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Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews (Review)

Mourad S, Brown J, Farquhar C

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[Overview of Reviews]

Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews

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ABSTRACT

Background

Ovarian hyperstimulation syndrome (OHSS) in assisted reproductive technology (ART) cycles is a treatment-induced disease that has an estimated prevalence of 20% to 33% in its mild form and 3% to 8% in its moderate or severe form. These numbers might even be higher for high-risk women such as those with polycystic ovaries or a high oocyte yield from ovum pickup.

Objectives

The objective of this overview is to identify and summarise all evidence from Cochrane systematic reviews on interventions for prevention or treatment of moderate, severe and overall OHSS in couples with subfertility who are undergoing ART cycles.

Methods

Published Cochrane systematic reviews reporting on moderate, severe or overall OHSS as an outcome in ART cycles were eligible for inclusion in this overview. We also identified Cochrane submitted protocols and title registrations for future inclusion in the overview. The evidence is current to 12 December 2016. We identified reviews, protocols and titles by searching the Cochrane Gynaecology and Fertility Group Database of Systematic Reviews and Archie (the Cochrane information management system) in July 2016 on the effectiveness of interventions for outcomes of moderate, severe and overall OHSS. We undertook in duplicate selection of systematic reviews, data extraction and quality assessment. We used the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) tool to assess the quality of included reviews, and we used GRADE methods to assess the quality of the evidence for each outcome. We summarised the characteristics of included reviews in the text and in additional tables.

Main results

We included a total of 27 reviews in this overview. The reviews were generally of high quality according to AMSTAR ratings, and included studies provided evidence that ranged from very low to high in quality. Ten reviews had not been updated in the past three years. Seven reviews described interventions that provided a beneficial effect in reducing OHSS rates, and we categorised one additional review as 'promising'. Of the effective interventions, all except one had no detrimental effect on pregnancy outcomes.

Evidence of at least moderate quality indicates that clinicians should consider the following interventions in ART cycles to reduce OHSS rates.

• Metformin treatment before and during an ART cycle for women with PCOS (moderate-quality evidence).

• Gonadotrophin-releasing hormone (GnRH) antagonist protocol in ART cycles (moderate-quality evidence).

• GnRH agonist (GnRHa) trigger in donor oocyte or 'freeze-all' programmes (moderate-quality evidence).

Evidence of low or very low quality suggests that clinicians should consider the following interventions in ART cycles to reduce OHSS rates.

• Clomiphene citrate for controlled ovarian stimulation in ART cycles (low-quality evidence).

• Cabergoline around the time of human chorionic gonadotrophin (hCG) administration or oocyte pickup in ART cycles (low-quality evidence).

• Intravenous fluids (plasma expanders) around the time of hCG administration or oocyte pickup in ART cycles (very low-quality evidence).

• Progesterone for luteal phase support in ART cycles (low-quality evidence).

• Coasting (withholding gonadotrophins) - a promising intervention that needs to be researched further for reduction of OHSS.

On the basis of this overview, we must conclude that evidence is currently insufficient to support the widespread practice of embryo cryopreservation.

Authors' conclusions

Currently, 27 reviews in the Cochrane Library were conducted to report on or to try to report on OHSS in ART cycles. We identified four review protocols but no new registered titles that can potentially be included in this overview in the future. This overview provides the most up-to-date evidence on prevention of OHSS in ART cycles from all currently published Cochrane reviews on ART. Clinicians can use the evidence summarised in this overview to choose the best treatment regimen for individual patients - a regimen that not only reduces the chance of developing OHSS but does not compromise other outcomes such as pregnancy or live birth rate. Review results, however, are limited by the lack of recent primary studies or updated reviews. Furthermore, this overview can be used by policymakers in developing local and regional protocols or guidelines and can reveal knowledge gaps for future research.

PLAIN LANGUAGE SUMMARY

Interventions for prevention of ovarian hyperstimulation syndrome in in vitro fertilisation cycles: an overview of Cochrane reviews

Overview question

This overview of Cochrane reviews aims to identify and summarise all evidence from Cochrane systematic reviews on interventions that could prevent or treat moderate, severe and overall ovarian hyperstimulation syndrome (OHSS) in couples with subfertility who are undergoing assisted reproductive technology (ART) cycles (i.e. in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI)).

Background

OHSS in ART cycles is an adverse event that follows ovarian stimulation for IVF. It is caused by a very high ovarian response to hormonal medication and results in enlarged ovaries and a fluid shift from blood vessels to the abdominal cavity, resulting in, for example, abdominal bloating, high risk of clots within the blood vessels (thrombosis) and decreased blood supply to important organs such as kidneys and liver. The mild form of OHSS is seen in almost 20% to 33% of cycles, whereas a moderate or severe form is found in approximately 3% to 8% of cycles and can lead to serious disease burden or even mortality if left untreated. It is therefore important to identify treatment regimens and interventions that can reduce the incidence of OHSS.

Study characteristics

We found a total of 27 Cochrane ART reviews of high quality that could be included for this overview. These reviews aimed to report on OHSS in cycles of IVF or ICSI. We did not include reviews of intrauterine insemination and ovulation induction. The evidence is current to 12 December 2016.

Key results

Of the 27 reviews included in this overview, 10 reviews had not been updated in the past three years.

Seven reviews described interventions that provided a beneficial effect in reducing OHSS rates, and we categorised one additional review as 'promising'. Of the effective interventions, all except one had no detrimental effect on pregnancy outcomes. *Evidence of at least moderate quality evidence* indicates that clinicians should consider the following interventions in ART cycles to reduce OHSS rates.

• Metformin treatment before and during an ART cycle in women with PCOS (moderate-quality evidence).

• Gonadotrophin-releasing hormone (GnRH) antagonist protocol in ART cycles (moderate-quality evidence).

• GnRH agonist (GnRHa) trigger in donor oocyte or 'freeze-all' programmes (moderate-quality evidence).

Evidence of low or very low quality evidence suggests that clinicians should consider the following interventions in ART cycles to reduce OHSS rates.

• Clomiphene citrate for controlled ovarian stimulation in ART cycles (low-quality evidence).

• Cabergoline around the time of human chorionic gonadotrophin (hCG) administration or oocyte pickup in ART cycles (low-quality evidence).

• Intravenous fluids (blood plasma expanders) around the time of hCG administration or egg pickup in ART cycles (very low-quality evidence).

• Progesterone for luteal phase support in ART cycles (low-quality evidence).

A promising intervention that needs to be researched further is coasting (withholding gonadotrophins) for reduction of OHSS. On the basis of this overview, we must conclude that evidence is currently insufficient to support the widespread practice of freezing all embryos and replacing them at a later time when OHSS has dissolved.

Clinicians can use the evidence summarised in this overview to choose the best treatment regimen for individual patients - a regimen that not only reduces the chance of developing OHSS but does not compromise pregnancy outcomes. However, results of this overview are limited by the lack of recent primary studies or updated reviews. Furthermore, this overview can be used by policymakers in developing local and regional protocols or guidelines and can reveal knowledge gaps for future research.

BACKGROUND

Description of the condition

Ovarian hyperstimulation syndrome (OHSS) is a serious complication of controlled ovarian hyperstimulation cycles used in assisted reproductive technologies (ART). OHSS is clinically characterised by abdominal tenderness and swelling due to increased ovarian volume along with a sudden increase in vascular permeability, which results in a shift of fluid to the extravascular space. However, the exact pathophysiology of OHSS has not been completely elucidated. Cases of spontaneous OHSS have been reported and are suspected to be linked to follicle-stimulating hormone (FSH) receptor gene mutations (Delbaere 2004). However, the development of OHSS during ART cycles is mainly an iatrogenic side effect of the high doses of gonadotropin used for ovarian stimulation, resulting in multi-follicular growth. A key role is suspected for vascular endothelial growth factor (VEGF), which is produced by multiple follicles following ovarian stimulation (Agrawal 1999). Higher VEGF levels induce hyperpermeability of ovarian blood vessels, which leads to a fluid shift from the intravascular to the third space. Also, the administration of human chorionic gonadotrophin (hCG) as an ovulation trigger or luteal phase support in high-risk women with extensive luteinisation and supraphysiological levels of oestradiol and progesterone in the presence of multiple corpora lutea can trigger OHSS (Delbaere 2005). Moreover, the extra hCG-rise accompanying (multiple) pregnancy after ART can aggravate already existing OHSS or induce late-onset OHSS.

Over the years, several criteria have been used to classify OHSS severity (Appendix 1; Aboulghar 2003; Golan 1989; Navot 1992; Schenker 1978). In general, when OHSS progresses to a moderate stage, women experience abdominal pain and nausea and vomiting, and ascites can be seen around the ovaries on vaginal ultrasonography. If the condition progresses to severe OHSS, extravascular fluid can be found in pleural and pericardial spaces, and several haemodynamic changes take place, such as intravascular

volume depletion, haemoconcentration, hypoalbuminaemia and electrolyte imbalances. These changes can lead to severe morbidity associated with thromboembolic events (Stewart 1997), respiratory distress and liver or renal failure. If left untreated, OHSS demonstrates rapid progression, with potentially life-threatening or lethal complications (Braat 2006).

The mild form of OHSS is common, is of less clinical importance and occurs in an estimated 20% to 33% of ART cycles. The more clinically relevant moderate and severe forms of OHSS occur in an estimated 3% to 8% of ART cycles (3% to 6% moderate and 0.5% to 5% severe forms) (Delvigne 2002; Golan 1989; Schenker 1994). These large differences in reported OHSS incidence occur mainly because most reports involve single-centre data, use different definitions of OHSS, do not require that diagnosis must be ascertained by a formal classification system or must have adequate follow-up and lack reporting of mild or moderate forms. A large European report on 2010 ART practice (Kupka 2014) provided OHSS data for 25 participating countries and revealed prevalence of 0.3% in 349,402 simulated ART cycles. However, this report lacked data for some countries with a high volume of ART cycles (e.g. France, Sweden, the Netherlands, UK) and for other countries reported extremely low rates of OHSS, possibly as the result of reporting bias. A large Swiss retrospective cohort study reported a decline in OHSS incidence from 3.6% to 1% from 2005 to 2009 (De Geyter 2015). Globally, the incidence of OHSS is declining; a steady decrease has been reported since its peak incidence in the 1990s, when the main goal of ART was to produce a high number of oocytes (Kol 2011), and the incidence of severe OHSS was considered to be around 0.2% to 1% (Abramov 1999). With the emergence of new treatment regimens, more judicious use of gonadotrophins, increased cycle monitoring and improved knowledge of OHSS risks, the incidence of this disorder fell gradually over subsequent decades.

Although it is relatively rare, OHSS in ART cycles is an iatrogenic disease, and women who are affected should be monitored carefully to avoid life-threatening complications. Early recognition of risk factors for OHSS can help clinicians tailor treatment regimens. Women with a priori risk for development of OHSS are those with polycystic ovaries (PCOs) (with or without PCO syndrome (PCOS)) or a high antral follicle count (e.g. at a young age). During a controlled ovarian stimulation cycle, women can acquire 'high risk' status when they prove to have high oestradiol levels, excessive growth of follicles or a large number of retrieved oocytes. Besides the early OHSS type that develops during, or immediately after, ovarian stimulation, we can distinguish a late type, which appears after embryo implantation has been established. The presence of a multiple gestation can trigger or exacerbate this late type of OHSS (Delbaere 2005; Mathur 2000).

Description of interventions and how the interventions might work

Interventions that aim to reduce OHSS incidence can target diverse portions of stimulated ART cycles.

- Selection or identification of 'high risk' populations for tailoring of stimulation regimens.
- Prevention of recurrent OHSS by adjustment of the dose of gonadotrophins in the next cycle.
- Prevention of large numbers of follicles by tailored ovarian stimulation for specific risk groups (e.g. use of different treatment regimens, use of adjuvant medication).
- Prevention of a rise in VEGF levels (e.g. by prevention of development of large numbers of follicles, by targeting of VEGF receptors (e.g. by dopamine agonists)).
- Dose reduction or withholding of hCG administration for ovulation trigger or luteal support.
- Prevention of a rise in oestradiol by withholding of gonadotrophins ('coasting').
- Prevention of a further rise in oestradiol and of ovulation triggering and pregnancy by cycle cancellation.
- Prevention of intravascular volume depletion by administration of plasma-expanding intravenous (IV) fluids.
- Prevention of pregnancy by freezing of all embryos and transfer back during a subsequent cycle.

