Ovarian Hyperstimulation Syndrome: Diagnosis, Prevention and Management

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially life-threatening iatrogenic complication of ovarian stimulation. The symptoms of OHSS typically present in the luteal phase or in early pregnancy and range from a mild, self-limiting disorder to a life-threatening illness. While the disease has been reported to occur spontaneously, or after clomiphene citrate treatment, it most commonly occurs after gonadotropin administration for ovarian stimulation.

The reported incidence of the mild form of OHSS is 8-33%, between 1-7% for the moderate form and 0.1 to 2% for the severe form.

This guideline reviews our current understanding of the risk factors, pathophysiology, prevention strategies, and management of OHSS; a disease that, if not completely preventable, can be minimized. Evidence is graded as outlined in the report of the Canadian Task Force on Preventative Health Care (Table 1).

<table>
<thead>
<tr>
<th>Quality of Evidence Assessment</th>
<th>Classification of Recommendations</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>A</td>
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<tr>
<td>II-1</td>
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<td>II-2</td>
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<td>II-3</td>
<td>D</td>
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<td>III</td>
<td>E</td>
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<td>III</td>
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</table>

Evidence obtained from a least one properly randomized controlled trial.
Evidence from well-designed controlled trials without randomization.
Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.
Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.
Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
There is good evidence to recommend the clinical preventative action.
There is fair evidence to recommend the clinical preventative action.
The existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventative action; however, other factors may influence decision-making.
There is fair evidence to recommend against the clinical preventative action.
There is good evidence recommend against the clinical preventative action.
There is insufficient evidence (in quantity and/or quality) to make a recommendation; however, other factors may influence decision-making.
**Pathophysiology**

Ovarian hyperstimulation syndrome is the clinical manifestation of increased vascular permeability that results in a shift of serum from the intravascular space to the third space. There are two main clinical consequences to this fluid shift: excess fluid in the third space, predominantly the abdominal and pleural cavities, and hemoconcentration with reduced organ perfusion.

While the precise etiology of OHSS remains unclear, the action of luteinizing hormone (LH) or LH-like exposure (e.g. human chorionic gonadotropin, hCG) on granulosa cells of stimulated ovaries is a prerequisite to disease development. LH or hCG induces the release of mediators that increase vascular permeability. The most strongly implicated mediator is vascular endothelial growth factor (VEGF) which acts on endothelial surface receptors to increase cellular junctions between endothelial cells resulting in increased vascular permeability. Serum and follicular fluid VEGF concentrations have been observed to predict the occurrence, severity, and progress of OHSS. Other mediators that have been implicated in the development of OHSS including interleukin-6, angiotension II, epidermal growth factor (EGF), transforming growth factors (TGF), and platelet-derived growth factor (PDGF).

**Secondary risk factors**, those identifiable after the onset of ovarian stimulation, include:
- absolute levels or rate of increase of serum estradiol,
- follicular size and number,
- number of oocytes collected, and
- pregnancy.

**Clinical Presentation**

There is a broad spectrum of clinical manifestations by which OHSS severity is classified and graded. OHSS was first classified by Rabau et al. in 1967. Since then, there have been several classification systems used. The Golan grading system is the most widely referenced and divides OHSS into mild, moderate and severe disease. The most recent modification of the Golan system was published in 2010 (Table 2). This system also divides OHSS into mild, moderate and severe disease but incorporates ultrasound and laboratory parameters into the classification system affording more objectivity.

Mild, moderate, and severe forms are distinguished by the extent of fluid shift into the third space. The symptoms of mild OHSS include abdominal distention and pelvic discomfort, and may include nausea, vomiting, and diarrhea. Progression of illness to moderate OHSS is marked by worsening symptoms, ascites evident on ultrasound examination and moderate hemoconcentration. In severe OHSS, more fluid shifts into the third space (predominately the peritoneal and pleural cavities), leading to hypovolemia and severe hemoconcentration. Life-threatening complications of severe OHSS include hepatorenal failure, acute respiratory distress syndrome, hemorrhage from ovarian rupture and thromboembolism.

