Cochrane Library

Cochrane Database of Systematic Reviews

Volume expanders for the prevention of ovarian hyperstimulation syndrome (Review)

Youssef MA, Mourad S

Youssef MA, Mourad S.
Volume expanders for the prevention of ovarian hyperstimulation syndrome.
Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD001302.
DOI: 10.1002/14651858.CD001302.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Volume expanders for the prevention of ovarian hyperstimulation syndrome

MA Youssef[1], Selma Mourad[2]

[1]Department of Obstetrics & Gynaecology, Faculty of Medicine, Cairo University, Cairo, Egypt. [2]Radboud University Medical Centre, Nijmegen, Netherlands

Contact: MA Youssef, Department of Obstetrics & Gynaecology, Faculty of Medicine, Cairo University, Cairo, Egypt. mohamedyoussef1973@gmail.com, m.a.youssef@amc.uva.nl.

Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 11, 2016.

Citation: Youssef MA, Mourad S. Volume expanders for the prevention of ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2016, Issue 8. Art. No.: CD001302. DOI: 10.1002/14651858.CD001302.pub3.

ABSTRACT

Background

Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially fatal complication of ovarian stimulation which affects 1% to 14% of all in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycles. A number of clinical studies with conflicting results have reported on the use of plasma expanders such as albumin, hydroxyethyl starch (HES), mannitol, polygeline and dextran as a possible intervention for the prevention of OHSS. Women with very high estradiol levels, high numbers of follicles or oocytes retrieved, and women with polycystic ovary syndrome (PCOS), are at particularly high risk of developing OHSS. Plasma expanders are not commonly used nowadays in ovarian hyperstimulation. This is mainly because clinical evidence on their effectiveness remains sparse, because of the low incidence of moderate and severe ovarian hyperstimulation syndrome (OHSS) and the simultaneous introduction of mild stimulation approaches, gonadotropin-releasing hormone (GnRH) antagonist protocols and the freeze-all strategy for the prevention of OHSS.

Objectives

To review the effectiveness and safety of administration of volume expanders for the prevention of moderate and severe ovarian hyperstimulation syndrome (OHSS) in high-risk women undergoing IVF or ICSI treatment cycles.

Search methods

We searched databases including the Cochrane Gynaecology and Fertility Group Specialised Register of controlled trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and trial registers to September 2015; no date restrictions were used as new comparators were included in this search. The references of relevant publications were also searched. We attempted to contact authors to provide or clarify data that were unclear from trial or abstract reports.

Selection criteria

We included randomised controlled trials (RCTs) comparing volume expanders versus placebo or no treatment for the prevention of OHSS in high-risk women undergoing ovarian hyperstimulation as part of any assisted reproductive technique.

Data collection and analysis

Two review authors independently selected the studies, assessed risk of bias and extracted relevant data. The primary review outcome was moderate or severe OHSS. Other outcomes were live birth, pregnancy and adverse events. We combined data to calculate pooled Peto odds ratios (ORs) and 95% confidence intervals (CIs) for each intervention. Statistical heterogeneity was assessed using the I^2 statistic. We assessed the overall quality of the evidence for each comparison, using GRADE methods.

Main results

We included nine RCTs (1867 women) comparing human albumin (seven RCTs) or HES (two RCTs) or mannitol (one RCT) versus placebo or no treatment for prevention of OHSS. The evidence was very low to moderate quality for all comparisons. The main limitations were imprecision, poor reporting of study methods, and failure to blind outcome assessment.

There was evidence of a beneficial effect of intravenous albumin on OHSS, though heterogeneity was substantial (Peto OR 0.67 95% CI 0.47 to 0.95, seven studies, 1452 high risk women; I^2 = 69%, very low quality evidence) . This suggests that if the rate of moderate or severe OHSS with no treatment is 12%, it will be about 9% (6% to12%) with the use of intravenous albumin. However, there was evidence of a detrimental effect on pregnancy rates (Peto OR 0.72 95% CI 0.55 to 0.94, I^2 = 42%, seven studies 1069 high risk women, moderate quality evidence). This suggests that if the chance of pregnancy is 40% without treatment, it will be about 32% (27% to 38%) with the use of albumin.

There was evidence of a beneficial effect of HES on OHSS (Peto OR 0.27 95% CI 0.12 to 0.59, I^2 = 0%, two studies, 272 women, very low quality evidence). This suggests that if the rate of moderate or severe OHSS with no treatment is 16%, it will be about 5% (2% to 10%) with the use of HES. There was no evidence of an effect on pregnancy rates (Peto OR 1.20 95% CI 0.49 to 2.93, one study, 168 women, very low quality evidence).

There was evidence of a beneficial effect of mannitol on OHSS (Peto OR 0.38, 95% CI 0.22 to 0.64, one study, 226 women with PCOS, low quality evidence). This means that if the risk of moderate or severe OHSS with no treatment is 52%, it will be about 29% (19% to 41%) with mannitol. There was no evidence of an effect on pregnancy rates (Peto OR 0.85 95% CI 0.47 to 1.55; one study, 226 women, low quality evidence).

Live birth rates were not reported in any of the studies. Adverse events appeared to be uncommon, but were too poorly reported to reach any firm conclusions.

Authors' conclusions

Evidence suggests that the plasma expanders assessed in this review (human albumin, HES and mannitol) reduce rates of moderate and severe OHSS in women at high risk. Adverse events appear to be uncommon, but were too poorly reported to reach any firm conclusions, and there were no data on live birth. However, there was evidence that human albumin reduces pregnancy rates. While there was no evidence that HES, or mannitol had any influence on pregnancy rates, the evidence of effectiveness was based on very few trials which need to be confirmed in additional, larger randomised controlled trials (RCTs) before they should be considered for routine use in clinical practice.

PLAIN LANGUAGE SUMMARY

Intravenous plasma expanders for preventing ovarian hyperstimulation syndrome (OHSS)

Review question

Researchers in the Cochrane Collaboration reviewed the evidence on different types of volume expanders in women at high risk of OHSS undergoing ovarian hyperstimulation as part of any assisted reproductive technique (ART). Women with very high estradiol levels, high numbers of follicles or oocytes retrieved, and women with polycystic ovary syndrome (PCOS), are at particularly high risk of developing OHSS.

