Review Article

Consensus statement on prevention and detection of ovarian hyperstimulation syndrome

Clare BOOTHROYD,[1] Sonal KARIA,[2,3] Natasha ANDREADIS,[1] Luk ROMBAUTS,[4] Neil JOHNSON,[5,6] and Michael CHAPMAN[7,8] on behalf of the Australasian CREI Consensus Expert Panel on Trial evidence (ACCEPT) group

[1]*Assisted Conception Australia, Brisbane, Queensland,* [2]*Genea,* [3]*Royal Prince Alfred Hospital, Sydney, New South Wales,* [4]*Monash IVF, Melbourne, Victoria, Australia,* [5]*Fertility Plus and Repromed Auckland, University of Auckland, Auckland, New Zealand,* [6]*Robinson Research Institute, University of Adelaide, Adelaide, South Australia,* [7]*Women's and Children's Health, University of New South Wales, and* [8]*IVF Australia, Sydney, New South Wales, Australia*

Background: Ovarian hyperstimulation syndrome is an important condition with considerable morbidity and a small risk of mortality, which most commonly results as an iatrogenic condition following follicular stimulation of the ovaries.
Aim: To produce evidence-based and consensus statements on the prevention and detection of ovarian hyperstimulation syndrome (OHSS).
Method: The CREI Consensus Group met in 2008 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: The group considered that there is a need for standardisation of the definition and classification of the clinical syndrome of OHSS to allow further conclusive research. Interventions with evidence of effect in reducing OHSS include the use of metformin in women with PCOS, use of GnRH antagonist rather than GnRH agonist and use of GnRH agonist triggers in GnRH antagonist stimulation cycles. The consensus view was that reducing the dose of FSH, freezing all embryos and transferring a single embryo were appropriate interventions to reduce OHSS. Agreement could not be reached on coasting, the lowest number of oocytes to consider freezing all embryos and management after cancellation of oocyte collection.
Conclusion: OHSS is a serious condition for which there are a number of proven preventative strategies. OHSS is an area requiring ongoing research and development of a universally agreed definition will allow development of optimal prevention strategies and facilitate improved early detection of women at risk.

Key words: diagnosis, ovarian hyperstimulation syndrome, prevention.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an important condition with considerable morbidity and a small risk of mortality, which most commonly results as an iatrogenic condition following follicular stimulation of the ovaries. The role of human chorionic gonadotrophin (hCG) and vascular endothelial growth factor (VEGF) are integral to the development of the syndrome.[1] It has been extensively reviewed and reported since its first recognition in 1943.[2] For the United Kingdom, the Green Top guidelines (2006)[3] discuss the management of OHSS. NICE Guidelines were published in 2004.[4] Guidelines for understanding the pathophysiology and risk features, clinical features, management and prevention of OHSS have been produced by the American Society of Reproductive Medicine in 2008.[5]

Specialist obstetricians and gynaecologists holding the Certificate of Reproductive Endocrinology and Infertility (CREI) formed the CREI Consensus Guidelines Group in 2008. The purpose of developing guidelines on the prevention and recognition of OHSS was to reduce the incidence of severe OHSS, to establish some framework for best practice in prevention of OHSS and treatment of severe OHSS, to define what is an acceptable level of OHSS in assisted reproductive technology (ART) and to identify areas needing further research.

Material and Methods

The CREI Consensus Group (later renamed the ACCEPT [Australasian CREI Consensus Expert Panel on

Correspondence: Dr Clare Boothroyd, Greenslopes Specialist Centre, 25/121 Newdegate Street, Greenslopes, Qld 4120, Australia. Email: fertility@ivfmed.com.au

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Trial evidence group]) met in 2008 and identified issues for inclusion and review. Review of the available evidence was prepared and presented to the CREI Consensus Group in 2009 and input sought from members of the group. The search strategy was searching Medline, EMBASE for the terms 'ovarian', 'hyperstimulation', 'syndrome', 'prevention' and 'diagnosis'. Specific searches were also conducted to areas of interest identified by the group such as the use of 'dopamine agonists'. The Cochrane Database was also searched for intervention studies. Where a systematic review was conducted, the primary references were reviewed by one or two members of the group. The search was last performed in July 2014. Ongoing literature review was conducted by nominated members to address specific questions at the request of the group. The evidence was further reviewed and presented in 2010 to the group and classified according to the levels of evidence detailed in Table 1. The wording of statements was vigorously debated until consensus was reached wherever possible. Areas of 'expert opinion' with the absence of evidence were discussed, and statements reflecting expert opinion were prepared as consensus statements. Voting on consensus statement was recorded as in Table 2, the adopted consensus grading of the ACCEPT Group.[6] Areas in which there was dissent of expert opinion and requiring further research were noted.

