



THE MANAGEMENT OF OVARIAN HYPERSTIMULATION SYNDROME.

This is the second edition of this guideline. The previous edition, entitled *Management and Prevention of Ovarian Hyperstimulation Syndrome*, was published in January 1995 and was archived in 1998, as the topic was to be discussed in the National Institute for Health and Clinical Excellence (NICE) Clinical Guideline No. 11, entitled *Fertility*. As the topic was not discussed in depth, this RCOG guideline has been produced to offer evidence-based support for those involved in the management of patients with ovarian hyperstimulation syndrome (OHSS).

1. Purpose and scope

The aim of this guideline is to provide clinicians with up-to-date information about the diagnosis and treatment of OHSS, based upon the best available evidence. This guideline covers outpatient management, criteria for hospital admission and basic inpatient management. Intensive care management of OHSS is not covered in detail. Prevention of OHSS lies outside the scope of this guideline and has been addressed by NICE Clinical Guideline No. 11, *Fertility*.

2. Background

OHSS is a systemic disease resulting from vasoactive products released by hyperstimulated ovaries. The pathophysiology of OHSS is characterised by increased capillary permeability, leading to leakage of fluid from the vascular compartment, with third space fluid accumulation and intravascular dehydration. Severe manifestations include a tendency to develop thrombosis, renal and liver dysfunction and acute respiratory distress syndrome (ARDS), causing serious morbidity. Although the true incidence of mortality from OHSS is unknown, and possibly under-reported, deaths from OHSS are rare. The reported causes of death include ARDS (two cases), cerebral infarction (two cases) and hepatorenal failure in a woman with pre-existing hepatitis C (one case).¹⁻⁴

Many staff who assess and manage women with OHSS will be unfamiliar with the condition, because assisted conception treatment frequently takes place outside the hospital setting and serious OHSS is uncommon. Thus, education and communication is particularly important in providing safe and effective care to women with OHSS.

3. Identification and assessment of evidence

Original articles considered when writing this guideline were obtained following a literature search of Medline January 1966–April 2006 and Embase January 1980–April 2006 electronic databases using the keyword ‘ovarian hyperstimulation syndrome’. This was complemented by hand searching from original references and reviews. Although the literature search revealed few comparative studies on best management, this guideline provides information to assist clinical management, linking recommend-

ations to both the evidence and reasoning of the guidelines development group. The definitions of the types of evidence used in this guideline originate from the US Agency for Health Care Policy and Research. No systematic reviews or meta-analyses were identified from the literature search.

4. Incidence of OHSS

What is the reported incidence of OHSS?

Women should be informed that mild forms of OHSS are common, affecting up to 33% of *in vitro* fertilisation (IVF) cycles and that 3–8% of IVF cycles are complicated by moderate or severe OHSS.

B

The incidence of OHSS varies between treatments and patient groups and accurate estimates from the literature are difficult owing to the variety of classification schemes used historically. The majority of cases of severe OHSS are seen following IVF treatment but the syndrome can occur after any form of supraphysiological ovarian stimulation, including clomifene and gonadotrophin ovulation induction. As many as 33% of IVF cycles have been reported to be associated with mild forms of OHSS.⁵ While these are often described as not being clinically significant, the severity of OHSS can worsen over time and even initially mild presentations should be kept under review. More severe OHSS has been reported in 3.1–8.0% of IVF cycles.⁵ The incidence of OHSS is increased in young women, women with polycystic ovaries and in cycles where conception occurs, particularly multiple pregnancies.

Evidence level III

5. Diagnosis of OHSS

How is OHSS diagnosed?

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

A diagnosis of OHSS is usually straightforward, given a history of ovarian stimulation, either by gonadotrophins or antiestrogens, followed by the typical symptoms of abdominal distension, abdominal pain, nausea and vomiting. Nevertheless, alternative diagnoses should always be considered, such as a complication of an ovarian cyst (torsion, haemorrhage), pelvic infection, intra-abdominal haemorrhage, ectopic pregnancy and appendicitis.

6. Assessing severity and reporting adverse outcomes

How is the severity of OHSS classified and reported?

Women with OHSS should have the severity of their condition assessed and documented as an aid to management. It should be remembered that the severity could worsen over time as the condition evolves. Each case should be classified according to the classification in Table 1.