Besides disease severity, OHSS is further categorized based on the onset of the syndrome in relation to oocyte retrieval and/or hCG administration. Two distinct clinical forms
of OHSS are recognized: early OHSS and late OHSS. Early OHSS is an acute effect of exogenous hCG administration, occurring within 9 days of administration and correlated with ovarian response to gonadotropins. In contrast, late OHSS occurs more than 10 days after hCG administration and does not correlate to the ovarian response. Late OHSS is related to hCG administered for luteal phase support and/or endogenous hCG produced by an implanting embryo.24,29,30

Table 2. Humaidan’s proposed new clinical grading system for OHSS.28

<table>
<thead>
<tr>
<th>Objective criteria</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid in Douglas pouch</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fluid around uterus (major pelvis)</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Fluid around intestinal loops</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit &gt;45%</td>
<td>✓</td>
<td>±a</td>
<td>✓</td>
</tr>
<tr>
<td>White blood cells &gt;15,000/mm3</td>
<td>±a</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Low urine output</td>
<td>±a</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>&lt;600 mL/24 h</td>
<td>±a</td>
<td></td>
<td>±</td>
</tr>
<tr>
<td>Creatinine &gt;1.5 mg/dL</td>
<td>±</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>±c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotting disorder</td>
<td>±c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>±c</td>
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<table>
<thead>
<tr>
<th>Subjective criteria</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal distention</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pelvic discomfort</td>
<td>±b</td>
<td>±b</td>
<td>✓</td>
</tr>
<tr>
<td>Breathing disorder</td>
<td>±b</td>
<td>±b</td>
<td>±b</td>
</tr>
<tr>
<td>Acute pain</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ovarian enlargement</td>
<td>±</td>
<td>±</td>
<td>✓</td>
</tr>
<tr>
<td>Pregnancy occurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The ± sign means may or may not be present.
a If two of these are present, consider hospitalization.
b If present, consider hospitalization.
c If present, consider intensive care.

Prevention

Primary prevention

Primary prevention strategies intend to avoid the development of OHSS by identifying women at high-risk who can benefit from specific preventive strategies.

The selection of the stimulation protocol plays an important role in determining the magnitude of the ovarian response and hence the risk of developing OHSS. Three major aspects of the stimulation protocol could affect the intensity of the ovarian response: the type of gonadotropin-releasing hormone (GnRH) analogue used to suppress ovulation (agonist or antagonist), the starting dose of gonadotropins, and the type of gonadotropins administered.

1. Type of protocol

Evidence from a meta-analysis of randomized controlled trials of normo-ovulatory women indicates that the use of GnRH-antagonists instead of GnRH-agonists during ovarian stimulation for IVF reduces the risk of severe OHSS (OR 0.43; 95% CI 0.33, 0.57). Importantly, there was no evidence of a statistically significant difference in live birth rates between women receiving the antagonist compared with the agonist protocols. The reduction in OHSS was particularly pronounced in patients with polycystic ovarian syndrome, a finding replicated in a separate meta-analysis. The reduction in OHSS observed with GnRH-antagonist protocols can be partially explained by a lower number of growing follicles in the antagonist protocol. On average, one oocyte less is retrieved after ovarian stimulation in a GnRH-antagonist protocol versus a GnRH-agonist protocol. Agonist triggering is feasible in a GnRH-antagonist protocol as the pituitary remains responsive to a bolus dose of GnRH-agonist leading to a reduction in endogenous LH levels, luteolysis and thereby a reduction in the incidence of OHSS.

Recommendation

The use of GnRH antagonist protocols should be considered for both normo-ovulatory women and women with polycystic ovarian syndrome undergoing IVF treatment who are at higher risk of OHSS. (IA)

2. Starting dose

Selecting the optimal dose of gonadotropins that will result in an acceptable number of oocytes is complicated. Several studies have observed that the dose of gonadotropins can be reduced without affecting the pregnancy rates in GnRH agonist or GnRH antagonist IVF cycles. These studies did not examine OHSS incidence, however, one observational study of IVF treatment and one randomized controlled trial of controlled ovarian stimulation with IUI observed that a reduction in the dose of gonadotropins significantly reduced the incidence of OHSS.