Background

OHSS is a serious complication of ovarian stimulation, which affects up to 14% of ART cycles. It is characterised by enlarged ovaries following excessive hormonal stimulation resulting in a shift of fluid from the blood vessels to the extracellular space. It can cause abdominal bloating, blood clots (thrombosis) and reduced perfusion of vital organs like the kidneys and liver. Several clinical studies have reported on the use of intravenous fluids such as albumin and hydroxyethyl starch (HES), as a possible way of preventing OHSS.

Study characteristics

We found nine randomised controlled trials (RCTs) which compared the use of volume expanders (albumin, HES and mannitol) for preventing moderate or severe OHSS. Control groups received no treatment or placebo. The studies included 1867 women at high risk of OHSS. The evidence is current to September 2015.

Key results

Evidence suggests that plasma expanders (human albumin, HES and mannitol) reduce rates of moderate and severe OHSS in women at high risk.

If the rate of OHSS without treatment is 12%, it will be about 9% (6% to 12%) with the use of intravenous albumin. If the rate of OHSS without treatment is 16%, it will be about 5% (2% to 10%) with the use of HES, and if the rate without treatment is 52%, it will be about 29% (19% to 41%) with mannitol.

Adverse events appear to be uncommon, but were too poorly reported to reach firm conclusions. No studies reported live birth, but there was evidence that human albumin reduces pregnancy rates. While there was no evidence that HES, or mannitol had any influence on pregnancy rates, the evidence of effectiveness was based on very few trials, and better evidence is needed before they should be considered for routine use in clinical practice.

Quality of the evidence

The evidence was very low to moderate quality for all comparisons. The main limitations were imprecision, poor reporting of study methods, and failure to blind outcome assessment.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Human albumin versus placebo or no treatment for the prevention of OHSS

Human albumin versus placebo or no treatment for the prevention of OHSS

Population: women at high risk of OHSS
Setting: ART clinics
Intervention: Human albumin
Comparison: placebo / no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo / no treatment	Risk with Human albumin			
Moderate or severe OHSS	122 per 1000	85 per 1000 (61 to 117)	OR 0.67 (0.47 to 0.95)	1452 (7 RCTs)	⊕⊝⊝⊝ VERY LOW [1 2 3]
Live birth	Not reported in the included studies				
Pregnancy rate assessed with: serum β-hCG or heartbeat on ultrasound	396 per 1000	321 per 1000 (265 to 381)	OR 0.72 (0.55 to 0.94)	1069 (7 RCTs)	⊕⊕⊕⊝ MODERATE [1]
Adverse effects	No reliable data as none of the studies specified adverse effects as an outcome				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the mean risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for serious risk of bias: associated with lack of blinding, inadequate reporting of allocation concealment, unclear risk of attrition bias
[2] Downgraded one level for serious imprecision: number of events < 300
[3] Downgraded one level for serious inconsistency: I^2= 69%

Summary of findings 2. HES versus placebo or no treatment for the prevention of OHSS

HES versus placebo or no treatment for the prevention of OHSS

Population: Women at high risk of OHSS
Setting: ART clinics
Intervention: HES
Comparison: placebo / no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo / no treatment	Risk with HES			
Moderate or severe OHSS	164 per 1.000	50 per 1000 (23 to 104)	OR 0.27 (0.12 to 0.59)	272 (2 RCTs)	⊕⊝⊝⊝ VERY LOW [1] [2]
Live birth	Not reported in the included studies				
Pregnancy rate assessed with: serum β-hCG or heartbeat on ultrasound	120 per 1.000	141 per 1000 (63 to 286)	OR 1.20 (0.49 to 2.93)	168 (1 RCT)	⊕⊝⊝⊝ VERY LOW [1] [2]
Adverse effects	No reliable data as none of the studies specified adverse effects as an outcome				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the mean risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded two levels for very serious risk of bias: associated with inadequate reporting of allocation concealment and blinding, and unclear risk of attrition bias
[2] Downgraded one level for serious imprecision: number of events <300

Summary of findings 3. Mannitol versus placebo / no treatment for the prevention of OHSS

Mannitol versus placebo or no treatment for the prevention of OHSS

Population: women at high risk of OHSS
Setting: ART clinics
Intervention: Mannitol
Comparison: placebo / no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo / no treatment	Risk with Mannitol			
Moderate or severe OHSS	517 per 1000	289 per 1000 (191 to 407)	OR 0.38 (0.22 to 0.64)	226 (1 RCT)	⊕⊕⊖⊖[1,2] LOW
Live birth	Not reported in the included studies				
Pregnancy rate assessed with: serum β-hCG or heartbeat on ultrasound	276 per 1000	245 per 1000 (152 to 371)	OR 0.85 (0.47 to 1.55)	226 (1 RCT)	⊕⊕⊖⊖[1,2] LOW
Adverse effects	No reliable data as none of the studies specified adverse effects as an outcome				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 Downgraded one level for risk of bias: inadequate reporting of allocation concealment,
2 Downgraded one level for serious imprecision: number of events < 300

BACKGROUND

Description of the condition

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic, serious and potentially fatal complication of ovarian stimulation which affects 1% to 14% of all in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycles (Garcia-Velasco 2003). OHSS may be associated with massive ovarian enlargement, extracellular exudate accumulation combined with profound intravascular volume depletion, ascites, hydrothorax, haemoconcentration, liver dysfunction and renal failure (Aboulghar 2003; Vloeberghs 2009). It can lead to cancellation of an IVF cycle and prolonged bed rest or hospitalisation, which may have significant emotional, social, and economic impacts (Delvigne 2002; Engmann 2008). OHSS can be classified into an early form that is related to the ovarian response and exogenous human chorionic gonadotrophin (hCG) administration, and is detected three to nine days after hCG administration. A late form of OHSS, diagnosed 10 to 17 days later, is due to endogenous hCG (Mathur 2000) and is categorised as mild, moderate, severe or life-threatening. The aetiology of OHSS is not completely clear at this moment; however the syndrome is strongly associated with serum hCG and certain vasoactive substances (Enskog 2001; Rizk 1997).

