Royal College of Obstetricians & Gynaecologists

The Management of Ovarian Hyperstimulation Syndrome

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The Management of Ovarian Hyperstimulation Syndrome

This is the third edition of this guideline, previously published in 2006 with the same title.

Executive summary of recommendations

Incidence of ovarian hyperstimulation syndrome (OHSS)

What is the reported incidence of OHSS?

Clinicians must remain alert to the possibility of OHSS in all women undergoing fertility treatment and women should be counselled accordingly. [*New 2016*] D

Diagnosis of OHSS

How is OHSS diagnosed and what differential diagnoses should be considered?

Clinicians need to be aware of the symptoms and signs of OHSS, as the diagnosis is based on clinical criteria. D

In women presenting with severe abdominal pain or pyrexia, extra care should be taken to rule out other causes of the patient's symptoms. The input of clinicians experienced in the management of OHSS should be obtained in such cases. [*New 2016*] D

Assessing severity and reporting adverse outcomes

How is the severity of OHSS classified?

The severity of OHSS should be graded according to a standardised classification scheme. D

How should OHSS be reported?

Licensed centres should comply with Human Fertilisation and Embryology Authority (HFEA) regulations in reporting cases of severe or critical OHSS among their patients. ✓

Units that treat women with OHSS should inform the licensed centre where the fertility treatment was carried out to promote clinical continuity and to allow the licensed centre to meet its legal obligations. ✓

Organisation of services

How should care be delivered for women at risk of OHSS?

Fertility clinics should provide verbal and written information concerning OHSS to all women undergoing fertility treatment, including a 24-hour contact telephone number. D

All acute units where women with suspected OHSS are likely to present should establish agreed local protocols for the assessment and management of these women and ensure they have access to appropriately skilled clinicians with experience in the management of this condition. ✓

Licensed centres that provide fertility treatment should ensure close liaison and coordination with acute units where their patients may present. [*New 2016*] ✓

Initial assessment

How should women suspected of suffering from OHSS be assessed?

Women presenting with symptoms suggestive of OHSS should be assessed face-to-face by a clinician if there is any doubt about the diagnosis or if the severity is likely to be greater than mild. [*New 2016*] D

Outpatient management of OHSS

Which patients with OHSS are suitable for outpatient care?

Outpatient management is appropriate for women with mild or moderate OHSS and in selected cases with severe OHSS. D

What management is appropriate in the outpatient setting for patients with OHSS?

Women undergoing outpatient management of OHSS should be appropriately counselled and provided with information regarding fluid intake and output monitoring. In addition, they should be provided with contact details to access advice. D

Nonsteroidal anti-inflammatory agents should be avoided, as they may compromise renal function. D

Women with severe OHSS being managed on an outpatient basis should receive thromboprophylaxis with low molecular weight heparin (LMWH). The duration of treatment should be individualised, taking into account risk factors and whether or not conception occurs. D

Paracentesis of ascitic fluid may be carried out on an outpatient basis by the abdominal or transvaginal route under ultrasound guidance. D

There is insufficient evidence to support the use of gonadotrophin-releasing hormone antagonists or dopamine agonists in treating established OHSS. [*New 2016*] D

How should women with OHSS managed on an outpatient basis be monitored?

Women with OHSS being managed on an outpatient basis should be reviewed urgently if they develop symptoms or signs of worsening OHSS (see Section 9.3). In the absence of these, review every 2–3 days is likely to be adequate. [*New 2016*] ✓

Baseline laboratory investigations should be repeated if the severity of OHSS is thought to be worsening. Haematocrit is a useful guide to the degree of intravascular volume depletion. [*New 2016*] D

Inpatient management

When should women with OHSS be admitted?

Hospital admission should be considered for women who: D

- **are unable to achieve satisfactory pain control**
- **are unable to maintain adequate fluid intake due to nausea**
- **show signs of worsening OHSS despite outpatient intervention**
- **are unable to attend for regular outpatient follow-up**
- **have critical OHSS. [*New 2016*]**

Who should provide care to women with OHSS?

Multidisciplinary assistance should be sought for the care of women with critical OHSS and severe OHSS who have persistent haemoconcentration and dehydration. D

Features of critical OHSS should prompt consideration of the need for intensive care. D

A clinician experienced in the management of OHSS should remain in overall charge of the woman's care. ✓

How should women with OHSS be monitored?

Women admitted with OHSS should be assessed at least once daily. More frequent assessment is appropriate for women with critical OHSS and those with complications. D

How should the symptoms of OHSS be relieved?

Analgesia and antiemetics may be used in women with OHSS, avoiding nonsteroidal agents and medicines contraindicated in pregnancy. D

What is the appropriate management of fluid balance?

Fluid replacement by the oral route, guided by thirst, is the most physiological approach to correcting intravascular dehydration. D

Women with persistent haemoconcentration despite volume replacement with intravenous colloids may need invasive monitoring and this should be managed with anaesthetic input. D

Diuretics should be avoided as they further deplete intravascular volume, but they may have a role in a multidisciplinary setting if oliguria persists despite adequate fluid replacement and drainage of ascites. ✓

How should ascites and effusions be managed?