Moreover, trials of interventions within an ART cycle that are not specifically aimed at preventing OHSS may report on OHSS as an outcome. These interventions are of interest to this overview and might reveal new mechanisms for lowering risk of OHSS.

Why it is important to do this overview

OHSS is an iatrogenic disease with an estimated incidence of 3% to 6% in ART cycles of the clinically relevant moderate or severe form (Delvigne 2002). If left untreated, OHSS can lead to severe morbidity and can be life-threatening. Multiple treatment options are available for prevention of OHSS in ART cycles; therefore, it is important to provide consumers, health professionals, policymakers and guideline developers with a summary of evidence on OHSS prevention obtained from the Cochrane Library. We will comment upon this evidence in light of the overall effectiveness of studied interventions in the separate reviews. By doing so, we will identify existing knowledge gaps or reporting flaws within the Cochrane systematic reviews published in the Cochrane Library on the topic of OHSS in ART cycles. This means that we can provide clear suggestions for future research.

OBJECTIVES

The objective of this overview is to identify and summarise all evidence from Cochrane systematic reviews on interventions for prevention or treatment of moderate, severe and overall OHSS in couples with subfertility who are undergoing ART cycles.

METHODS

Criteria for considering reviews for inclusion

Types of reviews

For this overview of reviews, we included all published Cochrane systematic reviews of randomised controlled trials (RCTs) that examined:

- interventions that aimed to prevent OHSS with reporting on the incidence of moderate, severe or overall OHSS as a primary outcome; and
- other interventions in ART cycles with reporting on the incidence of moderate, severe or overall OHSS as a secondary outcome.

Moreover, we listed the protocols of reviews and title registrations on OHSS prevention in a table included in the overview. Thus we will be able to identify and add new reviews, once published, at the time of the next overview update. We excluded reviews on non-ART cycles and reviews on ART cycles that did not report on OHSS as an outcome.

Types of participants

We included reviews that enrolled women who underwent fresh ART cycles, including those who acted as oocyte donors. We considered Cochrane systematic reviews that reported on 'high risk' subgroups (e.g. minimum number of follicles, minimum number of oocytes retrieved, minimum oestradiol level, women with PCOS) and those that reported on unselected populations. We excluded reviews of non-ART cycles, such as ovulation induction or intrauterine insemination cycles.

Types of interventions

We considered for inclusion reviews on two types of interventions.

- Interventions specifically aimed at prevention of OHSS for which OHSS was reported as a primary outcome.
- Any interventions in ART cycles for which OHSS was reported as a secondary outcome.

Search methods for identification of reviews

We searched for reviews within the *Cochrane Database of Systematic Reviews* and Archie (the Cochrane information management system) for the following keywords: in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI), ART, adverse events and OHSS (search dates 18/11/2015, 24/7/2016 and 12/12/2016). The overview 'Assisted reproductive technology: an overview of Cochrane Reviews' by Farquhar 2015 identified all current reviews on ART that reported on OHSS as a primary or secondary outcome, and we used this as complementary guidance.

Data collection and analysis

We based the methods used for data collection and analysis for this overview on Chapter 22 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Becker 2011; Higgins 2011*)*.

Primary outcomes

The primary outcome measure is the incidence of moderate, severe and overall OHSS per woman randomised.
The OHSS subgroups of moderate and severe are defined by the criteria set forth by Aboulghar 2003, Golan 1989, Navot 1992, Rabau 1967, Rizk 1999 and Schenker 1978, or by any other classification used in the included reviews (Appendix 1).

Secondary outcomes

Secondary outcomes studied were live birth rate, clinical pregnancy rate, miscarriage rate, multiple pregnancy rate and any reported adverse effects that derived from the interventions studied (as reported by separate reviews, e.g. side effects of medication, admission to the hospital).

Selection of reviews

Two overview authors independently selected reviews for inclusion according to the criteria stated. A third overview author acted as a referee and discussed disagreements that arose. We added the following to the overview for future overview updates: protocols of reviews and title registrations on prevention of OHSS submitted to the Cochrane Library, and reviews on ART interventions that will report on OHSS as a secondary outcome.

Data extraction and management

Two overview authors (SM and JB) performed data extraction using a Microsoft Excel spreadsheet. If data from the reviews were unclear or seemed to be missing, we contacted review authors for clarification, searched primary RCTs or contacted primary study authors for details. A third overview author (CF) acted as a referee and discussed discrepancies or disputes that arose.
We extracted and summarised the following data for the additional tables.

- Population demographics: participant characteristics, definition of high-risk groups when applicable.
- Review characteristics: number of included trials, number of participants, date the review was assessed as up-to-date (date of search), interventions and comparisons, all primary and secondary outcomes and limitations of the review.

- Timing of intervention: e.g. pretreatment selection of participants, pretreatment adjuvant therapy, stimulation phase, stimulation phase adjuvant treatment, ovulation trigger, embryo transfer phase, luteal support phase.
- Statistical summary: summary effects from relevant comparisons on our primary outcome of moderate, severe or overall OHSS.

We used the same summary effect measures as were used in the original reviews, in most cases odds ratios.

Assessment of methodological quality of included reviews

Two overview authors independently assessed the quality of the evidence derived from included systematic reviews. We resolved discrepancies by discussion, and a third overview author acted as an arbiter.

Quality of evidence from primary studies in included reviews

Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method, we summarised the quality of the evidence from primary studies in the included reviews (Guyatt 2008; Schünemann 2013). We prepared 'Summary of findings' tables using GRADEpro Guideline Development Tool (GDT) software (GRADEpro GDT) for overview outcomes for each comparison by taking ratings from the original review, or we appraised the review ourselves if the review had not yet been assessed through the GRADE approach.

- Risk of bias of included trials.
- Directness of the evidence.
- Precision of the evidence.
- Heterogeneity.
- Risk of publication bias.

We summarised the evidence for each of the selected clinical outcomes in a 'Summary of findings' table, to which we added the summary risk estimate and 95% confidence intervals. We allocated the quality of evidence for the clinical outcome with a score for strength of the evidence, ranging from 'high' to 'very low'.

Quality of included reviews

We assessed the methodological quality of included reviews using the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) instrument (Shea 2007). This instrument evaluates methods used in systematic reviews and the degree to which reviews are biased by comparing them on the basis of distinct criteria. Ratings used in AMSTAR include 'yes' (clearly done), 'no' (clearly not done), 'cannot answer' and 'not applicable' (Appendix 2).

Data synthesis

We undertook a narrative description of the included trials. We included an 'Overview of reviews' table, which shows the characteristics of included reviews. Moreover, we displayed a summary of the quality of evidence within individual reviews that was based on GRADE judgements, and we provided an AMSTAR rating for each included review.
We summarised the main results of the included systematic reviews and the effect on OHSS rates of their individual comparisons using the following framework.

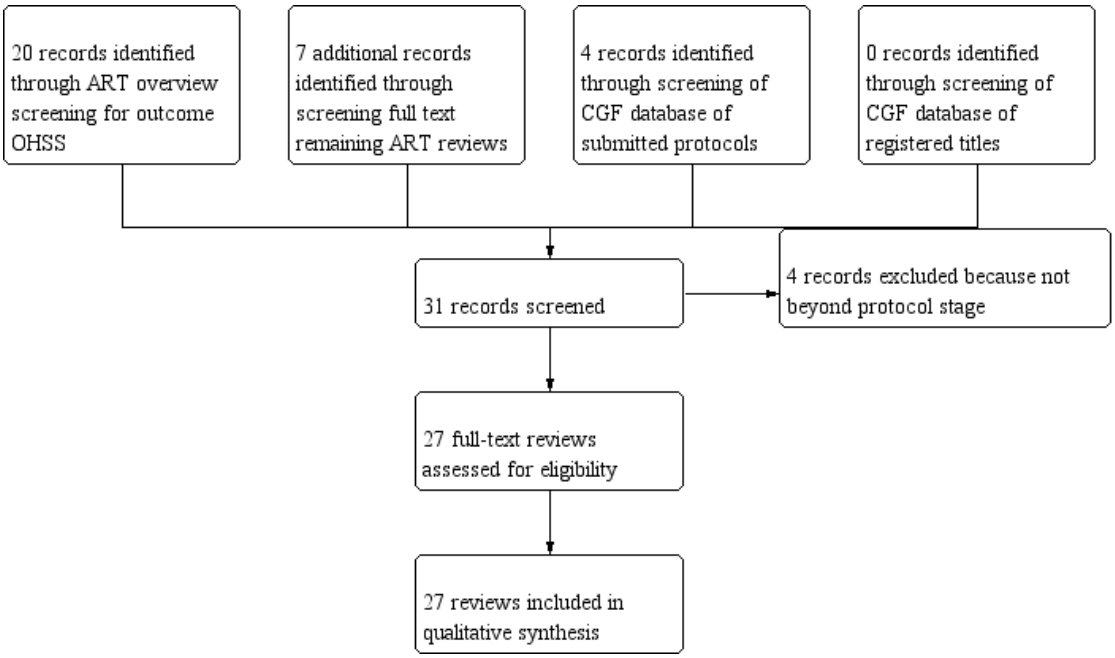
- Effective interventions: indicates that the review found evidence of effectiveness for an intervention.
- Promising interventions (more evidence needed): indicates that the review found some evidence of effectiveness for an intervention, but more evidence is needed.
- Ineffective interventions: indicates that the review found evidence of lack of effectiveness for an intervention.
- Probably ineffective interventions (more evidence needed): indicates that the review found evidence suggesting lack of effectiveness for an intervention, but more evidence is needed.
- No conclusions possible due to lack of evidence: indicates that the review found insufficient evidence for review authors to comment on the effectiveness of an intervention.

The choice of category to be allocated reflects the conclusions stated by authors of the individual reviews and our judgement as overview authors. We resolved disagreements by discussion.
We based our approach to summarising the evidence on the framework used for the ART overview (Farquhar 2015).

RESULTS

Upon screening the ART overview (Farquhar 2015), we identified a total of 20 reviews reporting on OHSS as an outcome. We subsequently screened full texts for remaining reviews in the ART overview reporting on OHSS or adverse events that could include OHSS as an outcome. By doing this, we identified an additional seven reviews (see flow diagram of included reviews, Figure 1). We excluded 33 reviews from the ART overview for not reporting on OHSS. From the Cochrane Gynaecology and Fertility (CGF) Database of registered titles, we identified no titles that were expected to report on OHSS in ART cycles as an outcome. From the CGF database of submitted protocols, we identified four protocols that potentially would report on OHSS in ART cycles as an outcome (Appendix 3). Most often, we excluded titles and protocols because they did not concern ART cycles or because they concerned laboratory interventions.

Figure 1. Flow diagram of included reviews.



Description of included reviews

In total, we included 27 Cochrane systematic reviews that reported on OHSS (85,497 participants). See Table 1 for a summary of the characteristics of these reviews (review title and author, numbers of randomised controlled trials and participants included, interventions and comparisons, outcomes, main limitations of each review). Of the 27 included reviews, two were empty reviews (reviews with no included studies), with last search dates in 2009 and 2011, respectively (Siristatidis 2009; Yossry 2006). We deemed two reviews to be stable, meaning that searches would be repeated only when review authors became aware of newly published evidence (D'Angelo 2007; Yossry 2006).

Pandian 2015 (IVF for unexplained subfertility) compared IVF versus IUI (we did not formally consider IUI a treatment for inclusion in this overview). As all studies also included a IVF/ICSI comparator group, we decided that we should include this review in the overview. Also, Cheong 2013 ('Acupuncture and assisted reproductive technology') could theoretically include studies on IUI or ovulation induction; however, all current comparisons in this review involve acupuncture around the time of oocyte retrieval and/or embryo transfer, which means that the current version of the review reports only on IVF/ICSI treatments.

Reporting on OHSS

A total of 15 reviews reported on OHSS as a primary outcome, and 12 reported on OHSS as a secondary outcome. The number of included primary studies per review ranged from zero to 94. We also noted large variation in the number of included primary studies that *actually* reported data on OHSS, which ranged from zero to 32 studies. For example, in the review that included 94 primary studies, only one study actually reported on OHSS (van der Linden 2015).