Attempts to develop a predictive model of gonadotropin effect and OHSS risk using patient variables have been unsuccessful in providing pregnancy rates comparable to physician determined gonadotropin dosing.

Recommendation

Administration of the lowest-effective dose of gonadotropins is reasonable to reduce the risk of OHSS. (II-3B)

3. Type of gonadotropin used

Evidence from two meta-analyses indicates that the choice of urinary or recombinant human menopausal gonadotropin or FSH does not influence the incidence of OHSS.
Recommendation

As there appears to be no difference in the risk of OHSS with the use of either urinary or recombinant gonadotropins, the choice of gonadotropin preparation should be based on other clinical parameters. (IA)

4. Metformin in women with PCOS

Insulin and insulin-like growth factors (IGFs) promote VEGF production by luteinized granulosa cells synergistically with LH exposure. An increase in serum VEGF levels in women with insulin-resistance, as seen in PCOS, may play a role in the increased risk of OHSS in PCOS women. By increasing insulin sensitivity, metformin may reduce VEGF production and OHSS in women with PCOS.

A meta-analysis of 4 RCTs comparing metformin versus no treatment or placebo in 449 women with PCOS undergoing IVF reported a significant reduction in the risk of OHSS in metformin treated women (OR = 0.27; 95% CI 0.16, 0.47). There was no difference in clinical pregnancy rates or live birth rates. A subsequent RCT comparing metformin to placebo found a similar reduction in the risk of OHSS in metformin treated women with PCOS (OR = 0.28; 95% confidence interval, 0.11, 0.67).

Recommendation

Metformin should be used to reduce the risk of OHSS in women with PCOS undergoing IVF. (IA)

5. Acetyl-salicylic acid (Aspirin)

Platelet activation is known to increase VEGF levels in OHSS. Activated platelets also release substances, such as lysophosphatidic acid and histamine that increase vascular permeability in OHSS. By blocking the formation of thromboxane A2 in platelets, aspirin inhibits platelet activation and the production of such vasoactive substances giving it a potential role in the prevention of OHSS.

In a randomized trial of 3154 women undergoing IVF, low dose aspirin (100mg per day) given during ovarian stimulation was observed to reduce the risk of OHSS in a high risk subgroup.

Recommendation

Low dose aspirin may be considered to reduce the risk of OHSS in women undergoing IVF treatment. (IB)

6. In Vitro Maturation

The only reliable way to eliminate the risk of OHSS is to avoid gonadotropin ovarian stimulation altogether. In vitro maturation (IVM) involves the retrieval of immature oocytes from unstimulated or minimally stimulated ovaries. These immature oocytes are then cultured, matured, and fertilized in vitro.

IVM was first performed on human oocytes by Edwards in 1965. Since that time, widespread application of IVM has been limited as the pregnancy rates from IVM are lower than those of in vivo stimulation cycles.

The incidence of OHSS in women with PCOS undergoing ovarian hyperstimulation can be as high as 30%. Two case-control studies observed a significant reduction in the risk of OHSS in women with PCOS undergoing IVM compared to IVF. However, there was also a reduction in implantation, clinical pregnancy and live birth rates with IVM. No other published studies have compared OHSS rates in women with PCOS undergoing IVM compared to IVF.

Although several centres have reported their IVM experience in ovulatory women with no cases of OHSS occurring, no studies have been published comparing OHSS rates with IVM versus IVF in this population.

Recommendation
Although there is a lack of published evidence, in vitro maturation minimizes ovarian stimulation, and therefore, can be considered for the prevention of OHSS. (III) (IL)

Secondary prevention

Secondary prevention strategies attempt to diagnose and treat an existing disease in its early stages before it results in significant morbidity.

