The Diagnosis and Management of Ovarian Hyperstimulation Syndrome

Evidence: Medline, Embase, and the Cochrane database were searched for relevant articles, using the key words “ovarian hyperstimulation syndrome” and “gonadotropins,” and guidelines created by other professional societies were reviewed.

Values: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care. Recommendations for practice were ranked according to the method described in that report (Table 1).

Recommendations
1. Once the diagnosis of ovarian hyperstimulation syndrome is made, disease severity should be classified as mild, moderate, severe, or critical. (III-B)
2. The physician prescribing gonadotropins should inform each woman of her personal risk for ovarian hyperstimulation syndrome. (III-A)
3. In areas where patients do not have ready access to physicians familiar with the diagnosis and management of ovarian hyperstimulation syndrome, the physician prescribing gonadotropins should ensure that women are made aware that they should contact a physician or a member of the team within the hospital unit who has relevant experience, should the need arise. (III-B)
4. Outpatient management is recommended for women with mild and moderate ovarian hyperstimulation syndrome. If outpatient management for more severe ovarian hyperstimulation syndrome is to be undertaken, the physician should ensure that the woman is capable of adhering to clinical instructions and that there is a system in place to assess her status every 1 to 2 days. (III-A)
5. Paracentesis should be performed in admitted patients with tense ascites to alleviate their discomfort. (II-2B)
6. Outpatient culdocentesis should be considered for the prevention of disease progression in moderate or severe ovarian hyperstimulation syndrome. (II-2B)
7. Women with severe and critical ovarian hyperstimulation syndrome should be admitted to hospital for intravenous hydration and observation. (III-A)
8. Intravenous hydration should be initiated with a crystalloid solution to prevent hemococoncentration and provide adequate end-organ perfusion. If end-organ perfusion is not maintained with a crystalloid solution, an alternate colloid solution should be administered. (II-2B)
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9. Pain relief in admitted patients should be managed with acetaminophen and/or opioid analgesics. (III-B) Non-steroidal anti-inflammatory drugs with antiplatelet properties should not be used. (III-B)

10. Women with severe ovarian hyperstimulation syndrome should be considered for treatment with prophylactic doses of anticoagulants. (II-2B)

11. Critical ovarian hyperstimulation syndrome should be managed by a multidisciplinary team, according to the end organ affected. (III-C)

INTRODUCTION

Ovarian hyperstimulation syndrome is an iatrogenic complication of supraphysiologic ovarian stimulation. The syndrome is almost exclusively associated with exogenous gonadotropin stimulation and is only rarely observed after clomiphene citrate treatment or spontaneous ovulation. Clinicians who prescribe gonadotropins should be knowledgeable about the prevention, diagnosis, and management of OHSS.

Most OHSS is mild and of little clinical concern. However, when OHSS is severe it is occasionally associated with severe morbidity, and fatalities have been reported. With rare exceptions, OHSS occurs only after a luteinizing hormone surge or exposure to hCG. After gonadotropin superovulation for IVF, the reported incidence of moderate OHSS is 3% to 6%, and for severe forms is 0.1% to 2%. The mild form, which has little clinical consequence, occurs in about 20% to 33% of IVF cycles.

As OHSS is iatrogenic, the goal for physicians prescribing gonadotropins should be to identify women at increased risk, apply preventive strategies, and identify for active management women who may be at risk of developing more severe OHSS.

PATHOPHYSIOLOGY OF OHSS

Severe OHSS is a systemic condition thought to result from vasoactive peptides released from the granulosa cells in hyperstimulated ovaries. Clinically, the fundamental physiologic change in severe OHSS is an increase in vascular permeability resulting in a fluid shift from intravascular to third space compartments such as the peritoneal and thoracic cavities. Studies have shown serum vascular endothelial growth factor levels to correlate with the severity of OHSS. Additionally, hCG has been shown to increase VEGF expression in human granulosa cells, which in turn raises serum VEGF concentration. Other mediators, such as angiotensin II, insulin-like growth factor 1, and interleukin-6, have also been implicated in the disease process.