Four reviews focused specifically on prevention of OHSS and compared the following interventions: coasting versus no/other treatment (D'Angelo 2011), embryo freezing versus fresh transfer or intravenous albumin plus fresh transfer (D'Angelo 2007), volume expanders versus placebo or no treatment (Youssef 2016b) and dopamine agonists versus placebo or no/other treatment (Tang 2016). These reviews included studies that identified high-risk groups on the basis of oestradiol levels, a minimum number of follicles of a certain size, a minimum number of retrieved oocytes or a diagnosis of PCOS. Some primary studies excluded extremely high risk groups on the basis of oestradiol levels.

Three reviews (D'Angelo 2007; D'Angelo 2011; Tang 2016) reported separately on the subgroups 'moderate' and 'severe' OHSS, and two reported only on 'severe OHSS' (Al-Inany 2016; Youssef 2016). The other 22 reviews were described as reporting 'total OHSS' with or without defining this as inclusion of mild, moderate or severe cases.

Timing of intervention

Timing of interventions in the included reviews differed (see Table 1) as follows.

- No reviews: interventions regarding pretreatment selection of participants.
- Five reviews: interventions regarding pretreatment adjuvant therapy (Duffy 2010; Showell 2013; Siristatidis 2009; Smulders 2010; Tso 2014).
- One review: the pituitary downregulation phase (Albuquerque 2013).
- No reviews: interventions regarding adjuvants during the stimulation phase.
- 11 reviews: interventions regarding the stimulation phase (Al-Inany 2016; Allersma 2013; Cheong 2013; D'Angelo 2011; Gibreel 2012; Kwan 2014; Martins 2013; Mochtar 2007; Pouwer 2015; Siristatidis 2015; van Wely 2011).
- Three reviews: the ovulation trigger phase (Tang 2016; Youssef 2014; Youssef 2016).
- Three reviews: the embryo transfer phase (Boomsma 2012; D'Angelo 2007; Youssef 2016b).
- One review: the luteal support phase (van der Linden 2015).

We could not classify the Yossry 2006 and Pandian 2015 reviews according to this framework because they studied IVF versus other strategies.

Main limitations of the reviews

The major and most frequent limitations of included reviews were the mere reporting of 'total OHSS', as opposed to reporting separately on the more clinically relevant subgroups 'moderate' and 'severe'; failure to include any or inclusion of only a few studies per comparison; and a generally low proportion of primary studies reporting data on OHSS.

The 12 reviews that did report on OHSS as a secondary outcome often described lack of statistical power for the outcome 'OHSS' due to the low incidence of the condition in general and more specifically in populations not selected for risk of developing OHSS. For example, given a population size of 2000 women undergoing ART, as well as a 5% margin of error and a 95% confidence interval, the required sample size would be 323 women. In light of the fact that the incidence of moderate to severe OHSS in this population would be set at 5% (range from literature 3% to 8%), at least 6460 women should be included in the study for enough women to develop OHSS that data would show differences in OHSS rates. For most countries and settings, this inclusion number is not realistically attainable for any study.

Last search date of the reviews

Table 2 shows the last search date per review. Only 17 of the 27 included reviews conducted a literature search within the past three years (to 12 December 2016), and overview authors deemed an additional two reviews (D'Angelo 2007; Yossry 2006) with an older literature search to be stable. At our third search date (12 December 2016), we became aware of four reviews that were in the process of being updated (D'Angelo 2011; Duffy 2010; Gibreel 2012; Mochtar 2007). Progress of these updates at the date of the search varied widely, from just starting the literature search to completing the final editorial phase.

Statistical summary

Quality of evidence from primary studies in included reviews

The quality of the evidence reported by primary studies in the included reviews assessed by the GRADE approach ranged from very low to high for individual comparisons. The main reasons for downgrading of reviews for quality included inadequate reporting of allocation concealment and randomisation methods, lack of blinding and imprecision. Eleven of the 27 reviews included fewer than 10 primary studies.

Methodological quality of included reviews

Quality of systematic reviews

We rated the quality of the included reviews using the AMSTAR tool (Shea 2007) and listed the domains per review in Table 3.

- All reviews had prespecified their clinical question and inclusion criteria.
- All reviews conducted study selection and data extraction in duplicate.
- All reviews conducted a comprehensive literature search.
- All reviews included searches of grey literature.
- All reviews listed included and excluded studies.
- All reviews described the characteristics of included studies.
- All reviews assessed study quality.
- All reviews combined studies using appropriate methods.
- A total of 25/27 reviews addressed the risk of reporting bias by using a statistical test when appropriate.
- All reviews addressed the potential for conflict of interest.

Effect of interventions

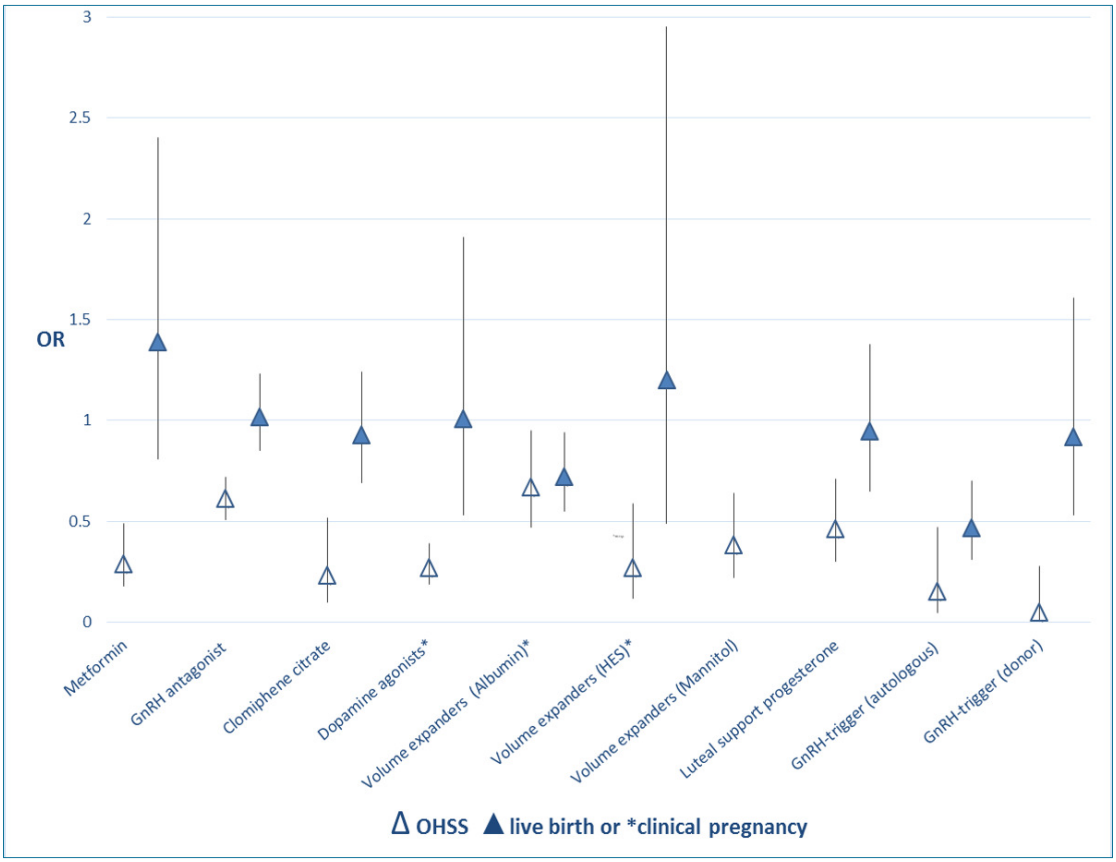
We categorised all included intervention reviews by effectiveness for reduction of OHSS and by effectiveness for the primary pregnancy outcome stated in the review. In total, with regard to reduction of OHSS rates, seven reviews showed a beneficial effect of the intervention on the incidence of OHSS, one was promising,13 were ineffective and six remained inconclusive. Of the effective interventions, one intervention did reduce OHSS rates but had a detrimental effect on pregnancy outcomes (Youssef 2014).

We listed effects of the interventions on the incidence of OHSS in the 'Summary of findings' table (Table 4). Most reviews did not report the incidence of OHSS as the (sole) primary outcome. This implies that the effectiveness of studied interventions can very well be different for the main primary outcome and for reduction of OHSS. Among the 25 non-empty reviews, the effect of the intervention on OHSS rates was beneficial in eight reviews, and the intervention had no effect on OHSS rates in 14 reviews. One review reported that the control group had lower OHSS rates than the intervention group; however, the only primary study in this review reporting on OHSS did not provide exact numbers, so we could not calculate the effect size (Siristatidis 2016). For three reviews, we could not calculate effect size because they included insufficient primary studies reporting on OHSS (Cheong 2013; Duffy 2010; Showell 2013).

We summarise here the effectiveness of interventions for both reduction of OHSS and pregnancy outcomes, ranked by timing of the intervention within an ART cycle.

Moreover, for interventions that had a beneficial effect on OHSS rate, Figure 2 shows the extent of this effect in relation to the effect on live birth rate (when reported) or clinical pregnancy.

Figure 2. Extent of effect of interventions on OHSS rate and live birth rate (when reported) or clinical pregnancy: OR and 95% CI.



Effective interventions for reduction of OHSS with no impact on nor improvement in pregnancy outcomes

Pretreatment adjuvant therapy

- Metformin treatment before and during IVF or ICSI in women with PCOS: No conclusive evidence suggests that

metformin treatment before or during ART cycles improved live birth rates (low-quality evidence). However, use of this insulin-sensitising agent increased clinical pregnancy rates and decreased the risk of OHSS (moderate-quality evidence) (Tso 2014). Evidence showed a beneficial effect of the intervention on OHSS rates.

Pituitary downregulation phase

- Gonadotrophin-releasing hormone (GnRH) antagonists for ART: Use of antagonists compared with long GnRHa protocols was associated with a large reduction in OHSS, and no evidence suggested a difference in live birth rates (moderate-quality evidence) (Al-Inany 2016). Evidence showed a beneficial effect of the intervention on OHSS rates.

Stimulation phase

- Clomiphene citrate for controlled ovarian stimulation in women undergoing IVF: This review suggested that regimens with clomiphene could be used in controlled ovarian stimulation for IVF treatment without a reduction in pregnancy rates. However, further evidence is required before these regimens can be recommended with confidence as alternatives to gonadotrophins alone in GnRH long or short protocols (low-quality evidence) (Gibreel 2012). Evidence showed a beneficial effect of the intervention on OHSS rates.

Ovulation trigger phase

- Dopamine agonists for preventing OHSS: Dopamine agonists appeared to reduce the risk of OHSS in high-risk women, especially for moderate OHSS. Use of dopamine agonists did not appear to affect clinical pregnancy rates or miscarriage rates, nor did they increase the risk of other adverse events (moderate-quality evidence) (Tang 2016). Evidence showed a beneficial effect of the intervention on moderate or severe OHSS rates.
- Volume expanders for prevention of OHSS: The volume expanders hydroxyethyl starch and mannitol decreased the incidence of moderate or severe OHSS without affecting pregnancy rates (very low-quality evidence) (Youssef 2016b). Evidence showed a beneficial effect of the intervention on moderate or severe OHSS rates.

Luteal support phase

- Luteal support phase in ART cycles: This review concluded that progesterone appears to provide the best method of providing luteal phase support, as it is associated with higher rates of live birth or ongoing pregnancy than placebo, and lower rates of OHSS than hCG. Addition of one or more doses of GnRH agonists to progesterone was associated with higher live birth and ongoing pregnancy rates than progesterone alone. Overall, addition of other substances such as oestrogen or hCG did not seem to improve outcomes, and hCG was associated with higher risk of OHSS. The route of progesterone administration did not seem to matter (quality of evidence was low for most comparisons) (van der Linden 2015). Evidence showed a beneficial effect of the intervention on OHSS rates for the comparison hCG versus placebo/no treatment. For the other comparisons, no evidence showed an effect on OHSS rates.

Effective interventions for reduction of OHSS with negative impact on pregnancy outcomes

Ovulation trigger phase

- GnRHa versus hCG for oocyte triggering in antagonist ART cycles: Evidence suggested a lower live birth rate, a reduced ongoing pregnancy rate and a higher miscarriage rate among women who received a GnRHa. However, OHSS rates were reduced with GnRHa triggering; therefore, clinicians should consider the tradeoff between benefits and harms (moderate-quality evidence) (Youssef 2014). Evidence showed a beneficial effect of the intervention on OHSS rates.
- Volume expanders for prevention of OHSS: Evidence suggested that human albumin decreased the incidence of moderate or severe OHSS. However, contrary to the (very low-quality) evidence found with hydroxyethyl starch (HES) and mannitol, human albumin appeared to have a detrimental effect on pregnancy rates (moderate-quality evidence) (Youssef 2016b).