In the UK, any death related to OHSS must be reported to the Confidential Enquiries into Maternal Deaths, irrespective of whether the woman was pregnant. Units should follow relevant Human Fertilisation and Embryology Authority (HFEA) guidelines for reporting severe untoward incidents.

C

Management of OHSS is guided by the severity of the condition. This may change over time. The classification scheme proposed here is based on several important studies.^{6–9}

OHSS was originally divided into six grades of severity,⁶ the first two grades of which were based on laboratory evidence of overstimulation. Women with only ‘biochemical’ overstimulation were excluded by subsequent researchers.⁸ In these studies, women with abdominal distension,

Evidence level IV

discomfort, nausea, vomiting or diarrhoea were classed as having mild OHSS, while ultrasonic evidence of ascites in the presence of these symptoms was designated as moderate OHSS. The presence of significant abdominal pain, nausea or diarrhoea may identify women who need closer monitoring of fluid and electrolyte balance. This is reflected in the modification to the classification system suggested by Mathur in 2005 detailed in Table 1.⁹ Women with these symptoms are placed in the category of moderate OHSS. The category of severe OHSS was modified in 1992⁸ to include a category of critical OHSS, highlighting women with the most serious manifestations of OHSS who may need intensive care management.

Evidence level IV

Grade	Symptoms
Mild OHSS	Abdominal bloating Mild abdominal pain Ovarian size usually <8 cm*
Moderate OHSS	Moderate abdominal pain Nausea ± vomiting Ultrasound evidence of ascites Ovarian size usually 8–12 cm*
Severe OHSS	Clinical ascites (occasionally hydrothorax) Oliguria Haemoconcentration haematocrit >45% Hypoproteinaemia Ovarian size usually >12 cm*
Critical OHSS	Tense ascites or large hydrothorax Haematocrit >55% White cell count >25 000/ml Oligo/anuria Thromboembolism Acute respiratory distress syndrome

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

A division of OHSS into ‘early’ and ‘late’, depending on the time of onset, may be useful in determining the prognosis. OHSS presenting within 9 days after the ovulatory dose of human chorionic gonadotrophin (hCG) is likely to reflect excessive ovarian response and the precipitating effect of exogenous hCG administered for final follicular maturation. OHSS presenting after this period reflects endogenous hCG stimulation from an early pregnancy.¹⁰ Late OHSS is more likely to be severe and to last longer than early OHSS.

Evidence level III

The HFEA *Standards for Assisted Conception Centres* states that all adverse incidents occurring at the treatment centre must be reported by telephone to the HFEA within 12 working hours of the identification of the incident and submission of an Incident Report Form within 24 working hours.¹¹

Evidence level IV

7. Women at risk of OHSS

What advice should women receive about the risk of OHSS?

Assisted conception units should provide women with written information about OHSS including risks, symptoms of OHSS, what action to take and a 24-hour contact number with prompt access to a clinician with the necessary expertise in the diagnosis and management of OHSS. Women should be advised to keep this information with them at all times and show it if they seek medical help.

C

All women undergoing ovarian stimulation should be considered at risk of OHSS and should be provided with clear face-to-face advice about the condition, backed up by written information. Women at higher risk of developing OHSS include those with polycystic ovaries, women under 30 years of age, use of GnRH agonists, development of multiple follicles during treatment, exposure to LH/hCG, and previous episodes of OHSS.

8. Outpatient management

How should the treatment for women with suspected OHSS be managed?

Units carrying out treatment that has a potential for resulting in OHSS should develop agreed protocols for referral of women with suspected OHSS to hospital care, including written protocols for initial OHSS management. Protocols should be available to referring practitioners, neighbouring gynaecology departments and accident and emergency departments in their catchment areas.

C

Treatment for women with mild OHSS and many with moderate OHSS can be managed on an outpatient basis.

✓

Analgesia using paracetamol or codeine is appropriate. Nonsteroidal anti-inflammatory drugs should not be used.

✓

Women should be encouraged to drink to thirst, rather than to excess.

✓

Strenuous exercise and sexual intercourse should be avoided for fear of injury or torsion of hyperstimulated ovaries.

✓

Women should continue progesterone luteal support but hCG luteal support is inappropriate.

✓

Assessment of the woman will usually involve clinical examination, which should include body weight and abdominal girth measurement, and pelvic ultrasound examination to measure ovarian size and check for ascites. Laboratory investigations that are helpful in assessing the severity of OHSS are haemoglobin, haematocrit, serum creatinine and electrolytes and liver function tests. Baseline values may help track the progress of the condition.