RISK FACTORS

Several factors independently increase the risk of developing severe OHSS. These include the following:

- Age < 30 years
- Polycystic ovaries or high basal antral follicle count on ultrasound
- Rapidly rising or high serum estradiol
- Previous history of OHSS
- Large number of small follicles (8 to 12 mm) seen on ultrasound during ovarian stimulation
- Use of hCG as opposed to progesterone for luteal phase support after IVF
- Large number of oocytes retrieved (> 20)
- Early pregnancy

CLINICAL PRESENTATION

OHSS is a clinical diagnosis and is divided into mild, moderate, severe, and critical (Table 2). The initial presentation of OHSS is most often abdominal bloating secondary to an increase in ovarian size; in more severe cases, the bloating may also be due to accumulation of intraperitoneal fluid. OHSS symptoms may begin as soon as 24 hours after hCG administration but become most severe 7 to 10 days after hCG, usually associated with the rise of endogenous hCG from an early pregnancy. When OHSS is classified as severe, the subsequent clinical picture is the result of increased vascular permeability and ascites leading to dehydration with hemoconcentration. The resulting decreased intravascular volume leads to oliguria.

The first sign of impending severe OHSS is usually abdominal bloating due to a small amount of ascites that can generally be detected by physical examination with abdominal percussion for shifting dullness or through ultrasound examination. Early intraperitoneal fluid accumulation can typically be visualized only through vaginal ultrasound, because enlarged superovulated ovaries make the pelvis difficult to image with transabdominal ultrasound. Once OHSS becomes severe, abdominal

ABBREVIATIONS

OHSS  Ovarian hyperstimulation syndrome
VEGF  vascular endothelial growth factor
distension due to ascites is more readily apparent. Ultrasound examination will usually show ovaries 10 to 12 cm in diameter filled with multiple luteal cysts. On gross examination, ascitic fluid is clear and straw coloured. Laboratory examination will show a high concentration of albumin and a low leukocyte count. Red blood cells are often found in the ascites, likely because of bleeding from the egg retrieval and/or the paracentesis procedure used to acquire the fluid sample. This extravascular albumin-rich exudate accumulates in the peritoneal cavity, occasionally in the pleura, and rarely in the pericardiac space. The loss of albumin from the intravascular compartment leads to decreased plasma oncotic pressure. The shift of intravascular fluid into extravascular compartments results in intravascular volume depletion and hemoconcentration with consequent hypercoagulability. An increase in urine specific gravity and hematocrit are useful in determining whether a patient is so dehydrated as to warrant hospital admission for intravenous hydration.

In general, leukocytosis is a harbinger of hemoconcentration and is thought to be due to monocyte tissue factor expression from the granulosa cells. In severe OHSS, electrolyte imbalance is also often observed.

If pleural effusion develops, women will present with tachypnea or shortness of breath. Drainage of abdominal ascites will also help resolve a pleural effusion. Large pleural effusions left untreated have resulted in adult respiratory distress syndrome.

Thromboembolic phenomena are the most severe complications of OHSS and can be fatal. To date, 8 fatalities resulting from OHSS have been reported, with the causes of death reported as thromboembolic disease, adult respiratory distress syndrome, and hepatorenal failure.

**DIAGNOSIS**

When OHSS is suspected, the managing clinician should seek out key historical and clinical findings. There must be a recent history of ovarian stimulation followed by ovulation or hCG administration. Classic symptoms of moderate to severe OHSS include a sensation of bloating, abdominal pain, rapid weight gain, and decreased urine output. Alternative diagnoses such as pelvic infection, intra-abdominal hemorrhage, ectopic pregnancy, appendicitis, and complications of ovarian cysts such as torsion or hemorrhage must be kept in mind.

