Prevention and management of ovarian hyperstimulation syndrome

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Abstract
Ovarian hyperstimulation syndrome (OHSS) is considered as one of the significant complications of assisted conception. Its presentation may vary in severity with the mild form affecting about 33% and the more severe forms seen in around 3–8% of in-vitro fertilization (IVF) cycles. Exact etiology of OHSS is unknown but it seems to be secondary to vasoactive products released by the ovaries after being exposed to human chorionic gonadotropin (hCG). This results in increased capillary permeability which in turn leads to leakage of fluid from the vascular compartment causing third space fluid accumulation and intravascular dehydration. Although mild and some moderate cases can be treated as outpatients, severe forms of OHSS need inpatient treatments which are mainly aimed at preventing complications like deep vein thrombosis, renal and liver dysfunction and acute respiratory distress syndrome (ARDS).

Keywords ovarian hyperstimulation syndrome; ovulation induction; polycystic ovaries

Introduction
The introduction of ovulation inducing agents has been a major stepping stone in the treatment of infertility. With these some degree of hyperstimulation is unavoidable but this must be distinguished from the clinical entity of ovarian hyperstimulation syndrome (OHSS) which is a systemic disease resulting from the release of vasoactive peptides from the stimulated ovaries. The treatment of OHSS is mainly empirical in order to prevent severe morbidity and mortality. Identification of patients who are at high risk of developing OHSS and taking some precautionary steps can reduce the incidence of severe forms of the disease.

Case 1
A 25-year-old woman with polycystic ovarian syndrome (PCOS) is planned to have ovulation induction. She has got a body mass index (BMI) of 32. Ultrasound examination shows polycystic ovaries. How will you manage this case?

The main aim in this case should be to achieve pregnancy and prevent OHSS. Although the predictive models are not very accurate, they do give some direction in optimizing treatment to the patient’s advantage. When taking history it is essential to identify the factors that might put patients in the high risk group. In this particular case, her age, BMI and history of PCOS put her at high risk of OHSS. Various methods have been used to predict and prevent OHSS depending on the type and timing of the ovarian stimulation (Table 1).

Prior to starting
Weight management: weight loss in obese women may remove the need for stimulation and help in resumption of ovulatory cycles. This basic principle should be kept in mind while counselling any couple prior to treatment of infertility.

During stimulation
Alternative methods of stimulation: ovulation induction using clomiphene instead of gonadotropins could be considered in appropriate cases, which, does not abolish but significantly reduces the chances of OHSS.

Minimal/no stimulation protocols: altering the stimulation protocol by considering natural cycle IVF or in-vitro maturation (IVM) is an option to reduce OHSS and is used in certain circumstances. This reduces the exposure to FSH thereby reducing the risk of OHSS; this however needs to be balanced with reduced success rates and increased chances of cycle cancellation.

Coasting: this involves withdrawing exogenous gonadotropins while maintaining pituitary suppression and withholding hCG until the patient’s serum oestradiol concentration falls to a safer level. It appears to cause atresia of small to intermediate sized follicles leading to reduction in the amount of vasoactive peptides released from the granulosa cells. Although coasting can significantly reduce the incidence of severe OHSS, it does not abolish the syndrome completely. The evidence in favour of coasting is still insufficient and more studies are required to optimize coasting guidelines for clinical practice.

Summary of preventive strategy for OHSS

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Table 1
Alternative stimulation protocols: gonadotropin releasing hormone (GnRH) antagonist protocols have shown to reduce the risk of hospitalization and severe OHSS in women having IVF. They suppress endogenous gonadotropin release without impairing the pituitary sensitivity to GnRH during ovarian stimulation. Hence a reduced dose of gonadotropins is required to achieve stimulation and there is the avoidance of initial flare seen in agonist cycles. However the clinical equivalence with GnRH agonist cycles is still debated with studies showing conflicting result.

Low dose step up protocol is another alternative in women with a high risk of OHSS. The stimulation process involves using a low dose of gonadotropin initially and slowly increasing this if required.

Triggering ovulation

Human chorionic gonadotropin (HCG) dose: HCG is routinely used to trigger ovulation in stimulated cycles. Due to its long half-life and luteolytic properties, it is thought to have a role in OHSS initiation. Withholding HCG administration used to be the most commonly used method of preventing OHSS but this often led to cancellation of cycle.

