Green-top Guideline No. 5
Peer Review Draft – May 2024

The Management of Ovarian Hyperstimulation Syndrome

H Hamoda, AJ Drakeley, K Brian, IO Evbuomwan, R Mathur on behalf of the Royal College of Obstetricians and Gynaecologists

Correspondence: Royal College of Obstetricians and Gynaecologists, 10–18 Union Street, London SE1 1SZ.
Email: clinicaleffectiveness@rcog.org.uk

This is the fourth edition of this guideline, previously published in 2016 with the same title.

Key recommendations

- Fertility clinics should provide verbal and written information about OHSS to all people undergoing fertility treatment, including a 24-hour contact telephone number. [Good Practice Point]
- Clinicians should be aware of the risk of OHSS in those undergoing fertility treatment, and people undergoing fertility treatment should be informed and counselled about this risk, as well as provided information about the key symptoms and signs of OHSS. [Grade D]
- The severity of OHSS should be graded according to a standardised classification and it is recommended to follow the classification used by the RCOG and the Human Fertilisation and Embryology Authority (HFEA). [Grade D]
- People undergoing fresh IVF treatment who experience symptoms of early OHSS before having their embryo transfer should be advised to avoid fresh embryo transfer and to have cryopreservation of embryos followed by interval frozen embryo replacement. [Grade D]
- Outpatient care is appropriate for people with mild or moderate OHSS and in selected cases with severe OHSS. [Grade D]
- People with OHSS should be evaluated for predisposing risk factors for thrombosis and consider thromboprophylaxis where appropriate to minimise the risk of thrombosis with OHSS. [Grade C]
- People with OHSS should be followed up until resolution of OHSS. This should ideally be carried out in the treating clinic and / or in the clinical setting where the woman is cared for. [Grade D]

1. Purpose and scope

This guideline is for healthcare professionals who care for women, non-binary and trans people with OHSS.

Ovarian hyperstimulation syndrome (OHSS) is a complication of fertility treatment with pharmacological ovarian stimulation to increase the number of oocytes and therefore embryos available during assisted reproductive technology (ART). In a minority of people undergoing treatment, the ovarian response is excessive and results in this clinical condition and 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 care and monitoring while awaiting resolution. Those with severe OHSS may require inpatient

treatment to manage symptoms and reduce the risk of further complications. The key principles of OHSS care are therefore early recognition, prompt assessment and treatment of moderate and severe OHSS.

The mechanism whereby OHSS develops has received plenty of interest in recent years and pro-inflammatory mediators are believed to be involved in the pathogenesis.[2,3] However, translating this basic scientific knowledge to inform the diagnosis and care of OHSS in clinical practice has so far proven difficult. Studies that have addressed the care of OHSS thus far, have been of suboptimal quality, and the subject remains of great significance not only to clinicians who provide assisted conception treatment, but also to those who look after affected people in emergency and gynaecology departments distinct from the treating fertility clinic. Often, people with OHSS present to clinicians who may not be fertility specialists.

Prevention of OHSS is outside the scope of this guideline and is covered by guidance from the British Fertility Society and European Society of Human Reproduction and Embryology.[4,5]

Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

2. Introduction and pathophysiology

OHSS is a systemic disease which principally affects people undergoing gonadotropin ovarian stimulation and arises from the effects of pro-inflammatory mediators produced by the hyperstimulated ovaries. Exposure of the ovaries to human chorionic gonadotrophin (hCG) and/or luteinising hormone (LH) following controlled ovarian stimulation by gonadotropin injections underlies most cases. In the absence of luteinisation induced by hCG or LH the syndrome does not occur.

Hyperstimulated ovaries exposed to hCG produce a number of proinflammatory mediators. Vascular endothelial growth factor (VEGF) predominates, but a variety of cytokines and secondary mediators are likely to be involved in the pathogenesis of OHSS.[1] Clinical features of OHSS are secondary to ovarian enlargement, as well as local and systemic effects of proinflammatory mediators (including increased vascular permeability and a prothrombotic effect)[3].

Increased vascular permeability leads to loss of fluid into the extravascular space, manifesting as ascites or, less commonly, pleural and pericardial effusions. People with severe OHSS experience symptoms and display signs of hypovolaemia and haemoconcentration, with a typical loss of 20% of their calculated blood volume in the acute phase of OHSS.[6] 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. This in turn leads to low osmolality and reduced sodium levels, as these patients remain able to concentrate and dilute their urine around the new, lower level of osmolality.[7,8]

This resetting of the osmotic thresholds is thought to explain the observed decreases in serum osmolality and sodium in the acute phase of severe OHSS, rather than due to electrolyte losses.[6,7,8]

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 October 2021. 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 and who is at risk?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
People undergoing fertility treatment should be informed and counselled about the risk of OHSS, with the incidence varying between 3-6%. **People undergoing fertility treatment should be provided with information on the key symptoms and signs of OHSS.**	**3**	**D**	The incidence of OHSS varies with different types of fertility treatment with those involving greater degrees of ovarian stimulation being associated with increased incidence.

Despite the growing number of cycles of assisted reproduction, the true incidence of OHSS remains unknown as 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 countries.[9,10]

Internationally, the quoted incidence of OHSS varies, with Japanese literature estimating the OHSS rate to be as high as 20%.

The incidence of OHSS varies between different types of fertility treatment, with those involving greater degrees of ovarian stimulation being associated with increased incidence. The true incidence of OHSS in assisted conception is unclear due to the lack of mandatory reporting of cases and the absence of a universally agreed classification scheme. In the UK, licensed clinics are mandated to report cases of severe or critical OHSS to the Human Fertilization and Embryology Authority (HFEA). In 2021-22, there were 66 reported cases, accounting for less than 0.1% of IVF cycles.[16]

Historically, around one-third of cycles of conventional in vitro fertilisation (IVF) were estimated to be associated with mild OHSS, while the combined incidence of moderate to severe OHSS varied from 3.1% to 8%.[14] The incidence of OHSS is lower when GnRH antagonist regimes are used compared to

the incidence in GnRH agonist cycles. The overall incidence of any grade of OHSS in randomised trials of GnRH antagonist regimens, comprising 4447 cycles, was 6% for moderate and 3% for severe OHSS.[15-17]

The incidence of OHSS may be lower with the use of certain measures used in current reproductive medicine practice, such as ovarian reserve test-based starting doses of FSH, gonadotrophin releasing hormone (GnRH)-agonist trigger and use of elective embryo cryopreservation followed by interval frozen embryo replacement.[16, 102] A recent single-centre UK study found a combined incidence of moderate to severe OHSS of 1.6% per cycle using GnRH antagonist with liberal application of such preventive measures.[17]

A national register-based historical cohort study in Denmark found an incidence of hospital admission due to OHSS of 1.2% of all stimulated cycles between 2001 to 2017 (2,261 admissions in 186 168 stimulated cycles). The annual incidence of hospital admissions varied from 0.9% to 1.4%. Admissions decreased in absolute numbers and rates between 2004 and 2008, but remained stable between 2008 and 2014.[19]

OHSS is rare following ovulation induction with clomifene citrate, aromatase inhibitors or mono-follicular ovulation induction with gonadotropins, but it has been reported. Clinicians should consider the possibility of OHSS in any treatment involving ovarian stimulation. [17-19 21–25]

Very rarely, OHSS may occur spontaneously in a naturally conceived pregnancy.[99-101]

Certain patient and cycle characteristics increase the risk of OHSS. These include a previous history of OHSS, polycystic ovary syndrome, increased antral follicle count (AFC) and high levels of anti-Müllerian hormone (AMH). 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.[16,18.]

GnRH antagonist cycles allow the use of a GnRH agonist trigger instead of hCG and cryopreservation of all embryos reducing OHSS risk. Severe OHSS, however, has still been reported with this approach.[20]

Single embryo transfer should be considered for those deemed at increased risk of OHSS, as the disease severity and duration are linked to hCG production.[21] For the same reason conditions that result in high hCG levels such as molar pregnancy increase the risk of OHSS. Despite PCOS being associated with an increased risk of OHSS, studies have suggested that obesity appears to be associated with lower OHSS complication rates in hospitalised patients. The mechanism of this association is unclear.[26]

5. Diagnosis of OHSS

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

Recommendation	Evidence quality	Strength	Rationale for the recommendation
There are no specific diagnostic tests for OHSS, however objective assessment should be made with	**3**	**D**	The diagnosis of OHSS is made on clinical grounds and objective assessment with blood tests.

physical examination, blood tests and imaging as considered appropriate.			However, there are no specific diagnostic tests for the condition.
In women and people who have had fertility treatment and present with severe abdominal pain or pyrexia, other causes should be rules out such as pelvic infection, ovarian torsion or ectopic pregnancy. Advice should be obtained from fertility specialists for their care.	**3**	**D**	The symptoms of OHSS are not specific. Hence, care must be taken to exclude other serious conditions that may present in a similar manner but require different management.