Description of the intervention

Many strategies have been tried to prevent OHSS and cycle cancellation such as coasting (withholding gonadotrophins before the ovulation trigger is given) (D'Angelo 2011), gonadotropin-releasing hormone (GnRH) agonist as an oocyte trigger in GnRH antagonist cycles (Kol 2008; Youssef 2014), natural cycle IVF (Edwards 2007), cabergoline (Tang 2012), embryo freezing (D'Angelo 2007), and in vitro oocyte maturation (Loutradis 2006). Unfortunately, none of the strategies currently employed completely prevent OHSS after hCG administration (Egbase 2000). Recently the role of vascular endothelial growth factor (VEGF), as mediator of hCG-dependent ovarian angiogenesis, has emerged (Cerrilo 2009). VEGF is expressed in human ovaries (Yan 1993) and levels significantly increase after hCG administration leading to increased vascular permeability (Foong 2006). It has been proposed that the administration of intravenous fluids such as human albumin, hydroxyethyl starch (HES), dextran or polygeline might result in a restoration of intravascular volume and inactivation of the vasoactive intermediates responsible for the pathogenesis of OHSS (Asch 1993; Chen 1997; Isik 1997; Kissler 2001; Shalev 1995).

How the intervention might work

Albumin has both osmotic and transport functions. It contributes about 75% of the plasma oncotic pressure and administration of 50 g human albumin solution will draw more than 800 mL of extracellular fluid into the circulation within 15 minutes (McClelland 1990). It has been suggested that the binding and transport properties of human albumin play a major role in the prevention of severe OHSS, as albumin may result in binding and inactivation of the vasoactive intermediates responsible for the pathogenesis of OHSS. The osmotic function is responsible for maintaining the intra-vascular volume in the event of capillary leakage, thus preventing the sequelae of hypovolaemia, ascites and haemoconcentration (Shalev 1995).

Hydroxyethyl starch (HES) is a plasma expander that has gained recent attention as an alternative to albumin in reducing the incidence of severe OHSS. Because HES is a non-biological substance, its use avoids any potential concern about viral transmission that may be present with albumin (Abramov 2001; Chen 2003a).

Dextran is a complex, branched glucan composed of chains of varying lengths. It is used as an antithrombotic, to reduce blood viscosity, and as a volume expander in anaemia (Endo 2004).

Polygeline is a type of intravenous colloid with 3.5% urea-linked gelatin used to treat OHSS (Gamzu 2002). It is used in the prevention or treatment of shock associated with reduction in effective circulating blood volume due to haemorrhage, loss of plasma or loss of water and electrolytes from persistent vomiting and diarrhoea.

Mannitol is a naturally occurring sugar alcohol used for its osmotic diuretic purposes; it is used as plasma expander for the protection of renal failure and in cases of intracerebral oedema (Shawkat 2012).

Why it is important to do this review

OHSS is one of the most common adverse effects of assisted reproductive technology-controlled ovarian hyperstimulation (ART-COH) cycles. OHSS can result in hospital admission and in some cases in critical illness. Therefore the aim of this review is to evaluate the evidence from randomised controlled trials (RCTs) to determine whether volume expanders can reduce the incidence of moderate and severe OHSS in high-risk women undergoing IVF/ICSI treatment This review provides a new evidence base for physicians and stakeholders considering the use of plasma expanders in women at high risk of developing OHSS who are undergoing IVF/ICSI treatment.

This is an update of a Cochrane review first published in 1999, and previously updated in 2002 and 2011. This is the first update that aims to report 'moderate or severe OHSS' as a primary outcome, as opposed to the original primary outcome of 'severe OHSS'.

OBJECTIVES

To investigate the effectiveness and safety of administration of volume expanders in the prevention of moderate and severe ovarian hyperstimulation syndrome (OHSS) in high-risk women undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) treatment cycles.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs).

We excluded non-randomised and quasi-randomised studies (e.g. studies with evidence of inadequate sequence generation such as alternate days, patient numbers) as they are associated with a high risk of bias.

Cross-over studies were not eligible for inclusion, as the design is not valid in this context.

Types of participants

Women of reproductive age who were having controlled ovarian hyperstimulation as part of any assisted reproductive technique and were considered to be at high risk of moderate or severe OHSS (as determined by either a diagnosis of polycystic ovary syndrome (PCOS) (criterion new to the 2016 update), a specific threshold serum estradiol level, a threshold number of follicles on day of human chorionic gonadotrophin (hCG) administration or threshold number of retrieved oocytes (as defined in individual studies).

Types of interventions

All kinds of volume expanders used in the prevention of OHSS versus placebo or no treatment. Administration can be at any time in the cycle (e.g. prior to or after oocyte pick-up).

For example:

- Intravenous albumin versus placebo or no treatment
- Hydroxyethyl starch (HES) versus placebo or no treatment
- Mannitol versus placebo or no treatment
- Polygeline versus placebo or no treatment
- Dextran versus placebo or no treatment

Types of outcome measures

Primary outcomes

1. Moderate or severe OHSS (as determined by established clinical criteria, such as Humaidan 2010; Rizk 1999; Navot 1992; Golan 1989; Schenker 1978; WHO 1973)

Secondary outcomes

2. Live birth rate per woman randomised

3. Pregnancy rate per woman randomised (as confirmed by β-hCG or pregnancy test or ultrasonic visualisation of fetal heart beat at a certain gestational age (as defined in the separate studies))

4. Adverse effects of treatment (e.g. allergic reaction)

Search methods for identification of studies

We searched for published and unpublished RCTs of diverse intravenous fluids versus placebo or no treatment using a systematic search strategy, without date or language restriction and in consultation with the Cochrane Gynaecology and Fertility (formerly Menstrual Disorders and Subfertility Group (MDSG)) Information Specialist.

Electronic searches

The following electronic databases, trial registers and websites were searched to September 2015.

- Ovid Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 2)
- Ovid MEDLINE (Appendix 3)
- Ovid Embase: Embase (Appendix 4)
- Ovid PsycINFO (Appendix 5)
- MEDLINE and Embase search strategies use different filters for identifying randomised trials. The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials which appears in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011).
- The Embase and CINAHL searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/mehodology/filters.html#random)
- Trial registers for ongoing and registered trials including www.controlled-trials.com/,https://clinicaltrials.gov and www.who.int/trialsearch/Default.aspx
- The Web of Knowledge (for conference abstracts, and to check citations of included studies)

Searching other resources

We hand searched the reference lists of all primary studies and review articles retrieved by the search, and checked the citation lists of relevant publications. We contacted known experts in the field and personal contacts regarding any unpublished materials.