Indications for paracentesis include the following: D

- **severe abdominal distension and abdominal pain secondary to ascites**
- **shortness of breath and respiratory compromise secondary to ascites and increased intra-abdominal pressure**
- **oliguria despite adequate volume replacement, secondary to increased abdominal pressure causing reduced renal perfusion.**

Paracentesis should be carried out under ultrasound guidance and can be performed abdominally or vaginally. C

Intravenous colloid therapy should be considered for women who have large volumes of fluid removed by paracentesis. D

How should the risk of thrombosis be managed?

Women with severe or critical OHSS and those admitted with OHSS should receive LMWH prophylaxis. C

The duration of LMWH prophylaxis should be individualised according to patient risk factors and outcome of treatment. [*New 2016*] D

Women with moderate OHSS should be evaluated for predisposing risk factors for thrombosis and prescribed either antiembolism stockings or LMWH if indicated. ✓

In addition to the usual symptoms and signs of venous thromboembolism (VTE), thromboembolism should be suspected in women with OHSS who present with unusual neurological symptoms, even if they present several weeks after apparent improvement in OHSS. D

When is surgical management indicated?

Surgery is only indicated in patients with OHSS if there is a coincident problem such as adnexal torsion, ovarian rupture or ectopic pregnancy and should be performed by an experienced surgeon. D

OHSS and pregnancy

What are the risks associated with pregnancy and OHSS?

Clinicians should be aware, and women informed, that pregnancies complicated by OHSS may be at increased risk of pre-eclampsia and preterm delivery. [*New 2016*] C

1. Purpose and scope

Ovarian hyperstimulation syndrome (OHSS) is a complication of fertility treatment, which uses pharmacological ovarian stimulation to increase the number of oocytes and therefore embryos available during assisted reproductive technology (ART). In a minority of women undergoing treatment, the ovarian response exceeds that aimed for and results in a clinical condition with a specific pathophysiology. OHSS is associated with significant physical and psychosocial morbidity and has been associated with maternal death.[1] However, in most cases OHSS is self-limiting and requires supportive management and monitoring while awaiting resolution. Women with more severe OHSS may require inpatient treatment to manage the symptoms and reduce the risk of further complications. The key principles of OHSS management therefore are early recognition and the prompt assessment and treatment of women with moderate or severe OHSS.

The mechanism whereby OHSS develops has received a lot of interest in recent years and key proinflammatory mediators are believed to be involved in the pathogenesis.[2,3] However, translating this basic scientific knowledge into clinical practice has so far proved difficult. There are few high quality studies that address the management of OHSS, and the subject remains of great significance not only to clinicians who provide assisted conception treatment, but also to those who look after affected women in emergency and gynaecology departments distinct from the treating clinic. Very often, women with

OHSS present to clinicians who are not fertility specialists or who do not undertake assisted conception. This guideline aims to review the literature and provide evidence-based advice to help clinicians diagnose and manage patients with OHSS. Prevention of OHSS is outside the scope of this guideline and is covered by guidance from the British Fertility Society.[4]

2. Introduction and background epidemiology

Exposure of ovaries to human chorionic gonadotrophin (hCG) or luteinising hormone (LH) following controlled ovarian stimulation by follicle-stimulating hormone (FSH) underlies most cases of OHSS. Exposure of hyperstimulated ovaries to hCG leads to the production of proinflammatory mediators. Chief among these is vascular endothelial growth factor (VEGF), but a variety of cytokines are likely to be involved in the pathogenesis and clinical features of OHSS.[1] The occurrence of ovarian enlargement with the local and systemic effects of proinflammatory mediators, including increased vascular permeability and a prothrombotic effect, is responsible for the clinical features of OHSS.

Increased vascular permeability leads to loss of fluid into the third space, manifesting as ascites or, less commonly, pleural and pericardial effusions. Women with severe OHSS demonstrate hypovolaemia, with a typical loss of 20% of their calculated blood volume in the acute phase of OHSS.[5] Accompanying this hypovolaemia is reduced serum osmolality and sodium. This paradoxical combination of hypovolaemia and hypo-osmolality has been ascribed to a 'reset' of the osmotic thresholds of vasopressin and thirst to lower osmolality and sodium levels as these women remain able to concentrate and dilute their urine around the new, lower, level of osmolality. The parallel resetting of the osmotic thresholds is thought to explain the observed decreases in serum osmolality and sodium as opposed to electrolyte losses.[6,7]

Despite the growing number of cycles of assisted reproduction, the true incidence of OHSS remains unknown because there is no mandatory reporting for mild and moderate cases. Furthermore, the lack of an internationally agreed classification system makes it difficult to compare data from different units.[8]

3. Identification and assessment of evidence

This guideline was developed in accordance with standard methodology for producing Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guidelines. MEDLINE, EMBASE and the Cochrane Library were searched. The search was restricted to articles published between January 2006 and May 2015. The databases were searched using the relevant Medical Subject Headings (MeSH) terms including all subheadings and this was combined with a keyword search. Search terms included 'ovarian hyperstimulation syndrome', 'ovary hyperstimulation', 'OHSS', 'hyperstimulation' and 'hyper-stimulation'. The National Guideline Clearinghouse, NICE Evidence Search, Trip and Guidelines International Network were also searched for relevant guidelines. Where possible, recommendations are based on available evidence. Areas lacking evidence are highlighted and annotated as 'good practice points' (GPP).