All consensus statements derived by the authors from the search outlined above were modified as required and voted on by the ACCEPT group in Sydney on 7/05/2010 and 18/06/2011 and further revised on 04/05/2013 and 16/08/2014. Those clinicians in attendance are listed below in Acknowledgements.

Results

Definition of OHSS

The group reviewed a number of definitions of OHSS and proposed the following definition of OHSS.

A syndrome characterised by ovarian enlargement and fluid accumulation within the peritoneal and/or pleural and/or (rarely) pericardial cavities, following treatment with ovarian stimulating hormones. The action of LH or hCG is required to develop the syndrome	Consensus grade α

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

Table 2 Classification of voting

Unanimous	α
Unanimous with caveat	β
Majority	γ
No consensus	δ

Clinical consequences of OHSS

The group discussed the clinical consequences of OHSS and considered that the following statement included those of greatest clinical significance.

Clinical consequences of OHSS are related to intravascular fluid depletion and include the following: 1 Hypotension 2 Haemoconcentration 3 Oliguria, renal impairment, hepato-renal syndrome 4 Thromboembolism 5 Respiratory distress	Consensus grade α

Subtypes of OHSS

OHSS can be divided into two types: early and late OHSS depending on the interval between oocyte retrieval or ovulation and the onset of symptoms. Papanikalaou *et al.*[7] presented a retrospective report of 2524 IVF-ICSI cycles among which 53 patients were hospitalised with OHSS. Thirty-one of these presented with early OHSS (1.2%; 95% CI 0.9–1.8), whereas the remaining 22 presented with late OHSS (0.9%; 95% CI 0.5–1.3). Late OHSS compared with early OHSS always occurred in a pregnancy cycle, had a higher probability of being severe and was more likely to occur with a multiple pregnancy. Mathur *et al.*[8] in a retrospective cohort study of 2362 IVF-ICSI cycles reported 78 (3.3%) cases of OHSS of which 48 (2.03%) were early onset and 30 (1.27%) were late onset.

Summary of the subtypes of OHSS

OHSS has been divided into two types: early and late Early onset OHSS occurs within nine days after oocyte retrieval or ovulation and relates to the use and action of LH or hCG to induce ovulation Late onset relates to rising hCG from pregnancy, is more severe and is more likely to occur in a multiple pregnancy	Level 3 evidence Consensus grade α

Classification of OHSS

A number of classification systems of OHSS have been developed and because of different classifications used, interpretation of the literature and in particular intervention studies is difficult.

The classifications are summarised in Table 3. The group reviewed the definitions and did not accept any one classification as ideal.

There is a need for consensus on the classification of the severity of OHSS. A uniform classification system will allow consistent evaluation of the incidence and effective prevention and treatment of clinically significant OHSS	Level of evidence 4 Consensus grade α

Mortality related to OHSS

OHSS is potentially a life-threatening condition although mortality related to OHSS is extremely rare. Venn *et al.*[9] conducted a comprehensive review of 47 000 IVF cycles in mid-1990s revealing 1 death, which was possibly but not definitely related to OHSS. A retrospective analysis of ~100 000 IVF cycles conducted in Netherlands by Braat *et al.*[9] in 2006 indicated 3 deaths related to OHSS. Balen 2008 estimated a risk of death of 1:30 000.[11]

The risk of dying from OHSS when undertaking an ART cycle is extremely rare	Level 3 evidence
There was consensus that an accurate risk estimate applicable in 2014 could not be made on the basis of the available evidence	Consensus grade α

Morbidity related to OHSS

The group considered the prior reviews and clinical experience and summarised the morbidity related to OHSS.

Severe morbidity related to OHSS relates to thrombo-embolic disease, adult respiratory distress syndrome, renal complications, ovarian torsion and bleeding	Level of evidence 4 Consensus grade α

Estimation of risk of OHSS prior to commencement of FSH or clomiphene stimulation

A retrospective analysis of 9175 IVF and ovulation induction (OI) cycles conducted in Finland prior to 2000 was reported.[12] Depending on the definition of OHSS, the admission rate for OHSS ranged from 1.4 to 1.9% in the first IVF cycle and 0.04–0.5% with OI.[12]

All women undergoing assisted reproductive technology (ART) using FSH are at risk of OHSS	Level 3 evidence Consensus grade α

Risk Factors

Age

The risk of admission for OHSS was 3.1% in women aged <35 years compared with 1% in women aged over 35[12] Enskog *et al.*[13] reported a cohort study involving 428 women undergoing IVF, 49 women developed OHSS of which 18 were severe (4.2%) and 31 were mild to moderate (7.3%). Women developing OHSS or signs that they were at risk of developing OHSS (and had management altered to reduce the chance of developing OHSS) were significantly younger (31.46 year vs 33.22 years) than women who did not have signs of developing or develop OHSS. This study did not evaluate ovarian reserve.