1. Low dose HCG triggering of final oocyte maturation

Critical to IVF success is the induction of final oocyte maturation and separation of the oocyte from the follicle wall using LH or an LH analogue. This is achieved most commonly with human chorionic gonadotropin (HCG). The most widely used dose of HCG in IVF is 10,000 IU. It can be expected that less aggressive stimulation of the corpora lutea with lower doses of hCG used to induce final oocyte maturation would result in a lower risk of OHSS. A decrease in the HCG serum concentration is associated with a reduced risk of OHSS while remaining sufficient to induce final oocyte maturation and achieve comparable pregnancy rates. However, the published literature on the influence of HCG dose on the incidence of OHSS is varied. Three randomized control trials have been published comparing lower to higher doses of HCG. Shaltout et al. compared 5000 IU to 10,000 IU HCG in 100 IVF patients and observed a higher incidence of mild OHSS in the group receiving 10,000 IU (8.3% vs. 2%). There were no cases of moderate or severe OHSS in either group. In contrast, Kolibianakis et al. randomized 80 women with PCOS to receive 10,000IU, 5000IU, or 2500IU HCG and documented no difference in the incidence of severe OHSS. Lin et al. randomized 164 women to receive either 6000 IU or 4000 IU HCG and, similarly, documented no difference in the moderate or severe OHSS risk. Although no statistical difference in moderate and severe OHSS rates was demonstrated, the incidence of OHSS was low in all trials. Reassuringly, the pregnancy rates in all three randomized controlled trials were similar between comparison groups. Non-randomized studies are similarly contradictory.

While it is biologically plausible that a reduction in the dose of HCG below 10,000 IU will reduce the incidence of OHSS yet not reduce pregnancy rates, further prospective randomized trials are needed before dosing recommendations can be made.

Recommendation

For the prevention of OHSS, effectiveness of the reduction of HCG dose below 10,000 IU for final oocyte maturation is not well established.

2. GnRH agonist triggering of final oocyte maturation

OHSS occurs after hCG administration as the LH activity of HCG potentiates the activity of corpora lutea. HCG levels remain elevated even after 6 days of administration due to its long half-life affecting the risk of OHSS development. In contrast to HCG, endogenous LH levels after GnRH agonist triggering return to baseline within 24 to 48 hours and thus there is no prolonged stimulation of the corpora lutea. After the endogenous LH levels return to baseline, GnRH agonist are functionally luteolytic due to their prolonged pituitary downregulation and suppression of LH as evidenced by the lower luteal progesterone and estradiol levels compared with cycles triggered with hCG. Such diminution of corpora lutea activity makes the use of a GnRH agonist for triggering oocyte maturation in antagonist IVF cycles a feasible option to reduce the incidence of OHSS.

It has been demonstrated that triggering final oocyte maturation with a GnRH agonist is an effective alternative to hCG for inducing
However, a significant reduction in pregnancy rates in GnRH agonist triggered cycles was initially reported as GnRH agonist triggering has a negative effect on the function of the corpus luteum and the endometrium. Luteal phase support with estradiol, progestins and low dose HCG have been shown to equalize pregnancy rates in more recent studies. Examples of published GnRH agonist triggering doses are presented in Table 3.

<table>
<thead>
<tr>
<th>Study</th>
<th>GnRH agonist trigger</th>
<th>Luteal Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babayof 2006 et al.</td>
<td>Triptorelin 0.2mg sc</td>
<td>50mg IM progesterone, estradiol 4mg</td>
</tr>
<tr>
<td>Beckers 2003 et al.</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Fauser 2002 et al.</td>
<td>Triptorelin 0.2mg sc</td>
<td>50mg IM progesterone</td>
</tr>
<tr>
<td>Humaidan 2010 et al.</td>
<td>Buserelin 0.5 mg sc</td>
<td>micronized progesterone 90mg od, estradiol 4mg daily and 1500IU HCG 35 hours after trigger</td>
</tr>
<tr>
<td>Kolibianakis 2005 et al.</td>
<td>Triptorelin 0.2mg sc</td>
<td>micronized progesterone 600mg</td>
</tr>
</tbody>
</table>

