Current management of ovarian hyperstimulation syndrome

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Ovarian hyperstimulation syndrome is an iatrogenic and usually self-limiting condition which can occasionally be life threatening. This article reviews methods of prevention and management of ovarian hyperstimulation syndrome.

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic and potentially life-threatening complication of superovulation. The incidence of OHSS varies between 0.6% and 10% of in-vitro fertilization (IVF) cycles (McDougall et al, 1992). Although more commonly seen in association with gonadotrophin use, it may rarely occur following treatment with anti-oestrogens like clomiphene citrate (Jenkins and Mathur, 1998).

Several risk factors have been associated with the development of OHSS (*Table 1*).

PATHOGENESIS

The exact pathogenesis of OHSS is still unknown. It is associated with luteinization, either as a result of exogenous human chorionic gonadotrophin (hCG) to trigger ovulation, or in the presence of pregnancy. Two clinical forms of the condition are commonly encountered. The first is early-onset OHSS that occurs 3–7 days after the ovulatory dose of hCG and is caused by excessive ovarian stimulation. The second or late-onset type OHSS is thought to be caused by a pregnancy-related rise in hCG and presents more than a week later (Mathur et al, 2000). The latter is more severe than the early-onset type and is associated with multiple pregnancy.

The basic pathology responsible for the clinical features of OHSS appears to be a shift of protein-rich fluid from the intravascular to the extravascular space. Possible causes include increased vascular permeability as a result of the release of vasoactive substances from the ovaries under the influence of hCG, alterations in osmoregulation, activation of the ovarian renin–angiotensin activation system and changes in systemic immunological hypersensitivity. Depletion of intravascular volume and increase of the extravascular volume leads to dehydration, oliguria, hypovolaemia, electrolyte imbalance (hyponatraemia and hyperkalaemia), leucocytosis and haemoconcentration. The consequences of these effects are hypercoagulability and thromboembolic sequelae, rapid weight gain, ascites, and pleural and pericardial effusions.

TABLE 1.
Risk factors for ovarian hyperstimulation syndrome

Young age (<30 years)
Lean physique
Polycystic ovary syndrome patients
High serum oestradiol levels (>2500 pg/ml or 9000 pmol/litre)
Rapidly increasing oestradiol levels (>75% from previous day)
Size and number of follicles and ultrasonographic ovarian 'necklace sign' of multiple small follicles
Human chorionic gonadotrophin administration
Number of oocytes retrieved (≥20)
Multiple pregnancy

From Whelan and Vlahos (2000)

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Adult respiratory distress syndrome and multiple organ failure may occur (Whelan and Vlahos, 2000) and this can ultimately lead to death.

Physical symptoms comprise bloatedness, nausea, vomiting, diarrhoea, and lethargy, with complete loss of appetite. Onset of vomiting or diarrhoea within 48 hours of hCG administration, shortness of breath and/or reduced urine output indicating accumulation of ascites suggest potentially severe disease. OHSS is classified into four categories: mild, moderate, severe and critical (Jenkins and Mathur, 1998) on the basis of clinical and laboratory parameters (*Table 2*).

MANAGEMENT

Prevention

Given the uncertainty surrounding the pathogenesis of this condition, specific treatment is difficult to formulate and the emphasis should be on prevention (*Table 3*). Ovulation induction should only be performed in dedicated centres with appropriate monitoring facilities like ultrasonography and serum oestradiol assay. In high-risk women, use of gonadotrophin-releasing hormone (GnRH) pumps, low-dose step-up regimens for gonadotrophin ovulation induction and identification of clinical and laboratory parameters predictive of a high response should guide the stimulation protocol. There is no evidence to support the superiority of a specific gonadotrophin (recombinant follicle-stimulating hormone *vs* human menopausal gonadotrophin or recombinant *vs* urinary preparations) in preventing OHSS (Daya et al, 1995; Daya and Gunby, 2001).