The diagnosis of OHSS is made on clinical grounds comprising both clinical features and the results of objective investigations (Tables 1 and 2). The typical presentation is abdominal distension and discomfort following the hCG trigger 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 timing of presentation following hCG trigger results in different categorisations of OHSS:

- Early OHSS, which usually presents within 7 days of the hCG injection and is usually associated with an excessive ovarian response.

- Late OHSS, which 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.[30–35]

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 care. Careful assessment by an experienced clinician is 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. Important differential diagnoses include pelvic infection, pelvic abscess, appendicitis, ovarian torsion or cyst rupture, bowel perforation[36] and ectopic pregnancy. Causes other than OHSS should therefore always be considered in women presenting with abdominal pain during fertility treatment. *[Evidence level 3]*

203 **Table 1. Initial assessment and history-taking for suspected OHSS**
204

History
Time of onset of symptoms relative to trigger Pituitary down-regulation regimen: Long- GnRH agonist, GnRH antagonist Medication used for trigger (higher OHSS risk with hCG. Significantly lower with GnRH agonist trigger) Number of follicles on final monitoring scan (≥20) Number of eggs collected (≥15) Whether the woman had an embryo transfer and how many embryos were replaced History of polycystic ovarian morphology on ultrasound scan/ polycystic ovary syndrome
Symptom
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

205

206 **Table 2. Examination and investigation for suspected OHSS**
207

Examination
General: assess for dehydration, oedema (pedal, pre-tibial, vulval and sacral); check heart rate, respiratory rate, blood pressure, body weight and temperature. Muffled heart sounds may suggest pericardial effusion. **Abdominal:** assess for ascites, palpable mass, peritonism; measure girth **Respiratory:** assess for pleural effusion, pneumonia, pulmonary oedema
Investigations
Full blood count (FBC) Haematocrit – as a reflection of haemoconcentration (High: greater than 0.45) C-reactive protein (severity) Urea and electrolytes (U&E) particularly to assess for hyponatraemia and hyperkalaemia Sodium - to rule out hyponatremia (<135 mmol/L) Potassium – to rule out hyperkalemia (>5.0mmol/l) Serum osmolality (hypo-osmolality <282 mOsm/kilogram) Liver function tests (LFT) to assess for elevated enzymes and reduced albumin Serum Albumin (Hypoalbuminemia <35 g/l) Coagulation profile (elevated fibrinogen and reduced antithrombin) – coagulation cascade changes can occur with OHSS and may be markers of worsening OHSS hCG (to determine outcome of treatment cycle) if appropriate Ultrasound scan: ovarian size, pelvic and abdominal free fluid
Other tests that may be indicated
If suspected PE / plural effusion / pericardial effusion: -Arterial blood gas D-dimer -Electrocardiogram (ECG)/echocardiogram -Chest X-ray -Computerised tomography pulmonary angiogram (CTPA) or ventilation/perfusion (V/Q) scan *If suspected ovarian torsion:* Clinical assessment for torsion / consider pelvic ultrasound or MRI *Non-gynaecological symptoms such as headache and unilateral neck pain should alert the clinician to rarer diagnoses such as internal jugular thrombosis*

6. Classifying severity and reporting adverse outcomes

6.1 How is the severity of OHSS classified?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
The severity of OHSS should be graded according to a standardised classification.	**4**	**D**	**Several schemes have been developed for classifying the severity of OHSS. The suggested classification in this guidance is that used by the RCOG and the Human Fertilisation and Embryology Authority (HFEA).**

Several schemes have been developed for classifying the severity of OHSS,[26-29] with no clear agreement between investigators. The scheme in Appendix 2 is the classification used by the RCOG and the Human Fertilisation and Embryology Authority (HFEA).

Rarely, OHSS may be associated with life-threatening complications, including renal failure, acute respiratory distress syndrome (ARDS), intra-abdominal haemorrhage from ruptured ovarian cysts/follicles, and thromboembolism.[1-2,37-42] 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.[43] The 2022 triennial MBBRACE report did not identify any maternal deaths due to OHSS in the UK in the period 2018 to 2021.[44] No mortality from OHSS has been reported to the HFEA since the last update of this guideline in 2016.

6.2 How should OHSS be reported?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Licensed fertility clinics should comply with the HFEA regulations in reporting cases of severe or critical OHSS.	**4**	**D**	UK clinics providing licensed fertility treatment are obliged to follow relevant HFEA regulations for reporting severe untoward incidents.
Fertility clinics should encourage patients to directly inform them of any hospital admissions in the first three months of completing fertility treatment.	**4**	**GPP**	Clinics providing fertility treatment are responsible for the risks resulting from fertility treatment and should be aware of their occurrence, in addition this helps with auditing and reporting of events to the HFEA.

If a person with OHSS presents to the hospital at a site other than the treating licensed fertility clinic, the hospital should endeavour to inform the fertility clinic and vice versa.	**4**	**GPP**	It is good clinical practice that the admitting centre informs the clinic where the treatment took place regarding any hopsital admissions to allow the clinic to fulfil its reporting duties to the HFEA.
Any deaths related to OHSS in the UK should be reported to MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK), irrespective of whether the person was pregnant.	**4**	**GPP**	To allow review of cases, improving future practice and for audit purposes. At present it is not a specified requirement to report deaths related to OHSS to MBRRACE-UK. It is however good clinical practice to report any deaths related to OHSS.

UK clinics providing licensed fertility treatment are obliged to follow relevant HFEA guidelines for reporting severe untoward incidents, which is co-ordinated through the Person Responsible who has overall responsibility for ensuring the clinic and its staff comply with the law and code of practice requirements. The HFEA requires licensed clinics to report cases of severe or critical OHSS (as per the classification above), regardless of whether or not 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 and near misses be reported verbally within 12 working hours, followed by an incident form within 24 working hours of the incident being identified. A specific proforma for reporting cases of critical or severe OHSS is required to be completed within 25 working days. Since people with OHSS are often admitted to centres other than the treating clinic, it is important for the admitting centre to inform the originating clinic so that the clinic can fulfil its duty to report cases of OHSS to the HFEA.[45-46]

Any deaths related to OHSS in the UK should be reported to MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK), irrespective of whether the person was pregnant.[44] At present it is not a specified requirement to report deaths related to OHSS to MBRRACE-UK. It is however good clinical practice to report to MBRRACE-UK any deaths related to OHSS.

7. Organisation of services

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

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Fertility clinics should provide verbal and written information about OHSS to all people undergoing fertility treatment, including a 24-hour contact telephone number.	**4**	**GPP**	**Early detection and intervention helps to reduce worsening of OHSS, therefore people should be asked to seek advice early if feeling unwell.**

All acute units where people with suspected OHSS are likely to present should establish agreed local protocols for the assessment and care of these patients and ensure they have access to appropriately skilled clinicians with experience in the care of this condition.	**4**	**GPP**	**To allow appropriate assessment and care of people presenting with suspected OHSS.**
Once the diagnosis of OHSS is made the appropriate reporting form should be completed.	**4**	**GPP**	**To allow the fertility clinic where the treatment was undertaken to review this as part of their clinical governance process.**

OHSS results from fertility treatment carried out in specialist clinics. In many cases, the treating clinic 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 woman with OHSS may lack experience in managing this condition. Efforts should be made to reduce the risk associated with this by empowering people undergoing fertility treatment through clear information, and coordination of services between licensed clinics and the acute units where women are likely to present through pathways and guidance.[45-46]

People undergoing fertility treatment should be informed of the symptoms of OHSS and of the importance of reporting these. Information concerning OHSS should be fully discussed with all patients undergoing fertility treatment, with verbal and written information provided 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 care of women presenting with suspected OHSS. Input should be available from 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 clinic should agree referral pathways and protocols with the acute units to ensure that specialists provide continuity of care for people with OHSS, particularly when patients 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 clinicians with appropriate expertise.