A meta-analysis of 11 randomized controlled trials comparing GnRH agonist with hCG for triggering final oocyte maturation reported a reduction in the incidence of moderate and severe OHSS (OR 0.10; 95% CI 0.01, 0.82). Of the 11 randomized control trials included in the analysis, 8 included fresh autologous IVF cycles and 3 included donor oocyte IVF cycles. In autologous cycles, the ongoing pregnancy rate (OR 0.45; 95% CI 0.31, 0.65) and live birth rates (OR 0.44; 95% CI 0.29, 0.68) were significantly reduced with the use of a GnRH agonist trigger. In the subgroup of donor oocyte IVF cycles, there was no reduction in ongoing pregnancy rates.

GnRH agonist triggering leads to a significant reduction in the circulating endogenous LH level compared with hCG triggering. Luteal LH plays a role not only for the steroidogenic activity of the corpus luteum, but also for the up-regulation of growth factors, such as VEGF, which are important for implantation.

Luteal supplementation of low dose HCG (e.g. 1000-1500 IU) has been shown to adequately support the luteal phase in GnRH agonist triggered cycles. A recent RCT reported a no difference in live birth rates between GnRH agonist triggering with HCG supplementation and hCG triggering and no cases of OHSS were observed in the GnRH agonist triggered group. GnRH agonist triggering combined with low-dose hCG supplementation rescues the luteal phase and achieves pregnancy rates similar to that seen after hCG triggering.

**Recommendation**

In GnRH antagonist protocols, triggering of final oocyte maturation with a GnRH agonist is recommended for the prevention of OHSS in women at higher risk. (IA)

### 3. Use of dopamine agonists

In OHSS, vascular permeability is increased due to activation of the VEGF-2 receptor. The dopamine agonist cabergoline can prevent this increase in vascular permeability by inactivating the VEGF-2 receptor while not disrupting VEGF-receptor mediated angiogenesis, which is important for pregnancy development.
Several trials have documented a reduction in the incidence, severity and duration of OHSS with the use of cabergoline around the time of ovulation induction. There is variability in the dose and duration of treatment published. Two recent meta-analyses of randomized controlled trials of carbergoline use in women at high risk of developing OHSS observed a significant reduction in the incidence of moderate OHSS. The reduction in severe OHSS was not significant in either analysis. There was no significant difference in pregnancy rate between those treated with cabergoline or placebo. Examples of cabergoline dosing regimes are presented in Table 4.

<table>
<thead>
<tr>
<th>Study</th>
<th>Dopamine agonist</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez 2007 et al.93</td>
<td>cabergoline 0.5mg po</td>
<td>daily for 8 days from the day of HCG</td>
</tr>
<tr>
<td>Carizza 2008 et al.94</td>
<td>cabergoline 0.5mg po</td>
<td>daily for three weeks from day after ooocyte retrieval</td>
</tr>
<tr>
<td>Salah Edeen 2009 et al.95</td>
<td>cabergoline 0.5mg po</td>
<td>daily for 2 days from the day of HCG and repeated after 1 week</td>
</tr>
<tr>
<td>Shaltout 2009 at al.96</td>
<td>cabergoline 0.25mg po</td>
<td>daily for 8 days from the day of HCG</td>
</tr>
</tbody>
</table>

**Recommendation**

The dopamine agonist cabergoline should be used to reduce the incidence of OHSS in women at higher risk. (IA)

**4. Withholding gonadotropins (coasting)**

Coasting is defined as withholding gonadotrophins for a variable number of days before administering hCG injection until safe estradiol levels are attained. This approach may prevent severe OHSS by reducing the FSH stimulation of granulosa cells thereby inhibiting their proliferation and reducing the number of granulosa cells and, consequently, the amount of vasoactive substances released in response to hCG.