4. Incidence of OHSS

4.1 What is the reported incidence of OHSS?

Clinicians must remain alert to the possibility of OHSS in all women undergoing fertility treatment and women should be counselled accordingly. D

It is known that the incidence of OHSS varies between different types of fertility treatment, with treatments involving greater degrees of ovarian stimulation being associated with a higher incidence. In cycles of conventional in vitro fertilisation (IVF), mild OHSS has been estimated

Evidence level 3

to affect around one-third of cycles, while the combined incidence of moderate or severe OHSS varies from 3.1% to 8%.[9] The 14th European IVF-Monitoring report,[10] analysing data from 25 European countries, found an incidence of hospitalisation due to OHSS of 0.3% in 2010. Data from the USA showed OHSS to be the commonest complication of IVF treatment,[11] with an incidence of moderate or severe OHSS in 2011 of 1.1%. OHSS is rare following ovulation induction with clomifene, or monofollicular ovulation induction with gonadotropins, but it has been reported. Very rarely, OHSS may occur spontaneously, in association with pregnancy.[12]

Evidence level 3

Certain patient and cycle characteristics increase the risk of OHSS; women with a previous history of OHSS, polycystic ovary syndrome, increased antral follicle count (AFC) or high levels of anti-Müllerian hormone (AMH) are at an increased risk of OHSS. Evidence from meta-analysis[13] also shows a reduced risk of OHSS in IVF cycles employing gonadotrophin-releasing hormone (GnRH) antagonists compared with cycles where GnRH agonists are used as part of the regimen for controlled ovarian hyperstimulation. However, OHSS still occurs despite these preventive measures and can occur in patients and treatment cycles that do not meet any criteria that might be considered 'high risk' for the development of OHSS. The outcome of treatment also influences the incidence, which is higher in cycles where conception occurs, compared with cycles without conception, and higher still in cycles resulting in multiple pregnancy, highlighting the important role of endogenous hCG.

Evidence level 2+

5. Diagnosis of OHSS

5.1 How is OHSS diagnosed and what differential diagnoses should be considered?

Clinicians need to be aware of the symptoms and signs of OHSS, as the diagnosis is based on clinical criteria. D

In women presenting with severe abdominal pain or pyrexia, extra care should be taken to rule out other causes of the patient's symptoms. The input of clinicians experienced in the management of OHSS should be obtained in such cases. D

The diagnosis of OHSS is made on clinical grounds (Tables 1 and 2). The typical patient presents with abdominal distension and discomfort following the trigger injection used to promote final follicular maturation prior to oocyte retrieval. There may be a preceding history of an excessive ovarian response to stimulation, but the absence of such a history does not rule out a diagnosis of OHSS. The time of presentation following trigger injection divides patients into two groups: early and late OHSS. 'Early' OHSS usually presents within 7 days of the hCG injection and is usually associated with an excessive ovarian response. 'Late' OHSS typically presents 10 or more days after the hCG injection and is usually the result of endogenous hCG derived from an early pregnancy. The preceding ovarian response in these women may be unremarkable. Late OHSS tends to be more prolonged and severe than the early form.[14]

Evidence level 3

The symptoms of OHSS are not specific and there are no diagnostic tests for the condition. Hence, care must be taken to exclude other serious conditions that may present in a similar manner but require very different management. Careful assessment by an experienced clinician may be needed, along with full blood count, serum electrolytes and osmolality, pelvic ultrasound scan and, in selected cases, abdominal imaging. The combination of elevated haematocrit and reduced serum osmolality and sodium is indicative of OHSS.[7] It should be remembered that OHSS by itself is not commonly associated with severe pain, pyrexia or signs of peritonism. The presence of these features should lead to a thorough clinical review and investigation to

rule out other diagnoses. Important differential diagnoses include pelvic infection, pelvic abscess, appendicitis, ovarian torsion or cyst rupture, bowel perforation[15] and ectopic pregnancy. OHSS should not, therefore, be the 'default diagnosis' for women presenting with abdominal pain during fertility treatment.

Evidence level 3

Table 1. Relevant history from a woman suspected to be suffering from OHSS

History
Time of onset of symptoms relative to trigger
Medication used for trigger (hCG or GnRH agonist)
Number of follicles on final monitoring scan
Number of eggs collected
Were embryos replaced and how many?
Polycystic ovary syndrome diagnosis?
Symptoms
Abdominal bloating
Abdominal discomfort/pain, need for analgesia
Nausea and vomiting
Breathlessness, inability to lie flat or talk in full sentences
Reduced urine output
Leg swelling
Vulval swelling
Associated comorbidities such as thrombosis

Table 2. Examination and investigation of women with suspected OHSS

Examination
General: assess for dehydration, oedema (pedal, vulval and sacral); record heart rate, respiratory rate, blood pressure, body weight
Abdominal: assess for ascites, palpable mass, peritonism; measure girth
Respiratory: assess for pleural effusion, pneumonia, pulmonary oedema
Investigations
Full blood count
Haematocrit (haemoconcentration)
C-reactive protein (severity)
Urea and electrolytes (hyponatraemia and hyperkalaemia)
Serum osmolality (hypo-osmolality)
Liver function tests (elevated enzymes and reduced albumin)
Coagulation profile (elevated fibrinogen and reduced antithrombin)
hCG (to determine outcome of treatment cycle) if appropriate
Ultrasound scan: ovarian size, pelvic and abdominal free fluid. Consider ovarian Doppler if torsion suspected
Other tests that may be indicated
Arterial blood gases
D-dimers
Electrocardiogram (ECG)/echocardiogram
Chest X-ray
Computerised tomography pulmonary angiogram (CTPA) or ventilation/perfusion (V/Q) scan