Cycle cancellation: Cancellation of a treatment cycle should be considered if serum oestradiol levels are excessively high and/or ovarian ultrasound reveals a large number of developing follicles. The principle behind this decision is to withhold the ovulatory trigger (hCG). In cycles where GnRH agonists have not been used this may not completely prevent early-onset OHSS as a natural luteinizing hormone surge may still occur (Jenkins and Mathur, 1998).

Coasting: Coasting involves discontinuation of gonadotrophins in cycles with an excessive response and delaying hCG administration, while continuing GnRH agonist administration in the presence of ultrasound and endocrine monitoring (Fluker et al, 1999). It is an alternative to cycle cancellation in situations where there is a substantial risk of OHSS associated with high serum oestradiol levels above 2500 pg/ml (9000 pmol/litre). The aim is to allow follicle-stimulating hormone levels to drop thus inhibiting granulosa cell proliferation and subsequent availability for luteinization. The patient is monitored until the oestradiol levels drop to safe levels (<2500 pg/ml or 9000 pmol/litre). Although shown to be effective in observational studies, coasting does not entirely abolish the risk of OHSS and there are no randomized trials to date to advocate its use in the prevention of OHSS. At the same time, it can potentially reduce the num-

TABLE 2.
Classification of severity of ovarian hyperstimulation syndrome

Mild	Abdominal bloating, mild pain
	Ovarian size usually <8 cm*
Moderate	Increased abdominal discomfort accompanied by nausea, vomiting and/or diarrhoea
	Ultrasound evidence of ascites
	Ovarian size usually 8–12 cm*
Severe	Clinical ascites, sometimes hydrothorax
	Haemoconcentration (haematocrit >45%, WBC > 15 000/ml)
	Oliguria with normal serum creatinine
	Liver dysfunction
	Anasarca
	Ovarian size usually >12 cm*
Critical	Tense ascites
	Haematocrit >55%, WBC >25 000/ml
	Oliguria with elevated serum creatinine
	Renal failure
	Thromboembolic phenomenon
	Ovarian size usually >12 cm*

From Jenkins and Mathur (1998). *Ovarian size may not correlate with severity of ovarian hyperstimulation syndrome in cases of assisted conception because of the effect of follicular aspiration. Nevertheless, recording ovarian measurements of ovarian size is not currently considered useful as a prognostic indicator nor as an indicator of the stage of the disease (Whelan and Vlahos, 2000). WBC = white blood cell count

TABLE 3.
Prevention of ovarian hyperstimulation syndrome

General measures	Choice of appropriate dose and protocol
	Constant vigilance
	Progesterone for luteal phase support
Specific measures	Cycle cancellation
	Coasting
	Defer embryo transfer
	Luteal phase support with progesterone
	Prophylactic albumin administration
	Use of GnRH antagonists
	Use of pulsatile GnRH instead of sequential FSH
	Role of follicular aspiration

FSH = follicle-stimulating hormone; GnRH = gonadotrophin releasing hormone

ber of oocytes recovered, and may even compromise pregnancy rates. A Cochrane review on the role of coasting in OHSS is currently in progress (D'Angelo and Amso, 2001).

Elective cryopreservation of all embryos: Following oocyte recovery in assisted reproductive treatments, fresh embryo transfer may be deferred if there are excessive numbers of follicles and oocytes recovered (>20). All embryos are cryopreserved and electively replaced at a later date. The idea is to prevent a conception cycle and hence late-onset OHSS. A recent systematic review has concluded that there is insufficient evidence to support routine cryopreservation in cases with a high risk of OHSS (D'Angelo and Amso, 2002).

Luteal phase support: A systematic review (Soliman et al, 1994) has confirmed the effectiveness of routine luteal phase support after embryo transfer in IVF cycles involving the use of gonadotrophin-releasing hormone agonists. The use of hCG in this situation can aggravate OHSS and progesterone should be the preparation of choice in high-risk women (Ludwig and Diedrich, 2001).