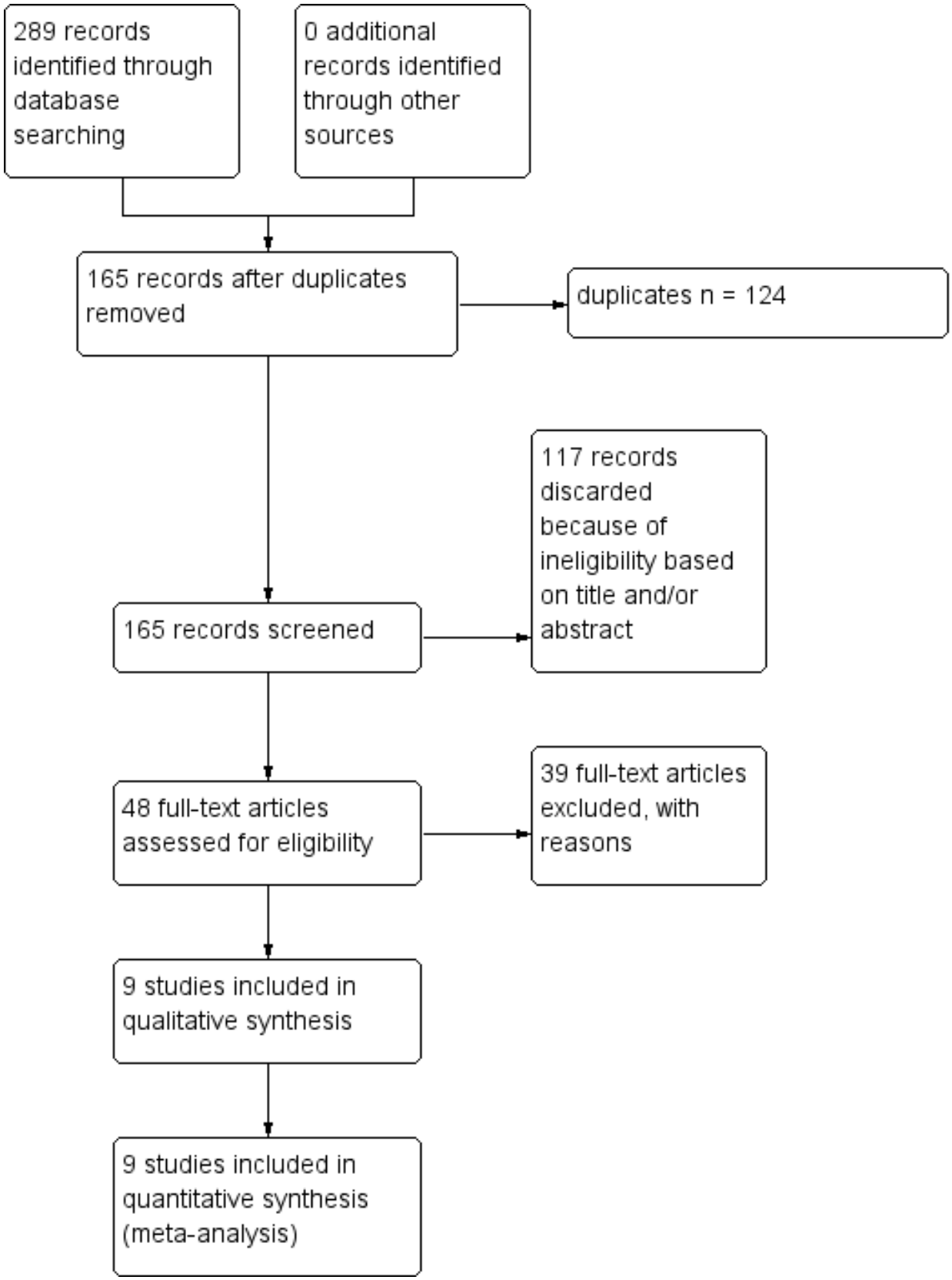
Data collection and analysis

Selection of studies

Thereview authors (MY or SM) independently reviewed the titles and abstracts of studies using the a priori criteria for inclusion. The full-text manuscripts of studies were obtained for the short-listed papers that were considered potentially eligible for inclusion. We sought further information from the authors of study reports that did not contain sufficient information to make a decision about eligibility. Thereview authors independently critically appraised these studies and any disagreements were resolved by discussion. The studies that were determined to be suitable for inclusion were assessed for risk of bias and data were extracted. Subsequently, a detailed 'Characteristics of excluded studies' table was constructed for those studies that did not satisfy the inclusion criteria. A similar 'Characteristics of included studies' table was constructed for those studies considered suitable for inclusion.

The 2016 selection process was documented with a study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

A standardised data extraction form was developed and piloted for consistency and completeness. Two review authors (MY, HG or SM) independently performed data extraction. The two sets of extracted data were compared and discrepancies were resolved by discussion. Where studies had multiple publications, the review authors collated multiple reports so that each study rather than each report was the unit of interest in the review; overlapping data were thus identified and duplicates were excluded.

We requested extra information about the methodological quality of some studies (Bellver 2003; Gokmen 2005; Isik 1996; Isikoglu 2007; Saremi 2003; Shalev 1995; Shoham 1994), however the only response we received was from the authors of Isikoglu 2007 and Saremi 2003.