6. Assessing severity and reporting adverse outcomes

6.1 How is the severity of OHSS classified?

The severity of OHSS should be graded according to a standardised classification scheme. **D**

Several schemes have been developed for classifying the severity of OHSS,[16–19] with no clear agreement between investigators. The scheme in Table 3 is based on the classification of OHSS severity proposed in the previous edition of the RCOG guideline combined with useful features from previous classifications. Evidence level 4

Table 3. Proposed RCOG classification of severity of OHSS

Category	Features
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 (± hydrothorax) Oliguria (< 300 ml/day or < 30 ml/hour) Haematocrit > 0.45 Hyponatraemia (sodium < 135 mmol/l) Hypo-osmolality (osmolality < 282 mOsm/kg) Hyperkalaemia (potassium > 5 mmol/l) Hypoproteinaemia (serum albumin < 35 g/l) Ovarian size usually > 12 cm[a]
Critical OHSS	Tense ascites/large hydrothorax Haematocrit > 0.55 White cell count > 25 000/ml Oliguria/anuria Thromboembolism Acute respiratory distress syndrome

[a] Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration. Women demonstrating any feature of severe or critical OHSS should be classified in that category.

Rarely, OHSS may be associated with life-threatening complications, including renal failure, acute respiratory distress syndrome (ARDS), haemorrhage from ovarian rupture, and thromboembolism.[1,2,20–22] The precise risk of mortality from OHSS is unknown, because there is no obligation to report such cases internationally. There were three deaths from OHSS between 1984 and 2008 in the Netherlands; it is estimated that 100 000 IVF cycles were performed during this period.[1] No deaths were reported in 209 cases of severe or critical OHSS arising from 73 492 cycles of IVF performed between 1987 and 1996 in 16 out of 19 tertiary centres in Israel.[23] The 2011 triennial report of the Confidential Enquiries into Maternal Deaths in the UK[24] did not identify any maternal deaths due to OHSS in the period 2006–08, during which time approximately 119 000 IVF and intracytoplasmic sperm injection (ICSI) cycles were carried out in 92 813 women. Evidence level 3

6.2 How should OHSS be reported?

Licensed centres should comply with Human Fertilisation and Embryology Authority (HFEA) regulations in reporting cases of severe or critical OHSS among their patients. ✓

Units that treat women with OHSS should inform the licensed centre where the fertility treatment was carried out to promote clinical continuity and to allow the licensed centre to meet its legal obligations. ✓

Any death related to OHSS in the UK must be reported to MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK),[25] irrespective of whether the woman was pregnant.

UK clinics providing licensed fertility treatment are obliged to follow relevant Human Fertilisation and Embryology Authority (HFEA) guidelines[26] for reporting severe untoward incidents. In the context of OHSS, this may be taken to include cases of severe or critical OHSS (as per the classification above) where hospitalisation is needed. Clinicians must recognise the importance of accurately reporting OHSS as a means of providing reliable data to help patients, researchers and commissioners of services. The HFEA requires that all incidents be reported verbally within 12 working hours, followed by a completed incident form within 24 working hours of the incident being identified.

Evidence level 4

Since women with OHSS are often admitted to centres other than the treating unit, it is important for the admitting centre to inform the originating clinic. The duty to report cases of OHSS to the HFEA, however, lies with the Person Responsible of the licensed centre providing the fertility treatment.

7. Organisation of services

7.1 How should care be delivered for women at risk of OHSS?

Fertility clinics should provide verbal and written information concerning OHSS to all women undergoing fertility treatment, including a 24-hour contact telephone number. D

All acute units where women with suspected OHSS are likely to present should establish agreed local protocols for the assessment and management of these women and ensure they have access to appropriately skilled clinicians with experience in the management of this condition. ✓

Licensed centres that provide fertility treatment should ensure close liaison and coordination with acute units where their patients may present. ✓

OHSS results from fertility treatment carried out, in the UK, in specialist units licensed for this purpose by the HFEA. In many cases, the treating unit is separate to, and some distance from, acute gynaecology or emergency departments where women may present with symptoms of OHSS. As a result, in certain situations the clinicians looking after a patient with OHSS may lack experience in managing this condition. Efforts should be made to reduce the risk associated with this by patient empowerment and coordination of services between licensed centres and the acute units where their patients are likely to present.

Women should be informed of the symptoms of OHSS and of the importance of reporting these. Information concerning OHSS should be delivered face-to-face to all patients undergoing fertility treatment, backed up with written information[27] and advice including a 24-hour contact. They should be advised to mention that they are undergoing fertility treatment even if they present with an apparently unrelated symptom, such as headache or visual disturbance.

Evidence level 4

Gynaecology and emergency departments in acute hospitals should develop evidence-based local protocols covering the assessment and management of women presenting with suspected OHSS. Input should be available from senior clinicians with experience of managing OHSS and, as soon as practicable, women with OHSS should be transferred to the care of such clinicians.