Optimal dose of HCG is still being debated (2000 IU vs 5000 IU vs 10 000 IU). It seems logical that lower the dose, lesser the chance of developing OHSS, but this may be at the expense of decreased number of oocytes retrieved.

Other triggers: use of GnRH agonist to induce ovulation in gonadotropin only or GnRH antagonist stimulated cycles has given some hope in preventing OHSS. When compared to HCG, GnRH agonists have shorter half-life. They cause an endogenous LH surge that helps trigger ovulation. GnRH agonist resulted in complete and quick luteolysis. Vice versa, studies have shown that administering GnRH antagonist in women pre-treated with long GnRH agonist protocol, resulted in rapid reduction of oestriadiol concentration. Once the oestriadiol fell below the critical level, HCG was administered to harvest the oocytes.

Recombinant LH instead of HCG is also being tried for final follicular maturation use GnRH agonists as it has a shorter half-life and a less marked luteotrophic effect compared with HCG. However its effect on OHSS reduction has not been conclusively proven.

Cycle cancellation

This is considered only in exceptional circumstances due to the emotional and to some extent financial implication associated with IVF cycles. However it remains as a useful method in selected cases with a high risk of developing OHSS such as women who have had similar response previously leading to severe OHSS. It should be noted that this will abolish the risk of early OHSS, ovulation can still occur and rarely followed by pregnancy if protection is not used which may be associated by late onset OHSS.

Egg collection

During the stage of egg collection: administration of albumin infusion has been tried to reduce the incidence of OHSS. Albumin was given intravenously at the time of oocyte retrieval to enhance oncotic pressure and hence helps retain fluid in the intravascular compartment. The risk of using albumin included side effects and sometimes allergic reaction and anaphylactic shock. As an alternative to albumin, hydroxyl ethyl starch (HES) solution has been tried with some promising results. However such therapies are not without their own risk and should be used with caution in women at high risk of OHSS.

Elective cryopreservation: embryo cryopreservation and reinitiating their use in future unstimulated cycles will reduce the incidence of late OHSS which is triggered by the rise of endogenous HCG that occurs with pregnancy. The patients need to counselled about the reduced success of frozen—thawed embryo replacement compared with fresh treatment cycles. Although the success rates of fresh and frozen cycles are now getting comparable with the development of vitrification which is the new technique of embryo freezing.

Luteal phase

Luteal phase support after controlled ovarian hyperstimulation is required as the supra-physiological levels of ovarian steroids can cause impairment of the luteal phase due to the negative feedback of pituitary. The use of progesterone instead of HCG has been shown to have similar efficacy and significantly lower OHSS rates. OHSS is believed to be induced by the ovarian release of vasoactive—angiogenic substances increasing the vascular permeability. Vascular endothelial growth factor (VEGF) has emerged as the main angiogenic factor. Compounds that block the release or action of these substances would appear suitable for preventing OHSS. Recent studies involving VEGF and the inhibition of its receptors by dopamine agonists (cabergoline) have brought new insights to the prevention and management of OHSS. Insulin sensitizing agents such as metformin that have been used with ovulation induction also appear to be effective in reducing OHSS. They have been reported to reduce the insulin response on vascular peptide VGEF (vascular endothelial growth factor) which contributes to OHSS by increasing the vascular permeability. However their primary role for this purpose needs to be investigated further. Immuno-modulation studies are currently in progress and this approach may be used in future to prevent severe OHSS in high risk patients. However more work is required prior to offering these therapies in the routine clinical setting.

In the scenario mentioned above, options to prevent OHSS would be to consider alternatives such as clomiphene induction of ovulation. If IVF is used as primary treatment, consideration should be given to use of antagonist protocol or minimal stimulation protocols. If during treatment there are signs pointing towards development of OHSS, then consider options such as coasting or cancellation of cycle. If the cycle is continued, consider altering the dose of HCG for triggering. Prophylactic albumin during egg collection is an option but is not without its side effects and decision should be based on risk—benefit assessment. Elective cryopreservation of all embryos is an option for those that show signs of significant early OHSS. If decision is made to carry on with replacement, the couple should be encouraged for replacement of single embryo. The luteal phase support should be delivered appropriately using progesterone.

