Clinical Opinion

RANZCOG CREI Consensus Statement on treatment of Ovarian Hyperstimulation Syndrome

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Background: Ovarian hyperstimulation syndrome (OHSS) is an uncommon but important iatrogenic condition associated with considerable morbidity and a small risk of mortality. This document gathers the consensus of a group of fertility subspecialists to aid health professionals in the development of protocols and guidelines for the management of women with OHSS.
Aim: To produce evidence-based consensus statements on the treatment of ovarian hyperstimulation syndrome (OHSS).
Methods: The CREI Consensus Group met in 2013 and 2014 and identified issues for inclusion and review. Review of the available evidence was conducted and consensus statements prepared. Areas of dissent of expert opinion and for further research were noted.
Results: There is a paucity of good data regarding the treatment of this condition, and much of the treatment is supportive in nature. Most of the management recommendations are based on good clinical practice points, rather than evidence from randomised trials.
Conclusion: OHSS is an uncommon but serious condition for which there are a number of proven preventative strategies. Once OHSS is present, the treatment of OHSS is mainly supportive, and more research is required to elucidate treatment options targeted specifically at the main causative factors, to better treat the condition.

Key words: hyperstimulation, ovarian, syndrome, treatment.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an important iatrogenic condition with considerable morbidity and a small risk of mortality. OHSS occurs following an exaggerated response to stimulation of the ovaries by follicle-stimulating hormone (FSH) when luteinising hormone (LH) or human chorionic gonadotrophin (hCG) is also present. OHSS rarely follows the use of clomiphene.

The pathogenesis of OHSS involves increased capillary permeability (which may result from increased vascular endothelial growth factor [VEGF]).[1] This results in leakage of fluid from the intravascular space into extravascular spaces. Haemoconcentration, hypoalbuminemia, ascites, sometimes pleural effusion and rarely pericardial effusion result. In severe cases, deep vein thrombosis, disturbances in renal and/or liver function or adult respiratory distress syndrome (ARDS) may occur. It is typically a self-limiting condition but persists if pregnancy occurs. OHSS can be graded depending on the severity of the symptoms, signs and laboratory findings. Current measures to prevent OHSS are not universally successful, and in Australia and New Zealand, there were 225 (0.54%) cases of OHSS requiring hospitalisation from 41,657 FSH-stimulated cycles during 2011.[2]

Guidelines for the management of OHSS have been prepared by specialty groups outside Australia.[3–5] Specialist obstetricians and gynaecologists holding a Certificate of Reproductive Endocrinology and Infertility (CREI) in Australia and New Zealand formed the CREI Consensus Guidelines Group in 2008 to develop guidelines on the management of OHSS in the Australasian setting (Fig. 1).

The definition and prevention of OHSS has been addressed in a separate publication.[6]

Materials and Methods

The CREI Consensus Group (later renamed the ACCEPT (Australasian CREI Consensus Expert Panel on Trial evidence group)) met in 2008 and identified