The licensed centre should agree referral pathways and protocols with the acute units to ensure that specialists provide continuity of care for their patients with OHSS, particularly when women are admitted to a centre without the required specialist expertise. Acute hospitals with assisted conception units should ensure that 24-hour input is available from relevant senior clinicians.

8. Initial assessment

8.1 How should women suspected of suffering from OHSS be assessed?

Women presenting with symptoms suggestive of OHSS should be assessed face-to-face by a clinician if there is any doubt about the diagnosis or if the severity is likely to be greater than mild. **D**

The aim of initial assessment is to establish the diagnosis (see section 5) and grade the severity of OHSS (see section 6). Women with symptoms of OHSS may in the first instance be assessed over the telephone. It is important for staff triaging women over the telephone to have a clear understanding of the women who will require face-to-face clinical review. Important points to be noted in the history are specified in Table 1. Specific enquiry should be made for significant abdominal pain, shortness of breath or a subjective impression of reduced urine output. These symptoms may indicate severe OHSS and the occurrence of specific respiratory, renal or ovarian complications.[21,22,28] Evidence level 3

Face-to-face clinical assessment allows examination and investigations with the aim of clarifying the diagnosis and severity of the patient's condition (Table 2).

9. Outpatient management of OHSS

9.1 Which patients with OHSS are suitable for outpatient care?

Outpatient management is appropriate for women with mild or moderate OHSS and in selected cases with severe OHSS. **D**

A number of retrospective observational series[29–31] have described outpatient management of severe OHSS. Lincoln et al.[30] reported a retrospective series of 48 women with moderate to severe OHSS managed on an outpatient basis with transvaginal paracentesis and rehydration. The mean number of outpatient visits was 3.4 ± 0.45 (range 1–14). Hospitalisation was required in 8.4% of women and no complications were noted. Smith et al.[31] reported a retrospective case series of 146 outpatient transvaginal paracenteses in 96 women with OHSS with no procedure-related complications. A retrospective UK series of 99 women at risk of developing OHSS was reported by Shukla et al.[32] Women received a daily telephone call by a nurse and were reviewed by a doctor where necessary. Women were followed up for a median of 8 days (range 4–31) after egg collection and no woman had complications related to OHSS. Paracentesis was carried out in 7.1% of women with a mean volume of fluid drained of 4543 ml (SD 2792 ml). Hospital admission was required in 4% of women, with a median length of admission of 2 days (range 2–5 days). Evidence level 3

9.2 What management is appropriate in the outpatient setting for patients with OHSS?

Women undergoing outpatient management of OHSS should be appropriately counselled and provided with information regarding fluid intake and output monitoring. In addition, they should be provided with contact details to access advice. D

Nonsteroidal anti-inflammatory agents should be avoided, as they may compromise renal function. D

Women with severe OHSS being managed on an outpatient basis should receive thromboprophylaxis with LMWH. The duration of treatment should be individualised, taking into account risk factors and whether or not conception occurs. D

Paracentesis of ascitic fluid may be carried out on an outpatient basis by the abdominal or transvaginal route under ultrasound guidance. D

There is insufficient evidence to support the use of GnRH antagonists or dopamine agonists in treating established OHSS. D

Women with OHSS should be provided with verbal and written information about their condition. There are no specific studies to guide advice regarding fluid intake. However, it appears reasonable to encourage patients to drink to thirst rather than a set amount.[7] Fluid intake of at least 1 litre a day should be advised. Outpatient management may be aided if patients are able to maintain fluid input–output charts. Urine output of less than 1000 ml per 24 hours or a positive fluid balance of greater than 1000 ml over 24 hours should prompt medical review to assess severity. Evidence level 3

Paracetamol and oral opiates including codeine can be offered to women for pain relief. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided as they may compromise renal function in women with OHSS.[28]

Women with severe OHSS are at increased risk of thromboembolism. Although there are no trials on this subject, thromboprophylaxis should be provided for these women in view of the serious nature of this complication[33] (see section 10.7). Evidence level 4

A number of retrospective case series describe outpatient paracentesis in women with severe OHSS.[30–32]

An observational study[34] has suggested that GnRH antagonist administration in women with established severe early OHSS may result in quicker regression of the syndrome. Small observational studies[35,36] also suggest that dopamine agonists may have a beneficial role in the treatment of established OHSS. Further research is required to evaluate these interventions. Evidence level 3

9.3 How should women with OHSS managed on an outpatient basis be monitored?

Women with OHSS being managed on an outpatient basis should be reviewed urgently if they develop symptoms or signs of worsening OHSS (see below). In the absence of these, review every 2–3 days is likely to be adequate. ✓

Baseline laboratory investigations should be repeated if the severity of OHSS is thought to be worsening. Haematocrit is a useful guide to the degree of intravascular volume depletion. D

In the majority of women with OHSS, the condition is self-limiting. The object of monitoring is to identify women who suffer an increasing severity of OHSS and may require further measures. In most women, the condition resolves over a period of 7–10 days.[37] If conception occurs, endogenous hCG can lead to a worsening of OHSS, whereas, in the absence of pregnancy, recovery is usually complete by the time of the withdrawal bleed.

Evidence level 3

Clinicians and patients should be vigilant for signs that the severity of OHSS is worsening. These include:[38,39]

- increasing abdominal distension and pain
- shortness of breath
- tachycardia or hypotension
- reduced urine output (less than 1000 ml/24 hours) or positive fluid balance (more than 1000 ml/24 hours)
- weight gain and increased abdominal girth
- increasing haematocrit (greater than 0.45).