Coasting was first described as a method to reduce the incidence of OHSS over 20 years ago. Since that time over 16 studies have examined coating; each using different coating techniques that can be broadly categorized as “early” or “late.” Early coating involves withholding gonadotropins once follicles reach 12-15mm in the presence of an elevated estradiol concentration. Late coating involves withholding gonadotropins once follicles are >15mm and the estradiol is markedly elevated. There is limited evidence to suggest one technique is superior to the other. A small retrospective study reported that both early and late coating were equivalent in reducing OHSS, with similar IVF outcomes. Most studies examined late coating.

A meta-analysis identified four randomized controlled trials of women at high risk of developing OHSS. There was no effect on the incidence of moderate to severe OHSS or in the achievement of clinical pregnancy when coating was compared with early unilateral follicular aspiration (two trials) or GnRH antagonist administration (one trial). A single trial found a benefit of coating over no coating for a reduction in moderate to severe OHSS (OR 0.17; 95% CI 0.03, 0.88) without effect on the clinical pregnancy rate (OR 0.56; 95% CI 0.20, 1.63).
Many, but not all observational studies have reported a significant reduction in OHSS with coasting compared to no coasting, and some have documented a decrease in clinical pregnancy rates after coasting, particularly if the duration of coast exceeds 3 days.

**Recommendation**

Coasting can be useful to reduce the incidence of moderate and severe OHSS. (IB)

5. **Freezing all embryos**

OHSS occurs in the luteal phase as a consequence of ovulatory or exogenous hCG, and in early gestation when endogenous hCG is produced. When OHSS develops in the luteal phase and pregnancy does not occur, the syndrome resolves spontaneously with the onset of the menses and only rarely progresses into severe disease. The elective cryopreservation of all embryos to avoid pregnancy and therefore, severe OHSS was first described in 1990.

A meta-analysis of two randomized controlled trials examined the effect of embryo cryopreservation on the risk of OHSS. One trial compared cryopreservation of all embryos with intravenous albumin infusion and subsequent fresh ET, and the second compared elective cryopreservation of all embryos with fresh ET, with both groups receiving albumin infusion on the day of egg retrieval. Both studies were of poor methodological quality with limited numbers of participants. Neither showed a statistically significant difference in the incidence of moderate or severe OHSS with cryopreservation of all embryos versus fresh embryo transfer in women at risk of OHSS.

While several non-randomized studies have highlighted similar pregnancy rates whether using elective cryopreservation of all embryos or fresh embryo transfer, the influence of a policy of elective cryopreservation of all embryos on cumulative pregnancy rate is unclear as embryo cryopreservation techniques and success rates vary among centres.

**Recommendation**

There is insufficient evidence to support the routine cryopreservation of all embryos to prevent the development of OHSS. (IIIL)

6. **IV Colloid infusions**

In the pathogenesis of OHSS, elevated levels of VEGF, and other vasoactive mediators, leads to increased vascular permeability. The administration of intravenous fluids such as human albumin is hypothesized to restore intravascular volume by increasing plasma colloid oncotic pressure preventing the sequelae of hypovolaemia, ascites and haemoconcentration. Albumin may also bind and inactivate VEGF and other such mediators of OHSS.

Two meta-analyses published in 2011 examined the use of intravenous albumin in women at high risk of developing OHSS for prevention of severe OHSS. Venetis et al. reported no difference in the risk of severe OHSS (OR, 0.80; 95% CI, 0.52, 1.22), early or late onset, and no difference was noted with varying albumin doses. Youssef et al. reported a borderline, statistically significantly lower incidence of severe OHSS in women that received IV albumin (OR 0.67; 95% CI 0.45, 0.99). While both meta-analyses included eight trials, Venetis et al. excluded one study included in Youssef et al. on the basis of overlapping publication, while Youssef et al. excluded one trial due to quasi-randomization. Sensitivity analysis with exclusion of potentially duplicated data was performed in the Youssef et al. meta-analysis showing a loss of significance in the reduction of severe OHSS with intravenous albumen (OR 0.75; 95% CI 0.47, 1.21).
In three randomized control trials there was evidence of a statistically significant reduction in the incidence of severe OHSS in women who received hydroxyethyl starch (HES) compared to placebo (OR 0.12; 95% CI 0.04, 0.40); however, two of the included trials may have overlapping data.115