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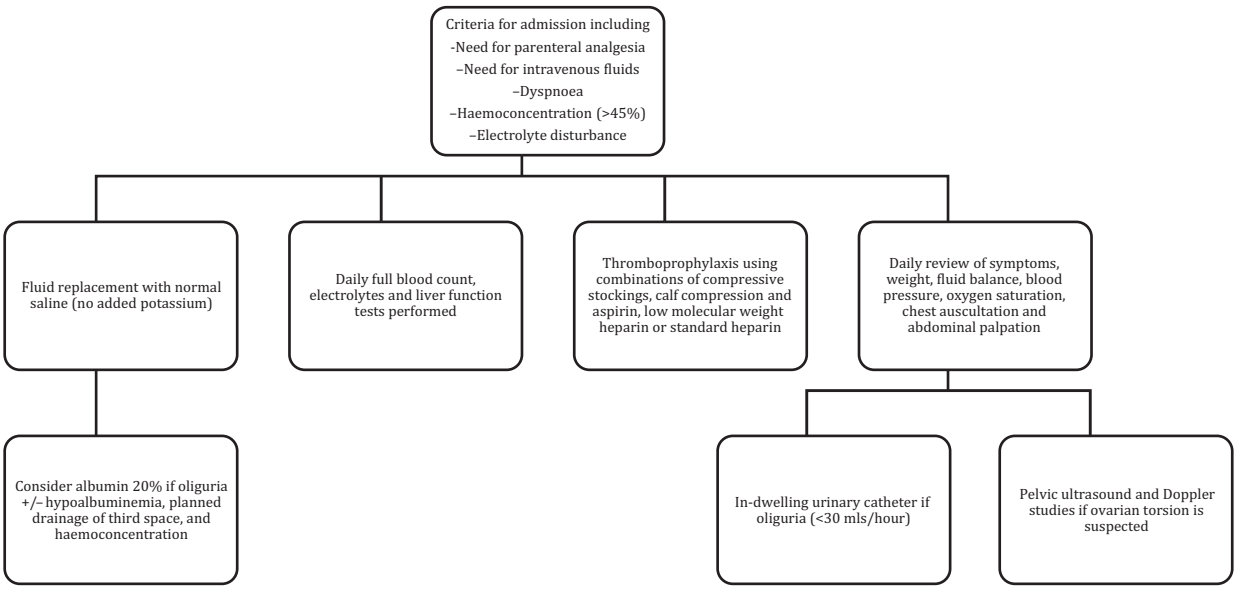

Figure 1 Criteria for admission, and initial in-patient investigations and management of women with OHSS.

issues for inclusion and review. Review of the available evidence was prepared and presented to the CREI Consensus Group in 2013 and input sought from members of the group. The search strategy involved searching Medline and PubMed for the terms 'ovarian', 'hyperstimulation', 'syndrome' and 'treatment'. The Cochrane Database of Systematic Reviews was also searched for intervention studies. Where a systematic review was conducted, the primary references were extracted and reviewed by one or two members of the group. The most recent literature search was performed in July 2014, with ongoing literature review conducted by nominated members to address specific questions at the request of the group.

The evidence was classified according to the 'levels of evidence' detailed in Table 1. Areas of 'expert opinion' with absence of evidence were discussed, and statements reflecting expert opinion were also prepared as consensus statements and labelled as a good practice point (GPP).

All consensus statements derived by the authors from the search outlined above were voted on by the ACCEPT group in Sydney in April 2013 and August 2014. Those clinicians in attendance are listed below in Acknowledgements. Voting on each consensus statement was recorded in accordance with the adopted consensus grading of the ACCEPT group (Table 2). Areas in which there was dissent of expert opinion and areas requiring further research were noted.

Table 1 Classification of levels of evidence

1a	Systematic review or meta-analysis of randomised controlled trials
1b	One or more randomised controlled trial/s
2a	One or more well designed study/studies, controlled, non-randomised
2b	One or more well-designed, quasi-experimental study/studies
3	One or more well-designed descriptive study/studies
4	Expert opinion

Results

Monitoring of OHSS symptoms in the outpatient setting

The majority of women with OHSS are managed in the outpatient setting. Daily communication with the woman is recommended by the American Society of Reproductive Medicine (ASRM).[5] The woman is advised to contact their health provider with any of the following: an increase in weight of one kilogram, increasing pain, increasing abdominal distension, subjective oliguria, symptoms suggestive of thrombosis or reduced mobility.[3,5]

There is general agreement that nausea, vomiting and dyspnoea are associated with increasing severity of OHSS,[6,7] although some consider that women with mild OHSS may also experience nausea and vomiting.[8]

As described in the ACCEPT group consensus statement on the prevention of OHSS, there is no

Table 2 Classification of voting

Unanimous	α
Unanimous with caveat	β
Majority	γ
No consensus	δ

universally agreed classification of the severity of OHSS;[6] however, it is generally agreed that a haematocrit >45% is a marker of moderately severe or severe OHSS.[8,9]