Younger women may be at a particularly increased risk of developing OHSS	Level 3 evidence Consensus grade α

Polycystic ovarian syndrome (PCOS)

There is no systematic review relating OHSS to PCOS. A review of the SART data base, including 214 219 ART cycles, revealed 11 523 reports of moderate OHSS and 655 reports of severe OHSS in which ovulation disorders and PCOS were associated with an increased risk of any OHSS and an increased risk of severe OHSS.[14] Ludwig *et al.*[15] in 1999 conducted a retrospective case control study involving 51 ICSI cycles in 31 women with PCOS compared with 105 controls and reported the rate of severe OHSS was significantly higher in the PCOS group (12% vs 3%, $P < 0.01$). A retrospective case control study by Esinler *et al.*[16] of patients undertaking ICSI with polycystic ovaries on ultrasound (PCO) (58 patients, 58 cycles), PCOS (99 patients, 109 cycles) and controls with male factor (210 patients, 232 cycles) reported four cycles (3.7%) in the PCOS group necessitating hospitalisation for OHSS. The corresponding figures in the PCO and control groups were 1 (1.7%) and 3 (1.3%). The group noted differing definitions of PCOS had been used in the available studies which had been retrospective in nature.

Table 3 Classification of OHSS

Study	Mild	Moderate	Severe		
Rabau et al. (1967)[17]	Grade 1: oestrogen >150 mg and pregnanediol >10 mg 24 h Grade 2: + enlarged ovaries and possibly palpable cysts Grade 1 and 2 were not included under the title of mild OHSS	Grade 3: grade 2+ confirmed palpable cysts and distended abdomen Grade 4: grade 3+ vomiting and possibly diarrhoea	Grade 5: grade 4+ ascites and possibly hydrothorax	Grade 6: grade 5+ changes in blood volume, viscosity and coagulation, time	
Schenker and Weinstein (1978)[18]	Grade 1: oestrogen >150 mg/24 h and pregnanediol >10 mg 24 h Grade 2: grade 1+ enlarged ovaries, sometimes small cysts	Grade 3: grade 2+ abdominal distension Grade 4: grade 3+ nausea, vomiting and/or diarrhoea	Grade 5: grade 4+ large ovarian cysts, ascites and/or hydrothorax	Grade 6: marked haemoconcentration + increased blood viscosity and possibly coagulation abnormalities	
Golan et al. (1989)[19]	Grade 1: abdominal distension and discomfort Grade 2: grade 1+ nausea, vomiting and/or diarrhoea, enlarged ovaries 5 ± 12 cm	Grade 3: grade 2+ ultrasound evidence of ascites	Grade 4: grade 3+ clinical evidence of ascites and/or hydrothorax and breathing difficulties	Grade 5: grade 4+ haemoconcentration, increase blood viscosity, coagulation abnormality and diminished renal perfusion	
Navot et al. (1992)[20]			Severe OHSS: variable enlarged ovary; massive ascites 6 hydrothorax; Hct >45%; WBC >15 000; oliguria; creatinine 1.0 ± 1.5; creatinine clearance >50 mL/min; liver dysfunction; anasarca	Critical OHSS: variable enlarged ovary; tense ascites 6 hydrothorax; Hct >55%; WBC >25 000; oliguria; creatinine >1.6; creatinine clearance <50 mL/min; renal failure; thromboembolic phenomena; ARDS	
Rizk and Aboulghar (1999)[21]		Discomfort, pain, nausea, distension, ultrasonic evidence of ascites and enlarged ovaries, normal haematological and biologicalprofiles	Grade A: Dyspnoea, oliguria, nausea, vomiting, diarrhoea, abdominal pain, clinical evidence of ascites, marked distension of abdomen or hydrothorax, US showing large ovaries and marked ascites, normal biochemical profile	Grade B: Grade A plus massive tension ascites, markedly enlarged ovaries, severe dyspnoea and marked oliguria, increased haematocrit, elevated serum creatinine and liver dysfunction	Grade C: Complications as respiratory distress syndrome, renal shut-down or venous thrombosis
Humaidan et al. (2000)[22]	Fluid in Pouch Of Douglas	(If two of these are present, consider hospitalisation)	Fluid in Pouch of Douglas Fluid around uterus (major pelvis) Fluid around intestinal loops		