Promising interventions for reduction of OHSS with no impact on or improvement in pregnancy outcomes (more evidence needed)

Ovulation trigger phase

- Coasting (withholding gonadotrophins) for preventing OHSS: Evidence was insufficient to show benefit derived from coasting done to prevent OHSS compared with no coasting or other interventions (very low-quality evidence) (D'Angelo 2011). Evidence showed a beneficial effect of the intervention on OHSS rates, but this was reported only in a single abstract on an RCT that provided insufficient methodological details.

Ineffective interventions for reduction of OHSS with no impact on or improvement in pregnancy outcomes

Pretreatment adjuvant therapy

- Oral contraceptive pill (OCP), progestogen or oestrogen pretreatment for ovarian stimulation protocols for women undergoing ARTs: Evidence suggested improved pregnancy outcomes with progestogen pretreatment and poorer pregnancy outcomes with combined OCP pretreatment (Smulders 2010). No evidence showed an effect of the intervention on OHSS rates.

Pituitary downregulation phase

- GnRHa protocols for pituitary suppression in ART cycles: The pregnancy rate was higher when GnRHa was used in a long protocol as compared with a short or ultra-short protocol (low-quality evidence) (Siristatidis 2015). No evidence showed an effect of the intervention on OHSS rates.
- Depot versus daily administration of GnRHa protocols for pituitary desensitisation in assisted reproduction cycles: No evidence suggested a significant difference in live birth or pregnancy outcomes between depot and daily GnRHa use for pituitary downregulation in IVF cycles using the long protocol, but substantial differences could not be ruled out (moderate-quality evidence) (Albuquerque 2013). No evidence showed an effect of the intervention on OHSS rates.

Stimulation phase

- FSH replaced by low-dose hCG in the late follicular phase versus FSH alone for ARTs: Review authors were very uncertain about effects on live birth, OHSS and miscarriage, but evidence suggested that this intervention did not reduce the chances of ongoing and clinical pregnancy, and that it was likely to result in retrieval of an equivalent number of oocytes with less FSH expended (very low-quality evidence) (Martins 2013). No evidence showed an effect of the intervention on OHSS rate.
- Recombinant versus urinary gonadotrophin for ovarian stimulation in ART cycles: It appeared that all available gonadotrophins were equally effective and safe. The choice of one or the other product would depend upon the availability of the product, the convenience of its use and associated costs. Any specific differences are likely to be too small to justify further research (high-quality evidence) (van Wely 2011). No evidence showed an effect of the intervention on OHSS rates.
- Long-acting FSH versus daily FSH for women undergoing assisted reproduction: A medium dose (150 to 180 μg) of long-acting FSH appeared to offer a safe treatment option that was as effective as daily FSH in women with unexplained subfertility. Evidence showed a reduced live birth rate among women receiving a low dose (60 to 120 μg) of long-acting FSH compared with daily FSH (moderate-quality evidence) (Pouwer 2015). No evidence showed an effect of the intervention on OHSS rates.
- Natural cycle IVF for subfertile couples: No evidence showed a significant difference between natural cycle and standard IVF for outcomes including live birth, OHSS, clinical pregnancy and multiple pregnancy (very low-quality evidence) (Allersma 2013). No evidence showed an effect of the intervention on OHSS rates.
- Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI): RCTs provided no evidence to support cycle monitoring by ultrasonography plus serum oestradiol as more efficacious than cycle monitoring by ultrasonography only for the outcomes of live birth and pregnancy. A large well-designed RCT is needed (low-quality evidence) (Kwan 2014). No evidence showed an effect of the intervention on OHSS rates.

Ovulation trigger phase

- Recombinant versus urinary hCG for final oocyte maturation triggering in IVF and ICSI cycles: Review authors concluded that urinary hCG remains the best choice for final oocyte maturation triggering in IVF and ICSI treatment cycles owing to availability and cost and no difference in live birth rates (moderate-quality evidence) (Youssef 2016). No evidence showed an effect of the intervention on OHSS rates.

Embryo transfer phase

- Peri-implantation glucocorticoid administration for ART cycles: Overall, no clear evidence suggests that administration of peri-implantation glucocorticoids in ART cycles significantly improved clinical outcomes (low-quality evidence) (Boomsma 2012). No evidence showed an effect of the intervention on OHSS rates.
- Embryo freezing for prevention of OHSS: Evidence was insufficient to show benefit for routine cryopreservation and the relative merits of intravenous albumin versus cryopreservation (low-quality evidence) (D'Angelo 2007). No evidence showed an effect of the intervention on OHSS rates.

Luteal support phase

- Recombinant luteinising hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles: No evidence suggested that coadministration of rLH and recombinant follicle-stimulating hormone (rFSH) in GnRHa-downregulated women resulted in more live births than were reported with controlled ovarian hyperstimulation (COH) with rFSH alone. Nevertheless, all pooled pregnancy estimates, although not significantly different, pointed towards a beneficial effect of cotreatment with rLH, in particular with respect to pregnancy loss (low-quality evidence) (Mochtar 2007). No evidence showed an effect of the intervention on OHSS rates.

ART versus other interventions

- In vitro fertilisation for unexplained subfertility: IVF may be more effective than IUI plus ovarian stimulation (low-quality evidence) (Pandian 2015). No evidence showed an effect of the intervention on OHSS rates.

Possibly ineffective interventions for reduction of OHSS with no impact on or improvement in pregnancy outcomes (more evidence needed)

- None were reported.

No conclusions possible on effectiveness for reduction of OHSS (lack of evidence)

For six reviews, review authors could provide no conclusions on the effects of interventions on OHSS rates.

Pretreatment adjuvant therapy

- Aspirin for IVF: Evidence from adequately powered RCTs was insufficient for review authors to reach a conclusion (Siristatidis 2016). No evidence showed an effect of the intervention on OHSS rates. No numbers were provided, so we could not calculate effect size.
- Antioxidants for female subfertility: Antioxidants were not associated with increased live birth or clinical pregnancy rates, although more evidence is needed (low-quality evidence) (Showell 2013). No trials reported actual numbers of cases of OHSS.
- Acupuncture and ART: No evidence suggested benefit for acupuncture in improving live birth or clinical pregnancy rates in assisted conception (low-quality evidence) (Cheong 2013). No trials reported on OHSS.

Stimulation phase

- Growth hormone for IVF: We could not calculate the effect of the intervention on OHSS rates. Use of growth hormone in poor responders was associated with significant improvement in live birth rates (moderate-quality evidence) (Duffy 2010).

- In vitro maturation in subfertile women with polycystic ovarian syndrome (PCOS) undergoing assisted reproduction: This is an empty review (Siristatidis 2009).

ART versus other interventions

- IVF versus tubal reanastomosis (sterilisation reversal) for subfertility after tubal sterilisation: This is an empty review (Yossry 2006).

DISCUSSION

Summary of main results

We found seven interventions that were effective in reducing the occurrence of ovarian hyperstimulation syndrome (OHSS) while not influencing or even improving pregnancy outcomes: metformin pretreatment in women with polycystic ovary syndrome (PCOS), use of a gonadotrophin-releasing hormone (GnRH) antagonist protocol for pituitary suppression, use of clomiphene citrate for controlled ovarian stimulation, use of dopamine agonists and the volume expanders hydroxyethyl starch (HES) and mannitol around the time of oocyte triggering, coasting before oocyte triggering and use of progesterone for luteal phase support (Al-Inany 2016; D'Angelo 2011; Gibreel 2012; Tang 2016; Tso 2014; van der Linden 2015; Youssef 2016b).
Two additional interventions - gonadotrophin-releasing agonist (GnRHa) versus human chorionic gonadotrophin (hCG) for oocyte triggering, and use of the volume expander human albumin around the time of ovulation triggering - proved effective in reducing OHSS but negatively impacted pregnancy outcomes in autologous cycles (Youssef 2014; Youssef 2016b).
Concerning the GnRHa trigger, this detrimental effect on pregnancy outcomes was not found in oocyte donation cycles. This would make the use of GnRHa for ovulation triggering suitable for oocyte donation programmes, as it would largely eradicate the chance of OHSS in the donor, without negatively influencing pregnancy outcomes in the recipient. GnRHa could also be useful in preventing OHSS in "freeze-all" programmes (i.e. embryo transfer is not performed in the fresh autologous cycle) - a regimen that is currently the topic of numerous research projects and new randomised controlled trials (RCTs).

Overall completeness and applicability of evidence

This overview of Cochrane reviews is complete and up-to-date as of December 2016. Only four reviews specifically addressed prevention of OHSS; by reporting all reviews on assisted reproduction technology (ART) that include OHSS as a primary or secondary outcome, we aimed to provide the most up-to-date overview of strategies to prevent OHSS currently included within the Cochrane Library. In keeping with the nature of a Cochrane overview, this body of work does not cover non-Cochrane reviews on OHSS. Moreover, alternative or emerging strategies for prevention of OHSS may not yet have been covered in a Cochrane review and therefore cannot be found in this overview, for example, use of calcium gluconate infusion or the dual GnRHa and hCG trigger. Once such strategies have been assessed in new reviews, we can and will update this overview accordingly.
Clinically relevant moderate OHSS and severe OHSS are still rare conditions; moreover, inclusion of 'high risk' groups was not based

on a variety of criteria and was not a prerequisite at all for many of the included reviews. In combination with the fact that most studies included OHSS as a secondary outcome, this means that most primary studies lacked statistical power to report on OHSS. However, as OHSS is an undesirable outcome in ART, it is unlikely that the prevalence will change, and it is considered unethical by many institutional ethics review boards to randomise very high-risk groups as a control in current and future studies. Unfortunately, this means that it will be difficult to nearly impossible for researchers to perform well-powered studies that address these shortcomings.

A major limitation of many of the included reviews is reporting of 'total OHSS' only. A total of three reviews reported separately on the subgroups 'moderate' and 'severe' OHSS. Three additional reviews reported only 'severe' OHSS; the remaining 21 reviews described that they reported on total 'OHSS' and provided no further explanation (e.g. this could have included moderate + severe, mild + moderate + severe, severe only). As almost all hyperstimulation cycles for in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) are accompanied by some form of discomfort and ovarian enlargement, the subgroup 'mild OHSS' does not seem to represent a very significant clinical outcome (for a description of subgroups, see Appendix 1). Reporting only on the total incidence of OHSS with no further specification of cases per subgroup biases the comparability of studies and actual reporting on clinically significant OHSS rates. For example, some studies could have found mainly, or only, mild cases of OHSS, whereas other studies might not have even included or assessed mild cases and would have reported only moderate and/or severe cases of OHSS. This would mean that the former study would overestimate the number of OHSS cases for which the latter finding is more precise. Also, a study that reports only on *hospitalised* cases might underestimate moderate cases, which we consider clinically significant too. Moreover, reviews reporting on interventions that aim to reduce the incidence of OHSS included only 'high risk' populations, whereas most of the other reviews did not select their population specifically for this criterion, which makes it difficult to compare the effectiveness of different interventions within this overview. This heterogeneous method of reporting fails to acknowledge the incidence of moderate and severe cases, resulting in an evidence gap for this important adverse outcome of ART cycles.

Currently, many ART clinics apply preventive strategies such as natural cycle/mild stimulation IVF or cryopreservation of all embryos (the 'freeze-all' approach) that have not been proven to have a beneficial effect on OHSS on the basis of low-quality evidence (Allersma 2013; D'Angelo 2007; D'Angelo 2011). However, theoretical considerations suggest that these strategies are probably effective, as they eliminate certain steps of an ART cycle (preventing multiple follicle growth and implantation, thereby preventing an hCG surge); additional RCTs are needed to provide a robust evidence base for these practices.

Quality of the evidence

All included systematic reviews were prepared according to Cochrane guidelines and were of high quality in most respects, although only 17 of 27 had conducted a literature search within the past three years. Moreover, the included primary studies might be significantly older than the review publication date, thus sometimes reflecting outdated clinical practice or stimulation regimens. This cannot be avoided in an overview, as we summarise available evidence from existing reviews, and sometimes few or no recent RCTs are available.