The measurement of serum albumin is not a criterion for severity of OHSS, and the predictive value of measuring serum albumin in the outpatient setting is uncertain.[6]

Women with OHSS often have pain related to abdominal distension and ascites, and paracetamol and opiates are often required for analgesia. Nonsteroidal anti-inflammatory drugs do not change the course of OHSS[10,11] and have the potential to adversely affect renal function.[12]

Admission for OHSS is indicated for intractable vomiting, abdominal pain not relieved by simple analgesics, significantly worsening abdominal distension, increasing dyspnoea, severe oliguria, patient anxiety, hypotension and syncope, hyponatraemia, hyperkalaemia, haematocrit >45% and abnormal liver function tests.[5,13]

Outpatients should be monitored daily, or if less frequently, women should be given clear criteria of when to contact their health service providers	Grade of evidence: 4 GPP Consensus grade α
Nausea is a symptom of OHSS and worsening nausea with or without anti-emetic therapy is a marker of disease progression.	Level of evidence: 4 Consensus grade α
The development of vomiting in a woman with OHSS implies that the maintenance of oral intake is compromised and the admission for intravenous fluids may be required.	Level of evidence: 4 Consensus grade α
Elevation of the haematocrit (>45%) is a marker of severe OHSS according to most of the classification systems available.	Level of evidence: 4 Consensus grade α
The role of serum albumin in evaluating OHSS which is being managed in the outpatient setting is uncertain. Members of the expert group use albumin in the management of OHSS	Level of evidence: 4 Consensus grade α
Use of paracetamol and opiates in OHSS is appropriate. There is need for further research into the use of nonsteroidal inflammatory drugs in women with OHSS.	Level of evidence: 4 GPP Consensus grade α
Indications for consideration of admission with OHSS include, but are not limited to, the following: –Need for parenteral analgesia –Need for intravenous fluids –Dyspneoa –Haemoconcentration –Electrolyte disturbance	Level of evidence: 4 GPP Consensus grade α

Advice given to women with OHSS

To avoid injury to the enlarged ovaries, women are advised to avoid strenuous physical activity and coitus.[3,5] However, as women with OHSS are also at risk of venous thromboembolism, women should be instructed to mobilise and avoid strict bed rest.[5]

Women should be encouraged to drink to thirst,[3] and fluid intake should be greater than one litre per day.[5] Although the ASRM recommends electrolyte solutions,[5] further research is needed to determine whether fluid intake and type of fluid intake influence the course of OHSS and the need for inpatient management.

There is no evidence to guide recommendations on the optimal level of activity for women with OHSS being managed as an outpatient.	Level of evidence 4 GPP Consensus grade α
Strenuous exercise should be avoided	Level of evidence 4 GPP Consensus grade α
Strict bed rest should not be recommended because of the increase in the predisposition to thrombosis.	Level of evidence 4 GPP Consensus grade α
Evidence-based recommendations for fluid intake during outpatient management cannot be made.	Consensus grade α
Expert opinion of the group is that the woman should drink according thirst.	Level of evidence 4 GPP Consensus grade α
There is no evidence to recommend electrolyte solutions over water as oral rehydrating solutions.	Level of evidence GPP Consensus grade α

Outpatient paracentesis

It is postulated that decreasing intra-abdominal pressure leads to an increase in renal blood flow, as well as an increase in venous return and therefore cardiac output.[13–16] Paracentesis may be performed transvaginally or transabdominally under ultrasound control under either local anaesthesia or light sedation. Several case series report the use of paracentesis to relieve symptoms and avoid hospital admission.[16–18] No randomised or multicentre studies have been reported. One prospective study involving 26 women (no control group) investigated transabdominal placement of a pigtail catheter for approximately two weeks with twice-daily drainage of fluid.[16] In another series, 96 women with OHSS had vaginal paracentesis (sometimes repeatedly) without adverse event.[17] Shrivastav *et al.* reported transabdominal paracentesis in 10 cases managed on an outpatient basis.[18] It is uncertain how much ascitic fluid can be removed safely following placement of the catheter although drainage of 7.5 L following catheter placement has been reported, with up to a total of 45 L removed over nine occasions.[19] Women who have repeated transabdominal paracenteses may require albumin infusions.[20]