Women who have underlying PCOS may be at particularly increased risk of developing OHSS	Level 3 evidence Consensus grade α

PCO morphology on ultrasound

Women with PCO but without PCOS are at risk of OHSS when undergoing ovarian stimulation for ART. A systematic review relating OHSS to PCO was conducted by Tummon *et al.*[23] in 2005, including 10 studies. Variable definitions of PCO and OHSS were used by different studies. A strong and consistent relationship was found between PCO and OHSS with a common odds ratio of 6.8 (95% CI 4.9–9.6).

Women with ultrasound evidence of PCO may be at particularly increased risk of developing OHSS	Level 1a evidence Consensus grade α

Past history of OHSS

The group noted the lack of evidence that women with a past history of OHSS were at risk of developing OHSS.

Women who have had past OHSS are at increased risk of OHSS with ovarian stimulation	Level 4 evidence Consensus grade α

High serum level of anti-Mullerian hormone (AMH)

AMH levels are a reflection of the ovarian reserve. To study the correlation between elevated baseline AMH levels and the risk of OHSS, Lee *et al.*[24] conducted a prospective case series of 262 women undertaking ART. All women underwent ovarian stimulation with long downregulation or flare protocol and 225 units of FSH. The FSH dose was adjusted after five days of stimulation according to the ovarian response. A total of 21 patients (8%) developed OHSS. The basal serum AMH (OR 1.7856, $P = 0.0003$) and the E2 levels on the day of hCG administration (OR 1.0005, $P = 0.0455$) were significant predictors of OHSS by logistic regression analysis. A basal serum AMH level of 3.36 ng/mL (23.99 pmol/L) had 90.5% sensitivity and 81.3% specificity for the prediction of OHSS.

Women with an elevated level of basal AMH may be at particularly increased risk of developing OHSS	Level 3 evidence Consensus grade α

Ovarian drilling

Ovarian drilling is a treatment for ovulatory dysfunction in women with PCOS. Fukaya *et al.*[25] reported a cohort study of 26 patients who had experienced grade 3 OHSS with hMG during a previous attempt at ovulation induction. These patients underwent ovarian drilling prior to further treatment. A total of 17 of these patients required hMG for ovulation induction post operatively. Only 3 of these developed mild OHSS in hMG cycles postdrilling.

There is a need for further research into the effect of ovarian drilling on reducing the risk of OHSS during IVF/ICSI treatment cycles.	Level 3 evidence Consensus grade γ

Lean body weight

There are conflicting studies on the influence of lean body weight on the risk of OHSS. Danninger *et al.*[26] followed a cohort of 101 women undergoing IVF for the development of OHSS. A number of variables were compared in patients who developed OHSS and those that did not. The average body weight of women who developed OHSS was significantly less than those who did not develop OHSS (55.4 ± 3.8 vs 62.8 ± 11 kg; $P = 0.011$). However, a meta-analysis of prospective and retrospective cohort and case control studies by Maheshwari *et al.*[27] showed that body mass index (BMI) greater than or less than 25 did not influence the risk of OHSS. Enskog *et al.*[13] conducted a prospective study of the clinical parameters of patients in whom OHSS developed during ovarian stimulation for ART. In the cohort of 428 women, there was no difference in BMI between those who developed OHSS and controls.

There are insufficient data on the influence of lean body weight on the risk of OHSS	Level of evidence 4 Consensus grade α

Ovarian reserve

Reduced ovarian reserve is associated with a reduced risk of OHSS. A review of the SART database by Luke *et al.*[14] suggested that diminished ovarian reserve was associated with 74% reduction in the risk of any OHSS (OR 0.26; 95% CI 0.20–0.34, $P < 0.0001$) and 80% reduction in the risk of severe OHSS (OR 0.20; 95% CI 0.12–0.33, $P < 0.0001$).