Evidence level 4

10. Inpatient management

10.1 When should women with OHSS be admitted?

Hospital admission should be considered for women who:

D

- **are unable to achieve satisfactory pain control**
- **are unable to maintain adequate fluid intake due to nausea**
- **show signs of worsening OHSS despite outpatient intervention**
- **are unable to attend for regular outpatient follow-up**
- **have critical OHSS.**

There is variability in the threshold for hospital admission between practitioners and it is not possible to be categorical about criteria for admission. The value of admission lies in the possibility of closer monitoring, ease of intervention and availability of multidisciplinary input. This is crucial in the care of women with critical OHSS, who may be at imminent risk of complications or who have already developed complications that may require intensive care. However, each case should be considered on its merits with reference to the clinical features, social factors and the expertise available. Women with less severe OHSS may also benefit from admission depending on their social situation and the availability of out-of-hours expertise.[38] The need for paracentesis is not in itself an absolute reason for admission, although it is recognised that several hospitals may not have easy access to outpatient paracentesis and volume replacement.

Evidence level 4

10.2 Who should provide care to women with OHSS?

Multidisciplinary assistance should be sought for the care of women with critical OHSS and severe OHSS who have persistent haemoconcentration and dehydration.

D

Features of critical OHSS should prompt consideration of the need for intensive care.

D

A clinician experienced in the management of OHSS should remain in overall charge of the woman's care.

✓

Patients with severe OHSS where dehydration and haemoconcentration persist despite adequate fluid replacement may need invasive haemodynamic monitoring, requiring input from anaesthetic/intensive care colleagues. Intensive care is also likely to be needed for women with critical OHSS, while specific complications such as thromboembolism, ARDS and renal failure require input from relevant specialties.[38]

Evidence level 4

Assisted reproduction centres should maintain close liaison with acute gynaecology and emergency units, so that appropriate expertise is available for the care of women admitted with OHSS.

10.3 How should women with OHSS be monitored?

Women admitted with OHSS should be assessed at least once daily. More frequent assessment is appropriate for women with critical OHSS and those with complications.

D

Inpatient monitoring of women with OHSS aims to track changes in the severity of the disease process and to identify any complications at an early stage. Body weight, abdominal girth, and fluid intake and output should be measured on a daily basis, along with full blood count, haematocrit, serum electrolytes, osmolality and liver function tests. Depending on the clinical features, arterial blood gases, ECG, chest X-ray and other imaging may be required. Increasing abdominal girth, weight gain, oliguria with positive fluid balance and elevated haematocrit are signs of worsening OHSS. Conversely, recovery is signalled by a diuresis, normalisation of haematocrit and a reduction in abdominal girth and body weight.[38,39] C-reactive protein levels have been shown to correlate with other markers of OHSS such as abdominal girth and weight, and may have a role in monitoring severity.[40]

Evidence level 3

10.4 How should the symptoms of OHSS be relieved?

Analgesia and antiemetics may be used in women with OHSS, avoiding nonsteroidal agents and medicines contraindicated in pregnancy.

D

Relief of abdominal pain and nausea forms an important part of the supportive care of women with OHSS. Analgesia with paracetamol and opiates, if required, is appropriate, while NSAIDs should be avoided as they may compromise renal function.[28] It should be borne in mind that severe pain may signal a complication such as ovarian torsion or rupture, or a coincident problem such as ectopic pregnancy or pelvic infection.

Evidence level 3

10.5 What is the appropriate management of fluid balance?

Fluid replacement by the oral route, guided by thirst, is the most physiological approach to correcting intravascular dehydration.

D

Women with persistent haemoconcentration despite volume replacement with intravenous colloids may need invasive monitoring and this should be managed with anaesthetic input.

D

Diuretics should be avoided as they further deplete intravascular volume, but they may have a role in a multidisciplinary setting if oliguria persists despite adequate fluid replacement and drainage of ascites.

✓

There are no trials on the optimum regimen for managing fluid balance in women with OHSS. Vigorous intravenous fluid therapy with crystalloids has the potential of worsening ascites in the presence of increased capillary permeability. Hence, the oral route should be used for hydration wherever practicable.[7] Some patients may need effective analgesia and antiemetics in order to be able to maintain adequate fluid balance.

Evidence level 4

Acutely dehydrated women may need intravenous fluid therapy to correct fluid balance, followed by oral fluids to maintain hydration. Crystalloids are useful for the initial correction of dehydration in women who are unable to maintain adequate oral intake. There are theoretical advantages to using colloids rather than crystalloids for initial rehydration. Human albumin and hexaethyl starch (HES) have been used for correction of dehydration in women with severe OHSS. However, HES has been withdrawn in the UK as a result of evidence showing increased mortality in critically ill and septic patients receiving HES compared with those receiving crystalloids. Human albumin solution 25% may be used as a plasma volume expander in doses of 50–100 g, infused over 4 hours and repeated 4- to 12-hourly.[38] Strict fluid balance recording should be followed for these patients.