**Evaluating Severity**

Once the diagnosis is established, the assessment of OHSS severity will direct further management. A practical classification of OHSS severity proposed by Navot et al. and modified by Mathur et al. is shown in Table 2. A distinction between “early onset” (occurring within 9 days of hCG administration) and “late onset” (occurring after 9 days of hCG administration) may be prognostic. In women who are not pregnant, early onset OHSS takes a milder course, resolving in a few days. In those who are pregnant, renewed ovarian stimulation from endogenous

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Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

<table>
<thead>
<tr>
<th>Quality of evidence assessment*</th>
<th>Classification of recommendations †</th>
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<tbody>
<tr>
<td>I: Evidence obtained from at least one properly randomized controlled trial</td>
<td>A. There is good evidence to recommend the clinical preventive action</td>
</tr>
<tr>
<td>II-1: Evidence from well-designed controlled trials without randomization</td>
<td>B. There is fair evidence to recommend the clinical preventive action</td>
</tr>
<tr>
<td>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group</td>
<td>C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making</td>
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<td>II-3: 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</td>
<td>D. There is fair evidence to recommend against the clinical preventive action</td>
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<tr>
<td>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees</td>
<td>E. There is good evidence to recommend against the clinical preventive action</td>
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<td></td>
<td>F. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making</td>
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*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.
†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.
hCG can lead to very severe OHSS that necessitates prolonged hospital care.

Patient Assessment
Careful assessment of the patient is needed to classify disease severity. This should include a review of her stimulation and a prediction of underlying risk based on age, onset of presentation, follicle number and size during stimulation, number of eggs retrieved, peak estradiol level, and estradiol level at trigger. The history should include an estimation of urine output and weight gain, and should seek to identify symptoms such as abdominal pain, bloating, shortness of breath, and the ability to maintain oral hydration.

Physical examination should include measurement of vital signs, body weight, abdominal girth at the umbilicus, and assessment for the presence of ascites, pleural effusion, and signs of venous thromboembolic disease, such as unilateral increase in calf diameter. Caution should be taken with pelvic examinations to minimize the risk of trauma to enlarged ovaries. Initial laboratory investigations should screen for hemoconcentration with a hematocrit and/or hemoglobin measurement and urine specific gravity.

### Recommendation

1. Once the diagnosis of ovarian hyperstimulation syndrome is made, disease severity should be classified as mild, moderate, severe, or critical. (III-B)

### MANAGEMENT

Very few comparative studies have been published on best management practices for OHSS. Therefore recommendations are predominantly based on the expert opinion of the authors and expert opinions voiced in review papers.

### Information and Communication

Women undergoing gonadotropin ovarian stimulation should be considered at risk for OHSS. Additional risk factors for developing OHSS include polycystic ovaries, age < 30, multiple developing follicles during stimulation, and previous OHSS. Every centre that offers assisted reproductive services should provide written information about OHSS including potential risks, signs and symptoms, and actions to take in case of symptoms. Patients should be told how they can contact a physician with expertise in the diagnosis and management of OHSS.

### Recommendations

2. The physician prescribing gonadotropins should inform each woman of her personal risk for ovarian hyperstimulation syndrome. (III-A)
3. In areas where patients do not have ready access to physicians familiar with the diagnosis and management of ovarian hyperstimulation syndrome, the physician prescribing gonadotropins should ensure that women are made aware that they should contact a physician or a member of the team within the hospital unit who has relevant experience, should the need arise. (III-B)

### Outpatient Management

Outpatient management is usually possible in women with mild and moderate OHSS. Women with severe disease may be considered for outpatient management if they are able to adhere to treatment and follow clinical instructions. Abdominal discomfort can be treated with acetaminophen with or without a narcotic agent. Non-steroidal anti-inflammatory drugs with antiplatelet properties should not be used as they may interfere with implantation and may also compromise renal function in patients with severe OHSS. To prevent additional hemoconcentration women should be encouraged to drink 2 to 3 litres of liquid per day.