Case 2

A 33-year-old woman presents herself to the emergency gynaecological admission unit 14 days after the ovulatory dose of HCG.
She was undergoing ovarian stimulation induction for her third IVF cycle. She complained of severe abdominal bloating, nausea, vomiting and reduced urinary output. Examination revealed clinical ascites. Blood picture showed a haematocrit of 48%. Ultrasound examination showed ovarian size of 16 cm. What would be your next step in the management of this woman?

The clinical picture is suggestive of late onset OHSS. Treatment is usually conservative with primary aim being symptomatic relief and then to prevent secondary life threatening complications. A diagnosis of OHSS is usually straightforward, given a history of ovarian stimulation followed by typical symptoms of abdominal distension, pain, nausea and vomiting. OHSS can also be classified as mild, moderate or severe and critical depending on the severity of haemoconcentration and ascites, ovarian size and any other complicating factors such as thrombosis (RCOG; green top guideline, no.5, September 2006). OHSS is a dynamic condition and although patients with mild to moderate OHSS can be monitored on an outpatient basis, they need to be aware of the changing conditions and counselled about warning symptoms. Furthermore, they should have access to emergency out of hours contact.

OHSS presenting within 9 days (early OHSS) after the ovulatory dose of HCG is likely to be due to excessive ovarian response and the precipitating effect of exogenous HCG administered to trigger ovulation. OHSS presenting after this period (late OHSS) is likely to be due to endogenous HCG stimulation from early pregnancy. Late OHSS is more likely to be severe and longer lasting than early OHSS.

Clinical examination
This gives information regarding the degree of hydration, cardio respiratory status, presence of clinical ascites and distension of abdomen. Observational chart should be commenced with measurement of blood pressure (BP), pulse, temperature, weight, urine analysis, abdominal girth and intake/output charting. In this situation, clinical examination will help confirm the history and provisional diagnosis and the requirement for hospital admission.

Investigations
The recommended baseline blood tests should assess the renal and liver functions including urea, electrolytes, albumin, liver enzymes and full blood count (to look for signs of haemoconcentration). Pelvic ultrasound should be performed to measure ovarian size and check for ascites. These may be repeated depending on clinical severity and requirement.

Apart from the above investigations offered routinely on all patients with OHSS, chest X-ray and electrocardiogram (ECG) may be required in women with respiratory symptoms to look at signs of effusion, infection and pulmonary embolism or in suspected cases of pulmonary embolism or pericardial effusion. The origin of hepatic abnormalities in OHSS is unknown but it seems to occur in 25–40% of severe OHSS cases. These usually normalize with resolution of the disease.

Monitoring
Daily monitoring should include intake/output chart, pulse and BP chart, weight and girth measurements (frequency being determined by the patient’s clinical condition).

Management
The management of OHSS is mainly supportive treatment until the condition resolves spontaneously.

Symptomatic relief: this is important, especially for pain and nausea to keep the patient comfortable. The use of simple analgesics like paracetamol and codeine is the preferred first line treatment. Non-steroidal anti-inflammatory drugs should be avoided as they may compromise renal function. Anti-emetic should be given if there is severe nausea or vomiting. These drugs should be appropriate keeping in mind the possibility of early pregnancy.

Thromboprophylaxis: thromboembolic accidents reported in around 0.7–10% of women with OHSS are a serious complication that despite appropriate treatment, can lead to the death of the patient. Predisposition to thrombosis is a combined effect of increased oestrogen level, dehydration and reduction of venous return caused by compression associated with ascites and enlarged ovaries. However, the predilection for unusual sites characteristics of these thromboses such as involvement of upper extremities and the arterial system is now thought to be due to a state of hypercoagulopathy. Hypercoagulopathy is explained by haemoconcentration resulting from extravasation of fluid into third space which seems to activate the coagulation cascade.

Routine anti-thrombotic prophylaxis with stockings and heparin should be commenced for all women requiring hospitalization for OHSS as in this case. The risk of thrombosis appears to persist into the first trimester of pregnancy and consideration should be given to risks and benefits of heparin prophylaxis. In women who do not conceive, thromboprophylaxis is discontinued with resolution of OHSS while those who conceive are advised to continue this until the end of first trimester and sometimes even longer depending on additional risk factors.