**Recommendation**

There is insufficient evidence to support the use of intravenous albumin or hydroxyethyl starch to prevent the development of severe OHSS. (IC)

**Management**

Patients with mild to moderate OHSS can generally be managed on an outpatient basis. Treatment usually requires only oral analgesics and counseling regarding the signs and symptoms of progressing illness. Fluid intake and weight should be monitored daily and the woman should be in regular communication with someone experienced in monitoring and managing OHSS.

1. **Hospitalization**

Hospitalization for severe OHSS is uncommon but should be considered if there is severe abdominal pain, intractable nausea and vomiting, dyspnea and tachypnea, elevated liver enzymes, decreased urine output (< 600 mL/24 hours), abnormal elevation of liver enzymes or other significant biochemical abnormality.

The inpatient management of OHSS includes careful monitoring of the woman’s vital signs, weight, fluid balance, abdominal circumference and oxygen saturation. A chest X-ray and echocardiogram should be considered if pleural or pericardial fluid is suspected. Frequent assessment of hematocrit, electrolytes, liver enzymes and creatinine levels will assist in monitoring disease progression and response to treatment.

2. **Fluid management**

A balance is made between intravascular volume maintenance to ensure adequate organ perfusion and minimizing third space fluid accumulation. Fluids should be strictly monitored and IV fluids titrated to maintain adequate urine output.

Crystalloids and colloids are commonly used but have not been compared in the management of OHSS. As colloid solutions are more effective in expanding the intravascular volume, if adequate volume expansion is not achieved with an initial crystalloid administration, IV colloids should be initiated. Both albumin and hydroxyethyl starch (HES) have been used in the treatment of severe OHSS. A single study of 16 women with severe OHSS compared human albumin and 6% HES. Women who received 6% HES had a higher urine output, needed less abdominal paracentesis and drainage of pleural effusions, and had a shortened hospital stay.118

**Recommendation**

If volume depletion persists despite IV crystalloids, IV 6% HES may be considered. (II-3C)

3. **Paracentesis**

Ultrasound guided paracentesis or culdocentesis is indicated if there is tense ascites, or compromised renal or pulmonary function. Several case reports have documented an improvement in severe OHSS after drainage of ascites. A randomized trial of 21 women comparing culdocentesis and expectant management with IV fluids observed more rapid improvement of symptoms, and a shorter hospital stay in the culdocentesis group.
No major complications were reported.\textsuperscript{119} Further, culdocentesis may reduce the progression of moderate to severe disease.\textsuperscript{120}

**Recommendation**

Paracentesis or culdocentesis should be considered in the management of moderate and severe OHSS. (IB)

**4. Thromboprophylaxis**

Thromboembolism is a rare, but life-threatening complication of severe OHSS. There are no comparative trials of the effectiveness of thromboprophylaxis in women with OHSS.

**Recommendation**

Venous support stockings and daily prophylactic heparin therapy should be considered. (III) (I)

**Complications**

Thromboembolism, pericardial effusion, renal failure and adult respiratory distress syndrome are potential life-threatening complications of OHSS. Prompt identification and management of such complications are critical to the successful management of OHSS.

**Conclusion**

OHSS is a serious and preventable, potentially life-threatening complication of ovarian stimulation. In the primary prevention of OHSS, the use of modest ovarian stimulation in a GnRH antagonist protocol and triggering final oocyte maturation with a GnRH agonists is an effective strategy. Metformin should be considered in women with PCOS and low-dose aspirin can be considered for those at high risk of developing OHSS. Secondarily, coasting and the use of cabergoline are currently supported by the available evidence.

Mild and moderate OHSS can generally be managed on an outpatient basis with close monitoring. Severe OHSS may require hospitalization.

The implementation of evidence-based prevention and management strategies should enable clinicians to significantly reduce the occurrence and severity of OHSS.
References


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