### Table 2. Classification of OHSS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
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<tr>
<td>Mild OHSS</td>
<td>Abdominal bloating</td>
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<td></td>
<td>Mild abdominal pain</td>
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<tr>
<td></td>
<td>Ovarian size usually &lt; 8 cm</td>
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<tr>
<td>Moderate OHSS</td>
<td>Moderate abdominal pain</td>
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<tr>
<td></td>
<td>Nausea ± vomiting</td>
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<tr>
<td></td>
<td>Ultrasound evidence of ascites</td>
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<tr>
<td></td>
<td>Ovarian size usually 8 to 12 cm</td>
</tr>
<tr>
<td>Severe OHSS</td>
<td>Clinical ascites (occasionally pleural effusion)</td>
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<tr>
<td></td>
<td>Oliguria</td>
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<tr>
<td></td>
<td>Hemoconcentration hematocrit (&gt; 45%)</td>
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<tr>
<td></td>
<td>Hypoproteinemia</td>
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<tr>
<td></td>
<td>Ovarian size usually &gt; 12 cm</td>
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<tr>
<td>Critical OHSS</td>
<td>Tense ascites or large pleural effusion</td>
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<tr>
<td></td>
<td>Hematocrit (&gt; 55%)</td>
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<tr>
<td></td>
<td>White cell count &gt; 25 000</td>
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<tr>
<td></td>
<td>Oliguria/anuria</td>
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<tr>
<td></td>
<td>Thromboembolism</td>
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<td>Acute respiratory distress syndrome</td>
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day. Women should not engage in vigorous exercise or sexual intercourse because of the possibility of rupture or torsion of enlarged hyperstimulated ovaries. Paracentesis by transvaginal ultrasound guidance can be done through the outpatient clinic.\(^2\)

If outpatient management is to be successful, the patient must demonstrate willingness to adhere to a management strategy and must maintain regular communication with an experienced member of the health care team who can monitor clinical progress and recognize any deterioration in her condition.\(^3\) Patient assessment requires physical examination by a physician to determine if hospital admission is needed. Outpatient communication should address several key points, and an accurate record of the patient's progress should be kept (Table 3).

### Recommendation

4. Outpatient management is recommended for women with mild and moderate ovarian hyperstimulation syndrome. If outpatient management for more severe ovarian hyperstimulation syndrome is to be undertaken, the physician should ensure that the woman is capable of adhering to clinical instructions and that there is a system in place to assess her status every 1 to 2 days. (III-A)

### Paracentesis

Patients with tense ascites causing significant pain and/or respiratory compromise benefit from paracentesis. Paracentesis will also improve oliguria that is secondary to reduced renal perfusion from ascites increasing intra-abdominal pressure and compromising blood flow to the kidneys.\(^2\)^\(^3\) Insertion of an indwelling pigtail catheter under ultrasound guidance circumvents the need for multiple attempts at drainage and limits potential infectious complications.\(^2\) The ascites output should be recorded daily. Clinical resolution is achieved when paracentesis output starts to decrease as urine output increases. When ascites output is < 50 mL/ day the catheter can be removed. Drainage of ascites will also generally resolve a pleural effusion.

<table>
<thead>
<tr>
<th>Table 3. Daily communication checklist</th>
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<tbody>
<tr>
<td>• Is the patient adequately hydrated?</td>
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<tr>
<td>○ Quantitative estimates of oral intake and urine output</td>
</tr>
<tr>
<td>• Can she maintain adequate oral hydration?</td>
</tr>
<tr>
<td>• What is her weight today?</td>
</tr>
<tr>
<td>• What is her abdominal girth measured at the umbilicus?</td>
</tr>
<tr>
<td>• Are there any manifestations of severe or critical OHSS? Does the patient have worsening shortness of breath, calf pain, or new neurological deficits?</td>
</tr>
</tbody>
</table>

### Recommendation

5. Paracentesis should be performed in admitted patients with tense ascites to alleviate their discomfort. (II-2B)

### Culdocentesis

Culdocentesis can be offered in an attempt to prevent disease progression from moderate to severe OHSS and keep the woman out of hospital.\(^3\)

In addition to alleviating discomfort, culdocentesis may precipitate diuresis in women who are oliguric, and it helps resolution of severe OHSS.\(^3\)

<table>
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<tr>
<td>6. Outpatient culdocentesis should be considered for the prevention of disease progression in moderate or severe ovarian hyperstimulation syndrome. (II-2B)</td>
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</table>

### Pleuracentesis

Symptomatic pleural effusions that persist despite paracentesis can also be drained.

### Inpatient Management

Women with OHSS who are unable to maintain adequate oral hydration to minimize hemoconcentration and/or unable to overcome the discomfort of abdominal distension with oral analgesia need to be admitted to hospital for IV hydration and possibly paracentesis.