This also has an impact on the quality of the evidence reported by primary studies in the included reviews. Using GRADE methods, we rated this quality level as very low to high. The main reasons for downgrading the quality of evidence included bias in the primary studies (inadequate reporting of allocation concealment and randomisation methods, lack of blinding) and imprecision. Evidence was frequently restricted to that provided by only a few included trials per comparison. Because clinically relevant OHSS is still a relatively rare outcome in ART cycles, and given that the primary study size and the number of studies per comparison have been limited for most reviews, the event rate of reported OHSS will remain low, as mild OHSS frequently is not reported. This implies that the quality of the evidence should be downgraded by one level (according to GRADE rules for downgrading dichotomous outcomes by one level for imprecision), and that the event rate < 300 and the total cumulative sample size were lower than the calculated optimal information size (OIS) (Schünemann 2013). As a result, the quality of the evidence on effectiveness of interventions for the outcome of OHSS remains 'very low' or 'low' for most interventions and comparisons.

Potential biases in the overview process

We identified no biases during the overview process.

Agreements and disagreements with other studies or reviews

Over the years, as new evidence from RCTs continues to emerge, a steady stream of publications aims to provide a comprehensive overview on the pathophysiology, prevention and treatment of OHSS. For example, in 2016 alone, Guo 2016 and Kwik 2016 were published, and recently, the American Society for Reproductive Medicine provided practice guidelines (ASRM 2016). In addition to this, an abundance of reviews have examined particular interventions covered in this overview, such as use of dopamine agonists (Baumgarten 2013; Kalampokas 2013; Kasum 2015; Leitao 2014).

Such publications encompass, for example, regional or national clinical practice guidelines or an overview of the literature. However, most also include data derived from retrospective and pop-

ulation-based longitudinal studies or non-randomised controlled trials. To our knowledge, this overview is the first to include solely systematic reviews on ART conducted according to rigorous Cochrane standards, thus showing high methodological quality. Moreover, we included not only reviews of interventions directly aiming to prevent OHSS, but also reviews of other ART interventions reporting on OHSS as an adverse effect, thus presenting a more complete overview of the literature currently available in the Cochrane Library.

AUTHORS' CONCLUSIONS

This overview provides the most up-to-date evidence on prevention of OHSS in ART cycles from all currently published Cochrane reviews on ART. Clinicians can use the evidence summarised in this overview to choose the best treatment regimen for individual patients: a regimen that not only reduces the chance of developing OHSS but does not compromise other outcomes such as pregnancy or live birth rate. Furthermore, policymakers can use this overview when developing local and regional protocols or guidelines, and investigators can use it to identify knowledge gaps for future research.

Implications for practice

Evidence of at least moderate quality shows that clinicians should consider the following interventions to reduce OHSS rates in ART cycles.

- Metformin treatment before and during an ART cycle for women with PCOS (moderate-quality evidence) (Tso 2014).
- Dopamine agonists around the time of hCG administration or oocyte pickup in ART cycles (moderate-quality evidence) (Tang 2016).
- GnRH antagonist protocol in ART cycles (moderate-quality evidence) (Al-Inany 2016).
- GnRHa trigger in donor oocyte or 'freeze-all' programmes, as it reduces OHSS and leads to lower pregnancy rates when embryo transfer is performed in the same cycle (moderate-quality evidence) (Youssef 2014).

All of the above mentioned interventions are preventive measures used to reduce OHSS rates.

Evidence of low or very low quality indicates that clinicians can consider the following interventions to reduce OHSS rates in ART cycles.

- Clomiphene citrate for controlled ovarian stimulation in ART cycles (low-quality evidence) (Gibreel 2012).
- Intravenous fluids (plasma expanders) around the time of hCG administration or oocyte pickup in ART cycles (very low-quality evidence) (Youssef 2016b).
- Progesterone for luteal phase support in ART cycles (low-quality evidence) (van der Linden 2015).

Among the interventions mentioned above, clomiphene for ovarian stimulation and progesterone for luteal support are preventive measures used to reduce OHSS rates; dopamine agonists and plasma expanders are considered treatments for women with OHSS.

On the basis of this overview, we must conclude that evidence is currently insufficient to support the widespread practice of embryo cryopreservation and coasting (withholding of gonadotrophins) for reduction of OHSS (D'Angelo 2007; D'Angelo 2011).

Implications for research

This overview clearly identifies ways in which current evidence on effectiveness of interventions for prevention of OHSS is lacking. First, it highlights the need for review authors to update existing ART reviews to decrease knowledge gaps on this topic. Second, it should motivate clinicians and researchers to generate larger RCTs of higher quality to perform comparisons of new and existing interventions intended to reduce the incidence of OHSS.

The following three interventions have been shown to reduce OHSS on the basis of low-quality or very low-quality evidence. The fourth intervention listed here has shown a *promising* effect on reduction of OHSS and should be prioritised for examination by researchers in new high-quality RCTs.

- Clomiphene citrate for controlled ovarian stimulation in ART cycles (low-quality evidence) (Gibreel 2012).
- Intravenous fluids (plasma expanders) around the time of hCG administration or oocyte pickup in ART cycles (very low-quality evidence) (Youssef 2016b).
- Progesterone for luteal phase support in ART cycles (low-quality evidence) (van der Linden 2015).
- Coasting (withholding gonadotrophins) before hCG triggering in ART cycles (very low-quality evidence) (D'Angelo 2011).

The uptake of subgroups 'moderate' and 'severe' OHSS in outcome reporting would be very useful for future studies and reviews, as these categories are the most clinically significant subgroups of OHSS. Reporting these subgroups separately provides clinicians

and policymakers with a far more balanced reflection of treatment risks than is provided by mere use of the outcome 'total OHSS', which also includes mild OHSS and might not be as clinically important. Furthermore, clinicians would benefit if new RCTs would distinguish early and late types of OHSS, as the time of development of OHSS could influence the choice of therapy.

Large, well-conducted RCTs are urgently needed to support the current evidence base for interventions described in this overview, including dose-finding studies and research to determine the optimal timing of interventions. These trials should first examine interventions that seem to be effective but for which only very low-quality, low-quality or moderate-quality evidence is available (Table 4).

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Review characteristics

Review ID	Number of included trials	Population *Definition of high risk for OHSS (where applicable)*	Intervention	Comparison intervention/ control	Primary outcomes[a]	Review limitations
ADA563 D'Angelo 2011 Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome	4 RCTs	340 women with PCOS downregulated by GnRHa, undergoing superovulation in IVF or ICSI cycles *High risk: women with PCOS*	Coasting when oestradiol levels were > 2500 pg/mL or > 9000 pmol/L	Early unilateral follicular aspiration No coasting or other interventions	OHSS[a] Live birth[a] Clinical pregnancy Number of oocytes retrieved Multiple pregnancy Miscarriage	Comparisons based on limited trial data Live birth reported in only 1 trial Trials lacked blinding, and half the trials lacked details on allocation concealment and incomplete outcome assessment
ADA561 D'Angelo 2007 Embryo freezing for preventing ovar-	2 RCTs	151 women downregulated by GnRHa, undergoing superovulation in IVF	Cryopreservation	Fresh embryo transfer Intravenous albumin	OHSS[a] Clinical pregnancy[a] Live birth	Evidence based on 2 trials, 1 for each comparison Live birth re-

Table 1. Review characteristics (*Continued*)

ian hyperstimulation syndrome		or ICSI cycles *High risk: as defined by included studies*			Admissions	ported in only 1 trial Issues around methodological quality of both trials
TH1338 Tang 2016 Dopamine agonists for preventing ovarian hyperstimulation syndrome	16 RCTs	2091 women at high risk of developing OHSS undergoing ART *High risk: as defined by included studies*	Cabergoline quinagolide, bromocriptine, cabergoline + albumin, cabergoline + HES	Placebo/no treatment/other treatment: Albumin alone HES Coasting Prednisolone	OHSS[a] Live birth[a] Clinical pregnancy Adverse effects Miscarriage Multiple pregnancy	Allocation concealment and blinding not adequately reported. One study used a co-intervention of albumin IV and 1 of HES Different regimens of cabergoline administration between included studies Live birth rate reported in only 2 studies Incomplete reporting of multiple pregnancy rate, adverse effects and miscarriage rate
PMA481 Youssef 2016b Volume expanders for prevention of OHSS	9 RCTs	1660 (albumin) + 487 (HES) women at high risk of developing OHSS undergoing ART cycles *High risk: determined as number of follicles or oestradiol levels on day of hCG, as defined by included studies*	Human albumin Hydroxyethyl starch (HES)	Placebo/no treatment	OHSS[a] Clinical pregnancy Number of oocytes retrieved Multiple pregnancy Miscarriage Live birth	No reporting of live birth rate Limited by incomplete data reporting and lack of (details on) blinding
HA413 Youssef 2016 Recombinant vs urinary hCG for	18 RCTs	2952 women undergoing ART	Recombinant hCG Recombinant	Urinary hCG	OHSS[a] Clinical pregnancy	Review authors combined ongoing preg-

Table 1. Review characteristics (*Continued*)

final oocyte maturation triggering in IVF and ICSI cycles			LH		Miscarriage Oocytes retrieved Tolerance Live birth	nancy and live births together Only 7 trials reported on live birth Trials lacked details on allocation concealment, randomisation and blinding
MM1690 Youssef 2014 GnRHa vs hCG for oocyte triggering in antagonist-assisted reproductive technology	17 RCTs	1847 women undergoing ART	GnRH agonist	hCG	OHSS[a] Live birth rate[a] Ongoing pregnancy Clinical pregnancy Multiple pregnancy Miscarriage rate	Risk of bias in included studies. Limitations included premature termination, failure to clearly report methods and substantial heterogeneity Adverse events such as multiple pregnancy rate were not well reported
AWP1710 Pouwer 2015 Long-acting FSH vs daily FSH for women undergoing assisted reproduction	6 RCTs	3753 women with subfertility	Long-acting FSH	Daily FSH	OHSS[a] Live birth rate[a] Ongoing pregnancy rate Clinical pregnancy rate Multiple pregnancy rate Miscarriage rate Adverse events Satisfaction	Limited by risk of attrition bias in some primary studies and by serious imprecision
LDT120 Tso 2014 Metformin treatment before and during IVF or ICSI in women with PCOS	9 RCTs	816 women with PCOS	Metformin	Placebo No treatment	OHSS[a] Live birth[a] Clinical pregnancy[a] Miscarriage Adverse events Number of oocytes	Half the trials were not blinded and lacked details on allocation concealment and randomisation

Table 1. Review characteristics (*Continued*)

					retrieved Total dose FSH (IU) Number of days gonadotrophin treatment Cycle cancellation rate Serum E2 level (nmol/L)	
AM1335 Gibreel 2012 Clomiphene citrate in combination with gonadotropins for controlled ovarian stimulation in women undergoing IVF	14 RCTs, 12 for meta-analysis	2536 (12 trials) Subfertile women undergoing ART	Clomiphene citrate ± additional treatments	Alternative treatments for COH	OHSS[a] Live birth rate[a] Miscarriage rate Ectopic pregnancy Foetal abnormality Ongoing pregnancy rate Cancellation rate	Live birth reported in only 5 trials Most studies suffered from suboptimal methods and information on some outcomes was insufficient
TA1860 Allersma 2013 Natural cycle IVF for subfertile couples	5 RCTs	382 subfertile women and couples undertaking IVF treatment	Natural cycle IVF Modified natural cycle IVF	COH IVF	OHSS[a] Live birth[a] Pregnancy Ongoing pregnancy Number of oocytes retrieved Time to live birth Number of cycles required to conceive Cumulative pregnancy/live birth rate Multiple pregnancy Lack of embryos for cryopreservation Cycle cancellation Gestational abnormalities Cancellation of	Few studies, live birth reported in only 1 very small trial Inclusion criteria differed