Reduced ovarian reserve is associated with reduction in the risk of OHSS	Level 3 evidence Consensus grade α

Identification of Women at Risk of OHSS During FSH Stimulation

Number of follicles on ultrasound scan

Number of growing ovarian follicles during follicular stimulation predicts OHSS and 13 follicles or more on the day of hCG administration predicted all cases of early OHSS and 87% of the severe cases[7]

The risk of OHSS increases with the number of growing ovarian follicles seen during follicular stimulation. These women may be candidates for interventions to reduce the incidence of severe OHSS	Level 4 evidence Consensus grade α

Oestradiol levels on the day of hCG administration and retrieved oocyte number as a predictor of OHSS

The use of oestradiol levels on the day of hCG trigger has been investigated as a predictor of the risk of both early and late OHSS.[7] None of the threshold oestradiol levels on the day of hCG trigger could predict late or severe OHSS and a cut-off of ≥ 2560 ng/L (9395 nmol/L) had a 67% sensitivity for predicting only early OHSS.[7] Association between the number of oocytes retrieved and the rate of OHSS in fresh autologous IVF cycles has been reported in a retrospective cohort study involving a review of the SART database, including 256 381 IVF cycles. The rate of OHSS was more clinically significant after retrieval of more than 15 oocytes (0–5 oocytes: 0.09%; 6–10 oocytes: 0.37%; 11–15 oocytes: 0.93%; 16–20 oocytes: 1.67%; 21–25 oocytes: 3.03%; >25 oocytes: 6.34%). The finding remained true after adjusting for age, BMI, basal FSH and smoking status. ROC curve calculation revealed that 15 is the number of retrieved oocytes that maximises sensitivity and specificity in the prediction of OHSS.[48]

Women with high levels of oestradiol on the day of hCG administration and/or who have large numbers of oocytes collected are at increased risk of OHSS. These women may be candidates for interventions to reduce the incidence of severe OHSS	Level 4 evidence Consensus grade α

Reduction in OHSS Risk Prior to Cycle Commencement

There are a number of strategies proposed to reduce the risk of OHSS.

Dose of FSH used during stimulation

Randomised controlled trials investigating the effect of different fixed doses of FSH have reported the incidence of OHSS as a secondary outcome. Selection criteria for entry to these studies excluded women with PCOS and/or a history of OHSS. The definition of OHSS has been variable and sometimes not described; however, OHSS of moderate or severe nature has been higher in the groups prescribed higher doses of FSH.[28–31] One study comparing an FSH dose 100 IU with an FSH dose of 200 IU did not find an association of dose of FSH and OHSS, but OHSS was not a prospectively defined outcome of the trial and the trial may have had Type II error for the outcome of OHSS.[32]

Higher dose of FSH used during ovarian stimulation is associated with increased risk of OHSS	Level 4 evidence Consensus grade α

Use of GnRH antagonists rather than GnRH agonists

GnRH analogues are used to prevent premature LH surge in ART cycles. GnRH agonists act by downregulation of the pituitary GnRH receptors and desensitisation of the gonadotropic cells, whereas GnRH antagonists bind competitively to the receptors. Use of GnRH antagonists to reduce the risk of premature LH surge has been reported as being associated with a reduced risk of OHSS. A Cochrane systematic review on the use of GnRH antagonists for ART, including 29 RCTs comparing GnRH antagonists and agonists with respect to the development of OHSS, revealed a statistically significant lower incidence of OHSS in the antagonist group (OR 0.43; 95% CI 0.33–0.57).[33]

A recent meta-analysis[60] of use of GnRH antagonists and GnRH agonists in women with PCOS suggested no benefit of GnRH antagonists in prevention of OHSS, but data extraction was not complete (two eligible studies were not included), intention to treat analysis was not used and graphs were mislabelled in this review. On that basis, the conclusion of the earlier Cochrane meta-analysis is accepted.

Use of GnRH antagonist rather than GnRH agonist during ovarian stimulation for ART reduces the incidence of OHSS	Level 1a evidence Consensus grade α

Concomitant use of metformin

Metformin is frequently used in women with PCOS to improve insulin sensitivity and ovulation. A systematic review of the relationship between metformin use during IVF and ICSI cycles in women with PCOS was reported by Tso *et al.*[34] The incidence of OHSS was significantly lower in the metformin group compared with the placebo

group with a pooled OR 0.27 (95% CI 0.16–0.47). The studies were heterogeneous with differing definitions of OHSS, different doses of metformin used and different duration of use of metformin. The optimal dose and timing of metformin is therefore uncertain.