8. Initial assessment

8.1 How should women with suspected OHSS be assessed and cared for?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
People presenting with symptoms suggestive of OHSS should be assessed by a suitably experienced health care professional.	**3**	**D**	**To establish the diagnosis and grade the severity of OHSS and to determine whether outpatient or inpatient care is needed.**
People undergoing fresh IVF treatment who experience symptoms of early OHSS before having their embryo transfer should be advised to avoid fresh embryo transfer and to have cryopreservation of embryos followed by interval frozen embryo replacement.	**3**	**D**	**This is likely to result in a lower risk of late OHSS and unlikely to compromise success rates.**

The initial assessment aims to establish the diagnosis (see section 5) and grade the severity of OHSS (see section 6). People with symptoms of OHSS may, in the first instance, be assessed over the telephone especially if symptoms are mild. It is important for staff triaging people over the telephone to identify patients who will require face-to-face clinical review. Important points to note in the history are specified in Table 1. A specific enquiry should be made for significant abdominal pain, shortness of breath, nausea, vomiting or a subjective impression of reduced urine output. These symptoms may indicate severe OHSS and the occurrence of specific respiratory, renal or ovarian complications.[36–41]

People undergoing fresh IVF treatment who experience symptoms of early OHSS before having their embryo transfer should be advised to avoid having fresh embryo transfer and to have cryopreservation of embryos followed by interval frozen embryo replacement. This is unlikely to compromise success rates and likely to result in a lower risk of late OHSS.[102]A meta-analysis of 11 studies including 5379 patients assessed outcomes with elective interval frozen embryo transfer compared with fresh embryo transfer in IVF/ICSI cycles. The meta-analysis showed significant reduction in the risk of moderate/severe OHSS with elective interval frozen embryo transfer compared with fresh embryo transfer (RR 0.42; 95% CI: 0.19-0.96). A significant increase in live birth rates was noted with elective interval frozen embryo transfer compared with fresh embryo transfer in the overall IVF/ICSI population (RR 1.12; 95% CI: 1.01-1.24). In addition, subgroup analyses showed higher live birth rates by elective interval frozen embryo transfer than by fresh embryo transfer in hyper-responders (RR 1.16; 95% CI: 1.05-1.28).[102]

9. Outpatient care of people with OHSS

9.1 When is outpatient care for people with OHSS appropriate?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Outpatient care is appropriate for people with mild or moderate OHSS and in selected cases with severe OHSS.	**3**	**D**	**To allow people to be cared for in their home environment.**

Outpatient care is appropriate for people with mild or moderate OHSS and in selected cases with severe OHSS (see appendix 2). This would allow outpatient management and avoid the need for care to take place in hospital. This, however, needs to be done following clear criteria with patient selection and access to hospital admission where required. Criteria for inpatient management are addressed in Section 10.

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

Recommendation	Evidence quality	Strength	Rationale for the recommendation
People undergoing outpatient care for OHSS should be appropriately counselled and provided with information regarding fluid intake and output monitoring. In addition, people should be provided with contact details (daytime and out of hours) to access advice.	**3**	**D**	**To allow safe monitoring and to have access to advice and support where required.**
People with moderate OHSS should be evaluated for predisposing risk factors for thrombosis and prescribed anti-embolism stockings and consideration given to the need for LMWH. **People with severe OHSS being cared for on an outpatient basis should be recommended thromboprophylaxis with LMWH. The duration of treatment should be individualised, considering risk factors and whether or not conception occurs.**	**4**	**C**	**People with moderate / severe OHSS are at increased risk of thromboembolism.**
Nonsteroidal anti-inflammatory agents should be avoided.	**3**	**D**	**These may compromise renal function.**
Paracentesis of ascitic fluid may be carried out on an outpatient basis by the abdominal or transvaginal route under ultrasound guidance.	**3**	**D**	**To minimise hospital admission**

People with OHSS should be provided with verbal and written information about their condition and be advised to alert the clinic if their symptoms worsen. There are no specific studies to guide advice regarding fluid intake. However, it appears reasonable to encourage people to drink to thirst rather than a set amount.[7]. Outpatient care may be aided if women 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.

Paracetamol and oral opiates including codeine can be offered to women for pain relief. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided as they may compromise renal function in women with OHSS.[53]

Those 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 (see section 10.7).[44]

A number of retrospective observational series[47-52] have described outpatient care of severe OHSS. Lincoln et al.[41] reported a retrospective series of 48 patients with moderate to severe OHSS cared for 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.[49] reported a retrospective case series of 146 outpatient transvaginal paracenteses in 96 people 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.[50] Patients received a daily telephone call by a nurse and were reviewed by a doctor where necessary. They were followed up for a median of 8 days (range 4–31) after egg collection and no one had complications related to OHSS. Paracentesis was carried out in 7.1% of patients with a mean volume of fluid drained of 4543 ml (SD 2792 ml). Hospital admission was required in 4%, with a median length of admission of 2 days (range 2–5 days). *[Evidence level 3]*

A systematic literature review reported on the outpatient care of severe OHSS.[52] The review included retrospective and observational non-controlled trials and did not identify any randomised trials comparing inpatient with outpatient care. In addition, the small number of patients assigned for outpatient care in all the included studies were too small to allow meta-analysis of the data. The review reported that outpatient care with early drainage of ascitic fluid, hydration and thromboprophylaxis, appeared to be associated with shortening of the treatment and follow up duration. Early aspiration of ascites appeared to be a successful and cost-effective intervention. The systematic review concluded that outpatient care is a safe option in appropriately selected patients, with no reported increase in morbidity or mortality.[52]

Observational studies[54–55] have suggested that GnRH antagonist administration in those with established severe early OHSS may result in quicker regression of the syndrome. Small observational studies[56-59] also suggest that dopamine agonists may have a beneficial role in the treatment of established OHSS. Further research is required to evaluate these interventions including the optimal dose and duration for use in this context.

9.3 Outpatient monitoring of people with OHSS

Recommendation	Evidence quality	Strength	Rationale for the recommendation
People with OHSS being cared for on an outpatient basis should be reviewed urgently by a suitably experienced healthcare professional if they develop symptoms or signs of worsening OHSS. In the absence of these, review every 2–3 days is likely to be adequate.	**4**	**GPP**	**To allow prompt assessment and management of worsening OHSS.**

Baseline laboratory investigations (FBC, U&E and LFT) should be repeated if the severity of OHSS is thought to be worsening.	**4**	**D**	**To complement clinical assessment and allow identification of worsening OHSS.**
People with OHSS should be followed up until resolution of OHSS. This should ideally be carried out in the treating clinic and / or in the clinical setting where the patient is managed.	**3**	**D**	**To monitor for changes in the clinical picture and provide advice and support.**

The objective of monitoring is to identify those who suffer increasing severity of OHSS and may require further measures. In most people, the condition resolves over a period of 7–10 days.[60-61] 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.

Clinicians and women should be vigilant for signs that the severity of OHSS is worsening. These include:[60-63]

- increasing abdominal distension and pain
- shortness of breath
- tachycardia or hypotension
- reduced urine output (less than 1000 ml/24 hours). Urine output less than 300ml/24 hours or a positive fluid balance of more than 1000ml/24 hours should prompt suspicion of severe OHSS.
- weight gain and increased abdominal girth
- increasing haematocrit (greater than 0.45L/L)

Ongoing patient contact should be arranged with the fertility clinic and treating centre (if in a different setting), until resolution of OHSS symptoms. Counselling and support should also be offered.

10. Inpatient care

10.1 When should women with OHSS receive inpatient care?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Hospital admission should be considered for people who: • **are unable to attend for regular outpatient follow-up.** • **are unable to achieve satisfactory pain control.** • **are unable to maintain adequate fluid intake due to nausea/vomiting.** • **have worsening OHSS symptoms despite outpatient intervention.**	**4**	**D**	**To allow safe assessment, monitoring and prompt management of worsening OHSS as some with severe OHSS will not be suitable for outpatient management.**

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 those with critical OHSS, and those who may be at imminent risk of complications or who have already developed complications that may require urgent clinical care. However, each case should be considered on its merits with reference to the clinical features, social factors and the expertise available. People with less severe OHSS may also benefit from admission depending on their social situation, geographical location and the availability of out-of-hours expertise. 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]*

Ongoing contact should be arranged after discharge with the fertility clinic or treating centre, (if in a different setting to where OHSS is managed) until resolution of symptoms. Counselling and support should also be offered.

10.2 How should people admitted with OHSS be monitored?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Those admitted with OHSS should be assessed at least daily for their symptoms. More frequent assessment is appropriate for people with critical OHSS and those with complications.	**4**	**GPP**	**To allow safe assessment monitoring and prompt management of worsening OHSS.**

Inpatient monitoring of people with OHSS aims to monitor changes in the severity of the disease process and to identify any complications at an early stage. Table 3 outlines what to consider in the monitoring of people with OHSS.