Table 1. Review characteristics (*Continued*)

					treatment Cost-effectiveness	
MV263 van der Linden 2015 Luteal phase support for ART cycles	94 RCTs	26,198 women with any cause of subfertility undergoing ART	Progesterone hCG	Placebo or no treatment hCG Progesterone + oestrogen Progesterone + GnRHa	Live birth[a] Clinical pregnancy Ongoing pregnancy Miscarriage OHSS Multiple pregnancy	Poor reporting of study methods and imprecision due to small sample sizes
HA412 Al-Inany 2016 Gonadotrophin-releasing hormone antagonists for ART	73 RCTs	12,212 women undergoing ART	GnRH antagonist	Long-course GnRHa	OHSS[a] Live birth[a] Ongoing pregnancy Clinical pregnancy Miscarriage Cycle cancellation	Only 12 trials reported live birth Trial methods limited by lack of blinding Poor reporting of study methods for OHSS
AMY731 Yossry 2006 IVF vs tubal re-anastomosis (sterilisation reversal) for subfertility after tubal sterilisation	No RCTs	NA	IVF	Tubal re-anastomosis	Live birth[a] Clinical pregnancy Multiple pregnancy Other serious maternal morbidity, (incl OHSS)	Empty review with no trials No longer being updated
ZP672 Pandian 2015 IVF for unexplained subfertility	6 RCTs	733 couples with unexplained subfertility	IVF	Expectant management Intrauterine insemination Intrauterine insemination + ovarian stimulation Clomiphene citrate	Live birth[a] OHSS Clinical pregnancy Multiple pregnancy	Some evidence was based on a single trial Limitations included imprecision and heterogeneity for some outcomes
LA541 Albuquerque 2013 Depot vs daily administra-	16 RCTs, 12 for meta-analysis	1811 couples with any cause of subfertility undergoing IVF with COH with	Pituitary down-regulation with depot administration of GnRHa	Daily administration of GnRHa	OHSS[a] Live birth[a] Clinical pregnancy[a]	S tudy quality unclear due to poor reporting. O nly

Table 1. Review characteristics (*Continued*)

tion of GnRHa protocols for pituitary desensitisation in assisted reproduction cycles		hFSH, hMG or rFSH			Miscarriage Multiple pregnancy	four stu dies reported live birth an d only five described adequate methods for allocation concealment
IOK973 van Wely 2011 Recombinant vs urinary gonadotrophin for ovarian stimulation in ART cycles	42 RCTs	9606 normogonadotrophic women undergoing fresh and/or frozen thawed IVF or ICSI cycles	Recombinant FSH	Urinary FSH	OHSS[a] Live birth[a] Clinical pregnancy Miscarriage Multiple pregnancy Adverse effects	No difference reported in moderate/severe OHSS
WPM1780 Martins 2013 FSH replaced by low-dose hCG in the late follicular phase vs continued FSH for ART	5 RCTs	351 women undergoing COH for ART	Low-dose hCG instead of FSH in late follicular phase	Continued FSH in late follicular phase	OHSS[a] Live birth[a] Clinical pregnancy Miscarriage	Small studies and low event rate Total OHSS incidence reported
DHH752 Smulders 2010 Oral contraceptive pill, progestogen or oestrogen pretreatment for ovarian stimulation protocols for women undergoing ART	23 RCTs	2596 women of any age with subfertility regardless of cause, undergoing ART	Pretreatment with combined oral contraceptive pills Pretreatment with progestogens	No pretreatment Placebo Progestogens Oestrogens	Live birth[a] OHSS Clinical pregnancy Miscarriage Multiple pregnancy Adverse effects	Only 3/23 studies reported on OHSS 2 of these 3 studies did not define how they diagnosed the condition
IOK972 Kwan 2014 Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI)	6 RCTs	781 women undergoing COH in an IVF/ICSI cycle	Transvaginal ultrasonography + Oestradiol measurement	Transvaginal ultrasonography	Live birth[a] OHSS Clinical pregnancy Miscarriage Multiple pregnancy Adverse effects	Only total OHSS reported, including mild OHSS
CMB1261 Boomsma 2012 Peri-implanta-	14 RCTs	1879 subfertile patients undergoing IVF/	Glucocorticoids in the peri-implantation phase	No glucocorticoids in the peri-implantation	Live birth[a] Multiple	Only 2 studies, pooled

Table 1. Review characteristics (*Continued*)

tion glucocorticoid administration for ART cycles		ICSI, regardless of cause of infertility		phase	pregnancy[a] OHSS Clinical pregnancy Miscarriage Adverse effects	total OHSS
VJP951 Siristatidis 2016 Aspirin for IVF	13 RCTs	2653 women undergoing IVF/ICSI and their partners	Aspirin	No treatment Placebo	Live birth[a] OHSS Clinical pregnancy Miscarriage Multiple pregnancy Adverse effects	Only 1 of 13 studies reported on OHSS and without exact numbers or explanation for numerators/denominators
CS1400 Siristatidis 2009 In vitro maturation in subfertile women with PCOS undergoing assisted reproduction	None	0 women with PCOS and subfertility	In vitro maturation + IVF/ICSI in women with PCOS	Conventional IVF/ICSI in women with PCOS	Live birth[a] OHSS Effectiveness Clinical pregnancy Miscarriage Adverse effects	Empty review
IRS911 Cheong 2013 Acupuncture and ART	20 RCTs	4544 women undergoing ART, any type of acupuncture at any time point before, after or during ART, intended to improve ART outcome	Acupuncture of men, women or both during COH Acupuncture + ART Acupuncture alone	No treatment Placebo Sham acupuncture Acupuncture + ART	Live birth[a] OHSS Clinical pregnancy Miscarriage Multiple pregnancy Adverse effects	No trials reported on OHSS
MHM931 Mochtar 2007 Recombinant luteinising hormone (rLH) for COH in assisted reproductive cycles	14 RCTs	2612 subfertile ovulatory women undergoing IVF or ICSI High risk: NA	Combination of rLH and rFSH for COH in IVF/ICSI followed by ET in GnRHa and GnRH antagonist protocols	rFSH alone for COH in IVF/ICSI followed by ET in GnRHa and GnRH antagonist protocols	OHSS[a] Live birth[a] Clinical pregnancy Miscarriage	Only 4/14 trials reported on OHSS Pooled OHSS No GRADE assessment in old version
KH291 Duffy 2010 Growth hormone for IVF	10 RCTs	440 women part of a subfertile couple undergoing IVF	Adjuvant growth hormone during conventional	Conventional IVF	Live birth[a] OHSS Clinical	Only 4 of 10 RCTs reported on adverse events

Table 1. Review characteristics (*Continued*)

			IVF		pregnancy Adverse effects	(which could include OHSS) 1 study actually mentioned OHSS (however, no cases); pooled OHSS
SD265 Siristatidis 2015 GnRHa protocols for pituitary suppression in assisted reproduction	37 RCTs	3872 women/couples with all types of infertility undergoing ART and using GnRHa for pituitary downregulation	Long protocol Long luteal protocol Short protocol Dose continued Dose continued after hCG administration Pretreatment 2 weeks	Short protocol Ultrashort protocol Long follicular phase protocol Ultrashort protocol Dose stopped Dose reduced Dose discontinued after hCG administration Pretreatment 3 weeks	Live birth[a] OHSS Clinical pregnancy Adverse effects	Only 2 of 37 included RCTs reported on OHSS for 2 of 9 compared regimens
JC1630 Showell 2013 Antioxidants for female subfertility	28 RCTs	3548 subfertile women referred to fertility clinic who might or might not undergo ART (IVF, ICSI or IUI)	Adjuvant antioxidants in females	No treatment Placebo Another antioxidant	Live birth[a] Clinical pregnancy Miscarriage Multiple pregnancy Adverse effects (incl OHSS)	Only 3 studies reported: 1 no data and 2 no cases

[a] Primary review outcome.
ART: artifical reproductive technology.
COH: controlled ovarian hyperstimulation.
ET: embryo transfer.
FSH: follicle-stimulating hormone.
GnRHa: gonadotrophin-releasing hormone agonist.
hCG: human chorionic gonadotrophin.
HES: hydroxyethyl starch.
hFSH: human follicle-stimulating hormone.
hMG: human menopausal gonadotrophin.
ICSI: intracytoplasmic sperm injection.
IUI: intrauterine insemination.
IVF: in vitro fertilisation.
LH: luteinising hormone.
NA: not applicable.
OHSS: ovarian hyperstimulation syndrome.
PCOS: polycystic ovary syndrome.
RCT: randomised controlled trial.

rFSH: recombinant follicle-stimulating hormone.
rLH: recombinant luteinising hormone.

Table 2. Last search date assessment

Review no.	First review author	Review title	Date last assessed up to date	< 3 years since last assessed up to date or deemed stable
ADA561	D'Angelo 2007	Embryo freezing for preventing OHSS	26/11/2010	**Stable**
ADA 563	D'Angelo 2011	Coasting (withholding of gonadotrophins) for preventing OHSS	19/07/2010	**X**
TH1338	Tang 2016	Dopamine agonists for preventing OHSS	15/08/2016	✓
PMA481	Youssef 2016b	Volume expanders for prevention of OHSS	21/09/2016	✓
HA413	Youssef 2016	Recombinant vs urinary hCG for final oocyte maturation triggering in IVF and ICSI cycles	23/04/2015	✓
MM1690	Youssef 2014	GnRHa vs hCG for oocyte triggering in antagonist-assisted reproductive technology	08/09/2014	**X**
LDT1201	Tso 2014	Metformin treatment before and during IVF or ICSI in women with PCOS	15/10/2014	✓
AWP1710	Pouwer 2015	Long-acting FSH vs daily FSH for women undergoing assisted reproduction	8/06/2015	✓
AM1335	Gibreel 2012	Clomiphene citrate in combination with gonadotrophins for controlled ovarian stimulation in women undergoing IVF	23/03/2012	**X**
TA1860	Allersma 2013	Natural cycle IVF for subfertile couples	5/03/2013	✓
MV263	van der Linden 2015	Luteal phase support for ART cycles	25/11/2014	✓

Table 2. Last search date assessment (*Continued*)

HA412	Al-Inany 2016	Gonadotrophin-releasing hormone antagonists for ART	28/04/2016	✓
AMY731	Yossry 2006	IVF vs tubal re-anastomosis (sterilisation reversal) for subfertility after tubal sterilisation	15/05/2009	**Empty, stable**
ZP672	Pandian 2015	IVF for unexplained subfertility	4/05/2015	✓
LA541	Albuquerque 2013	Depot vs daily administration of GnRHa protocols for pituitary desensitisation in assisted reproduction cycles	3/07/2012	✓
IOK973	van Wely 2011	Recombinant vs urinary gonadotrophin for ovarian stimulation in ART cycles	20/10/2010	**X**
WPM1780	Martins 2013	FSH replaced by low-dose hCG in late follicular phase vs continued FSH for ART	5/02/2013	✓
DHH752	Smulders 2010	Oral contraceptive pill, progestogen or oestrogen pretreatment for ovarian stimulation protocols for women undergoing ART	16/11/2008	**X**
IOK972	Kwan 2014	Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI)	30/05/2014	✓
CMB1261	Boomsma 2012	Peri-implantation glucocorticoid administration for ART cycles	20/09/2011	**X**
VJP951	Siristatidis 2016	Aspirin for IVF	9/05/2016	✓
CS1400	Siristatidis 2009	In vitro maturation in subfertile women with PCOS undergoing assisted reproduction	17/02/2011	**Empty**
IRS911	Cheong 2013	Acupuncture and ART	22/07/2013	✓

Table 2. Last search date assessment (*Continued*)

MHM931	Mochtar 2007	Recombinant luteinising hormone (rLH) for COH in assisted reproductive cycles	25/01/2007	**X**
KH291	Duffy 2010	Growth hormone for IVF	20/07/2009	**X**
SD265	Siristatidis 2015	GnRHa protocols for pituitary suppression in assisted reproduction	23/04/2015	✓
JC1630	Showell 2013	Antioxidants for female subfertility	15/04/2014	✓

ART: artifical reproductive technology.
COH: controlled ovarian hyperstimulation.
FSH: follicle-stimulating hormone.
GnRHa: gonadotrophin-releasing hormone agonist.
hCG: human chorionic gonadotrophin.
ICSI: intracytoplasmic sperm injection.
IUI: intrauterine insemination.
IVF: in vitro fertilisation.
OHSS: ovarian hyperstimulation syndrome.
PCOS: polycystic ovary syndrome.
rLH: recombinant luteinising hormone.