Concomitant use of metformin in women with PCOS undertaking an IVF or ICSI cycle reduces the incidence of OHSS	Level 1a evidence Consensus grade α

Concomitant use of aspirin

There is some evidence to suggest that increased platelet activation correlates with increase in VEGF as well as release of histamine, serotonin, platelet-derived growth factors and other substances which may further potentiate the pathologic mechanisms involved in the development of OHSS. On this basis, a role of aspirin has been studied for the prevention of OHSS. Varnagy *et al.*[35] report a quasi-randomised controlled trial of 1503 women undertaking IVF using GnRH antagonist protocol. Aspirin 100 mg/day was introduced on day 1 of menstrual bleeding and continued till the fetal heart was identified. No placebo was administered. Forty-five cases of severe OHSS were identified in the study, of which only two cases were in the group taking aspirin.

There is one poorly designed study suggestive of the benefit of the use of aspirin in OHSS and further research is needed.	Level 2a evidence Consensus gradeα

Withholding the administration of hCG to induce ovulation (cycle cancellation)

As the action of hCG is required for the development of OHSS, withholding hCG is a means of preventing OHSS. Subsequent management after withholding hCG was discussed.

The expert group considered that OHSS after withholding hCG is very rare (α)	Level 4 evidence Consensus grade α
There was no consensus that following withholding hCG, strategies to prevent a spontaneous surge of LH will further reduce the risk of OHSS	Level 4 evidence Consensus grade δ

Coasting to reduce OHSS

Coasting involves withholding gonadotropins prior to initiating ovulation. Coasting does not have a precise definition. There are many clinical protocols described as 'coasting'.[36]

One small randomised trial suggests a reduction in the risk of OHSS with coasting[37] (that if greater than ten follicles size 11–14 mm are found on day 7 and coasting is performed, a reduced number of oocytes will be collected, without compromise in live birth rate but with reduction in the risk of severe OHSS). In a retrospective case control study by Chahvar *et al.*, the effect of coasting (withdrawal of exogenous gonadotropins for one to four days before administration of hCG) on blastocyst development and live birth rates in women at increased risk of moderate–severe OHSS ($n = 389$) was compared with a control group matched for age and basal FSH that did not undergo coasting ($n = 386$). There was no difference in the biochemical pregnancy, clinical pregnancy and live birth rates. There were four cases of OHSS (1%) in the coasted group and 6 in the control group (1.6%).[55]

There is currently insufficient evidence to support coasting as a means of reducing the risk of OHSS. However, some experts use coasting	Level 1b evidence Consensus grade δ
The expert group was unable to reach consensus on the role of coasting	
There is a need for further research into the role of coasting	Level 4 Consensus grade α

Use of recombinant hCG or recombinant LH vs urinary hCG to induce ovulation

Urinary hCG has been to induce oocyte maturation and ovulation. Recombinant hCG and hLH have now been developed for the same purpose. A Cochrane systematic review Youssef *et al.*[38] of 14 studies with a total of 2306 patients was conducted to compare the effects of urinary and recombinant preparations of hCG. Pooled results showed no significant difference between the drugs with respect to the occurrence of OHSS (3 RCTs; OR 1.47; 95% CI 0.37–4.1, $P = 0.37$). Similarly, comparison between recombinant LH and urinary hCG did not reveal significant difference in the development of OHSS (OR 0.82; 95% CI 0.39–1.69).

There is no evidence that use of recombinant hCG compared to urinary hCG reduces the risk of OHSS	Level 1a evidence Consensus grade α
There is no evidence that the use of recombinant LH compared with urinary hCG reduces the risk of OHSS	Level 1a evidence Consensus grade α

Reduction in dose of urinary hCG to induce ovulation

Two randomised controlled trials address the incidence of OHSS in high-risk women with reduction in the dose of urinary hCG to induce ovulation.[39]

There is no evidence that reduction in dose of hCG reduces the risk of OHSS	Level 1b evidence Consensus grade α

Use of GnRH agonist to induce ovulation in antagonist cycles

The initial flare effect of GnRH agonists can induce maturation of oocytes and ovulation in women with intact pituitary reserve where GnRH antagonists have been used to block premature LH surge. A Cochrane systematic review of 5 randomised controlled trials of 504 women reported reduced incidence of OHSS in the group allocated to GnRH agonist to induce ovulation.[40] The incidence of OHSS was significantly lower in the GnRH agonist group (5 RCTs, OR 0.1; 95% CI 0.01–0.82), but this was also associated with a reduction in the live birth rate. However, the two studies reporting the seven cases of OHSS in the group allocated hCG did not predefine OHSS as a secondary outcome and did not use a definition of OHSS.[41] It is also uncertain whether the OHSS was early or late in onset in either of the two studies. A further shortcoming of the meta-analysis is the variable luteal support used in the trials.

