Prevention and management of ovarian hyperstimulation syndrome

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is a complication of fertility treatment involving ovarian stimulation. Patient characteristics and treatment cycle parameters have a limited accuracy in predicting the risk of OHSS. In women at increased risk of OHSS, a lower starting dose of follicle stimulating hormone and use of gonadotrophin releasing hormone (GnRH) antagonist rather than GnRH agonist may lower the risk of OHSS. Cycles where ovarian response is excessive may be managed by coasting or, in severe cases, cancellation. Human chorionic gonadotrophin should be avoided for luteal support. All women at risk of OHSS should have adequate information and access to 24 h care. Mild and moderate OHSS can be managed on an outpatient basis with close monitoring, while severe OHSS merits admission. Non-steroidals and diuretics should be avoided, thromboprophylaxis provided and a close watch kept on fluid balance, allowing patients to drink to thirst. Ascites may require paracentesis. A prolonged course is expected if conception occurs, but recovery is the rule in the overwhelming majority of cases.

Keywords ascites; coasting; human chorionic gonadotrophin; ovarian hyperstimulation syndrome; thrombosis

Background

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic, systemic disease which can occur as a complication when the ovaries are stimulated for fertility treatment. This most often occurs in the context of assisted conception, such as in-vitro fertilization (IVF), but it can occur after any form of ovarian stimulation, including clomifene and gonadotrophin ovulation induction. Significant OHSS has been reported in 3.1–8% of IVF cycles and 0.04–2% of ovulation induction cycles.

The critical factor triggering OHSS is exposure to human chorionic gonadotrophin (hCG). The source of hCG can be either exogenous, administered for follicular maturation/ovulation, or endogenous, from a pregnancy. OHSS can occur in two forms, distinguished by time of onset, which reflect the source of the hCG trigger. 'Early' OHSS presents within 9 days of the ovulatory dose of hCG and is related to exogenous hCG stimulation on a background of ovaries that have been overstimulated by follicle stimulating hormone (FSH). 'Late' OHSS occurs 10 or more days after the ovulatory dose of hCG and is triggered by hCG from an early pregnancy. Late OHSS is more difficult to predict from commonly used parameters of ovarian response and is significantly more likely to be clinically severe.

Hyperstimulated ovaries release a number of vasoactive mediators under the influence of hCG. These include vascular endothelial growth factor (VEGF) and several pro-inflammatory cytokines that interact to produce the characteristic pathophysiology of OHSS. This is marked by increased capillary permeability, leakage of fluid from the vasculature, third space fluid accumulation and intravascular dehydration. OHSS is classified based on clinical and laboratory features reflecting worsening pathophysiology (Table 1). In severe cases the features may include renal and hepatic dysfunction, thrombosis and pulmonary oedema, cerebral infarction; adult respiratory distress syndrome and hepatorenal failure are serious complications which have been reported as causes of rare mortality from OHSS.

This review examines the evidence for various methods of prevention of OHSS and offers general guidance for managing this condition.

Classification of ovarian hyperstimulation syndrome (OHSS): OHSS may be early onset (within 9 days of hCG trigger) or late onset (after 9 days from HCG trigger) with severity as indicated below

Mild
- Abdominal bloating
- Mild abdominal pain
- Ovarian size usually <8 cm*

Moderate
- Moderate abdominal pain
- Nausea ± vomiting
- Ultrasound evidence of ascites
- Ovarian size usually 8–12 cm*

Severe
- Clinical ascites (occasionally hydrothorax)
- Oliguria
- Haemoconcentration haematocrit >45%
- Hypoproteinaemia
- Ovarian size usually >12 cm*

Critical
- Tense ascites or large hydrothorax
- Haematocrit >55%
- WCC >25 000/ml
- Oligo/anuria
- Thromboembolism
- Adult respiratory distress syndrome (ARDS)

*Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration.

Table 1

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Prevention

Identifying the patient at risk

Younger women and women with polycystic ovaries (PCO) are at greater risk of developing OHSS, possibly related to the increased sensitivity of their ovaries to exogenous FSH stimulation. A previous history of OHSS is a risk factor for developing OHSS in subsequent ovarian stimulation cycles. These factors should be taken into account in deciding the treatment and the stimulation regimen for individual cycles.

Features may become apparent during an induction cycle that indicate a high risk of developing OHSS in that particular treatment episode. These include a large number of ovarian follicles, high oestradiol concentrations and a large number of eggs. Unfortunately, there is no agreement in the literature as to what constitutes a useful cut-off for follicle or oocyte numbers or oestradiol concentration and the predictive value of these parameters for OHSS is poor.