Table 3. Monitoring and assessment of inpatients with OHSS

Objective of inpatient monitoring of people with OHSS: to monitor changes in the severity of the disease process and to identify any complications at an early stage.
Inpatient monitoring of OHSS should include daily recording of: • body weight • abdominal girth • fluid balance • full blood count noting the haematocrit • serum electrolytes • liver function tests • clotting Depending on the clinical features: • arterial blood gases • ECG • chest X-ray • other imaging such as chest ultrasound may be required
Signs of worsening OHSS include: • increasing abdominal girth • weight gain • oliguria with positive fluid balance • elevated / increase in haematocrit
Conversely, recovery is signalled by: • Diuresis • normalisation of haematocrit • normalising of serum electrolytes and osmolality • reduction in abdominal girth and body weight
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.[95] *[Evidence level 3]*

10.3 How should the symptoms of OHSS be treated?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Analgesia and antiemetics may be used in people with OHSS, avoiding non-steroidal agents and medicines contraindicated in pregnancy.	**4**	**D**	**NSAIDs should be avoided as they may compromise renal function. Medicines contraindicated in pregnancy should be avoided in people who had embryo transfer.**

Relief of abdominal pain and nausea forms an important part of the supportive care of people with OHSS. Analgesia with paracetamol and opiates, if required, is appropriate, while NSAIDs should be avoided as they may compromise renal function.[53] Severe pain should prompt a medical review to

assess for other differentials such as ovarian torsion, bleeding from a ruptured ovarian cyst, or a concurrent problem such as ectopic pregnancy or pelvic infection. *[Evidence level 3]*

10.4 What is the appropriate inpatient fluid balance regime?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Fluid replacement by the oral route, guided by thirst, is the most physiological approach to correcting intravascular dehydration.	**4**	**D**	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.
Human albumin may be used for correction of dehydration in people with severe OHSS with persistent haemoconcentration, despite volume replacement with intravenous crystalloids.	**4**	**D**	To correct intravascular volume depletion.
People with persistent haemoconcentration despite volume replacement with intravenous colloids may need invasive monitoring and this should be managed with multidisciplinary specialist input which may include anaesthetic, ITU and renal input.	**4**	**D**	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.
The use of diuretics in managing fluid balance in people with OHSS should only be considered in a multidisciplinary setting and with central venous monitoring in place.	**4**	**D**	These can further deplete intravascular volume, but may have a role in multidisciplinary settings 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 feasible.[7] Some women may need effective analgesia and antiemetics in order to be able to maintain adequate fluid balance.

Acutely dehydrated people 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 people 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 people with severe OHSS. However, HES has been withdrawn in the UK as a result of evidence showing increased mortality in critically ill and septic people receiving HES compared to those receiving crystalloids. Human albumin solution 20% may be used as a plasma volume expander in doses of 50–100g (100ml), infused over 4 hours and can be repeated 4 to 12 hourly as required. Strict fluid balance recording should be followed.

Persistent haemoconcentration or low urine output despite apparent adequate volume replacement with 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. Small non-randomised studies[58-59] 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 people with OHSS, but their use has not been subjected to controlled studies. There is a risk of worsening intravascular hypovolaemia if diuretics are administered without correcting dehydration. However, careful use of diuretics may be appropriate in people who continue to exhibit oliguria despite adequate fluid replacement, particularly if any tense ascites that may have been contributing to oliguria has been drained.[60]

10.5 How should ascites and effusions be managed?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Paracentesis is indicated when abdominal pressure due to ascites leads to the following: – **severe abdominal distension and pain.** – **shortness of breath and respiratory compromise.** – **oliguria despite adequate volume replacement.**	**4**	**D**	To lower intra-abdominal pressure in people with moderate to severe OHSS.
Paracentesis should be carried out under ultrasound guidance and can be performed abdominally or vaginally.	**4**	**C**	To avoid trauma to the enlarged, vascular ovaries. Both abdominal and transvaginal routes are suitable options.
Intravenous colloid therapy should be considered when have large volumes of fluid removed by paracentesis.	**4**	**D**	To replenish intravascular volume.

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.

Paracentesis should be carried out in settings where local expertise is available either in the fertility centre or in the local hospital where the patient is referred to.

Pigtail catheters to allow free drainage of ascites have been used successfully in a case series of 63 women, without an increase in fetal or maternal complications. The comparison group was 126 women with OHSS who did not need ascitic drainage.[66]

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.[49-65-66]

Smith et al.[49] reported a series of 146 outpatient transvaginal paracenteses performed to care for OHSS in 96 cases. The mean volume of fluid removed was 2155 ml (range 500–4500 ml) with no complications reported. Ozgun et al.[67] reported the drainage of 7.5 litres on one occasion over 3 hours, and a total of 45 litres by serial vaginal paracentesis with supportive fluid replacement with no adverse outcome. People 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 people with malignant ascites who may experience significant fluid shifts in such situations.[68]

It has been suggested that early drainage of ascites to lower the intra-abdominal pressure in women with moderate to severe OHSS may prevent disease progression and lower the risk of severe complications associated with this condition.[68] Drainage of 2000 ml of ascitic fluid in women with severe OHSS produced significant reductions in intra-abdominal pressure and renal vascular resistance.[54] Koike et al.[69] described autotransfusion of ultrafiltered ascitic fluid into the venous circulation and their observational study showed reduced haemoconcentration, improved urine output and quicker recovery following this procedure compared to 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[70] describes autotransfusion of concentrated ultrafiltered ascitic fluid protein, aiming to replenish albumin levels using the patient's own protein, reducing the risk of infection and allergic reaction to exogenous albumin.

10.6 When is multi-disciplinary care indicated?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Multidisciplinary assistance (anaesthetic, intensivists, renal, haematology) should be sought for the care of any person with critical OHSS and severe OHSS who have persistent haemoconcentration and dehydration. Features of critical OHSS should prompt consideration of the need for intensive care.	**4**	**D**	**To allow access to specialist assessment and management of worsening OHSS.**

People with severe OHSS where dehydration and haemoconcentration persist despite adequate fluid replacement may need invasive haemodynamic monitoring and anaesthetic/intensive care specialist input. Intensive care is also likely to be needed for people with critical OHSS, while specific complications such as thromboembolism, ARDS and renal failure require input from relevant specialties. *[Evidence level 4]*

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

10.7 How can the risk of thromboembolism be reduced in people with OHSS?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
People with OHSS should be evaluated for predisposing risk factors for thrombosis and consider anti-embolism stockings / LMWH.	**4**	**GPP**	**OHSS is a prothrombotic state due to haemoconcentration and vascular endothelial dysfunction.**
People admitted to hospital with OHSS should receive LMWH prophylaxis.	**4**	**C**	**To minimise the risk of thrombosis.**
The duration of LMWH prophylaxis should be individualised according to risk factors for the individual and outcome of treatment.	**4**	**D**	**To allow adjusting for individual background risk and minimise the risk of thrombosis.**
People with OHSS who are pregnant should receive thromboprophylaxis with LMWH for the first trimester.	**2**	**C**	**To minimise the risk of thrombosis.**
In addition to the typical symptoms and signs of venous thromboembolism (VTE), thromboembolism should be suspected in people with OHSS who present with unusual neurological symptoms such as dizziness, loss of vision and neck pain. This may present several weeks after apparent improvement in OHSS.	**4**	**D**	**Thrombosis in people with OHSS may affect upper body sites and can involve the arterial system. Therefore, clinicians should remain vigilant of people presenting with unusual symptoms such as dizziness, loss of vision and neck pain.**

OHSS is a prothrombotic state due to haemoconcentration and vascular endothelial dysfunction. The incidence of thrombosis has been estimated to lie between 0.7% and 10% of cases of OHSS.[96-97] Rova et al.[71] reported on the risk of VTE in early pregnancy in relation to IVF and OHSS. The review included all births 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, while the incidence in IVF pregnancies with no OHSS was 0.8 per 1000

cases (OR 4.8, 95% CI 2.7–8.7), compared to 16.8 VTE events per 1000 cases for those who developed OHSS (OR 99.7, 95% CI 61.6–161.1).

There are no comparative studies addressing the value of thromboprophylaxis in those with severe OHSS. However, the incidence of this complication and its potentially life-threatening nature mean that thromboprophylaxis with antiembolism stockings and LMWH should be given to people with severe OHSS, and those with risk factors such as:

- reduced mobility
- obesity
- pre-existing thrombophilia
- OHSS requiring admission to hospital
- People with OHSS who are pregnant [72-73]

There is no agreement on the duration of thromboprophylaxis in people with OHSS. Several case reports describe thromboembolism occurring weeks after the apparent resolution of OHSS, particularly in association with pregnancy. The majority of delayed thrombosis events are reported to have occurred in the first trimester of pregnancy. Hence, in people with severe OHSS who conceive, thromboprophylaxis should be considered at least until the end of the first trimester.[72-73] In general, the duration of thromboprophylaxis should be based on individual risk factors and whether or not conception occurs. Liaison with a haematology specialist may be beneficial in individualising therapy.

Thrombosis in those with OHSS may affect upper body sites and frequently involves the arterial system. Therefore, clinicians should remain vigilant of women presenting with unusual symptoms such as dizziness, loss of vision and neck pain. Patients may present with thromboembolism several weeks after apparent resolution of OHSS.[74] If a thrombosis is suspected, then therapeutic anticoagulation should be instigated, while appropriate imaging is arranged. These people should be cared for in collaboration with specialist haematology and maternal medicine input.