✓ under 3 years since last assessed as up to date
X over 3 years since last assessed as up to date

Table 3. AMSTAR assessment per review

Review no.	First review author + year	Review title	AMSTAR criteria									
			Pre-specified question and inclusion criteria	Duplicate study selection and data extraction	Comprehensive literature search	Grey literature included	Lists included and excluded studies	Describes characteristics of included studies	Study quality assessed	Studies combined using appropriate methods	Likelihood of publication bias considered/ tested	Potential for conflict of interest addressed
ADA561	D'Angelo 2007	Embryo freezing for pre-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3. AMSTAR assessment per review (*Continued*)

		venting ovarian hyper-stimu-lation syn-drome										
ADA 563	D'Angelo 2011	Coast-ing (with-holding go-nadotropl for pre-venting ovarian hyper-stimu-lation syn-drome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TH1338	Tang 2016	Dopamin agonists for pre-venting ovarian hyper-stimu-lation syn-drome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PMA481	Youssef 2016b	Vol-ume ex-panders for the pre-vention of ovar-ian hy-per-stimu-lation syn-drome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3. AMSTAR assessment per review (*Continued*)

HA413	Youssef 2016	Recombinant versus urinary human chorionic gonadotropl for final oocyte maturation triggering in IVF and ICSI cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MM169(	Youssef 2014	Gonadotropi releasing hormone agonist versus hCG for oocyte triggering in antagonist-assisted reproductive technology	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
LDT120	Tso 2014	Metformin treatment before and during IVF or ICSI in	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3. AMSTAR assessment per review (*Continued*)

		women with poly-cystic ovary syn-drome										
AWP171(	Pouwer 2015	Long-acting FSH versus daily FSH for women under-going assisted repro-duction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AM1335	Gibreel 2012	Clomiphe citrate in combi-nation with go-nadotropl for con-trolled ovarian stimu-lation in women under-going in vitro fertili-sation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TA1860	Allersma 2013	Natu-ral cycle IVF for subfer-tile cou-ples	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3. AMSTAR assessment per review (*Continued*)

MV263	van der Linden 2015	Luteal phase support for ART cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HA412	Al-Inany 2016	Gonadotropl releasing hormone antagonists for assisted reproductive technology	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AMY731	Yossry 2006	In vitro fertilisation versus tubal re-anastomosis (sterilisation reversal) for subfertility after tubal sterilisation	✓	✓	✓	✓	✓	**NA**	**NA**	**NA**	**NA**	✓
ZP672	Pandian 2015	In vitro fertilisation for unexplained subfertility	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3. AMSTAR assessment per review (*Continued*)

LA541	Albuquerque 2013	Depot versus daily administration of gonadotropl releasing hormone agonist protocols for pituitary desensitisation in assisted reproduction cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IOK973	van Wely 2011	Recombinant versus urinary gonadotropl for ovarian stimulation in assisted reproductive technology cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
WPM17	Martins 2013	FSH replaced by low-dose hCG in the late fol-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3. AMSTAR assessment per review (*Continued*)

		licular phase versus continued FSH for assisted reproductive techniques										
DHH752	Smulders 2010	Oral contraceptive pill, progestogen or oestrogen pretreatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IOK972	Kwan 2014	Monitoring of stimulated cycles in assisted reproduction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3. AMSTAR assessment per review (*Continued*)

		(IVF and ICSI)										
CMB126	Boomsma 2012	Peri-implantation glucocorticoid administration for assisted reproductive technology cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
VJP951	Siristatidis 2016	Aspirin for in vitro fertilisation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CS1400	Siristatidis 2009	In vitro maturation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction	✓	✓	✓	✓	✓	**NA**	**NA**	**NA**	**NA**	✓
IRS911	Cheong 2013	Acupuncture and assisted	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3. AMSTAR assessment per review (*Continued*)

		reproductive technology										
MHM93	Mochtar 2007	Recombinant luteinising hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles	✓	✓	✓	✓	✓	✓	✓	✓	X	✓
KH291	Duffy 2010	Growth hormone for in vitro fertilisation	✓	✓	✓	✓	✓	✓	✓	✓	X	✓
SD265	Siristatidis 2015	Gonadotropl releasing hormone agonist protocols for pituitary suppression in assisted reproduction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3. AMSTAR assessment per review (*Continued*)

JC1630	Showell 2013	Antioxidants for female subfertility	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Search date: 24/07/2016.
ART: artifical reproductive technology.
FSH: follicle-stimulating hormone.
hCG: human chorionic gonadotrophin.
ICSI: intracytoplasmic sperm injection.
IUI: intrauterine insemination.
IVF: in vitro fertilisation.
NA: not applicable.
rLH: recombinant luteinising hormone.

Table 4. Summary of findings for OHSS: per review and/or per intervention

	Review title and comparison intervention/control	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
D'Angelo 2007	Embryo freezing for preventing ovarian hyperstimulation syndrome *(Embryo freezing vs fresh transfer)*	Overall OHSS: 60 per 1000	Overall OHSS: 125 per 1000 (62 to 240)	OR 1.12 (0.01 to 2.29)	125 (1 study)	Low	Imprecision, number of events < 300 Evidence based on a single open-label study with insufficient methodological details provided
D'Angelo 2007	Embryo freezing for preventing ovarian hyperstimulation syndrome *(Em-*	Moderate or severe OHSS: 77 per 1000	Moderate or severe OHSS: 308 per 1000 (41 to 824)	OR 5.33 (0.51 to 56.24)	26 (1 study)	Very low	Imprecision, number of events < 300 Evidence based on a single open-label

Table 4. Summary of findings for OHSS: per review and/or per intervention (*Continued*)

	bryo freezing vs intravenous albumin)						trial
D'Angelo 2011	Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome	Moderate or severe OHSS: 265 per 1000	Moderate or severe OHSS: 58 per 1000 (11 to 241)	OR 0.17 (0.03 to 0.88)	68 (1 study)	Very low	Imprecision, number of events < 300 Evidence based on a single conference abstract Insufficient methodological details provided
Tang 2016	Dopamine agonists for preventing ovarian hyperstimulation syndrome	Moderate or severe OHSS: 286 per 1000	Moderate or severe OHSS: 97 per 1000 (71 to 135)	OR 0.27 (0.19 to 0.39)	2091 (16 studies))	Moderate	Imprecision, number of events < 300 Lack of details for allocation concealment and blinding, selective reporting
Youssef 2016b	Volume expanders for the prevention of ovarian hyperstimulation syndrome *(human albumin vs placebo/ no treatment)*	Moderate or severe OHSS: 122 per 1000	Moderate or severe OHSS: 85 per 1000 (61 to 177)	OR 0,67 (0.47 to 0.95)	1452 (7 studies)	Very low	Imprecision, number of events < 300 Lack of details on allocation concealment and selective reporting
Youssef 2016b	Volume expanders for the prevention of ovarian hyperstimulation syndrome *(HES vs placebo)*	Moderate or severe OHSS: 164 per 1000	Moderate or severe OHSS: 50 per 1000 (23 to 104)	OR 0.27 (0.12 to 0.59	272 (2 studies)	Very low	Imprecision, number of events < 300 Lack of details on allocation concealment and selective reporting

Table 4. Summary of findings for OHSS: per review and/or per intervention (*Continued*)

Youssef 2016b	Volume expanders for the prevention of ovarian hyperstimulation syndrome *(mannitol vs placebo)*	Moderate or severe OHSS: 517 per 1000	Moderate or severe OHSS: 289 per 1000 (191 to 407)	OR 0.38 (0.22 to 0.64)	226 (1 study)	Low	Imprecision, number of events < 300 Lack of details on allocation concealment and selective reporting
Youssef 2016	Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles *(r-hCG vs u-hCG)*	Overall OHSS: 27 per 1000	Overall OHSS:40 per 1000 (15 to 102)	OR 0.39 (0.25 to 0.61)	374 (3 studies)	Moderate	Imprecision, number of events < 300 One of the trials lacked methodological details on randomisation, allocation concealment and blinding
Youssef 2016	Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles *(r-LH vs u-hCG)*	Overall OHSS: 10 per 1000	Overall OHSS: 17 per 1000 (11 to 84)	OR 1.76 (0.37 to 8.45)	417 (3 studies)	Low	Imprecision, number of events < 300 One of the trials lacked adequate methodological details
Youssef 2014	Gonadotropin-releasing hormone agonist versus hCG for oocyte triggering in antagonist-assisted reproductive technology	Overall OHSS: 5 per 1000	Overall OHSS: 1 per 1000 (0 to 2)	OR 0.15 (0.05 to 0.47)	989 (9 studies)	Moderate	Imprecision, number of events < 300 All studies at high risk of bias in 1 or more domains None clearly reported blinded

Table 4. Summary of findings for OHSS: per review and/or per intervention (*Continued*)

							outcome assessment
Tso 2014	Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome	Overall OHSS: 270 per 1000	Overall OHSS: 97 per 1000 (62 to 153)	OR 0.29 (0.18 to 0.49)	798 (8 studies)	Moderate	Imprecision, number of events < 300
Pouwer 2015	Long-acting FSH versus daily FSH for women undergoing assisted reproduction (*low dose*)	Overall OHSS: 47 per 1000	Overall OHSS: 57 per 1000 (26 to 125)	RR 1.22 (0.56 to 2.66)	645 (3 studies)	Moderate	Imprecision, number of events < 300
Pouwer 2015	Long-acting FSH versus daily FSH for women undergoing assisted reproduction (*medium dose*)	Overall OHSS: 63 per 1000	Overall OHSS: 60 per 1000 (45 to 85)	RR 0.96 (0.68 to 1.35)	3075 (5 studies)	Low	Imprecision, number of events < 300 Confidence intervals compatible with clinically meaningful benefit in either arm or with no effect, plus high risk of attrition bias in 2 studies
Pouwer 2015	Long-acting FSH versus daily FSH for women undergoing assisted reproduction (*high dose*)	Overall OHSS: 0 per 1000	Overall OHSS: 0 per 1000 (0 to 0)	RR 1.73 (0.09 to 32.75)	33 (1 study)	Very low	Imprecision, number of events < 300 High risk of attrition bias

Table 4. Summary of findings for OHSS: per review and/or per intervention (*Continued*)

Gibreel 2012	Clomiphene citrate in combination with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilisation *(clomiphene + gonadotropins vs gonadotropins)*	Overall OHSS: 50 per 1000	Overall OHSS:12 per 1000 (5 to 27)	OR 0.23 (0.1 to 0.52)	1559 (5 studies)	Low	Imprecision, number of events < 300 Very wide 95% confidence interval crossing the threshold points of appreciable benefit or harm, which is 25%
Allersma 2013	Natural cycle IVF for subfertile couples *(natural cycle vs conventional IVF)*	Overall OHSS: 67 per 1000	Overall OHSS: 13 per 1000 (1 to 393)	OR 0.10 (0.01 to 4.06)	60 (1 study)	Very low	Imprecision, number of events < 300 Only 1 study reporting on OHSS Allocation concealment method not reported
van der Linden 2015	Luteal phase support for ART cycles *(hCG versus placebo/ no treatment)*	Overall OHSS: 41 per 1000	Overall OHSS: 155 per 100 (76 to 292)	OR 4.28 (1.191 to 9.6)	387 (1 study)	Low	Imprecision, number of events < 300 Poor reporting of study methods
van der Linden 2015	Luteal phase support for ART cycles *(progesterone vs hCG regimens)*	Overall OHSS: 126 per 1000	Overall OHSS: 72 per 1000 (31 to 162)	OR 0.54 (0.22 to 1.34)	615 (4 studies)	Low	Imprecision, number of events < 300 Poor reporting of study methods
van der Linden 2015	Luteal phase support for ART cycles *(progesterone +*	Overall OHSS: 50 per 1000	Overall OHSS: 50 per 1000 (17 to 137)	OR 1.00 (0.33 to 3.01)	300 (1 study)	Very low	Imprecision, number of events <

Table 4. Summary of findings for OHSS: per review and/or per intervention (*Continued*)

	GnRH agonist)						300 Poor reporting of study methods
van der Linden 2015	Luteal phase support for ART cycles *(progesterone vs progesterone + oestrogens)*	Overall OHSS: 39 per 1000	Overall OHSS: 22 per 1000 (8 to 62)	OR 0.56 (0.2 to 1.63)	461 (2 studies)	Low	Imprecision, number of events < 300 Poor reporting of study methods
Al-Inany 2016	Gonadotrophin-releasing hormone antagonists for assisted reproductive technology *(GnRH antagonist vs GnRH agonist)*	Overall OHSS: 114 per 1000	Overall OHSS: 73 per 1000 (62 to 85)	OR 0.61 (0.51 to 0.72)	7944 (36 studies)	Moderate	Methodological limitations including poor allocation concealment and lack of blinding
Yossry 2006	In vitro fertilisation versus tubal reanastomosis (sterilisation reversal) for subfertility after tubal sterilisation *(IVF vs tubal reanastomosis)*	NA	NA	NA	NA	NA	Empty review
Pandian 2015	In vitro fertilisation for unexplained subfertility *(IVF vs IUI + gonadotropins/ clomiphene citrate)*	Overall OHSS: 58 per 1000	Overall OHSS: 66 per 1000 (26 to 158)	OR 1.15 (0.43 to 3.06)	324 (2 studies)	Low	Imprecision, number of events < 300 Only 2 studies on OHSS reported
Albuquerque 2013	Depot versus daily administration of gonadotrophin	Overall OHSS: 3 per 100	Overall OHSS: 2 per 100	OR 0.84 (0.29 to 2.42)	570 (5 studies)	Low	Most studies were classified as at unclear