<table>
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<td>7. Women with severe and critical ovarian hyperstimulation syndrome should be admitted to hospital for intravenous hydration and observation. (III-A)</td>
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### Fluids and electrolytes

Women should drink according to their thirst. In addition, IV hydration with a crystalloid solution (100 to 150 mL/hr) should be instituted until diuresis occurs. If clinical and laboratory findings indicate persistent intravascular volume depletion despite aggressive IV fluid hydration, IV albumin (15 to 20 mL/hr of 25% albumin over 4 hours) should be initiated and repeated until hydration status improves.\(^3\) Diuretics should not be used as they can further deplete intravascular volume.
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Recommendation
8. Intravenous hydration should be initiated with a crystalloid solution to prevent hemoconcentration and provide adequate end-organ perfusion. If end-organ perfusion is not maintained with a crystalloid solution, an alternate colloid solution should be administered. (II-2B)

Pain relief
Symptomatic relief of abdominal pain can be achieved with acetaminophen and if necessary oral or parenteral opiates. Non-steroidal anti-inflammatory agents with antiplatelet properties should not be used because they may interfere with implantation and may also compromise renal function in women with severe OHSS.

Recommendation
9. Pain relief in admitted patients should be managed with acetaminophen and/or opioid analgesics. (III-B) Non-steroidal anti-inflammatory drugs with antiplatelet properties should not be used. (III-B)

Nausea and/or vomiting
Antiemetic agents considered to be safe in early pregnancy should be used to alleviate nausea and/or vomiting.

Prevention of thromboembolic complications
Hospitalized patients should be considered at risk of thrombosis secondary to hemoconcentration and immobilization. Daily prophylactic doses of low-molecular-weight heparin (e.g., dalteparin sodium 5000 IU/day) and use of thromboembolic deterrent stockings should be considered on admission and continued until discharge. However, there are no RCTs demonstrating that prophylactic anticoagulation prevents venous thromboembolism in cases of severe OHSS. In addition, there have been several reports of thromboembolism in women with OHSS treated with thromboprophylaxis.

Recommendation
10. Women with severe ovarian hyperstimulation syndrome should be considered for treatment with prophylactic doses of anticoagulants. (II-2B)

Monitoring
Admitted patients should be assessed by a physician at least once daily, with more frequent assessment in cases of critical OHSS. Weight and urine specific gravity should be recorded daily. Vital signs, urine output, and fluid balance should also be recorded. Urine output should be maintained at a minimum of 30 mL/hour. Physical examination should assess hydration, cardiorespiratory status, degree of ascites, and signs of thromboembolism. Daily monitoring of hemoglobin, hematocrit, creatinine, electrolytes, and albumin is useful to document disease progress. A weekly measurement of liver enzymes may also be useful.

Management of Complications
Renal failure, thromboembolism, pericardial effusion, and adult respiratory distress syndrome are potential life-threatening complications of OHSS. These conditions should be diagnosed early and managed by a multidisciplinary team possibly in an ICU setting.

Recommendation
11. Critical ovarian hyperstimulation syndrome should be managed by a multidisciplinary team, according to the end organ affected. (III-C)

Counselling
Women should be counselled, and their partners should be made aware, that the management of OHSS is primarily supportive until the condition resolves spontaneously. Women should be counselled regularly about the natural history of OHSS and advised that their clinical course may be prolonged should they become pregnant: they may have to be admitted to hospital for only a few days, but they may have to stay in hospital for as long as 4 weeks. It is also important to provide reassurance that pregnancy would not be adversely affected by the OHSS if complications of critical OHSS do not occur.

Conclusion
The key pathophysiological feature of OHSS is a fluid shift with extravascular fluid accumulation combined with intravascular volume depletion and hemoconcentration. This state of effective dehydration (and its detection and management) is the main clinical problem in the care of women with OHSS. Knowledge of OHSS risk factors, clinical presentation, and classification of severity are essential to the effective diagnosis and management of this disease. Mild manifestations of OHSS are common, occurring in up to one third of women being stimulated for IVF. Worsening symptoms can usually be managed on an outpatient basis if frequent monitoring and assessment is possible. Hospitalization may occasionally be necessary to prevent deterioration to critical disease.

Continued research will further our understanding of the pathophysiology of OHSS and may advance our ability to predict and prevent this potentially serious illness.
REFERENCES