10.8 When is surgical intervention indicated?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Surgery is indicated in the presence of a suspected adnexal torsion, internal bleeding from ruptured ovarian cyst or ectopic pregnancy.	**4**	**D**	**Differential diagnosis should be considered in the presence of worsening symptoms.**

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 patients with OHSS, particularly in the presence of pregnancy. Laparoscopic detorting of hyperstimulated ovaries has been described. The presence of ovarian enlargement and ascites should be kept in mind when considering a diagnosis of ectopic pregnancy.[75-79, 98]

In very rare cases of critical OHSS, termination of pregnancy as an exceptional live saving intervention has been reported in the situation of progressive thrombosis despite anticoagulation, and there have been cases reported of removal of the ovaries (bilateral oophorectomy) for intractable OHSS; however, this is not a recommended treatment option, but a treatment of last resort in exceptional cases.[87-88]

Torsion should be considered in the presence of progressively worsening pain with a rise in inflammatory markers. Successful detorsion has been described 72 hours after symptom onset and can be performed in early pregnancy. Ectopic pregnancy can be concurrent with OHSS, and a standard care approach should be taken, with extra vigilance that the ovaries will be enlarged and hyperaemic. Other possible causes of abdominal pain such as appendicitis should also be considered in those with OHSS and could be concurrent. Patients should be counselled about potential risks of anaesthesia and surgery in early pregnancy where applicable. Ascitic drainage of foul-smelling turbid fluid with rising pyrexia and continued pain should alert the clinician to bowel perforation. Obstructive uropathy, requiring bilateral percutaneous nephrostomies has been reported and a urological opinion should be considered, should the enlarged ovaries compress the kidneys or ureters and show early evidence of hydronephrosis on ultrasound scan. Early signs of acute kidney injury include a rising creatinine and white cell count. Accidental bladder trauma caused by ascites drainage can rarely lead to a haematocele resulting in haematuria, dysuria and urinary retention. In most cases, care is conservative.

Vulval oedema can be a common feature of OHSS, sometimes requiring catheterisation due to the inability to pass urine. If unilateral labial swelling is seen, this can be associated with an occult inguinal hernia, especially if movement is painful. Mechanical thrombectomy has been described for middle cerebral artery occlusion[79-80] and vena cava filters for venous thromboembolic events in pregnancy.[75-86]

11. OHSS and pregnancy

11.1 What additional problems can occur in people with OHSS and concurrent pregnancy?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Clinicians should be aware, and patients informed, that pregnancies complicated by OHSS may be at increased risk of pre-eclampsia and preterm birth.	**4**	**C**	**Observational studies suggest OHSS may be associated with an increased risk of pre-eclampsia and preterm birth.**

Controlled studies do not suggest an increase in the risk of miscarriage in pregnancies arising from ART cycles complicated by OHSS compared to cycles without OHSS, although some reports have suggested an increased rate of early (biochemical) pregnancy loss in those with early, but not late, OHSS.[89-93]

Data concerning later gestational complications in pregnancies complicated by OHSS are limited. Courbierre et al.[91] found a higher incidence of pre-eclampsia (21.2% versus 9.2%) and preterm birth (36% versus 10.7%) in 40 OHSS pregnancies compared to 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.[92] 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 to the corresponding non-OHSS controls. In a retrospective cohort study using National Assistant Reproductive Technology Surveillance System (NASS) data, Schirmer III et al. also found an increased risk of prematurity and low birth weight in

singleton pregnancies, and in addition, an increased risk of second trimester loss in twin pregnancies complicated by OHSS.[93]

12. The patient perspective

12.1 Information provision and awareness

It is important not to forget the emotional impact of OHSS on fertility patients. OHSS is associated with abdominal discomfort, and the symptoms can cause significant distress to patients and their partners/support network. The swelling, sickness and bloating are often unpleasant even when OHSS is classified as mild or moderate. People are not always sure whether to contact a healthcare professional when they start to experience symptoms and clear guidance on this should be provided to all patients undergoing fertility treatment for the early and progressing signs of OHSS for which they should alert their clinic or GP. This should be both verbally and in written formats.

People are often worried that having OHSS will reduce their chances of a successful outcome from treatment, or affect the pregnancy if they have already had a positive test result. When treatment has to be halted, delays may cause concern especially given the emotional, physical and often the financial, investment in the fertility treatment. Making a clear plan and explaining the pathway is helpful and enables patients to have a better understanding of what is happening.

All people undergoing fertility treatment should be informed about OHSS and their individualised risks and the signs to look out for. People who are at higher risk of OHSS should be informed of their increased background risk before treatment starts.

People need to understand when they should report symptoms of OHSS and who they should turn to if they experience them. They should be given access to a 24-hour contact so they can get in touch at any time.

12.2 Support for people with OHSS

Recommendation	Evidence quality	Strength	Rationale for the recommendation
People diagnosed with OHSS should be signposted to appropriate counselling and support services.	**4**	**GPP**	**It can be distressing with symptomatic OHSS and disappointing with fresh embryo transferred not occurring.**

People who present with OHSS should be provided information about the interventions that they may be offered and any impact this may have on their fertility treatment.

Advice about what an individual can do themselves to help with OHSS should be clear and evidence-based. Recognising the emotional impact of OHSS is vital, and it may be beneficial to remind patients how to access fertility counselling or peer support.[94]

13. Recommendations for future research

- More research is required to clarify changes in the osmoregulatory system in people at different phases of OHSS, using well-defined cohorts of women with severe disease who are followed through the course of OHSS.
- There is a need to compare outpatient and inpatient care of severe OHSS in terms of safety, efficacy, patient acceptability and health economic assessment. A multi-centre trial comparing outpatient care of severe OHSS with conventional care was started in the UK but stopped early in 2023 due to low recruitment numbers.
- Further research is required to evaluate the role of GnRH antagonists, dopamine agonists and aromatase inhibitors in the care of people with established OHSS.
- There is a need for assessment of the feasibility of having a national OHSS registry to allow a better understanding of the incidence and outcomes of OHSS cases of all degrees of severity.
- HFEA data on the incidence and features of cases of OHSS (including incidence by ethnic group) should be published and made available for statistical analysis

14. Auditable topics

- Proportion of people 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 clinics 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 units should ensure licensed clinics have been informed regarding all cases seen with a suspected diagnosis of OHSS (100%).
- Effectiveness of outpatient care of severe OHSS against locally agreed standard. (100%)
- People admitted to hospital should have daily clinical review with weight and abdominal girth measurements and monitoring of intake and output of fluid (100%).
- All people with severe or critical OHSS should be prescribed LMWH, unless there is a contraindication, whether admitted to hospital or not (100%).

15. Useful links and support groups

- British Fertility Society. Ovarian hyperstimulation syndrome (OHSS) http://britishfertilitysociety.org.uk/downloads/ms_3642.pdf
- RCOG Ovarian Hyperstimulation Syndrome (OHSS) Patient Information Leaflet Ovarian hyperstimulation syndrome (OHSS) patient information leaflet | RCOG
- Infertility Network UK. Fact Sheet: Ovarian Hyper Stimulation Syndrome (OHSS) https://fertilitynetworkuk.org/wp-content/uploads/2016/09/FACTSHEET-PCOS-Polycystic-Ovary-Syndrome-September-2016.pdf

687 **References**
688
689 1. Braat DD, Schutte JM, Bernardus RE, Mooij TM, van Leeuwen FE. Maternal death related to IVF
690 in the Netherlands 1984–2008. Hum Reprod 2010;25:1782–6.
691 2. Whelan JG 3rd, Vlahos NF. The ovarian hyperstimulation syndrome. Fertil Steril 2000;73:883–
692 96.
693 3. Ata B, Tulandi T. Pathophysiology of ovarian hyperstimulation syndrome and strategies for its
694 prevention and treatment. Expert Rev Obstet Gynecol 2009;4:299–311.
695 4. Mathur RS, Tan BK. British Fertility Society Policy and Practice Committee: prevention of ovarian
696 hyperstimulation syndrome. Hum Fertil (Camb) 2014;17:257–68.
697 5. Guideline on Ovarian Stimulation in IVF ICSI. 2019. https://www.eshre.eu/Guidelines-and-
698 Legal/Guidelines/Ovarian-Stimulation-in-IVF-ICSI
699 6. Evbuomwan IO, Davison JM, Murdoch AP. Coexistent hemo concentration and hypoosmolality
700 during superovulation and in severe ovarian hyperstimulation syndrome: a volume homeostasis
701 paradox. Fertil Steril 2000;74:67–72.
702 7. Evbuomwan IO, Davison JM, Baylis PH, Murdoch AP. Altered osmotic thresholds for arginine
703 vasopressin secretion and thirst during superovulation and in the ovarian hyperstimulation
704 syndrome (OHSS): relevance to the pathophysiology of OHSS. Fertil Steril 2001;75:933–41.
705 8. Evbuomwan I. The role of osmoregulation in the pathophysiology and management of severe
706 ovarian hyperstimulation syndrome. Hum Fertil (Camb) 2013; 16:162–7.
707 9. Zegers-Hochschild F, Mansour R, Ishihara O, Adamson GD, de Mouzon J, Nygren KG, et al.
708 International Committee for Monitoring Assisted Reproductive Technology: world report on
709 assisted reproductive technology, 2005. Fertil Steril 2014;101:366–78.e14.
710 10. Humaidan P, Nelson SM, Devroey P, Coddington CC, Schwartz LB, Gordon K, Frattarelli JL,
711 Tarlatzis BC, Fatemi HM, Lutjen P, Stegmann BJ. Ovarian hyperstimulation syndrome: review
712 and new classification criteria for reporting in clinical trials. Hum Reprod. 2016 Sep;31(9):1997-
713 2004. doi: 10.1093/humrep/dew149. Epub 2016 Jun 23. PMID: 27343272.
714 11. Ishihara O, Arce JC; Japanese Follitropin Delta Phase 3 Trial (STORK) Group. Individualized
715 follitropin delta dosing reduces OHSS risk in Japanese IVF/ICSI patients: a randomized controlled
716 trial. Reprod Biomed Online. 2021 May;42(5):909-918. doi: 10.1016/j.rbmo.2021.01.023. Epub
717 2021 Feb 9. PMID: 33722477.
718 12. Ishihara O, Nelson SM, Arce JC. Comparison of ovarian response to follitropin delta in Japanese
719 and White IVF/ICSI patients. Reprod Biomed Online. 2022 Jan;44(1):177-184. doi:
720 10.1016/j.rbmo.2021.09.014. Epub 2021 Sep 23. PMID: 34799275.
721 13. Qiao J, Zhang Y, Liang X, Ho T, Huang HY, Kim SH, Goethberg M, Mannaerts B, Arce JC. A
722 randomised controlled trial to clinically validate follitropin delta in its individualised dosing
723 regimen for ovarian stimulation in Asian IVF/ICSI patients. Hum Reprod. 2021 Aug
724 18;36(9):2452-2462. doi: 10.1093/humrep/deab155. PMID: 34179971; PMCID: PMC8373472.
725 14. HFEA State of the Sector Report October 2022, https://www.hfea.gov.uk/about-
726 us/publications/research-and-data/state-of-the-fertility-sector-2021-2022/
727 15. HFEA: State of the fertility sector 2019/2020. https://www.hfea.gov.uk/about-
728 us/publications/research-and-data/state-of-the-fertility-sector-2019-2020/
729 16. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome
730 (OHSS): a review. Hum Reprod Update 2002;8:559–77.
731 17. Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin-
732 releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst
733 Rev. 2016 Apr 29;4(4):CD001750. doi: 10.1002/14651858.CD001750.pub4. PMID: 27126581;
734 PMCID: PMC8626739.