Review every 2–3 days is likely to be adequate. However, urgent clinical review is necessary if the woman develops increasing severity of pain, increasing abdominal distension, shortness of breath and a subjective impression of reduced urine output. If the woman conceives, prolonged monitoring may be appropriate, whereas, in the absence of pregnancy, resolution would be anticipated by the time of the withdrawal bleed.

9. Inpatient management

9.1 When should women with OHSS be admitted?

Hospital admission should be recommended to women with severe OHSS. Women should be kept under review until resolution of the condition.

✓

Women with severe OHSS require inpatient management. In addition, women with moderate OHSS who are unable to achieve control of their pain and/or nausea with oral treatment should also be admitted. Admission should also be considered where there are difficulties in ensuring adequate ongoing monitoring, until resolution commences.

9.2 Who should provide care to women with OHSS?

Multidisciplinary assistance should be sought for all women with critical or severe OHSS who have persistent haemoconcentration and dehydration.



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



A doctor experienced in managing OHSS should remain in overall charge to provide information concerning OHSS to other personnel, who may not have experience of managing this condition.



Women with critical OHSS require multidisciplinary care including specialists with appropriate expertise in intensive care. Specific complications, such as ARDS, renal failure and thromboembolism may require intensive care management. Anaesthesia and medical colleagues should be involved at an early stage in all cases of critical OHSS. Assistance should also be sought in women with severe OHSS where initial crystalloid and colloid therapy fails to correct dehydration and haemoconcentration.

Evidence level IV

9.3 How can the symptoms of OHSS be relieved?

Pain relief is best provided with paracetamol and if necessary oral or parenteral opiates. Nonsteroidal anti-inflammatory agents are not recommended.



Antiemetic drugs used should be those appropriate for the possibility of early pregnancy, such as prochlorperazine, metoclopramide and cyclizine.



The management of OHSS is essentially supportive until the condition resolves spontaneously. Symptomatic relief is important, particularly regarding pain and nausea. Discomfort may be relieved with paracetamol or opiate medications if severe. If opiates are used, particularly in women with reduced mobility, care should be taken to avoid constipation. Nonsteroidal anti-inflammatory agents are not recommended, because they may compromise renal function in patients with OHSS.¹² Nausea is usually related to the accumulation of ascites and so measures described to reduce abdominal distension should provide relief. Counselling support for both the woman and her partner provides reassurance and information to allay anxiety.

Evidence level III

9.4 How should women with OHSS be monitored?

Women admitted to hospital with OHSS should be assessed at least daily, with more frequent assessment of those with critical OHSS.



Increasing abdominal pain, oliguria, weight gain, increased girth measurement and breathlessness point to worsening OHSS. Clinical examination includes an assessment of hydration and cardiorespiratory system. Abdominal examination should note the degree of distension, palpable ovaries, presence or absence of ascites and paralytic ileus.

Abdominal girth and weight should be recorded at admission and daily until resolution. Fluid intake and output should be recorded and monitored on at least a daily basis, with more frequent assessment if the woman is dehydrated or receiving intravenous fluids. Urine output of less than 1000 ml/day or a persistent positive fluid balance is a cause for concern.

Haemoconcentration is a measure of the severity of OHSS and may be measured by raised haemoglobin and haematocrit.¹³ An increase in the white cell count may indicate an ongoing systemic stress response. Hyponatraemia, observed in 56% cases of severe OHSS, may be dilutional as a result of antidiuretic hormone hypersecretion.¹⁴ Although reduced renal

Evidence level III

perfusion secondary to hypovolaemia or tense ascites may lead to oliguria in about one-third of women with severe OHSS, acute renal failure is rare. Abnormal liver function tests can be found in 25–40% of severe OHSS cases and usually normalise with resolution of the disease.¹⁵

Evidence level III

Ultrasound of the pelvis assesses the extent of ovarian enlargement and the degree of abdominal fluid accumulation. Chest X-ray is indicated in women with respiratory symptoms and signs suggestive of hydrothorax, pulmonary infection or pulmonary embolism. Chest ultrasonography can assist diagnosis of hydrothorax. An electrocardiogram (ECG) should be carried out if pulmonary embolism or pericardial effusion is suspected. A pericardial effusion may present with quieter heart sounds and reduced QRS voltages on ECG. A chest radiograph would demonstrate an increased size in the cardiac shadow, with the heart appearing globular or pear shaped. Echocardiography confirms the diagnosis of pericardial effusion.¹⁶