Prophylactic albumin administration: It has been suggested that administration of intravenous albumin around the time of oocyte recovery could be used as a preventative measure in the high-risk patient. The exact mode of action of albumin is unknown, but it is thought to bind to vasoactive substances involved in the pathogenesis of OHSS. It also increases the intravascular oncotic pressure, thereby preventing the loss of water from the intravascular compartment (Whelan and Vlahos, 2000).

The results of a recently updated systematic review (Aboulghar et al, 2002) indicate that the use of intravenous albumin at the time of oocyte retrieval significantly reduces the incidence of severe OHSS in high-risk women undergoing IVF. However, the optimal timing and dose of albumin are unclear as is its effect on implantation. There are also growing concerns about the possibility of febrile reactions, anaphylactic shock and the potential risk of virus and prion transmission (Ben-Chetrit et al, 2001). According to Aboulghar et al (2002) eighteen women at risk need to be treated with albumin infusion in order to prevent a single case of severe OHSS. This needs to be taken into account in the context of clinical decision making.

The alternative to albumin is infusion of hydroxyethyl starch solution, which is a plasma colloidal substitute. It is likely to be a safer, cheaper and equally effective method (Gokmen et al, 2001), but there are concerns about its interaction with the blood coagulation system (Kissler et al, 2001).

Role of follicular aspiration: Recovery of immature oocytes (which can then be cultured in vitro and subsequently used for IVF) has been suggested as a means of preventing OHSS (Coskun et al, 1998). However, follicular aspiration alone cannot be relied on to avert the development of OHSS or to arrest clinical deterioration in a pre-existing case. Despite this, practitioners are known to attempt meticulous puncture and aspiration of all stimulated follicles at time of oocyte recovery in the belief that this interferes with the mechanisms leading to production of the ovarian mediators of OHSS (Whelan and Vlahos, 2000).

Other methods: A number of other methods of preventing OHSS have been advocated. These include the use of recombinant luteinizing hormone (Shoham et al, 1995) and GnRH antagonists like ganirelix or cetrorelix (Ludwig et al, 2000; Fluker et al, 2001). A meta-analysis of five randomized controlled trials suggests a significant reduction in the incidence of severe OHSS in women treated with GnRH antagonists in comparison with those treated with agonists (Al-Inany and Aboulghar, 2001).

Treatment

Treatment of OHSS is mainly supportive (*Table 4*). Multidisciplinary local protocols involving gynaecologists, anaesthetists and haematologists should be generated and strictly followed. The condition is self-limiting and resolution parallels the decline in serum hCG levels (about 7 days in non-pregnant, 10–20 days in pregnant). Mild OHSS is usually benign and resolves with the onset of the first period. Moderate to severe cases need hospital admission and monitoring. Women normally present to the nearest hospital, which may not be the unit involved with ovarian stimulation, so

TABLE 4.
Treatment of ovarian hyperstimulation syndrome

Mainly supportive treatment
Analgesia and antiemetics – antiprostaglandins are contraindicated
Fluid replacement – mainly crystalloids. Diuretics are contraindicated
Thromboprophylaxis
Ultrasound-guided paracentesis if indicated

appropriate communication with the centre initiating treatment is advisable. Monitoring should include daily physical examination, checking of vital signs every 4 hours, tabulation of fluid balance every 4 hours, and measurement of daily weight and abdominal girth. In addition, serial ultrasound scans may be helpful in quantifying ovarian size and ascites (Jenkins and Mathur, 1998).

The frequency of the investigations in *Table 5* will depend on the clinical circumstances but should occur on a daily basis in severe cases. In addition, chest X-ray, electrocardiogram and assessment of blood oxygen saturation are indicated if the patient develops breathlessness which is suggestive of pleural effusion and pulmonary embolism. It is important to be aware of the possibility of pregnancy if an X-ray is contemplated.

Biochemical indicators of severe disease include the following: leucocytosis >22 000/mm^3, haematocrit >45%, serum creatinine level >1.2 mg/dl, serum sodium level <135 meq/litre and serum potassium level >5.0 meq/litre (Jenkins and Mathur, 1998).