18. Sood A, Goel A, Boda S, Mathur R. Prediction of significant OHSS by ovarian reserve and ovarian response - implications for elective freeze-all strategy. Hum Fertil (Camb). 2020 Aug 24:1-7. doi: 10.1080/14647273.2020.1809021. PMID: 32835544.
19. Tomás C, Colmorn L, Rasmussen S, Lidegaard Ø, Pinborg A, Andersen AN. Annual incidence of severe ovarian hyperstimulation syndrome. Dan Med J. 2021 Jan 26;68(2):A12190738. PMID: 33543701.
20. Karimbil B, Maydanovych S, Hingorani J, et al. Ovarian hyperstimulation syndrome (OHSS) in a spontaneous pregnancy with persistent maternal tachycardia, acute renal failure, multiple VTEs (venous thromboembolism) and fetal mirror syndrome: diagnosis and management dilemma. BJOG. 2019;126:23–3.
21. Yang L, Wang R, Wang F, Wang F, Zou L. Ovarian hyperstimulation syndrome in a frozen-thawed embryo transfer pregnancy: a rare case report. BMC pregnancy and childbirth. 2020 May 20;20(1):313. https://pubmed.ncbi.nlm.nih.gov/32434545/
22. K A, Bs L, G B. Ovarian hyperstimulation syndrome as a complication of molar pregnancy. Cleveland Clinic journal of medicine. 2016 Jul 1;83(7). https://pubmed.ncbi.nlm.nih.gov/27399862/
23. Gaggero C r, Bogliolo S, Sala P, Molinari C, Motzo M, Fulcheri E, et al. Diginyc partial hydatidiform mole with increased fetal nuchal translucency and ovarian hyperstimulation syndrome. Clinical and Experimental Obstetrics & Gynecology. 2016;43(3):467–9. https://pubmed.ncbi.nlm.nih.gov/27328519/
24. Wu X, Zhu J, Zhao A. Ovarian hyperstimulation syndrome in a spontaneous pregnancy with invasive mole. Journal of Obstetrics and Gynaecology Research. 2014 Dec 10;41(5):817–22.
25. Wali S, Wild M. Maternal complications of fetal triploidy: a case report. BMJ Case Reports. 2020 Oct;13(10):e236950.
26. Mandelbaum RS, Bainvoll L, Violette CJ, Smith MB, Matsuzaki S, Klar M, et al. The influence of obesity on incidence of complications in patients hospitalized with ovarian hyperstimulation syndrome. Archives of Gynecology and Obstetrics. 2021 Jul 9; https://pubmed.ncbi.nlm.nih.gov/34241687/
27. Ovarian Stimulation TEGGO, Bosch E, Broer S, Griesinger G, Grynberg M, Humaidan P, Kolibianakis E, Kunicki M, La Marca A, Lainas G, Le Clef N, Massin N, Mastenbroek S, Polyzos N, Sunkara SK, Timeva T, Töyli M, Urbancsek J, Vermeulen N, Broekmans F. ESHRE guideline: ovarian stimulation for IVF/ICSI†. Hum Reprod Open. 2020 May 1;2020(2):hoaa009. doi: 10.1093/hropen/hoaa009. Erratum in: Hum Reprod Open. 2020 Dec 29;2020(4):hoaa067. PMID: 32395637; PMCID: PMC7203749.
28 Kupka MS, Ferraretti AP, de Mouzon J, Erb K, D'Hooghe T, Castilla JA, et al.; European IVF-Monitoring Consortium, for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE. Hum Reprod 2014;29:2099–113.
29. Kawwass JF, Kissin DM, Kulkarni AD, Creanga AA, Session DR, Callaghan WM, et al.; National ART Surveillance System (NASS) Group. Safety of assisted reproductive technology in the United States, 2000-2011. JAMA 2015;313:88–90.
30. Al-Inany HG, Youssef MA, Aboulghar M, Broekmans F, Sterrenburg M, Smit J, et al. GnRH antagonists are safer than agonists: an update of a Cochrane review. Hum Reprod Update 2011;17:435.
31. Mathur RS, Akande AV, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. Fertil Steril 2000;73:901–7.
32. Schenker JG, Weinstein D. Ovarian hyperstimulation syndrome: a current survey. Fertil Steril 1978;30:255–68.

33. Golan A, Ron-el R, Her man A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. Obstet Gynecol Surv 1989;44:430–40.
34. Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. Fertil Steril 1992;58:249–61.
35. Mathur R, Evbuomwan I, Jenkins J. Prevention and management of ovarian hyperstimulation syndrome. Curr Obstet Gynaecol 2005;15:132–8.
36. Memarzadeh MT. A fatal case of ovarian hyperstimulation syndrome with perforated duodenal ulcer. Hum Reprod 2010;25:808–9.
37. ESHRE Capri Workshop Group. Venous thromboembolism in women: a specific reproductive health risk. Hum Reprod Update 2013;19:471–82.
38. Petrie KF, Carter RMP, Carter RMP, Sadighi A, Choong AMTL, Davies AH, et al. An IVF pregnancy, a neck lump and shortness of breath. Clinical Medicine (London, England). 2015 Dec 1;15(6):562–4. https://pubmed.ncbi.nlm.nih.gov/26621946/
39. Zosmer A, Katz Z, Lancet M, Konichezky S, Schwartz-Shoham Z. Adult respiratory distress syndrome complicating ovarian hyperstimulation syndrome. Fertil Steril 1987;47:524–6.
40. Balasch J, Carmona F, Llach J, Arroyo V, Jové I, Vanrell JA. Acute prerenal failure and liver dysfunction in a patient with severe ovarian hyperstimulation syndrome. Hum Reprod 1990;5:348–51.
41. Abramov Y, Elchalal U, Schenker JG. Pulmonary manifestations of severe ovarian hyperstimulation syndrome: a multicenter study. Fertil Steril 1999;71: 645–51.
42. Al Omari W, Ghazal-Aswad S, Sidky IH, Al Bassam MK. Ovarian salvage in bilaterally complicated severe ovarian hyperstimulation syndrome. Fertil Steril 2011;96:e77–9.
43. Abramov Y, Elchalal U, Schenker JG. Severe OHSS: An 'epidemic' of severe OHSS: a price we have to pay? Hum Reprod 1999;14:2181–3.
44. MBRRACE-UK Saving Lives, Improving Mothers' Care Report 2021. https://www.npeu.ox.ac.uk/mbrrace-uk
45. Human Fertilisation and Embryology Authority [http://www.hfea.gov.uk/docs/Latest_long_term_data_ analysis_report_91-06.pdf.pdf].
46. Human Fertilisation and Embryology Authority [http://www.hfea.gov.uk/docs/General_Directions_0011_ -_Reporting_adverse_incidents_and_near_misses_V3.pdf].
47. Shrivastav P, Nadkarni P, Craft I. Day care management of severe ovarian hyperstimulation syndrome avoids hospitalization and morbidity. Hum Reprod 1994;9:812–4.
48. Lincoln SR, Opsahl MS, Blauer KL, Black SH, Schulman JD. Aggressive outpatient treatment of ovarian hyper stimulation syndrome with ascites using transvaginal culdocentesis and intravenous albumin minimizes hospitalization. J Assist Reprod Genet 2002;19:159–63.
49. Smith LP, Hacker MR, Alper MM. Patients with severe ovarian hyperstimulation syndrome can be managed safely with aggressive outpatient transvaginal paracentesis. Fertil Steril 2009;92:1953–9.
50. Shukla U, Deval B, Hamoda H, Savvas M, Narvekar N. A programme of outpatient surveillance for women at risk of severe OHSS following IVF: a prospective follow-up review of 99 cases. Hum Fertil (Camb) 2011;14 Suppl 1:7.
52. Gebril A, Hamoda H, Mathur R. Outpatient management of severe ovarian hyperstimulation syndrome: a systematic review and a review of existing guidelines. Hum Fertil (Camb). 2018 Jun;21(2):98-105. doi: 10.1080/14647273.2017.1331048. Epub 2017 May 29. PMID: 28554223.
53. Maslovitz S, Jaffa A, Eytan O, Wolman I, Many A, Lessing JB, et al. Renal blood flow alteration after paracentesis in women with ovarian hyperstimulation. Obstet Gynecol 2004;104:321–6.