Evidence level III

Assessment	Measurements
History and Examination	Pain
	Breathlessness
	Hydration
	Weight
	Cardiovascular
	Heart rate, blood pressure
	Abdominal girth, distension, ascites
	Intake and output chart
Investigations	Full blood count
	Haemoglobin, haematocrit, white cell count
	Urea & electrolytes
	Liver function tests
	Baseline clotting studies
	Pelvic ultrasound (for ascites and ovarian size)
	Chest X-ray or ultrasonography (if respiratory symptoms)
	ECG and echocardiogram (if suspect pericardial effusion)

9.5 What is the appropriate management of fluid balance?

Allowing women to drink according to their thirst represents the most physiological approach to replacing volume.

C

Women with severe OHSS with persistent oliguria and haemoconcentration despite initial colloid volume expansion may need invasive monitoring and should be discussed with an anaesthetist.

✓

Diuretics should be avoided as they deplete intravascular volume, although they may have a role with careful haemodynamic monitoring in cases where oliguria persists despite adequate intravascular volume expansion and a normal intraabdominal pressure.

C

Evidence to support specific regimens of fluid replacement in women with OHSS is lacking. Allowing women to drink to their thirst represents the most physiological approach to fluid volume replacement,¹⁷ avoiding the risk of hypervolaemia and worsening ascites that may occur with vigorous intravenous therapy. Women may need antiemetics and analgesics to enable them to tolerate oral fluid intake satisfactorily. However, where oral intake cannot be maintained, intravenous crystalloids, such as normal saline, should be used. Most women will need a fluid intake of 2–3 litres in 24 hours, guided by a strict fluid balance chart.

Evidence level IV

Women with haemoconcentration (haemoglobin greater than 14g/dl, haematocrit greater than 45%) may need more intensive initial rehydration, such as 1 litre of physiological saline over 1 hour. Women with persistent haemoconcentration and/or urine output less than 0.5 ml/kg/hour may benefit from colloids. Human albumin, 6% hydroxyethylstarch (HES), dextran, mannitol and Haemaccel® have been used for this purpose. Few comparative data exist to support the use of any one of these over the other in the specific situation of severe OHSS. HES has been reported to be associated with a higher mean daily urine output, fewer paracenteses and shorter hospital stay than human albumin.¹⁸ HES is of non-biological origin and with a higher molecular weight than human albumin. If haemoconcentration and/or oliguria persist despite these measures, paracentesis should be considered. Further fluid management may be guided by central venous pressure monitoring and anaesthetists should be involved.

Evidence level III

Diuretics should not be used in women with oliguria secondary to a reduced blood volume and decreased renal perfusion, as they may worsen intravascular dehydration. Where oliguria persists despite adequate rehydration (preferably judged by invasive haemodynamic monitoring), rarely there may be a role for the judicious use of diuretics with senior multidisciplinary involvement and usually after paracentesis.

9.6 How should ascites or effusions be managed?

Paracentesis should be considered in women who are distressed due to abdominal distension or in whom oliguria persists despite adequate volume replacement.

B

Paracentesis should be performed under ultrasound guidance to avoid inadvertent puncture of vascular ovaries distended by large luteal cysts.

B

Intravenous colloid replacement should be considered for women who have large volumes of ascitic fluid drained.

B

Where women have significant discomfort or respiratory embarrassment because of severe abdominal distension, abdominal paracentesis should be considered.¹⁹⁻²¹ It should also be considered for women who remain oliguric despite adequate fluid replacement, as the relief of intraabdominal pressure may promote renal perfusion and improve urine output. Intra-abdominal pressure may be measured via a urinary catheter with pressures greater than 20 mmHg suggestive of the need for decompression.²²

Evidence level III

To avoid cardiovascular collapse from massive fluid shifts, the rate of ascitic fluid drainage should be controlled, intravenous colloid should be administered and blood pressure and pulse should be monitored. Aspiration of ascites should take place under ultrasound guidance to minimise the risk of injury to enlarged, vascular ovaries. Transabdominal aspiration is likely to be better tolerated than a vaginal approach. Repeated paracenteses may be avoided by the use of pigtail or suprapubic catheter that can be left in place.²³

Evidence level III

Drainage of ascites alone may suffice to resolve hydrothorax, if present,²⁴ but symptomatic hydrothorax that persists despite abdominal paracentesis may be drained directly.