Abdominal (placement under local anaesthetic and ultrasound guidance) or vaginal paracentesis (under sedation) may be associated with improvement in severe OHSS.	Level of Evidence: 4 Consensus grade α
Hospital admission should be considered for women with OHSS who have ascites requiring paracentesis.	Level of Evidence: 4 GPP Consensus grade α
There is a need for further research to define the optimal timing and role of paracentesis in the management of OHSS	Consensus grade α

Thromboprophylaxis in outpatient management of OHSS

Thromboprophylaxis for women with OHSS being managed as outpatients has not been studied, although low molecular weight heparin has been administered to women with a haematocrit >50%.[17]

Thromboprophylaxis in women with OHSS managed in the outpatient setting is not usually indicated.	Level of evidence: 4 Consensus grade ß (caveat: further research is required)

Dopamine and dopamine agonists to treat OHSS

Women with OHSS have elevated intraperitoneal levels of VEGF, and dopamine reduces the expression of VEGF receptors.[21] All the studies reporting the use of dopamine and dopamine agonists are uncontrolled observational reports.

Two studies have reported the use of cabergoline in the treatment of clinically diagnosed early OHSS. Rollene *et al.* describe four women who took 500 mcg cabergoline and gonadotrophin-releasing hormone (GnRH) antagonist daily for seven days from the onset of OHSS symptoms 1–2 days after oocyte retrieval and resolution of OHSS symptoms occurred after a mean of 5.75 days.[22] Ata *et al.* describe a single case of a woman who took 1 mg cabergoline daily following oocyte retrieval until the positive pregnancy test and had rapid resolution of OHSS symptoms.[23]

Ferraretti *et al.* administered intravenous dopamine to seven women with OHSS and reported symptom regression within 1–2 days. Five women were pregnant, and no adverse effects were reported.[24]

Tsunoda *et al.* administered docarpamine (a derivative of dopamine with good oral bioavailability) 750 mg every 8 h from five days after oocyte retrieval to 27 symptomatic women. They describe improvement of ascites, but the duration of treatment was not stated.[25]

An early study suggested that cabergoline is not teratogenic when used in the early first trimester (50 patients);[26] however, two recent large cohort studies have demonstrated that cabergoline use in the first trimester may be associated with an increased risk of early fetal loss.[27,28]

There is a need for further research into the role of dopamine agonists with/without GnRH antagonist in the treatment of early onset severe OHSS when all embryos are cryopreserved.	Level of evidence 3 Consensus grade α
There is a need for further research into the role of dopamine agonists in the treatment of severe OHSS associated with pregnancy (late onset OHSS).	Level of evidence 3 Consensus grade α

Inpatient management of OHSS

The in-patient management of OHSS is largely based on expert opinion rather than strong evidence. It has been suggested that women should have daily abdominal palpation, abdominal girth measurements at the level of the umbilicus, daily weight recorded, chest auscultation and peripheral oxygen saturation levels checked.[5,14,29] Recommendations for the frequency of general observations also vary between 2 and 8 h,[5,29] and keeping of a strict fluid balance record is recommended.[4]

Daily venepuncture to analyse a full blood count and serum biochemistry has been recommended,[5] and some treatment protocols recommend measurement of albumin levels in the assessment of inpatients with OHSS.[3,5] Coagulation studies will not predict thrombotic events and therefore are not recommended.[30]

Fluid resuscitation to maintain the haematocrit at <40% has been proposed.[13] Other recommendations include placement of an in-dwelling urinary catheter if oliguria is present,[14,29] a pelvic ultrasound scan[4] and performing a chest X-ray if pleural or pericardial effusion is suspected.[4]