A retrospective analysis of donor oocyte cycles comparing the use of GnRH agonist and hCG to induce ovulation showed a reduction in the risk of OHSS after use of GnRH agonist without a reduction in live birth rate.[42] As live birth rates are affected in cycles using GnRH antagonist with GnRH agonist to induce ovulation, modified luteal support has been attempted for patients undergoing fresh embryo transfer. Imbar *et al.* reported a retrospective cohort analysis of patients at risk of OHSS undertaking fresh embryo transfer with modified luteal support or cryopreservation and frozen embryo transfer after GnRH agonist use to induce ovulation. Participants were included based on risk factors for OHSS. A daily dose of 50 mg IM progesterone in oil and 6 mg of oral 17-β-estradiol was initiated on oocyte retrieval day in women undergoing fresh embryo transfer ($n = 70$). Women undergoing frozen embryo transfer ($n = 40$) were compared. There was no significant difference in the live birth rates [27.1% in the fresh vs 20% in the frozen ET group, $P = 0.4$, rate ratio 1.36 (0.65–2.81)]. There were no cases of OHSS in either group.[50]

The use of GnRH agonist trigger with cryopreservation of all embryos does not completely eliminate OHSS. Fatemi *et al.*[57] reported two cases of severe OHSS, requiring hospitalisation and peritoneal drainage following use of GnRH agonist to induce ovulation.

Griesinger *et al.*[58] also reported a single case of severe early onset OHSS in a cohort of 48 women who were at risk of OHSS undergoing ovarian stimulation in a GnRH antagonist protocol and receiving a GnRH agonist and cryopreservation of all embryos.

The use of GnRH agonists to induce ovulation/final oocyte maturation in cycles where a GnRH antagonist is used is associated with a reduction in the risk of moderate and severe OHSS (although the risk is not completely eliminated) and a reduction in the live birth rate in fresh embryo replacement cycles	Level 1a evidence Consensus grade α
The use of GnRH agonists in donor oocyte cycles to induce ovulation/final oocyte maturation in cycles where a GnRH antagonist is used is associated with a reduction in the risk of OHSS without a reduction in live birth rate	Level 2 evidence Consensus grade α

Actions to Reduce OHSS at Time of OPU

The role of intravenous albumin at the time of oocyte retrieval has been reviewed in a Cochrane systematic review of 5 RCTs by Alboulghar *et al.*[43] The results revealed a significantly lower incidence of OHSS in the albumin group compared with placebo (OR 0.28; 95% CI 0.11–0.73). The number needed to treat was 18. Intravenous hydroxyethyl starch (HES) at the time of oocyte retrieval has also been used to reduce the incidence of OHSS. A more recent Cochrane systematic review Youssef *et al.*,[44] including 9 RCTs with 1660 (albumin v/s placebo) and 487 (HES v/s placebo), revealed a borderline significant reduction in the incidence of severe OHSS with intravenous albumin (8 RCTs; OR 0.67; 95% CI 0.45–0.99) as well as with HES (3 RCTs; OR 0.12; 95% CI 0.04–0.4); however, this review has been updated and shows no benefit of the administration of intravenous albumin (personal communication, Cochrane Collaboration, C. Farquhar).

Contrary to these findings, a systematic review and metaanalysis conducted by Venetis *et al.*, including 8 RCTs with a total of 1199 patients to evaluate the role of administration of IV albumin in high-risk patients for the prevention of OHSS, revealed no significant difference in the occurrence of severe OHSS in patients receiving IV albumin ($n = 595$) compared with those who did not ($n = 604$, OR 0.80; 95% CI 0.52–1.22).[49]

Administration of albumin at or around the time of OPU is not associated with reduction in the risk of severe OHSS	Level 1a evidence Consensus grade α
Administration of HES at or around the time of OPU is associated with reduction in the risk of severe OHSS	Level 1a evidence Consensus grade α

Actions to Reduce the Risk of late Onset OHSS

One randomised controlled trial of 125 women at high risk of OHSS (greater than 15 oocytes collected) had embryo cryopreservation and intravenous albumin or embryo

transfer. The risk of late and severe OHSS was reduced in the embryo cryopreservation group.[45]

Freezing all embryos for high-risk patients will reduce the incidence of late onset OHSS	Level 1b evidence Consensus grade α

Prediction of risk of late onset OHSS is difficult	Level 4 evidence Consensus grade α

Transfer of a single embryo will reduce the risk of late onset OHSS	Level 4 evidence Consensus grade α