Evidence level 3

Persistent haemoconcentration or low urine output despite apparent adequate volume replacement by colloids is an indication to seek multidisciplinary assistance. In these cases, continuous urine output measurement and invasive haemodynamic monitoring may help guide fluid management more accurately. Oliguria despite adequate fluid replacement may in some cases respond to paracentesis.[41] Small nonrandomised studies[42,43] describe the use of dopamine infusion or oral docarpamine in treating severe OHSS. It is not possible to be categorical about the value of these interventions in the absence of adequate trials and they should only be undertaken in the multidisciplinary setting under close monitoring.

Diuretics have been used in managing fluid balance in women with OHSS, but their use has not been subjected to controlled studies. There is a risk of worsening hypovolaemia if diuretics are administered without correcting dehydration. However, careful use of diuretics may be appropriate in women who continue to exhibit oliguria despite adequate fluid replacement, particularly if any tense ascites that may have been contributing to oliguria has been drained.[38,44]

Evidence level 4

10.6 How should ascites and effusions be managed?

Indications for paracentesis include the following: D

- **severe abdominal distension and abdominal pain secondary to ascites**
- **shortness of breath and respiratory compromise secondary to ascites and increased intra-abdominal pressure**
- **oliguria despite adequate volume replacement, secondary to increased abdominal pressure causing reduced renal perfusion.**

Paracentesis should be carried out under ultrasound guidance and can be performed abdominally or vaginally. C

Intravenous colloid therapy should be considered for women who have large volumes of fluid removed by paracentesis. D

Paracentesis should be carried out under ultrasound guidance to avoid trauma to the enlarged, vascular ovaries. Both abdominal and transvaginal routes are well described. Abdominal paracentesis allows the insertion of an indwelling catheter and this may minimise the need for repeat paracentesis. Raziel et al.[45] reported on the transvaginal insertion of an indwelling catheter in an obese woman, using a guide wire and an indwelling catheter fixed to the woman's thigh. Most other reports on transvaginal paracentesis, however, describe aspirations in a single sitting.

Evidence level 4

There is little evidence to guide clinical practice regarding the optimal amount of ascitic fluid to be removed on any one occasion, the time over which ascites should be drained or the route of drainage. Smith et al.[31] reported a series of 146 outpatient transvaginal paracenteses performed to manage OHSS in 96 patients. The mean volume of fluid removed was 2155 ml (range 500–4500 ml) with no complications reported. Ozgun et al.[46] reported the drainage of 7.5 l on one occasion over 3 hours, and a total of 45 l by serial vaginal paracentesis with supportive fluid replacement with no adverse outcome. Patients with OHSS are generally a younger age group, and are likely to tolerate the removal of large volumes of ascites in a different way to elderly patients with malignant ascites who may experience significant fluid shifts in such situations.[38,47]

It has been suggested that early drainage of ascites to lower the intra-abdominal pressure in patients with moderate to severe OHSS may prevent disease progression and lower the risk of severe complications associated with this condition.[48] Drainage of 2000 ml of ascitic fluid in women with severe OHSS produced significant reductions in intra-abdominal pressure and renal vascular resistance.[41] Koike et al.[49] described autotransfusion of ultrafiltered ascitic fluid into the venous circulation and their observational study showed reduced haemo-concentration, improved urine output and quicker recovery following this procedure compared with a conservative treatment regime of diuretics, fluid restriction and intravenous albumin (without paracentesis). It is not clear to what extent the benefit of this treatment method lies in drainage of the ascites as opposed to autotransfusion. A further study[50] describes autotransfusion of concentrated ultrafiltered ascetic fluid protein, aiming to replenish the woman's albumin levels using her own protein, reducing the risk of infection and allergic reaction to exogenous albumin.

Evidence level 3

10.7 How should the risk of thrombosis be managed?

Women with severe or critical OHSS and those admitted with OHSS should receive LMWH prophylaxis. C

The duration of LMWH prophylaxis should be individualised according to patient risk factors and outcome of treatment. D

Women with moderate OHSS should be evaluated for predisposing risk factors for thrombosis and prescribed either antiembolism stockings or LMWH if indicated. ✓

In addition to the usual symptoms and signs of venous thromboembolism (VTE), thromboembolism should be suspected in women with OHSS who present with unusual neurological symptoms, even if they present several weeks after apparent improvement in OHSS. D

Severe OHSS is a prothrombotic state due to haemoconcentration and vascular endothelial dysfunction. The incidence of thrombosis been estimated to lie between 0.7% and 10% of cases of OHSS. Rova et al.[51] reported on the risk of VTE in early pregnancy in relation to IVF and OHSS. The review included all deliveries in Sweden (n = 964 532) during the period 1999–2008. Of these, 19 162 were IVF pregnancies compared to 935 178 non-IVF pregnancies. The incidence of VTE in the first trimester in non-IVF pregnancies was 0.2 per 1000 women, while the incidence in IVF pregnancies with no OHSS was 0.8 per 1000 women (OR 4.8, 95% CI 2.7–8.7), compared with 16.8 VTE events per 1000 women for those who developed OHSS (OR 99.7, 95% CI 61.6–161.1).