Inpatients should have daily review, with particular emphasis on symptoms, weight, fluid balance, blood pressure, oxygen saturation, chest auscultation and abdominal palpation	Level of evidence: 4 Consensus grade α
Inpatients should have daily full blood count, electrolytes and liver function tests performed.	Level of evidence: 4 Consensus grade α
Inpatients should have a chest X-ray only if clinically indicated	Level of evidence: 4 Consensus grade α
Inpatients should have an in-dwelling urinary catheter if oliguric (<30 ml/h)	Level of evidence: 4 Consensus grade α
Inpatients should have a pelvic ultrasound and Doppler studies if ovarian torsion is suspected.	Level of evidence: 4 Consensus grade α

Inpatient thromboprophylaxis

The options for thromboprophylaxis include mobilisation, graduated calf compression stockings, aspirin, low

molecular weight heparin, heparin and the maintenance of intravascular volume.

Recently, Fleming *et al.* reported 29 cases of internal jugular vein thrombosis associated with OHSS; however, there are no studies reporting on the best form of thromboprophylaxis for these women.[31]

There are no studies on the optimal combination of interventions to reduce the risk of thrombosis in OHSS.	
As thrombosis is associated with morbidity and mortality, combinations of compressive stockings, calf compression and aspirin, low molecular weight heparin or standard heparin in prophylactic dose is indicated.	Level of evidence: 4 Consensus grade α
The optimal duration of anticoagulant therapy is uncertain.	Grade of evidence: 4 Consensus grade α
The place of new oral anticoagulants such as rivaroxaban and dabigatran etexilate is unknown.	Consensus grade α

Inpatient paracentesis

General comments on paracentesis are included in 'outpatient paracentesis' above.

Paracentesis has been associated with a shorter hospital stay (reduction of seven days) when compared with women who do not have paracentesis.[32] Qublan *et al.* studied 65 inpatients who had multiple transvaginal paracenteses and found they had significantly shorter lengths of stay and significantly lower intravenous fluid replacement when compared to inpatients who had <3 paracenteses.[33]

Takamizawa *et al.* reported the return of aspirated peritoneal fluid back to the systemic circulation in 10 patients;[34] however, this carries a risk of infection and may cause an increase in plasma levels of inflammatory cytokines and worsen capillary permeability.[35]

Ultrasound guided abdominal or vaginal paracentesis may be performed for symptomatic relief of tense ascites and is associated with shorter duration of hospital admission	Grade of evidence: 3 Consensus grade α

Inpatient fluid replacement for OHSS

Optimal fluid management for patients with OHSS has not been studied prospectively. Suggested regimens recommend an initial fluid bolus of one litre,[5,13] followed by titration of fluid replacement according to the urine output, to maintain urine output between 20–30 mL/h[4] and 50 mL/h[29].

Potassium supplementation should be avoided as patients with OHSS may already be hyperkalaemic.[14,15] Oral intake should be increased if possible particularly when diuresis and recovery occurs.[5,13]

Fluid management of women with severe OHSS is difficult, and they are at increased risk of increased third space losses and pulmonary oedema. Assessment and management should be conducted by clinicians with experience in the management of OHSS.	Level of evidence: 4 Consensus grade α
Initial intravenous fluid resuscitation should be performed with normal saline to counter haemoconcentration and maintain urine output.	Level of evidence: 4 Consensus grade α
Potassium supplementation should not be given routinely.	Level of evidence: 4 Consensus grade α
It is uncertain whether fluid should be restricted to a particular volume per day or whether intravenous fluid should be given according to urine output.	Consensus grade α

The role of albumin

The use of a plasma expander to increase intravascular volume is debatable. The most commonly used plasma expander is albumin; however, there is a lack of consensus regarding the level of serum albumin at which an albumin infusion should be commenced. Albumin infusions have been recommended when the serum albumin level is <20 g/L[13], or <30 g/L, when the haematocrit is >45% or when severe ascites is present.[14,15,29]