Assessment of risk of bias in included studies

The review authors independently evaluated the included studies for risk of bias using the Cochrane 'Risk of bias' assessment tool (Higgins 2011) to assess: selection (random sequence generation and allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome assessors); attrition (incomplete outcome data); reporting (selective reporting); and other bias. Disagreements were resolved by discussion. We described all judgements fully and presented the conclusions in 'Risk of bias' tables (Figure 2; Figure 3), which were incorporated into the interpretation of review findings by means of sensitivity analyses.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

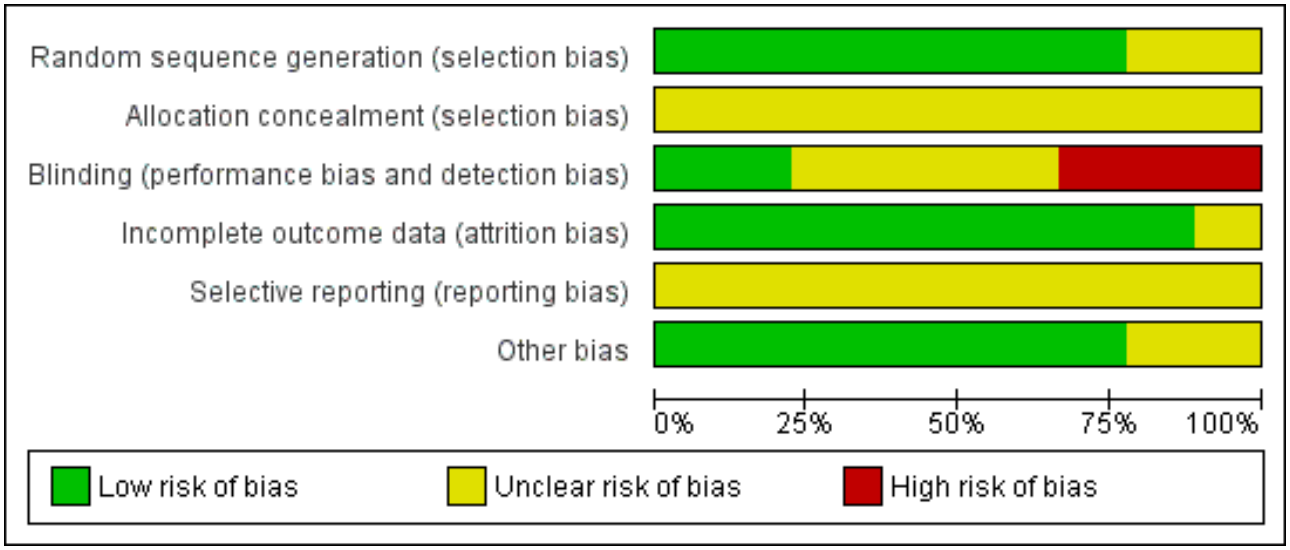
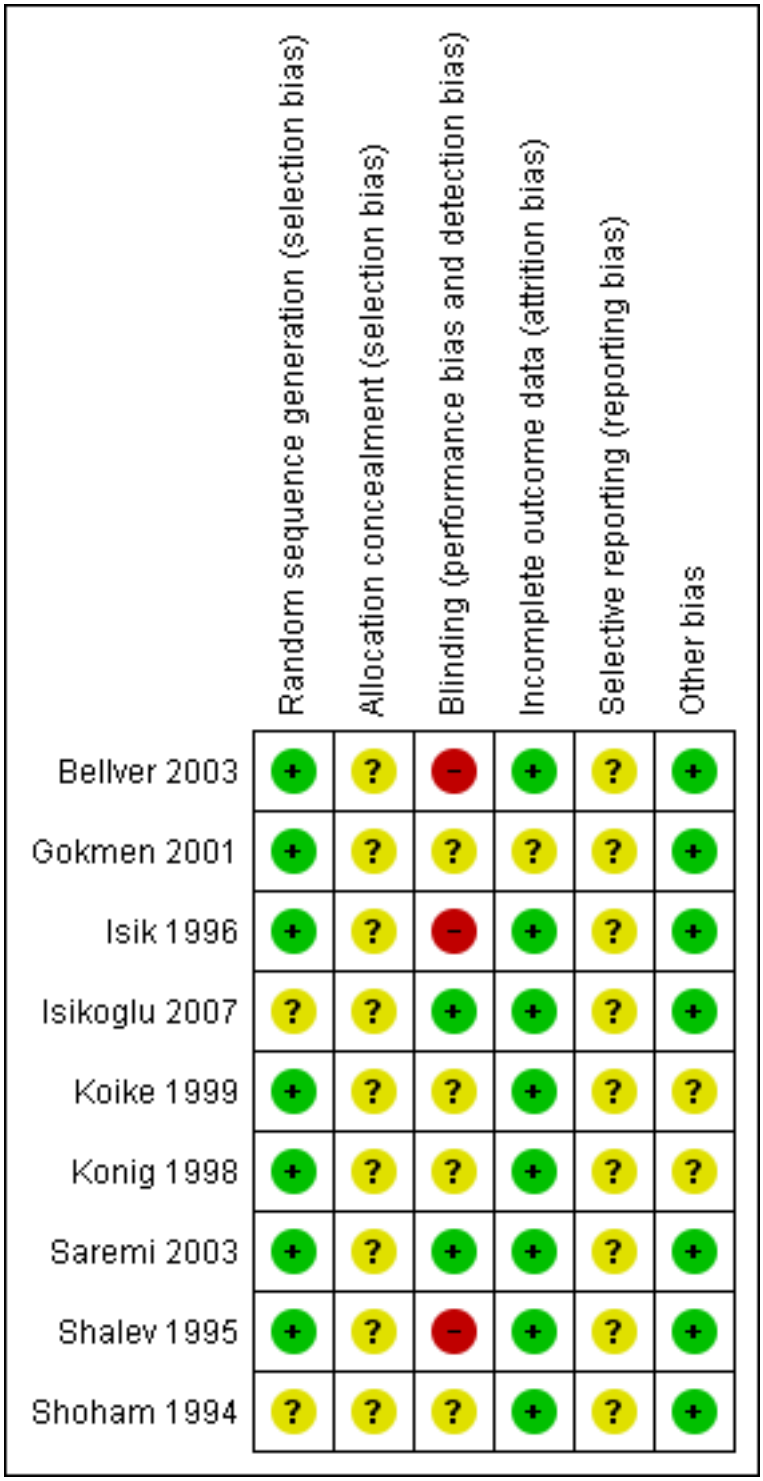


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Measures of treatment effect

All data were dichotomous. The numbers of events in the control and intervention groups of each study were used to calculate Peto odds ratios (ORs) for each comparison, with 95% confidence intervals (CIs).

Unit of analysis issues

The primary analysis was per woman randomised. Only one cycle per woman could be included.