Evidence level 2+

There are no comparative studies addressing the value of thromboprophylaxis in women with severe OHSS. However, the incidence of this complication and its potentially life-threatening nature mean that thromboprophylaxis should be given to women with severe OHSS and those with risk factors such as reduced mobility, obesity or a pre-existing thrombophilia. Antiembolism stockings should be used in patients admitted to hospital with OHSS for whom chemical thromboprophylaxis is contraindicated, as they are likely to have reduced mobility.[33]

There is no agreement on the duration of thromboprophylaxis in women with OHSS. Several case reports describe thromboembolism occurring weeks after the apparent resolution of OHSS, particularly in association with pregnancy. The majority of delayed thromboses are reported to have occurred in the first trimester of pregnancy. Hence, in women with severe OHSS who conceive, thromboprophylaxis should be considered at least until the end of the first trimester.[33,52] In general, the duration of thromboprophylaxis should be based on individual risk factors and whether or not conception occurs. Liaison with a specialist haematologist may be beneficial in individualising therapy.

Evidence level 3

Thrombosis in women with OHSS frequently affects upper body sites and frequently involves the arterial system. Therefore clinicians should remain vigilant of patients presenting with unusual symptoms such as dizziness, loss of vision and neck pain. Women may present with thromboembolism several weeks after apparent resolution of OHSS.[9,52] If a thrombosis is suspected, then therapeutic anticoagulation should be instigated, while appropriate imaging is arranged. These patients should be managed in collaboration with colleagues in haematology and maternal medicine.

10.8 When is surgical management indicated?

Surgery is only indicated in patients with OHSS if there is a coincident problem such as adnexal torsion, ovarian rupture or ectopic pregnancy and should be performed by an experienced surgeon. **D**

Hyperstimulated ovaries are likely to be highly vascular and liable to damage on handling. The risk of ovarian torsion or rupture appears to be increased in women with OHSS, particularly in the presence of pregnancy.[22,53] Laparoscopic 'untwisting' of torted hyperstimulated ovaries has been described.[54] The presence of ovarian enlargement and ascites should be kept in mind when considering a diagnosis of ectopic pregnancy.

Evidence level 4

In rare cases of critical OHSS, termination of pregnancy has been reported in the situation of progressive thrombosis despite anticoagulation,[55] and there have been cases reported for removal of the ovaries (bilateral oophorectomy) for intractable OHSS;[56] however, this is not a recommended treatment option.[57]

11. OHSS and pregnancy

11.1 What are the risks associated with pregnancy and OHSS?

Clinicians should be aware, and women informed, that pregnancies complicated by OHSS may be at increased risk of pre-eclampsia and preterm delivery. C

Controlled studies do not show an increase in the risk of miscarriage in pregnancies arising from assisted reproduction cycles complicated by OHSS compared to cycles without OHSS,[58–60] although some reports have suggested an increased rate of preclinical pregnancy loss in women with early, but not late, OHSS.[59]

Data concerning later gestational complications in pregnancies complicated by OHSS are limited. Courbierre et al.[60] found a higher incidence of pre-eclampsia (21.2% versus 9.2%) and prematurity (36% versus 10.7%) in 40 OHSS pregnancies compared with a control group of 80 IVF pregnancies without OHSS.The proportions of multiple pregnancies were similar between the two groups. A larger study by Haas et al.[61] comparing the obstetric outcomes of 125 pregnancies complicated by severe OHSS with 157 IVF pregnancies without OHSS found an increased risk of prematurity in singleton, but not multiple, pregnancies with OHSS compared with the corresponding non-OHSS controls. Evidence level 2+

12. Recommendations for future research

- More research is required to clarify changes in the osmoregulatory system in women at different phases of OHSS, using well-defined cohorts of women with severe disease who are followed through the course of the OHSS.
- There is a need to compare outpatient and inpatient management of severe OHSS in terms of safety, efficacy, patient acceptability and health economic assessment. Such a trial could compare a 'conventional' approach of inpatient management with conservative indications for abdominal paracentesis with a more 'active' approach emphasising earlier paracentesis on an outpatient basis.
- Further research is required to evaluate the role of GnRH antagonists and dopamine agonists in the management of women with established OHSS.

13. Auditable topics

- Proportion of women undergoing stimulated assisted reproduction treatment who are provided with verbal and written information about symptoms of OHSS and 24-hour contact details (100%).
- Formal agreements between licensed centres providing treatment that may lead to OHSS and acute units in their catchment area (100%).
- Reporting of cases of severe and critical OHSS admitted to hospital in accordance with HFEA regulations (100%). Responsibility for reporting lies with the licensed centre.
- Acute unit to inform licensed centre regarding all patients seen with a suspected diagnosis of OHSS (100%).
- Effectiveness of outpatient management of severe OHSS against locally agreed standard.
- Women admitted to hospital should have daily clinical review with weight and abdominal girth measurements and monitoring of intake and output of fluid (100%).
- All women with severe or critical OHSS should be prescribed LMWH, unless there is a contraindication, whether admitted to hospital or not (100%).

14. Useful links and support groups

- British Fertility Society. *Ovarian hyperstimulation syndrome (OHSS)* [http://britishfertilitysociety.org.uk/downloads/ms_3642.pdf].
- Infertility Network UK. *Fact Sheet: Ovarian Hyper Stimulation Syndrome (OHSS)* [http://www.infertilitynetworkuk.com/uploaded/Fact%20Sheets/Ovarian%20Hyper%20Stimulation%20Syndrome%20(OHSS).pdf].

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Appendix I: Explanation of guidelines and evidence levels

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group

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The final version is the responsibility of the Guidelines Committee of the RCOG.

The review process will commence in 2019, unless otherwise indicated.