Use of Dopamine Agonists to Prevent OHSS

Cabergoline is potentially a new strategy to reduce the incidence and severity of OHSS. Cabergoline is a D2 receptor agonist and may prevent the increase in vascular permeability observed in OHSS. Three systematic reviews on the role of cabergoline in prevention of OHSS have been reported.[46,51,52] The most recent review included 7 RCTs of 858 women and studied cabergoline (alone or combined with other intervention) vs placebo, no treatment or other treatment for reducing the risk of OHSS.[52] Cabergoline resulted in the reduction in moderate–severe OHSS (RR 0.38, 95% CI 0.29–0.51, NNT for moderate OHHS – 6, NNT for severe OHSS – 18) with no effect on clinical pregnancy rates or number of oocytes retrieved. The impact on live birth rates, miscarriage rates and congenital anomalies remained uncertain.[52] The optimal dose and timing of cabergoline are uncertain from the available data, but most studies reported a dose of 0.5 mg/day for seven to 21 days. Cabergoline has a dose-related side effect of valvular fibrosis.[47] The stimulation of serotonin receptor subtype 5-HT2b in valvular cardiac tissue may lead to proliferation of fibroblasts, which is believed to lead to valvular fibrosis and the significance of this for women who may be given cabergoline to prevent OHSS is uncertain.

Use of Other Dopamine Agonists to Prevent OHSS

The use of other dopamine agonists for prevention of OHSS has been less extensively studied. Women at risk of OHSS ($n = 182$) were randomised to either placebo or three different doses of quinagolide (50, 100 and 200 μg/day) starting on the day of hCG administration until the day of the pregnancy test. A significant reduction in the incidence of OHSS was observed with all quinagolide doses (OR 0.28, 95% CI 0.09–0.81, excluding late onset OHSS), but the difference in severe OHSS was not statistically significant.[53] This study is a prospective cohort study assessing the effect of bromocriptine on OHSS. In the intervention group, the incidence of clinically significant OHSS was 17.5% as compared to 40.9% in the historical control group.[54]

There is evidence that the incidence of early onset moderate and severe OHSS is reduced with the use of cabergoline after oocyte collection. Appropriate dose of cabergoline is 0.5 mg/day although the duration remains uncertain (seven to 21 days in different studies). There is no evidence that the risk of late onset OHSS is reduced with use of cabergoline There is insufficient evidence currently to recommend use of bromocriptine or quinagolide in the prevention of OHSS	Level 1a evidence Consensus grade α

Calcium Gluconate Infusion to Prevent OHSS

Among the various pathophysiological mechanisms leading to OHSS, one observation was the stimulatory role of low intracellular calcium on adenylyl cyclase resulting in cAMP synthesis and thus renin release. A quasi-randomised trial, including 202 women at risk of OHSS, was conducted to compare the effectiveness of intravenous calcium gluconate infusion in comparison with cabergoline for prevention of OHSS (98 in calcium gluconate group and 104 in the cabergoline group). A total of nine women in the calcium gluconate group developed OHSS compared with 16 in the cabergoline group (9.2% vs 15.4%).[56]

Gurgan *et al.* reported a retrospective comparative study in PCOS patients. A total of 84 women were administered intravenous calcium gluconate for prevention of OHSS, and those in the control group ($n = 371$) had no intervention for prevention of OHSS. OHSS was found in 16.2% (60 patients) in the latter, whereas in the former, only three patients (3.6%) developed OHSS, all three being mild.[59]

There is limited evidence for the role of calcium gluconate infusion in the prevention of OHSS	Level 2b evidence Consensus grade α

Conclusion

The group considered that there is a need for standardisation of the definition and classification of the clinical syndrome of OHSS to allow further conclusive research. Interventions with evidence of effect in reducing OHSS include the use metformin in women with PCOS,

use of GnRH antagonist rather than GnRH agonist, the use of GnRH agonist triggers in GnRH antagonist cycles, the use of intravenous HES at the time of oocyte collection and the use of cabergoline for prevention of early onset moderate OHSS. The consensus view was that reducing the dose of FSH, freezing all embryos and transferring a single embryo were appropriate interventions to reduce the risk of OHSS. Agreement could not be reached on the role of coasting, the lowest number of oocytes to consider freezing all embryos and management after cancellation of oocyte collection. There is a need for further research on the optimal dose and timing of metformin, use of aspirin and effect of ovarian drilling on OHSS. OHSS is a serious condition requiring ongoing research and universally agreed definition to allow the development of optimal preventative strategies. Future developments to prevent OHSS may include the use of *in vitro* maturation in women with PCOS or newer methods of induction of ovulation using kispeptin.

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