Dealing with missing data

The data were analysed on an intention-to-treat basis as far as possible and attempts were made to obtain missing data from the original trials. Where these were unobtainable, only the available data were analysed.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity by visual inspection of the forest plots, and used the I^2 statistic (Higgins 2011) to quantify any apparent inconsistency, interpreted in the broad terms:

- 0% to 40% might not be important;
- 30% to 60% represented moderate heterogeneity;
- 50% to 90% represented substantial heterogeneity;
- 75% to 100% represented considerable heterogeneity.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, the review authors aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. Had there been 10 or more studies in an analysis, we planned to use a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies)

Data synthesis

If the studies were sufficiently similar, data from primary studies were combined using a fixed-effect model to compare intravenous (IV) intervention fluids versus no treatment or placebo. We considered each type of volume expander in a separate comparison.

Subgroup analysis and investigation of heterogeneity

We considered whether the effect of the intervention on OHSS rates was different in studies that only measured severe (as opposed to moderate or severe) OHSS.

We also considered whether the effect of the intervention on pregnancy rates was different in studies that diagnosed pregnancy by ultrasonic visualisation of fetal heart beat rather than by pregnancy test.

Had we detected substantial heterogeneity, we planned to explore possible explanations in sensitivity analyses and to take any statistical heterogeneity into account when interpreting the results.

Sensitivity analysis

Sensitivity analyses were conducted for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding eligibility and in the analysis. These analyses included consideration of whether conclusions would have differed if:

- the summary effect measure was risk ratio rather than Peto odds ratio;
- eligibility was restricted to studies without high risk of bias;
- eligibility was restricted to full-text published studies.

Overall quality of the body of evidence: 'Summary of findings' table

Two review authors working independently prepared a 'Summary of findings' table using Guideline Development Tool software and Cochrane methods (Higgins 2011)This table evaluated the overall quality of the body of evidence for all outcomes for the three review comparisons using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate, low or very low) were justified, documented, and incorporated into reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

2016 update

Two hundred and eighty-nine studies were retrieved by the search; a total of 124 duplicates were discarded, leaving 165 studies for screening of title and abstract. Two new studies were identified concerning the infusion of mannitol (Saremi 2003) and calcium gluconate (El-Khayat 2015). However, calcium gluconate has a very different pathophysiological mechanism than the other IV fluids used, which all are volume expanders. We excluded El-Khayat 2015. A discussion on this topic took place between the authors and led to a decision to maintain a focus on volume expanders only; therefore, we amended the protocol and changed the title accordingly.

The data from Gokmen 2005 (conference abstract) were excluded from this update of the review, as there was serious concern that the data overlapped with the Gokmen 2001 publication, which was published as a full paper. We tried to contact the author to clarify potential duplication of data but did not succeed.

In total, nine studies were included in this review (Figure 1).

2014 update

Two hundred and seventy-three records were retrieved by the search and were screened. One unpublished study was deemed potentially eligible and was awaiting classification. The rest were discarded as clearly ineligible based on the title or abstract.

Searches prior to 2014

In earlier versions of the review a total of 43 articles were identified as potentially eligible and retrieved in full text. Of these, 34 articles (32 studies) were further assessed and excluded. Eight studies (nine articles) were included.

Included studies

See Characteristics of included studies

Design

- The nine included studies (n = 1867 women) were all single-centre studies. Eight studies were parallel-group RCTs comparing a single intervention versus placebo or a no treatment group; the Gokmen 2001 study had a three-armed design with two different intervention groups versus placebo.

- Eight studies were published as full papers and one as a 'letter to the editor' (Koike 1999).

Participants

All the studies used strict inclusion criteria for participant selection (see Characteristics of included studies).

- Two studies used estradiol (E2) as the basic risk factor of ovarian hyperstimulation syndrome (OHSS) (7000 pmol/L in Shoham 1994, 11,010 pmol/L in Isik 1996), both in combination with 'multifollicular response'; however no specific number of follicles was mentioned.
- Two studies used the number of retrieved oocytes as the main risk factor (Bellver 2003; Koike 1999).
- Four studies used both E2 level and number of follicles or oocytes as inclusion criteria; high E2 *or* number of follicles on day of human chorionic gonadotrophin (hCG) administration/ number of retrieved oocytes in Gokmen 2001, Isikoglu 2007 and Konig 1998; high E2 level *and* number of follicles in Shalev 1995.
- Where E2 levels were (partly) used to define the 'high-risk' population, cut-off levels varied (1906 pg/mL in Shoham 1994, > 2506 pg/mL in Shalev 1995, > 3000 pg/mL in Gokmen 2001, > 1500 pg/mL in Konig 1998, > 3000 pg/mL in Isik 1996, > 4000 pg/mL in Isikoglu 2007, > 9200 pg/mL in Koike 1999 ; where necessary pmol/L was converted to pg/mL).
- One study included women with polycystic ovary syndrome (PCOS) as their 'high-risk' group (Saremi 2003), without taking E2 levels or number of follicles/oocytes into account.
- One study excluded women with very high E2 levels and performed cycle cancellation for this extremely high-risk group for E2 > 7000 pmol/L (Shoham 1994).
- Mean female age was around 30 years in all studies (mean age range was 27.5 to 32.6 years). The intervention and control groups were largely similar regarding the number of ampoules of human menopausal gonadotropin (hMG) used for controlled ovarian hyperstimulation, number of oocytes retrieved and number of embryos. However, in five studies (Bellver 2003; Gokmen 2001; Koike 1999; Shalev 1995; Saremi 2003), there was no mention of the number of ampoules between intervention and control group.

See the table Characteristics of included studies for details.

Interventions

- Seven studies compared albumin versus placebo (Gokmen 2001; Isikoglu 2007; Koike 1999; Shoham 1994) or no treatment (Bellver 2003; Isik 1996; Shalev 1995).
- Two studies compared hydroxyethyl starch (HES) versus placebo (Gokmen 2001; Konig 1998).
- One study made both comparisons (Gokmen 2001).
- One study compared mannitol versus no treatment (Saremi 2003).
- Placebo (saline) was used in the control group of five studies (Gokmen 2001; Isikoglu 2007; Koike 1999; Konig 1998; Shoham 1994).