Fluid electrolyte balance: a strict fluid balance chart should be commenced and women should be encouraged to drink to thirst, rather than to excess. If not careful, there is a serious risk of over hydration in OHSS. In this pathological process, fluid is transferred rapidly from the vascular space into the body cavities resulting in ascites, pleural effusion and pericardial effusion with potentially fatal outcome. Where oral intake cannot be maintained, intravenous crystalloids and/or colloids should be used. This should be guided by the fluid balance chart.

Women with haemoconcentration requiring intense initial rehydration are done with crystalloids strictly guided by fluid balance. Those that persist to be haemoconcentrated or oliguric may benefit from colloids. Various agents have been used for this purpose including human albumin, hydroxyethylstarch (HES), dextran, mannitol and haemaccel. HES is of non-biological origin and hence produce lesser side effects and allergic reactions when compared to albumin. It has also been shown to be associated with higher mean daily urine output, fewer paracentesis and shorter hospital stay.

Hyponatremia and hyperkalaemia are the main electrolyte disturbances seen in OHSS that usually respond to hydration. Hyponatremia may be due to the dilution resulting from hyper secretion of ADH with water resorption exceeding the sodium resorption. This can occur in about 56% cases of severe OHSS. Diuretics should be avoided in women with oliguria secondary to reduced circulating volume and decreased renal perfusion, as they may worsen intravascular dehydration. If oliguria persists
despite hydration then invasive hemodynamic monitoring should be considered and diuretics can be used judiciously guided by central venous pressure. Such complex management should be done in the realms of a multidisciplinary setting. Even in a multidisciplinary setting the IVF specialist remains overall in-charge of management to ensure communication between various members of the team. The breakdown of this communication has been sited as contributory to mortality following OHSS in recent years.

**Paracentesis:** there are a few scenarios where paracentesis may be considered to improve symptoms. These include significant abdominal discomfort due to distension, respiratory distress and in women who remain oliguric despite adequate fluid replacement. There are various mechanisms by which paracentesis appear to improve urine production including reduction in the vena cava compression which increases cardiac output and renal perfusion. Furthermore it helps decompression of the ureters and removes fluid rich in mediators of OHSS. If required, paracentesis should be performed under ultrasound guidance so as to avoid injury to the highly vascular and enlarged ovaries. At this stage it is very important to highlight that paracentesis should not be delayed unnecessarily. Most mortalities that have occurred resulted from paracentesis being done too late. Repeated paracentesis can be avoided using either pigtail or suprapubic catheter. Any associated hydrothorax tends to resolve after drainage of ascites, but if symptomatic hydrothorax persists, it may be drained separately.

**Surgery:** surgery in OHSS should be avoided unless there is a suspicion of ovarian torsion or haemorrhage secondary to follicular rupture. Worsening pain especially unilateral, further ovarian enlargement, nausea, leucocytosis and anaemia should raise the suspicion of torsion. Colour Doppler assessment of ovarian blood flow may help in diagnosis. In these cases surgery should be conservative with minimum invasive manipulations so as to preserve maximum ovarian integrity. Surgery should be performed by a senior person as complications can arise because of ovaries being very vascular and friable.

The above patient needs assessment and possibly hospital admission to investigate, monitor and treat her initial symptoms. If these improve with conservative management, she may be discharged and followed up on an outpatient basis with low threshold for readmission if required. It is worth remembering that the severity could worsen overtime as the condition evolves in spite of the supportive measures. Worsening symptoms i.e. pain, vomiting, breathlessness along with oliguria, weight gain and increased abdominal girth are indicators of worsening OHSS. Urine output of less than 1000 ml/day or a persistent negative fluid balance is a cause for concern. OHSS is a dynamic condition that can change and evolve over a period of time, hence close monitoring is required to tailor treatment accordingly.

**FURTHER READING**

**Practice points**
- Ovarian hyperstimulation is considered as the most serious complication of ovarian stimulation. Detection of early warning signs and taking adequate precautions can prevent development of severe OHSS in majority of cases.
- Clinical picture of OHSS may vary depending on severity and is linked to excessive vascular permeability leading to fluid shifts, third space formation and significant fluid electrolyte imbalance.
- Treatment is mainly aimed at relieving symptoms and prevention of life threatening complications.