Table 4. Summary of findings for OHSS: per review and/or per intervention (*Continued*)

	releasing hormone agonist protocols for pituitary desensitization in assisted reproduction cycles *(depot vs daily gonadotropins)*		(1 to 6)				risk of bias for all domains Imprecision, number of events < 300 Studies were insufficient to assess publication bias
van Wely 2011	Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles *(rFSH vs HMG/HMG-HP)*	Overall OHSS: 17 per 1000	Overall OHSS: 17 per 1000 (10 to 28)	OR 1.00 (0.58 to 1.71)	3197 (11 studies)	High	Imprecision, number of events < 300
van Wely 2011	Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles *(rFSH vs FSH-P)*	Overall OHSS: 28 per 1000	Overall OHSS:49 per 1000 (25 to 95)	OR 1.79 (0.89 to 3.62)	1490 (6 studies)	High[a]	Imprecision, number of events < 300
van Wely 2011	Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles *(rFSH vs FSH-HP)*	Overall OHSS: 28 per 1000	Overall OHSS: 31 per 1000 (20 to 48)	OR 1.11 (0.70 vs 1.75)	3053 (14 studies)	High[a]	Two additional trials excluded in sensitivity analyses because it was unclear if data were reported according to ITT analysis (those were included for "Overall OHSS")

Table 4. Summary of findings for OHSS: per review and/or per intervention (*Continued*)

van Wely 2011	Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles *(rec-hCG vs u-hCG)*	Overall OHSS: 19 per 1000	Overall OHSS: 22 per 1000 (16 to 30)	OR 1.18 (0.86 vs 1.61)	7740 (32 studies)	High[a]	Imprecision number of events < 300
Martins 2013	FSH replaced by low-dose hCG in the late follicular phase versus continued FSH for assisted reproductive techniques *(low-dose hCG vs FSH in late follicular phase)*	Overall OHSS: 3 per 100	Overall OHSS: 1 per 100 (0 to 4)	OR 0.30 (0.06 to 1.59)	351 (5 studies)	Very low	Imprecision, number of events < 300 Inconsistency, high risk of bias
Smulders 2010	Oral contraceptive pill, progestogen or oestrogen pre- treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques *(OAC plus antagonist vs antagonist)*	Overall OHSS: 17 per 1000	Overall OHSS: 25 per 1000 (5 to 133)	OR 1.5 (0.26 to 8.8)	234 (1 study)	Very low	Single study reporting on OHSS Imprecision, number of events < 300 Wide confidence intervals that cross line of no effect High risk of attrition bias
Smulders 2010	Oral contraceptive pill, progestogen or oestrogen pre- treat-	Overall OHSS: 55 per 1000	Overall OHSS: 35 per 1000 (12 to 100)	OR 0.63 (0.21 to 1.92)	290 (2 studies)	Very low	Imprecision, number of events < 300

Table 4. Summary of findings for OHSS: per review and/or per intervention (*Continued*)

	ment for ovarian stimulation protocols for women undergoing assisted reproductive techniques *(OAC plus antagonist vs agonist)*						One study at high risk of attrition bias
Kwan 2014	Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI) *(transvaginal ultrasound + estradiol vs transvaginal ultrasound)*	Overall OHSS: 36 per 1000	Overall OHSS: 36 per 1000 (18 to 75)	OR 1.03 (0.48 to 2.20)	781 (6 studies)	Low	Imprecision, number of events < 300 with wide confidence intervals Methods of randomisation inadequately described in 3 of 6 trials, allocation concealment inadequately described in all 6 trials and blinding inadequately described in 5 of 6 trials No definition of OHSS provided by authors of these 6 studies
Boomsma 2012	Peri-implantation glucocorticoid administration for assisted reproductive technology cycles *(adjuvant glucocorticoids vs no glucocorti-*	Overall OHSS: 194 per 1000	Overall OHSS: 159 per 1000 (64 to 392)	OR 0.82 (0.33 to 2.02)	151 (2 studies)	Low	Imprecision, number of events < 300

Table 4. Summary of findings for OHSS: per review and/or per intervention (*Continued*)

	coids)						
Siristatidis 2016	Aspirin for in vitro fertilisation *(aspirin vs no treatment/ placebo)*	NA	NA	NA	NA	NA	Only 1 study reported on OHSS; no exact numbers or explanation of numerators/denominators given
Siristatidis 2009	In vitro maturation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction *(IVM vs conventional IVF)*	NA	NA	NA	NA	NA	Empty review
Cheong 2013	Acupuncture and assisted reproductive technology *(acupuncture vs no acupuncture/sham acupuncture)*	NA	NA	NA	NA	NA	No studies reported on OHSS
Mochtar 2007	Recombinant luteinizing hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles *(combined rLH + FSH vs FSH)*	Overall OHSS: 20 per 1000	Overall OHSS: 27 per 1000 (12 to 59)	OR 1.34 (0.58 to 3.09)	986 (7 studies)	Low	Imprecision, number of events < 300 Some methodological details unclear
Duffy 2010	Growth hormone for in vitro fertiliza-	NA	NA	NA	NA	NA	Only 1 study reported on OHSS; how-

Table 4. Summary of findings for OHSS: per review and/or per intervention (*Continued*)

	tion *(growth hormone vs no treatment/ placebo)*						ever, no cases of OHSS were reported
Siristatidis 2015	Gonadotropin-releasing hormone agonist protocols for pituitary suppression in assisted reproduction *(different protocols vs other protocol)*	Overall OHSS: 20 per 1000	Overall OHSS: 27 per 1000 (12 to 59)	OR 1.34 (0.58 to 3.09)	986 (7 studies)	Low	Imprecision, number of events < 300 Some methodological details unclear
Showell 2013	Antioxidants for female subfertility *(antioxidants vs no treatment/ placebo/other antioxidant)*	NA	NA	NA	NA	NA	Although 3 studies reported on OHSS, no numbers were given, so effect size could not be calculated

[a] Review authors GRADED these outcomes as 'high quality'; however, the total event rate < 300 would justify downgrading for this to moderate-quality evidence.

ART: artifical reproductive technology.
FSH: follicle-stimulating hormone.
FSH-HP: highly purified FSH.
hCG: human chorionic gonadotrophin.
HES: hydroxyethyl starch.
ICSI: intracytoplasmic sperm injection.
IUI: intrauterine insemination.
IVF: in vitro fertilisation.
IVM: in vitro maturation.
NA: not applicable.
OAC: oral anticoagulant.
OHSS: ovarian hyperstimulation syndrome.
OR: odds ratio.
rFSH: recombinant follicle-stimulating hormone.
r-hCG: recombinant human chorionic gonadotrophin.
rLH: recombinant luteinising hormone.
Total: any grade of OHSS.

u-hCG: urinary human chorionic gonadotrophin.

APPENDICES

Appendix 1. Clinical classification of ovarian hyperstimulation syndrome (OHSS) (from Aboulghar and Mansour 2003)

Study	Mild	Moderate	Severe	
Rabau et al (1967)	Grade 1: oestrogen > 150 µg and pregnanediol > 10 mg/24 h Grade 2: + enlarged ovaries and possibly palpable cysts Grades 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)	Grade 1: oestrogen > 150 µg/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)	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, increased blood viscosity, coagulation abnormality and diminished renal perfusion
Navot et al (1992)			Severe OHSS: variable enlarged ovary; massive ascites ± hydrothorax; Hct > 45%; WBC > 15 000; oliguria; creatinine 1.0-1.5; creatinine clearance ≥ 50 mL/min; liver	Critical OHSS: variable enlarged ovary; tense ascites ± hydrothorax; Hct > 55%; WBC > 25 000; oliguria; creatinine > 1.6; creatinine clearance < 50 mL/min; renal

(*Continued*)

			dysfunction; anasarca	failure; thromboembolic phenomena; ARDS
Rizk and Aboulghar (1999)		Discomfort, pain, nausea, distension, ultrasonic evidence of ascites and enlarged ovaries, normal haematological and biological profiles	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 hematocrit, elevated serum creatinine and liver dysfunction	Grade C: complications such as respiratory distress syndrome, renal shut-down or venous thrombosis

Footnotes

ARDS: acute respiratory distress syndrome.
Hct: hematocrit.
OHSS: ovarian hyperstimulation syndrome.
US: ultrasonography.
WBC: white blood cell count.

Appendix 2. AMSTAR ratings

1.	Was an 'a priori' design provided? (Yes: the research question and inclusion criteria were established before conducting the review.)
2.	Was there duplicate study selection and data extraction? (Yes: at least two people working independently extracted the data and the method was reported for reaching consensus if disagreements arose.)
3.	Was a comprehensive literature search performed? (Yes: at least two electronic sources were searched; details of the databases, years searched and search strategy were provided; the search was supplemented by searching reference lists of included studies and specialised registers, and by contacting experts.)
4.	Was status of publication used as an exclusion criterion? (Yes: the authors stated that they excluded studies from the review based on publication status. No: authors searched for reports irrespective of publication type. They did not exclude reports based on publication from the systematic review.)

(*Continued*)

5.	Was a list of studies (included and excluded provided)? (Yes: a list was provided.)
6.	Were the characteristics of the included studies provided? (Yes: data on participants, interventions and outcomes were provided, and the range of relevant characteristics reported.)
7.	Was the scientific quality of the included studies assessed and reported? (Yes: predetermined methods of assessing quality were reported.)
8.	Was the scientific quality of the included studies used appropriately in formulating conclusions? (Yes: the quality, and limitations, of included studies were used in the analysis, conclusions and recommendations of the review.)
9.	Were the methods used to combine the findings of studies appropriate? (Yes: if results were pooled statistically, heterogeneity was assessed and used to inform the decision of the statistical model to be used. If heterogeneity was present, the appropriateness of combining studies was considered by review authors.)
10.	Was the likelihood of publication bias assessed? (Yes: publication bias was explicitly considered and assessed.)
11.	Was the conflict of interest stated? (Yes: sources of support were clearly acknowledged.)

Footnotes

Appendix 3. ART protocols and titles for potential future inclusion

(date of search 24 July 2016)

- No titles were registered that were expected to potentially list OHSS as an outcome.
- Four registered protocols, upon title screening, were judged as potentially reporting on OHSS as an outcome. When these reviews are published as a full review, they can be assessed for the future update of this overview.

Review registration number	Lead review author	Review title
IDG1973	Gallos	Controlled ovarian stimulation protocols for assisted reproduction: a network meta-analysis
MGS1974	Showell	Inositol for subfertile women with polycystic ovary syndrome
SHJ 881	Jaafar	Long-term GnRH agonist therapy before in vitro fertilization (IVF) for improving fertility outcomes in women with endometriosis
LC1971	Craciunas	Oxytocin antagonists for assisted reproduction

CONTRIBUTIONS OF AUTHORS

SM drafted first versions of the protocol and overview manuscripts. All three overview authors (SM, JB, CF) contributed to preparation of the protocol, data extraction and analysis of reviews for this overview. JB and CF contributed to the definitive version of the manuscript.

DECLARATIONS OF INTEREST

All three overview authors (SM, JB,CF) were co-review authors on several of the included reviews. CF is a director/shareholder of a small day stay surgical unit and gynaecology clinic and undertakes private practice within these facilities. She has received travel/ accommodation/meeting expenses from ESHRE or ASRM for attendance at scientific meetings. She does not receive any industry or commercial payments for research or travel. SM and JB report no conflicts of interest regarding industry.

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Internal sources

- Department of Obstetrics and Gynaecology, University of Auckland, New Zealand.

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External sources

- None, Other.

INDEX TERMS

Medical Subject Headings (MeSH)

Ergolines [therapeutic use]; Gonadotropin-Releasing Hormone [agonists; therapeutic use]; Metformin [therapeutic use]; Ovarian Hyperstimulation Syndrome [etiology; *prevention & control; therapy]; Progesterone [therapeutic use]; Reproductive Techniques, Assisted [*adverse effects]; Review Literature as Topic

MeSH check words

Female; Humans; Pregnancy