The dose and timing of the interventions varied between studies but all were given in a relatively early phase (i.e. day of hCG administration or oocyte retrieval) to try to prevent early onset OHSS: Shoham 1994 used 50 g albumin two hours before oocyte retrieval; Koike 1999 used 37.5 g albumin just after oocyte retrieval; Shalev 1995 used 20 g albumin just after oocyte retrieval; and Isik 1996 used 10 g albumin two hours before oocyte retrieval; Gokmen 2001 and Isikoglu 2007 used 10 g albumin immediately after oocyte retrieval; and Bellver 2003 used 40 g of albumin immediately after oocyte retrieval. In Gokmen 2001, 6% hydroxyethyl starch (200/0.5) (500 mL) was used immediately after oocyte retrieval, and in Konig 1998 it was used 48 hours after the oocyte retrieval. Saremi 2003 used mannitol 3 g/kg bodyweight daily infusions (each 100 mL infusion containing 20 g mannitol and water for injection), starting the day after hCG injection until the third day after embryo transfer (lasting five to seven days depending on day of embryo transfer).

Outcomes

All nine studies reported the incidence of severe OHSS and five studies additionally reported on the incidence of moderate OHSS (Bellver 2003; Gokmen 2001; Isik 1996; Konig 1998; Saremi 2003). Diagnosis of severity of OHSS was done according to the criteria of Schenker 1978 in three studies (Gokmen 2001; Isik 1996; Shoham 1994), while Shalev 1995 and Isikoglu 2007 used the criteria of Navot 1988, Bellver 2003 used the criteria of Golan 1989, and Koike 1999 used those of Ben-Rafael 1995. Konig 1998 used the criteria of WHO 1973. Saremi 2003 did not explicitly state the reference but describes criteria similar to Golan 1989.

Eight studies reported pregnancy rates. Diagnosis of pregnancy was determined using serum ß-hCG in all studies except Isikoglu 2007 and Saremi 2003, which used "presence at ultrasound of a gestational sac with positive fetal heart rate".

Most studies mentioned adverse events in their results or discussion sections, but none of the studies prespecified adverse events as an outcome, or reported comparative data on adverse effects in all study groups.

Excluded studies

We excluded 39 studies which did not meet the inclusion criteria for this review, in most cases because they did not make any comparisons of interest or were not randomised. See Characteristics of excluded studies for details.

Risk of bias in included studies

Allocation

Sequence generation

Seven studies used adequate methods of sequence generation and were rated as at low risk of bias (Bellver 2003; Gokmen 2001; Isik 1996; Koike 1999; Konig 1998; Saremi 2003; Shalev 1995). Two studies did not report details of the methods used and were rated as at unclear risk of bias (Isikoglu 2007; Shoham 1994).

Allocation concealment

None of the studies clearly described an acceptable method of allocation concealment and all were rated as at unclear risk of bias in this domain.

Blinding

We considered that lack of blinding might influence outcome assessment for the outcomes of OHSS and adverse events.

One study clearly blinded both participants and outcomes assessors, and was rated as at low risk of bias (Isikoglu 2007). One study stated that "*physicians were blinded to the allocated groups and a nurse performed the protocol" (* Saremi 2003 *),* and we considered this study also to be at low risk of bias. Four studies did not mention blinding, and were rated as at unclear risk (Gokmen 2001; Koike 1999; Konig 1998; Shoham 1994). Three studies were unblinded and were rated as at high risk of bias (Bellver 2003; Isik 1996; Shalev 1995)

Incomplete outcome data

All studies appeared to include all randomised women in analysis. All were rated as at low risk of attrition bias apart from one (Gokmen 2001). An abstract from a conference held in 2005 (Gokmen 2005) appears to relate to the same study but has a larger sample size and reports two additional events. We attempted to contact the study authors to query this but did not receive a reply. We therefore rated this study as at unclear risk of attrition bias.

Selective reporting

Although most studies either stated that no events were observed, or mentioned events in one or both arms, it was unclear whether data on adverse events were collected prospectively or systematically. All studies were rated as at unclear risk of bias in this domain.

Other potential sources of bias

No other potential source of bias was identified in any of the studies, and they were rated as at low risk in this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Human albumin versus placebo or no treatment for the prevention of OHSS; **Summary of findings 2** HES versus placebo or no treatment for the prevention of OHSS; **Summary of findings 3** Mannitol versus placebo / no treatment for the prevention of OHSS

1. Human albumin versus placebo or no treatment

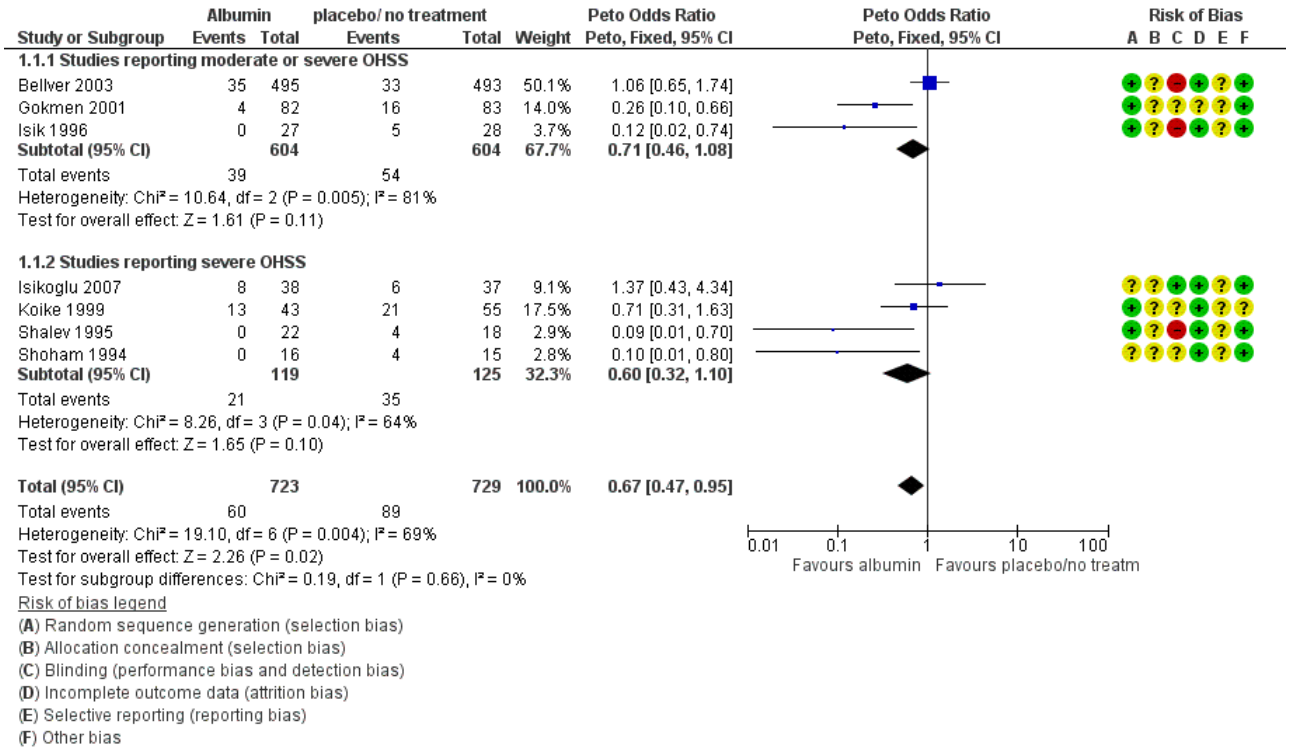
Seven studies compared albumin versus placebo (Gokmen 2001; Isikoglu 2007; Koike 1999; Shoham 1994) or no treatment (Bellver 2003; Isik 1996; Shalev 1995).