54. Lee D, Kim SJ, Hong YH, Kim SK, Jee BC. Gonadotropin releasing hormone antagonist administration for treatment of early type severe ovarian hyperstimulation syndrome: a case series. Obstet Gynecol Sci. 2017 Sep;60(5):449-454. doi: 10.5468/ogs.2017.60.5.449. Epub 2017 Sep 18. PMID: 28989921; PMCID: PMC5621074.
55. Lainas GT, Kolibianakis EM, Sfontouris IA, Zorzovilis IZ, Petsas GK, Tarlatzi TB, et al. Outpatient management of severe early OHSS by administration of GnRH antagonist in the luteal phase: an observational cohort study. Reprod Biol Endocrinol 2012;10:69.
56. Rollene NL, Amols MH, Hudson SB, Coddington CC. Treatment of ovarian hyperstimulation syndrome using a dopamine agonist and gonadotropin releasing hormone antagonist: a case series. Fertil Steril 2009;92:1169.e15–17.
57. Baumgarten M, Polanski L, Campbell B, Raine-Fenning N. Do dopamine agonists prevent or reduce the severity of ovarian hyperstimulation syndrome in women undergoing assisted reproduction? A systematic review and meta-analysis. Hum Fertil (Camb) 2013;16:168–74.
58. Ferraretti AP, Gianaroli L, Diotallevi L, Festi C, Trounson A. Dopamine treatment for severe ovarian hyperstimulation syndrome. Hum Reprod 1992;7:180–3.
59. Tsunoda T, Shibahara H, Hirano Y, Suzuki T, Fujiwara H, Takamizawa S, et al. Treatment for ovarian hyperstimulation syndrome using an oral dopamine prodrug, docarpamine. Gynecol Endocrinol 2003;17:281–6.
60. Nouri K, Tempfer CB, Lenart C, Windischbauer L, Walch K, Promberger R, et al. Predictive factors for recovery time in patients suffering from severe OHSS. Reprod Biol Endocrinol 2014;12:59.
61. Practice Committee of the American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. Fertil Steril 2008;90 Suppl 5:S188–93.
62. Fábregues F, Balasch J, Manau D, Jiménez W, Arroyo V, Creus M, et al. Haematocrit, leukocyte and platelet counts and the severity of the ovarian hyperstimulation syndrome. Hum Reprod 1998;13:2406–10.
63. Nowicka MA, Fritz-Rdzanek A, Grzybowski W, Walecka I, Niemiec KT, Jakimiuk AJ. C-reactive protein as the indicator of severity in ovarian hyperstimulation syndrome. Gynecol Endocrinol 2010;26:399–403.
64. Grossman LC, Michalakis KG, Browne H, Payson MD, Segars JH. The pathophysiology of ovarian hyperstimulation syndrome: an unrecognized compartment syndrome. Fertil Steril 2010;94:1392–8.
65. Raziel A, Friedler S, Schachter M, Strassburger D, Bukovsky I, Ron-El R. Transvaginal drainage of ascites as an alternative to abdominal paracentesis in patients with severe ovarian hyperstimulation syndrome, obesity, and generalized edema. Fertil Steril 1998;69:780–3.
66. Çağlar Aytaç P, Kalaycı H, Yetkinel S, Alkaş D, Yüksel Şimşek S, Haydardedeoğlu B, Bulgan Kılıçdağ E. Effect of pigtail catheter application on obstetric outcomes in in vitro fertilization/intracytoplasmic sperm injection pregnancies following hyperstimulation syndrome. Turk J Obstet Gynecol. 2017 ;14(2):94-99. doi: 10.4274/tjod.33340. Epub 2017 Jun 15. PMID: 28913144; PMCID: PMC5558420.
67. Ozgun MT, Batukan C, Oner G, Uludag S, Aygen EM, Sahin Y. Removal of ascites up to 7.5 liters on one occasion and 45 liters in total may be safe in patients with severe ovarian hyper stimulation syndrome. Gynecol Endocrinol 2008;24:656–8.
68. Royal College of Obstetricians and Gynaecologists. Manage ment of Ascites in Ovarian Cancer Patients. Scientific Impact Paper No. 45. London: RCOG; 2014.
69. Koike T, Araki S, Minakami H, Ogawa S, Sayama M, Shibahara H, et al. Clinical efficacy of peritoneovenous shunting for the treatment of severe ovarian hyperstimulation syndrome. Hum Reprod 2000;15: 113–17.

70. Zhang Q, Xia L, Gao G. A new effective method in the treatment of severe ovarian hyperstimulation syndrome. Iran J Reprod Med 2012;10:589–94.
71. Rova K, Passmark H, Lindqvist PG. Venous thrombo-embolism in relation to in vitro fertilization: an approach to determining the incidence and increase in risk in successful cycles. Fertil Steril 2012;97:95–100.
72. ESHRE Capri Workshop Group. Venous thromboembolism in women: a specific reproductive health risk. Hum Reprod Update 2013;19:471–82.
73. Royal College of Obstetricians and Gynaecologists. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium. Green-top Guideline No. 37a. London: RCOG; 2015.
74. Mitchell-Jones N, McEwan M, Johnson M. Management of venous thromboembolism secondary to ovarian hyperstimulation syndrome: A case report documenting the first use of a superior vena caval filter for upper limb venous thromboembolism in pregnancy, and the difficulties and complications relating to anticoagulation in antenatal and peri-partum periods. Obstetric Medicine. 2016 Jun 1;9(2):93–5. https://pubmed.ncbi.nlm.nih.gov/27512501/
75. Gelbaya TA. Short and long-term risks to women who conceive through in vitro fertilization. Hum Fertil (Camb) 2010;13:19–27.
76. Gorkemli H, Camus M, Clasen K. Adnexal torsion after gonadotrophin ovulation induction for IVF or ICSI and its conservative treatment. Arch Gynecol Obstet 2002;267: 4–6.
77. Narayansingh G, Hoh J. The eventual successful management of ovarian torsion in a hyperstimulated ovary following in vitro fertilization: A case report. Case Reports in Women's Health. 2020 Apr 1;(26):e00166. https://pubmed.ncbi.nlm.nih.gov/32071888/
78. Kanayama S, Kaniwa H, Tomimoto M, Zhang B, Nishioka K, Oi H. Laparoscopic detorsion of the ovary in ovarian hyperstimulation syndrome during the sixth week of gestation: A case report and review. International Journal of Surgery Case Reports. 2019; 59:50–3. https://pubmed.ncbi.nlm.nih.gov/31103953/
79. Orvieto R, Vanni VS. Ovarian hyperstimulation syndrome following GnRH agonist trigger—think ectopic. Journal of Assisted Reproduction and Genetics. 2017 Jun 9;34(9):1161–5.
80. Cupisti S, Emran J, Mueller A, Dittrich R, Beckmann MW, Binder H. Course of ovarian hyperstimulation syndrome in 19 intact twin pregnancies after assisted reproduction techniques, with a case report of severe thromboembolism. Twin Res Hum Genet 2006;9:691–6.
81. Bouzari Z, Yazdani S, Sadeghi T. Concurrent ovarian hyperstimulation syndrome with perforated appendicitis following induction ovulation with HMG and HCG. The American Journal of Emergency Medicine. 2016 Oct;34(10):2051.e5–6.
82. Moon A, Tez D, Naisby G, Garthwaite M. Obstructive uropathy secondary to ovarian hyperstimulation syndrome (OHSS). Journal of Clinical Urology. 2015 Dec 30;10(3):254–6.
83. Ke X, Lin Y-H, Wang F. Non-surgical treatment for hematocele in the bladder associated with ascites puncture in a patient with ovarian hyperstimulation syndrome: a case report. Postgraduate Medicine [Internet]. 2021 Jan 1;133(1):112–6. https://pubmed.ncbi.nlm.nih.gov/32969742/
84. Kalafat E, Acar D, Aytac R. Swollen labia majora: An unusual presentation of occult inguinal hernia secondary to ovarian hyperstimulation syndrome. Taiwanese Journal of Obstetrics & Gynecology.. 2016 Jun 1;55(3):446–7. https://pubmed.ncbi.nlm.nih.gov/27343335/
85. Li X, Zheng J. Mechanical thrombectomy for middle cerebral artery occlusion associated with ovarian hyperstimulation syndrome: case report and review of the literature. Annals of Palliative Medicine. 2021 Mar;10(3):3504–9.