Dextran has been associated with ARDS in OHSS patients,[5,36] and fresh-frozen plasma (FFP) has been found to have no advantage over albumin.[15]

Albumin infusion (preferably 20%) should be considered as a plasma expander. Settings in which members of the CREI group use albumin infusion include oliguria with or without hypoalbuminemia, planned drainage of third space and haemoconcentration.	Level of evidence: 4 Consensus grade α

The role of adjuvant treatments

The use of diuretics in OHSS is controversial. Those who advocate the use of diuretics prescribe them once the haematocrit reaches 36–38%.[5,14,15,37] Balasch *et al.* conducted a prospective longitudinal study of 25 women with OHSS and reported improved symptoms and laboratory parameters after day days of treatment with albumin and frusemide.[38] However, diuretics may also aggravate hypovolaemia and haemoconcentration[14,15] and may have no effect on ascites[29] or the course of the condition.[39]

Low-dose dopamine

Low-dose dopamine may increase renal blood flow and glomerular filtration rate, and its use in seven severely oliguric women has been reported.[24]

Angiotensin converting enzyme (ACE) Inhibitors

OHSS is associated with the activation of the renin-angiotensin system, and therefore, ACE inhibitors may be beneficial. Case reports of the use of captopil in OHSS are favourable;[14,15,40] however, as ACE inhibitors are teratogenic, and as severe and prolonged OHSS is usually associated with pregnancy, the place of ACE inhibitors is limited.

Antihistamines

There is no evidence that antihistamines provide benefit in the treatment of OHSS in animal studies.[41]

There is no indication for the routine use of diuretics in patients with OHSS.	Level of evidence: 4 Consensus grade α

ACE inhibitors should not be used in the treatment of OHSS	Level of evidence: 4 Consensus grade α
Antihistamines should not be used in the treatment of OHSS	Level of evidence: 4 Consensus grade α
The role of low-dose dopamine infusion in severe OHSS is uncertain.	Level of evidence: 3 Consensus grade α

Surgery in OHSS

There is no role for wedge resection of ovaries or follicular aspiration in the treatment of OHSS, and surgery should be reserved for the potential complications of enlarged ovaries, which include adnexal torsion, cyst rupture or cyst haemorrhage. Rarely, termination of pregnancy is also an option if worsening symptoms threaten the life of the woman.[5,14,15]

Surgery has no role in the routine management of OHSS.	Level of evidence: 4 Consensus grade α
Surgery should be performed for adnexal torsion.	Level of evidence: 4 Consensus grade α
Surgery may rarely be needed for ovarian cyst rupture and haemorrhage and should be performed with great care because of the risk of uncontrolled bleeding from hyperstimulated ovaries.	

Future considerations

The use of a GnRH antagonist in the luteal phase to treat early OHSS is worthy of research as it will reduce the endogenous levels of LH, a putative stimulant to the development of OHSS. Twelve women who received 0.25 mg GnRH antagonist daily from day 5 to day 8 after oocyte retrieval were reported.[42] The women did not have a fresh embryo transfer, and decline in serum VEGF level with resolution of symptoms occurred.[42] However, these findings may be due to spontaneous resolution, as the study did not have a control arm for comparison.

Strategies to reduce the production or effect of VEGF may have a role in the treatment of severe OHSS.

Conclusion

The ACCEPT group of subspecialists in Reproductive Endocrinology and Infertility considered that there is currently a lack of good evidence to guide the treatment of OHSS. However, they were able to determine good practice points based upon the limited evidence and their clinical experiences. With the advent of proven strategies to prevent OHSS, the incidence of OHSS should reduce. However, the prevention of OHSS has not been universally successful and therefore, development of treatment protocols and research into the optimal treatment of this serious condition remain a priority for clinicians practicing reproductive medicine.

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