Ovarian Hyperstimulation Syndrome

Ovarian hyperstimulation syndrome (OHSS) is the most serious consequence of induction of ovulation, as part of assisted conception techniques.

It may occur after stimulation of the ovaries into superovulation with drugs such as human chorionic gonadotrophin (hCG) and human menopausal gonadotrophin. It is rare with clomifene except in polycystic ovarian syndrome (PCOS).

Many women with OHSS will be seen by doctors unfamiliar with the condition. This is because assisted conception treatment frequently takes place outside hospitals and also because serious OHSS is uncommon. Education and good communication are particularly important in providing safe and effective care to women with OHSS.[1]

Pathogenesis[2, 3]

The ovaries may form 20 follicles or more and swell following an increase in serum levels of hCG. OHSS is a systemic disease. Vasoactive mediators are released from the hyperstimulated ovaries, causing an increase in capillary permeability. This causes fluid shift from the intravascular compartment to third space compartments such as the peritoneal or thoracic cavities. Morbidity and even mortality can then be caused by effusions (pericardial, pleural, ascites), haemoconcentration (causing increased risk of thrombosis and coagulopathy) and liver or kidney dysfunction.

Classification[1, 4]

OHSS may be classified as mild, moderate or severe. Although mild cases are common and may not have any clinical significance, severe cases can be life-threatening.

<table>
<thead>
<tr>
<th>Grade and associated clinical features</th>
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<tbody>
<tr>
<td>Mild OHSS</td>
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<tr>
<td>• Abdominal bloating.</td>
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<tr>
<td>• Mild abdominal pain.</td>
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<tr>
<td>• Ovarian size usually &lt;8 cm.</td>
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<tr>
<td>Moderate OHSS</td>
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<tr>
<td>• Moderate abdominal pain.</td>
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<tr>
<td>• Nausea ± vomiting.</td>
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<tr>
<td>• Ultrasound evidence of ascites.</td>
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<tr>
<td>• Ovarian size usually 8-12 cm.</td>
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<tr>
<td>Severe OHSS</td>
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<tr>
<td>• Clinical ascites (occasionally hydrothorax).</td>
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<tr>
<td>• Oliguria.</td>
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<tr>
<td>• Haemoconcentration haematocrit &gt;45%.</td>
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<tr>
<td>• Hypoproteinaemia.</td>
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<tr>
<td>• Ovarian size usually &gt;12 cm.</td>
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<tr>
<td>Critical OHSS</td>
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<tr>
<td>• Tense ascites or large hydrothorax.</td>
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<tr>
<td>• Haematocrit &gt;55%.</td>
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<tr>
<td>• White cell count &gt;25 x 10⁹/L.</td>
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<tr>
<td>• Oligo-anuria.</td>
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<tr>
<td>• Thromboembolism.</td>
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<tr>
<td>• Adult respiratory distress syndrome (ARDS).</td>
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</table>

Epidemiology[1, 4]

• Despite careful monitoring, a mild degree of OHSS occurs in up to 33% of in vitro fertilisation (IVF) cycles.
• A moderate degree occurs in 3-6% of treatment cycles but can be higher in high-risk women.
• It may be severe in 0.1 to 2% of IVF cycles.

Risk factors[2, 4]

• PCOS.
• Age under 30.
• Rapidly rising oestrogen levels and a large number of follicles.
The use of hCG for luteal phase support.
Low body weight.

Presentation
The diagnosis of OHSS is based on clinical criteria and therefore clinicians should be aware of the signs and symptoms:[1]

- Symptoms may start within 24 hours of hCG administration but become severe after 7-10 days.
- Bloating is often the first symptom due to increased ovarian size in mild cases, or due to ascites in more severe cases. There may be associated pain.
- In 1% or 2% of cases with very enlarged ovaries, the patient is ill with severe pain, nausea and vomiting.
- There may also be pleural effusions with fluid passing from the abdomen into the pleural cavity.
- Extravasation of fluid can cause haemoconcentration and hypercoagulability with risk of thrombosis.

If a woman who is undergoing IVF treatment presents with severe bloating, nausea and vomiting, shortness of breath and reduced urine output, urgent assessment in hospital is required.

Investigations
Careful monitoring of the ovaries by ultrasound during treatment is mandatory. The rate of growth of follicles is measured and treatment is cut back if stimulation seems excessive. In severe OHSS, investigations include:

- Ultrasound of the ovaries and abdomen for fluid. A possible risk in this condition is torsion of the ovary and ultrasound scan may suggest this.
- FBC, as there may be haemoconcentration. Serious findings are haematocrit above 45% and white cell count above $15 \times 10^9/L$.
- U&E and creatinine, as renal function may be impaired.
- Coagulation screen.
- LFTs.
- CXR and lateral (to assess any pleural effusion).
- Measurement of abdominal girth daily.