It must be remembered that women can develop OHSS even in the absence of these risk factors and that every cycle involving ovarian stimulation is at some degree of risk of OHSS.

Alternatives to ovarian stimulation

Depending on the clinical circumstances, alternatives which do not involve ovarian stimulation and do not carry a significant risk of OHSS should be considered. Extremes of body weight may be associated with ovulatory dysfunction, and optimizing this may restore ovulation without the need for further risky intervention. Avoidance of excessive exercise may have a similar role in some women. In women with polycystic ovarian syndrome (PCOS) there is a role for anti-oestrogens and insulin sensitizing agents as first-line pharmacological approaches to inducing ovulation. Laparoscopic ovarian diathermy can lead to ovulation in women with PCOS without a risk of OHSS. In other clinical situations, gonadotrophin releasing hormone (GnRH) pump and antidopiminergic agents are useful. The risk of OHSS is an important reason to consider other treatments before progressing to IVF.

Gonadotrophin ovulation induction cycles

In cycles where gonadotrophins are used to achieve ovulation, the aim should be to induce a monofollicular response, using a 'step-up' regimen. Ovarian stimulation is initiated with a low dose of FSH, followed by small incremental increases 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 higher and is decreased once ovarian response is initiated. Randomized trials show a lower risk of overstimulation with the step-up as compared to the step-down protocol.

Superovulation and IVF cycles

The majority of cases of OHSS in clinical practice arise from cycles of assisted conception, where exogenous ovarian stimulation is used to increase the number of oocytes available for fertilization. However, a number of measures are available to reduce the incidence of OHSS in women undergoing these treatments:

FSH dose

The dose of FSH administered for controlled ovarian hyperstimulation should take into account factors that may increase the risk of evoking an excessive ovarian response, particularly PCO, previous history of OHSS and young age. In these situations, a lower starting dose of FSH is usually recommended, with very cautious increases if the ovarian response is not judged sufficient.

GnRH antagonist

Prevention of a spontaneous luteinizing hormone (LH) surge in IVF cycles can be achieved either with GnRH agonists (GnRH-a) or antagonists. GnRH antagonists are associated with a shorter duration of stimulation, lower oestradiol levels and recruitment of a smaller number of ovarian follicles. Research indicates a potentially lower risk of OHSS with GnRH antagonists, in particular cetrorelix, as compared to agonists.

Metformin co-treatment

A systematic review shows that the risk of OHSS in women with PCOS undergoing IVF is reduced by co-treatment with metformin. Metformin-induced improvements in insulin resistance and hypersinulinaemia may underlie this phenomenon, as insulin is known to promote VEGF synthesis and secretion.

Coasting

Coasting is applicable in cycles where the ovarian response is thought to be excessive, as judged by serum oestradiol (E_2) and the number of developing ovarian follicles on transvaginal ultrasound scan. FSH injections are withheld, while maintaining pituitary suppression. Daily serum E_2 estimation and follicular tracking are carried out until E_2 drops to a 'safe' level. hCG is then administered, followed by oocyte retrieval and embryo transfer. Serum FSH levels decline significantly during the coasting period. Larger follicles have a lower dependence on FSH than smaller follicles and are capable of continuing their growth and maturation, while small and intermediate follicles undergo atresia. The concentrations of vasoactive mediators such as VEGF are also reduced during coasting. Retrospective studies suggest that coasting reduces, but does not abolish, the risk of OHSS and is one of the commonest preventative methods in clinical use.

Follicle aspiration prior to hCG

The rationale for this method is to reduce the total pool of ovarian granulosa cells, which are targets for hCG and the source of mediators that cause OHSS. The evidence regarding the preventative value of follicular aspiration prior to hCG is uncertain. The strategy involves an extra invasive procedure which may make it less acceptable to patients than coasting.

Reducing hCG exposure

hCG dose. hCG is commonly used as an LH surrogate to induce final follicular maturation prior to egg retrieval. There appears to be a correlation between the degree of exposure to hCG and the risk of OHSS. Hence, the lowest effective dose of hCG should be used, with the evidence suggesting that a dose of 5000 IU for final follicular maturation is reasonable, particularly in high-risk patients.

Cycle cancellation. OHSS is dependent on exposure to hCG, either exogenous or endogenous from a pregnancy. Hence, the most effective measure for preventing OHSS in cycles where the risk is believed to be high is to withhold hCG and cancel the treatment