Ovarian hyperstimulation syndrome: clinical features, prevention and management

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Abstract

Women undergoing fertility treatment involving ovarian stimulation with gonadotrophins are at risk of developing Ovarian Hyperstimulation Syndrome (OHSS), characterized by ovarian enlargement, increased vascular permeability, third space fluid accumulation and intravascular dehydration. Serious complications include thromboembolism, respiratory failure and renal failure. OHSS occurring in association with pregnancy has a more severe and prolonged course than in the absence of conception. Patient characteristics and parameters of ovarian response may help identify situations where the risk of developing OHSS is increased. Measures shown to be useful in preventing OHSS include the use of gonadotrophin-releasing hormone (GnRH) antagonist, which may be combined with GnRH agonist triggering of follicular maturation. In women with polycystic ovaries, a lower starting dose of Follicle-Stimulating Hormone (FSH) and metformin may reduce the risk of OHSS. Cycles where the ovarian response is excessive may be managed by coasting or by cryopreservation of all embryos, avoiding luteal hCG. Cancellation of the treatment cycle (avoiding hCG completely) prevents OHSS but results in 'wastage' of the treatment cycle. Dopamine agonists show promise as a preventative method. Mild cases of OHSS may be managed as outpatients with frequent monitoring. Patients of severe OHSS usually need hospital admission for close monitoring of fluid balance, analgesia and drainage of ascites. Thromboprophylaxis should be provided for all inpatients with OHSS. Multidisciplinary and intensive care management should be available for cases with complications.

Keywords in-vitro fertilization; ovarian hyperstimulation syndrome; polycystic ovarian syndrome

Introduction

Fertility treatment often involves the use of exogenous gonadotrophins to stimulate the ovaries, a process referred to as Controlled Ovarian Hyperstimulation. However, the ovarian response to stimulation may exceed safe limits, which are not precisely defined, resulting in a clinical condition called Ovarian Hyperstimulation Syndrome (OHSS). Rarely, OHSS may occur without fertility treatment, in association with pregnancy in women with gonadotrophin receptor mutations. However, most cases of OHSS are iatrogenic and occur in the context of elective, non-lifesaving treatment. Patients are at risk of significant morbidity and, in rare cases, even mortality. These factors impose a significant ethical responsibility on clinicians providing fertility treatment to minimize the incidence and severity of OHSS.

This review covers the clinical presentation of OHSS, measures to prevent it and principles of managing OHSS according to its severity. For an understanding of the pathophysiology of OHSS and the role of vasoactive molecules in the development of the disease process, the reader is referred to a review by Gomez et al (2010). The typical pathological changes in patients with OHSS include ovarian enlargement, increased vascular permeability and their sequelae. The increase in vascular permeability leads to the loss of fluid into the third space, causing effusions and intravascular dehydration.

Clinical features and classification

OHSS typically develops in women who have undergone ovarian stimulation with gonadotrophins, but only after exposure to human Chorionic Gonadotrophin (hCG) or, less frequently, following exposure to Luteinizing Hormone (LH). HCG is commonly used as an LH surrogate to induce final follicular maturation before oocyte collection or insemination; a further source of hCG is pregnancy. 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 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

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Classification of ovarian hyperstimulation syndrome

Mild OHSS
Abdominal bloating
Mild abdominal pain
Ovarian size usually <8 cm[a]

Moderate OHSS
Moderate abdominal pain
Nausea ± vomiting
Ultrasound evidence of ascites
Ovarian size usually 8–12 cm[a]

Severe OHSS
Clinical ascites (occasionally hydrothorax)
Oliguria
Haemoconcentration haematocrit >45%
Hypoproteinaemia
Ovarian size usually >12 cm[a]

Critical OHSS
Tense ascites or large hydrothorax
Haematocrit >55%
WCC >25000/ml
Oligo/anuria
Thromboembolism
Adult respiratory distress syndrome

OHSS may be early onset (within 9 days of hCG trigger) or late onset (after 9 days from hCG trigger) with severity as indicated in the table. This table has been reproduced with permission from Mathur and Sumaya (2007).
[a] Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration.

Table 1

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 fertilization (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 rate of hospitalization for OHSS following ovulation induction was 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. One study found 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 emphasizes 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 optimization 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. Randomized 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,