopping all stimulation and continuing pituitary down-regulation – abolishes the risk of OHSS, albeit at the cost of ‘wasting’ a treatment cycle. Short of this, measures can be taken to reduce the hCG exposure to the extent possible. Recombinant LH may be used in place of hCG for inducing final follicular maturation, but studies have failed to show a reduced risk of OHSS, despite the shorter half-life and less marked luteotrophic effect of LH compared with hCG. An alternative to hCG in GnRH antagonist cycles is the use of GnRH agonist to cause an endogenous LH surge. Further research is required on the optimum method of luteal support if this approach is used, to obviate the effect of inadequate corpus luteum development. An alternative to cancellation in cycles with an excessive ovarian response is elective cryopreservation of all embryos, thereby avoiding endogenous hCG. This clearly avoids the risk of late OHSS, but early OHSS risk is unaffected. Finally, progesterone is as effective as hCG for luteal support with a lower risk of OHSS and should be the recommended form of luteal phase support.

Adjuvants

The elevated risk of OHSS in women with PCOS may be related to increased VEGF activity. Insulin is known to stimulate VEGF protein expression and secretion. Co-administration of metformin for women with PCOS undergoing IVF shows a reduced incidence of OHSS (pooled odds ratio [OR] 0.27, 95% confidence interval [CI] 0.16–0.47). Dopamine agonists, cabergoline and quinagolide have been studied as preventative measures, having been found to exert a specific effect on vascular permeability without affecting luteal angiogenesis. However, the magnitude of protection and whether or not dopamine agonists protect against late OHSS is not clear. Future developments may include applications for specific antagonists for VEGF and hCG. In the animal model, hCG antagonist reduces vascular permeability and VEGF expression dramatically and does not appear to have
any effect on blastocyst development when used after hCG administration.16

Management

OHSS arises from fertility treatments often carried out in free-standing units, which may not have the facilities to look after patients with severe OHSS. Hence, close liaison is called for between fertility units and acute hospitals where patients with OHSS may present. All units that may potentially see patients with OHSS should put in place protocols for managing such patients and have access to specialised expertise in an emergency. Patient awareness regarding the symptoms of OHSS is key and all patients should have access to an emergency contact out of hours. The RCOG has produced a patient information leaflet on OHSS which can be used to educate patients and provide necessary advice, including symptoms indicative of worsening OHSS that should prompt urgent medical attention.17

The management of OHSS depends on the severity of the condition (Table 1). Symptomatic patients should be seen to establish a diagnosis and assess the severity of OHSS. Diagnostic confusion may arise between OHSS and other causes of abdominal pain and distension. It should be kept in mind that uncomplicated OHSS is not commonly associated with severe pain. The presence of significant pain and tenderness should lead to a suspicion of co-existing problems such as pelvic infection, ovarian torsion and ectopic pregnancy.

Patients with mild OHSS can be managed on an outpatient basis, with symptomatic relief, monitoring, counselling and support. Analgesia is provided by paracetamol and codeine. Non-steroidal anti-inflammatory medications should be avoided as they may compromise renal function. Anti-emetics may be needed to allow oral intake guided by thirst. Resolution of symptoms usually occurs in 7 to 10 days if treatment has not resulted in pregnancy. The course may be prolonged if pregnancy occurs and there is a risk of increased severity due to endogenous hCG stimulation.

Patients of severe OHSS and those with significant pain or nausea limiting oral intake are usually managed as inpatients. Monitoring and supportive care while awaiting spontaneous improvement is the mainstay of management. This involves a strict fluid balance record, 4 hourly pulse and blood pressure measurement, daily weight and abdominal girth measurement and daily assessment of electrolytes, liver function and full blood count. Catheterisation is sometimes required for accurate monitoring of fluid balance. Clinical assessment of respiratory function is prudent as pleural effusion is not uncommon in patients with severe OHSS. Respiratory rate and oxygen saturation values form a basic part in monitoring these women and if abnormal, chest X-ray may be indicated.

OHSS appears to cause a fundamental alteration in osmoregulation18 which makes management of fluid balance in such individuals difficult. Characteristic problems of electrolyte imbalance include hyponatraemia and hyperkalaemia in about 50% of women with severe OHSS. These usually respond to correction of dehydration. Oral fluid intake, guided by the patient’s thirst, is a physiological approach to fluid replacement and is the preferred method of fluid management. Pain relief and anti-emetic therapy may be required to help the patient achieve oral hydration. Intravenous fluid therapy in the presence of increased capillary permeability carries a risk of increasing ascites and effusions. However, intravenous fluids have a role where the patient is unable to drink, or for initial rehydration when the patient presents with severe haemoconcentration. Initial fluid replacement is usually with crystalloids. Initial crystalloid rehydration not followed by improvement in haemoconcentration (haematocrit >45%) or persistent oliguria (urine output <30 ml/hr) warrants a reassessment of the situation; colloids such as albumin or hydroxyethyl starch should then be considered. Diuretics should generally be avoided as they may worsen hypovolaemia, although there may be a role for diuretic use in a high-dependency setting if urine output remains poor despite adequate fluid replacement (as judged by invasive hemodynamic monitoring such as central venous pressure measurements) and paracentesis.

Paracentesis should be considered in patients with respiratory embarrassment due to abdominal distension and in those who remain oliguric despite adequate rehydration, which occurs due to a reduction of renal preload. This should be done under ultrasound guidance to avoid injury to the enlarged ovaries. There is some evidence that paracentesis shortens the course of the disease and there may be a role for this in patients with a prolonged course of OHSS.19

Rarely,
pleural effusions causing respiratory compromise unresolved by ascitic tap may need to be drained separately.

Thrombosis is a serious complication of OHSS with a reported incidence of 0.7–10%. A recent review suggested that arterial thrombosis usually occurs with the clinical manifestation of OHSS while venous thrombosis may occur weeks after apparent resolution of symptoms. Thromboembolism may be a life threatening complication of severe OHSS and prophylactic measures are warranted despite the lack of clinical studies on the value of thromboprophylaxis. Venous support stockings and prophylactic low molecular weight heparin should be used in all women with severe OHSS and those who are admitted to hospital or have reduced mobility. Current RCOG guidance suggests consideration for continuing prophylactic heparin 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 if complicated by other thrombophilic conditions. In women who do not conceive, thromboprophylaxis is usually discontinued at the time of the withdrawal bleed. 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. Atypical presentations of thrombosis should be kept in mind in women with OHSS, with frequent involvement of the arterial system and upper body vessels.

Enlarged ovaries are normal in OHSS and do not require surgery. Indications for surgery in women with OHSS include coincidental ovarian torsion and ectopic pregnancy. Hyperstimulated ovaries are very friable and vascular; hence any surgery if required should only be undertaken by an experienced surgeon.

Conclusion

Close monitoring of patients of severe OHSS and the use of a modified early warning score chart may help identify deteriorating patients who need high-dependency care. Women with critical OHSS may require management in an intensive-care setting. A gynaecologist with specialist knowledge and experience of OHSS should coordinate care, which usually requires multidisciplinary input from physicians, renal specialists and intensivists.

Conflict of interest

None declared.

References