86. Kuwano A, Kubota Y, Nonaka T, Miyao S, Nakamoto H, Kawamata T. Mechanical Thrombectomy for Middle Cerebral Artery Occlusion Suspected of Ovarian Hyperstimulation Syndrome: Case Report and Review of the Literature. World Neurosurgery. 2019 Dec 1;132:300–2. https://pubmed.ncbi.nlm.nih.gov/31525479/
87. Amarin ZO. Bilateral partial oophorectomy in the management of severe ovarian hyperstimulation syndrome. An aggressive, but perhaps life-saving procedure. Hum Reprod 2003;18:659–64.
88. Bellver J, Escudero E, Pellicer A. Bilateral partial oophorectomy in the management of severe ovarian hyperstimulation syndrome (OHSS): ovarian mutilating surgery is not an option in the management of severe OHSS. Hum Reprod 2003;18:1363–7.
89. Mathur RS, Jenkins JM. Is ovarian hyperstimulation syndrome associated with a poor obstetric outcome? BJOG 2000;107:943–6.
90. Papanikolaou EG, Tournaye H, Verpoest W, Camus M, Vernaeve V, Van Steirteghem A, et al. Early and late ovarian hyperstimulation syndrome: early pregnancy outcome and profile. Hum Reprod 2005;20:636–41.
91. Courbiere B, Oborski V, Braunstein D, Desparoir A, Noizet A, Gamerre M. Obstetric outcome of women with in vitro fertilization pregnancies hospitalized for ovarian hyper stimulation syndrome: a case-control study. Fertil Steril 2011;95:1629–32.
92. Haas J, Yinon Y, Meridor K, Hershko-Klement A, Orvieto R, Schiff E, et al. Is severe ovarian hyperstimulation syndrome associated with adverse pregnancy outcome? Evidence from a large case-control study. Am J Obstet Gynecol 2014;210 Suppl 1:S329–30.
93. Schirmer III D, Kulkarni A, Zhang Y, Kawwass J, Boulet S, Kissin D. Ovarian hyperstimulation syndrome after assisted reproductive technologies: trends, predictors, and pregnancy outcomes. Fertl Steril 2020;114: 567-78.
94. Royal College of Obstetricians and Gynaecologists. Information for you: Ovarian hyperstimulation syndrome. London: RCOG; 2016. https://www.rcog.org.uk/for-the-public/browse-all-patient-information-leaflets/ovarian-hyperstimulation-syndrome-patient-information-leaflet/.
95. Korhonen KV, Savolainen-Peltonen HM, Mikkola TS, Tiitinen AE, Unkila-Kallio LS. C-reactive protein response is higher in early than in late ovarian hyperstimulation syndrome. Eur J Obstet Gynecol Reprod Biol. 2016 Dec;207:162-168. doi: 10.1016/j.ejogrb.2016.10.051. Epub 2016 Oct 31. PMID: 27865939.
96. Schenker JG, Polishuk WZ. Ovarian hyperstimulation syndrome. Obstet Gynecol. 1975 Jul;46(1):23-8. doi: 10.1097/00006250-197507000-00004. PMID: 1153133.
97. Wormer KC, Jangda AA, El Sayed FA, Stewart KI, Mumford SL, Segars JH. Is thromboprophylaxis cost effective in ovarian hyperstimulation syndrome: A systematic review and cost analysis. Eur J Obstet Gynecol Reprod Biol. 2018 May;224:117-124. doi: 10.1016/j.ejogrb.2018.03.028. Epub 2018 Mar 19. PMID: 29602141; PMCID: PMC5973799.
98. Tobiume T, Shiota M, Umemoto M, Kotani Y, Hoshiai H. Predictive factors for ovarian necrosis in torsion of ovarian tumor. Tohoku J Exp Med. 2011 Nov;225(3):211-4. doi: 10.1620/tjem.225.211. PMID: 22041520.
99. Chai W, He H, Li F, Zhang W, He C. Spontaneous ovarian hyperstimulation syndrome in a nonpregnant female patient: a case report and literature review. J Int Med Res. 2020;48(9):300060520952647. doi:10.1177/0300060520952647
100. Sridev S, Barathan S. Case report on spontaneous ovarian hyperstimulation syndrome following natural conception associated with primary hypothyroidism. J Hum Reprod Sci 2013;6:158–61.

101. Santos-Ribeiro S, Polyzos NP, Stouffs K, et al. Ovarian hyperstimulation syndrome after gonadotropin-releasing hormone agonist triggering and "freeze-all": in-depth analysis of genetic predisposition. J Assist Reprod Genet. 2015;32(7):1063-1068. doi:10.1007/s10815-015-0498.

102. Roque M, Haahr T, Geber S, Esteves SC, Humaidan P. Fresh versus elective frozen embryo transfer in IVF/ICSI cycles: a systematic review and meta-analysis of reproductive outcomes. Hum Reprod Update. 2019 Jan 1;25(1):2-14. doi: 10.1093/humupd/dmy033. PMID: 30388233.

Appendix 1: Explanation of grades and evidence levels

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 Recommendation

A At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs 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 Points

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

*on the occasion when the guideline development group find there is an important practical point that they wish to emphasise but for which there is not, nor is there likely to be any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. These are marked in the guideline, and are indicated by ✓. It must be emphasised that these are NOT an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue

Appendix 2. RCOG classification of severity of OHSS

Category of OHSS	Symptoms	Ultrasound	Haematological	Fluid homeostasis
Mild	**Mild abdominal pain** **Abdominal bloating**	**Ovarian size < 8cm in diameter**	**HCT <0.40L/L**	
Moderate	**Moderate abdominal pain** **Nausea +/- vomiting**	**Ovarian size usually 8-12cm** **Ultrasound evidence of ascites**	**HCT <0.45L/L**	
Severe	**Clinical ascites**	**Ovarian size usually >12cm**	**HCT >0.45L/L**	**Sodium <135 mmol/L** **Serum Osmolality <282 mOsm/kg** **Potassium >5.0mmol/l** **Serum Albumin <35 g/l** **Oliguria (<300mls/day, or <30mls/hr)**
Critical	**Tense ascites, Pleural effusions**		**HCT > 0.55L/L** **White cell count > 25 000/ml**	**Anuria** **Thrombosis** **ARDS**

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

997 **Glossary**

998

Ovarian hyperstimulation syndrome (OHSS)	OHSS is a complication of fertility treatment with pharmacological ovarian stimulation to increase the number of oocytes and therefore embryos available during assisted reproductive technology (ART). It may be classified as mild, moderate or severe. OHSS is associated with significant physical and psychosocial morbidity.
Assisted reproductive technology (ART).	Assisted reproduction techniques include intrauterine insemination (IUI), in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI) and donor insemination (DI). ART often includes pharmacological treatment with the intention of inducing the development of ovarian follicles.
Embryo transfer	The procedure in which one or more embryos are placed in the uterus.
Egg / embryo cryopreservation	The freezing and storage of embryos or eggs for future use in IVF treatment cycles.

999

This guideline was produced on behalf of the Royal College of Obstetricians and Gynaecologists by: **Dr H Hamoda FRCOG, London; Prof AJ Drakeley FRCOG, Liverpool; Ms K Brian, London; Dr IO Evbuomwan FRCOG, Gateshead and Dr R Mathur FRCOG, Manchester.**

Peer reviewers: XX

Committee lead reviewers were: Miss N Potdar FRCOG, Leicester and Dr G Ahmad FRCOG, Manchester.

The chair of the Guidelines Committee was: Dr MA Ledingham FRCOG[1], Glasgow; Dr B Magowan FRCOG[1], Melrose; Miss N Potdar FRCOG[2], Leicester and Mr Alastair McKelvey FRCOG[2], Norwich.
[1]until June 2021; [2]from June 2021

All RCOG guidance developers are asked to declare any conflicts of interest. A statement summarising any conflicts of interest for this guideline is available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg5.

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

The guideline will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.

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 and 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, as they are not 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.