Analgesia: Adequate pain relief should be provided with paracetamol and oral or parenteral opiates as indicated. Antiprostaglandins should be avoided if possible as they may precipitate renal failure by inhibiting renal prostaglandins which help maintain renal blood flow despite hypovolaemia. Pain disproportionate to the ovarian enlargement should raise the suspicion of torsion, rupture or haemorrhage in the enlarged ovaries. Ectopic pregnancy may also need to be excluded.

Fluid replacement: Fluid replacement to counter haemoconcentration plays a crucial role in the treatment of OHSS. It is vital to maintain a strict fluid balance chart. An intake of <1000 ml/day, urine output of <1000 ml/day, or a discrepancy in the daily fluid balance >1000 ml/day are disconcerting features of this condition. Fluids may be given orally in mild or moderate cases but the intravenous route is essential in severe cases where oral intake is not tolerated. Crystalloids can be used initially, the target being an intake of 3 litres in 24 hours. Normal saline is the crystalloid of choice and potassium-containing fluids should be avoided as women with OHSS could develop hyperkalaemia (Jenkins and Mathur, 1998).

In more severe cases, with significant hypovolaemia, haemoconcentration (haematocrit >45%), hypoalbuminaemia (serum albumin <30 g/dl) or severe ascites, 500 ml of 4.5% isotonic intravenous albumin can be given over 2 hours as a plasma expander. Owing to the hyperpermeable state of the vasculature, infusion of large volumes of crystalloids in severe hypovolaemia requires close monitoring in order to avoid fluid overload. Other plasma expanders such as dextran (which can precipitate adult respiratory distress syndrome), mannitol and fresh frozen plasma have also been used in this setting.

Thromboprophylaxis: Early mobilization, use of thromboembolic stockings, correction of haemoconcentration and in severe cases, administration of prophylactic anticoagulants should be part of routine care.

Management of extravascular fluid in body cavities: Ultrasound-guided abdominal or vaginal paracentesis is often helpful in cases where ascites is a significant cause of pain or respiratory embarrassment. In this context, aspiration of ascitic fluid improves pulmonary compliance, relieves pain caused by tense ascites and reduces pressure on the inferior vena cava and renal veins, thus improving the venous return. Diuretics are contraindicated as they cause further depletion of the intravascular volume. Similarly, pulmonary compromise caused by pleural effusion may be treated by pleural tap.

Role of surgery: As the enlarged ovaries are friable and easily traumatized, pelvic surgery should be avoided if possible. In the presence of ovarian torsion, rupture or haemorrhage, intervention is best undertaken by an experienced

TABLE 5.
Recommended investigations for ovarian hyperstimulation syndrome

Haemoglobin, haematocrit, leukocyte count, platelet count
Serum creatinine and electrolytes (sodium and potassium)
Liver function tests including serum albumin
Coagulation profile – prothrombin time and partial prothrombin time (generally if the liver function tests are normal, then this may not be required on a daily basis)
Abdominal ultrasound for ascites

surgeon. It is important that the theatre team is aware of potential anaesthetic complications associated with pulmonary effusion, reduced pulmonary functional residual capacity and existing fluid imbalance.

CONCLUSIONS

OHSS is an iatrogenic potentially life-threatening condition. It is usually self-limiting and hence treatment is supportive. A number of methods of prevention and treatment have been suggested mainly on the basis of observational studies. Well-conducted double blind randomized control trials are required to evaluate the relative effectiveness of these interventions. HM

Conflict of interest: none.

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KEY POINTS

- Ovarian hyperstimulation syndrome (OHSS) is unpredictable – high oestradiol levels with multiple small or intermediate-sized follicles are the best predictors.
- Prevention is better than cure for this iatrogenic condition.
- Appropriate protocols and close monitoring are essential during controlled ovarian stimulation.
- If the possibility of OHSS is suspected, the cycle should be cancelled or embryo transfer deferred.
- Treatment principles are supportive based on fluid replacement, thromboprophylaxis and management of ascites.

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