Management[1, 4]
Management is essentially supportive until the condition resolves spontaneously. This often involves a multidisciplinary approach and should follow agreed protocols.

Currently risks are monitored by blood oestrogens and ultrasound scans, although a Cochrane review shows that it is probably sufficient to monitor with scans alone.[3] If blood oestrogens and ultrasound scans show a high risk of severe OHSS, hCG should be withheld. Egg collection and insemination may occur but any viable embryos should be frozen. Fresh embryo transfer should not occur in that cycle but frozen embryo transfer may take place in a subsequent treatment cycle. Routine freezing rather than fresh transfer as a matter of routine was not supported by a Cochrane review.[3] "Coasting" is the term used for stopping the gonadotrophin stimulation and continuing the agonist suppression until oestrogen levels decline to acceptable values before proceeding to egg collection. A 2011 Cochrane review found no evidence of benefit for this strategy.[4] Other reviews, however, have found weak evidence that coasting may reduce the incidence of severe OHSS.[7]

Management of mild-to-moderate cases
- Analgesia should take the form of paracetamol and/or opiates. Non-steroidal anti-inflammatory agents (NSAIDs) should be avoided.
- Antiemetics considered safe in early pregnancy should be used where need be.
- Women should be encouraged to increase oral fluids and drink according to their thirst.
- Where managed in the community, women should be monitored every 1-2 days and be made aware of symptoms which should prompt immediate assessment.
- In moderate cases admission to hospital for thromboprophylaxis and monitoring may be judicious.

Management of severe cases
- An intensive care setting may be required.
- Careful monitoring of fluid balance is needed. Intravenous (IV) fluids should be used if hydration cannot be maintained orally. A colloid such as albumin is given if, despite intensive IV fluid input, a woman remains fluid-depleted.
- Electrolytes require careful monitoring - hyponatraemia is common.
- Diuretics should be avoided.
- Aspiration of ascites or pleural effusion can relieve symptoms.
- Intense monitoring (as per the 'Investigations' section, above) is needed so that complications such as acute kidney injury (AKI), thromboembolism, pericardial effusion and ARDS are diagnosed early and managed appropriately.

Complications
Thromboembolism.
ARDS.
AKI.
Ovarian torsion.

Death has occurred but is rare.

Prevention[2, 7]

OHSS is an iatrogenic condition and large numbers of strategies have been investigated to try to reduce the incidence. Techniques which may reduce risk include:

- Individualised stimulation regimes dependent on risk stratification. Step-up regimens of gonadotrophin.
- Use of gonadotrophin-releasing hormone (GnRH) agonists rather than hCG as an ovulation trigger. This has been shown to reduce OHSS but also reduces live birth rates.[6] (No reduction of live birth rate if embryos are frozen and not used in that cycle, or in donor-recipient IVF cycles.)
- Freezing embryos and implanting in another cycle. In itself this does not reduce the risk significantly but in combination with the use of GnRH agonists virtually eliminates it.[5]
- Use of progesterone rather than hCG for luteal phase support. This significantly lowers the risk.[8]
- Use of metformin in women with PCOS. This has been found to reduce the risk of OHSS, but does not improve live birth rates.[10]
- Use of cabergoline in women at high risk, starting from the day of hCG administration.[11] Cabergoline is a dopamine antagonist which reduces the risks of increased vascular permeability and has been shown to protect against moderate OHSS in women at higher risk.
- Use of GnRH antagonists to reduce endogenous gonadotrophin release in women at high risk. When used with long GnRH agonist protocols, there has been shown to be a reduction of OHSS without impact on live birth rates.[12]
- Use of infusions of hydroxyethyl starch (HES) as a plasma expander preventatively in women at high risk.[13]

Techniques which have been investigated but efficacy found to be lacking include:

- Preventative infusions of albumin.[13]
- Coasting (withholding gonadotrophins as described in ‘Management’, above).[6]
- Use of recombinant vs urinary gonadotrophins does not appear to have an effect either way.
- Aromatase inhibitors in women with PCOS.[14]

Further reading & references

- Fertility - Assessment and treatment for people with fertility problems; NICE Guidance (February 2013, updated Aug 2016)
- The Management of Ovarian Hyperstimulation Syndrome; Royal College of Obstetricians and Gynaecologists (2016)

4. The diagnosis and management of ovarian hyperstimulation syndrome; Joint Society of Obstetricians and Gynaecologists (SOG) and Canadian Fertility and Andrology Society (CFAS) (November 2011)

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