Evidence level III

9.7 How should the risk of thrombosis be managed?

Routine screening for thrombophilia in all women undergoing assisted conception is not warranted, although testing may be helpful for those with a personal or family history of thrombosis.

B

Thromboprophylaxis should be provided for all women admitted to hospital with OHSS. This should be continued at least until discharge from hospital and possibly longer, depending on other risk factors.

B

Unusual neurological symptomatology following ovarian stimulation should raise the possibility of a thrombotic episode in an uncommon location, prompting referral for appropriate expert opinion.

B

The reported incidence of thrombosis with OHSS ranges between 0.7% and 10%, with an apparent preponderance of upper body sites and frequent involvement of the arterial system.¹⁵ Mechanisms contributing to thrombosis in women with OHSS include haemoconcentration, altered coagulation system and reduced venous return secondary to enlarged ovaries, ascites and immobility.^{25,26}

Evidence level III

There are no firm data indicating either the value of diagnostic tests or heparin prophylaxis to prevent thromboembolic complications. However, as thromboembolism is a potentially life-threatening complication, prophylactic measures should be provided for all women hospitalised with OHSS, particularly with a personal or family history of thromboembolic events, thrombophilia or vascular anomalies. Full-length venous support stockings and prophylactic heparin therapy may be used. The use of an intermittent pneumatic compression device may be helpful when symptoms prevent ambulation and confine the patient to bed. In women who do not conceive, thromboprophylaxis may be discontinued with resolution of OHSS. The risk of thrombosis appears to persist into the first trimester of pregnancy and consideration should be given to the risks and benefits of heparin prophylaxis until the end of the first trimester, or even longer, depending on the presence of risk factors and course of the OHSS. If thromboembolism is suspected, therapeutic anticoagulation should be commenced, and additional diagnostic measures performed such as arterial blood gases, and ventilation/perfusion scan.

9.8 When is surgical management indicated?

Pelvic surgery should be restricted to cases with adnexal torsion or co-incident problems requiring surgery and only undertaken by an experienced surgeon following careful assessment.

C

OHSS, particularly if associated with pregnancy, may be a risk factor for ovarian torsion.^{27,28} Torsion should be suspected in the presence of further ovarian enlargement, worsening particularly unilateral pain, nausea, leucocytosis and anaemia.¹⁴ Colour Doppler assessment of ovarian blood flow may help in diagnosis.²⁹ Untwisting of the twisted adnexa followed by observation of improved colour at laparoscopy or laparotomy is associated with a favourable prognosis for ovarian function.³⁰

Evidence level III

10. OHSS and pregnancy

What are the risks associated with pregnancy and OHSS?

Women should be reassured that pregnancy may continue normally despite OHSS, and there is no evidence of an increased risk of congenital abnormalities.

B

Severe OHSS is commonly associated with pregnancy. Data on the outcome of pregnancies conceived in cycles complicated by OHSS are inconclusive. High rates of miscarriage, pregnancy-induced hypertension and premature birth in women with severe OHSS³¹ have not been confirmed by controlled studies.³²⁻³⁴

Evidence level IIIa

11. Auditable standards

Some audits would be suitable for individual clinics but others would require collaboration between a number of centres possibly on a national basis.

- Percentage of women attending for IVF who are given written advice about OHSS, explaining what to look out for and what action to take.

- Percentage of women attending for IVF who are admitted to hospital with OHSS and number of days as inpatient.
- Percentage of women receiving thromboprophylaxis following hospital admission with OHSS.
- Thromboembolic complications following OHSS.
- Pregnancy outcome following OHSS, including miscarriage, hypertension, placental abruption, preterm delivery, low birth weight.

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APPENDIX

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: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/clingov1). 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	Grades of recommendations
Ia Evidence obtained from meta-analysis of randomised controlled trials.	A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
Ib Evidence obtained from at least one randomised controlled trial.	B Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
IIa Evidence obtained from at least one well-designed controlled study without randomisation.	C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)
IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.	Good practice point
III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.	<input checked="" type="checkbox"/> Recommended best practice based on the clinical experience of the guideline development group.
IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.	

This Guideline was updated on behalf of the Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists by:
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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG

Valid until September 2009
 unless otherwise indicated

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians, gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, not being intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.