Primary outcome

1.1 Moderate or severe OHSS

There was evidence of a difference between the groups, though (Peto OR 0.67 95% CI 0.47 to 0.95, seven studies, 1452 women; I^2 = 69%, very low quality evidence). Heterogeneity was substantial, and there was no obvious explanation for this (Figure 4; Analysis 1.1). This suggests that if the rate of moderate or severe OHSS with no treatment is 12%, it will be about 9% (6% to 12%) with the use of intravenous albumin.

Figure 4. Forest plot of comparison: 1 Human Albumin vs placebo / no treatment, outcome: 1.1 Total OHSS.



Subgroup and sensitivity analyses

Subgroup analysis showed no evidence that findings differed in studies that only reported severe OHSS (test for subgroup differences: Chi^2 = 0.19, df = 1 (P = 0.66), I^2 = 0%).

Use of a risk ratio reduced heterogenity to I^2=57%. Sensitivity analysis by study risk of bias was not possible as no studies were at low risk of bias in most domains.

Secondary outcomes

1.2 Live birth

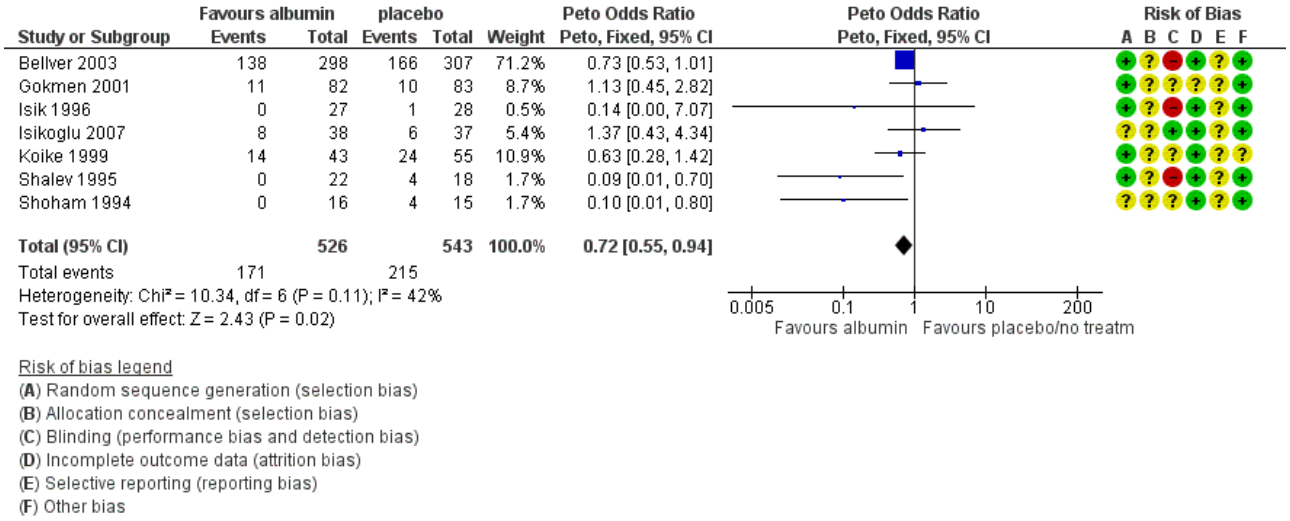
None of the studies reported live birth as an outcome.

1.3 Pregnancy

Seven studies reported data for this outcome.

There was evidence of a detrimental effect on pregnancy rates for the use of albumin (Peto OR 0.72 95% CI 0.55 to 0.94, I^2 = 42%, seven studies, 1069 women, moderate quality evidence) (Figure 5;Analysis 1.2; Summary of findings for the main comparison).

Figure 5. Forest plot of comparison: 1 Human Albumin vs placebo / no treatment, outcome: 1.2 Pregnancy rate.



Subgroup analysis

We examined whether effects differed according to the method used for diagnosing pregnancy (by β-hCG: Gokmen 2001; Isik 1996; Koike 1999; Shalev 1995; Shoham 1994) or heartbeat on ultrasound (Bellver 2003 (only pregnancy data for autologous cycles considered); Isikoglu 2007) and found no evidence of a difference between the subgroups (test for subgroup differences: Chi^2 = 0.78, df = 1 (P = 0.38), I^2 = 0%

1.4 Adverse effects

None of the studies explicitly mentioned 'adverse effects' as a prespecified outcome, though most commented (in the results or discussion section) on adverse events related to the interventions. Among women receiving albumin, in one study (Gokmen 2001), a woman developed an anaphylactoid reaction with hypotension and laryngospasm. In a second study (Isik 1996), two women developed mild urticaria. Four studies (Bellver 2003, Isikoglu 2007, Shalev 1995, Shoham 1994), noted that no side effects or hypersensitivity reactions were detected in association with the intervention. Koike 1999 did not mention adverse effects.

2. Hydroxyethyl starch (HES) versus placebo or no treatment

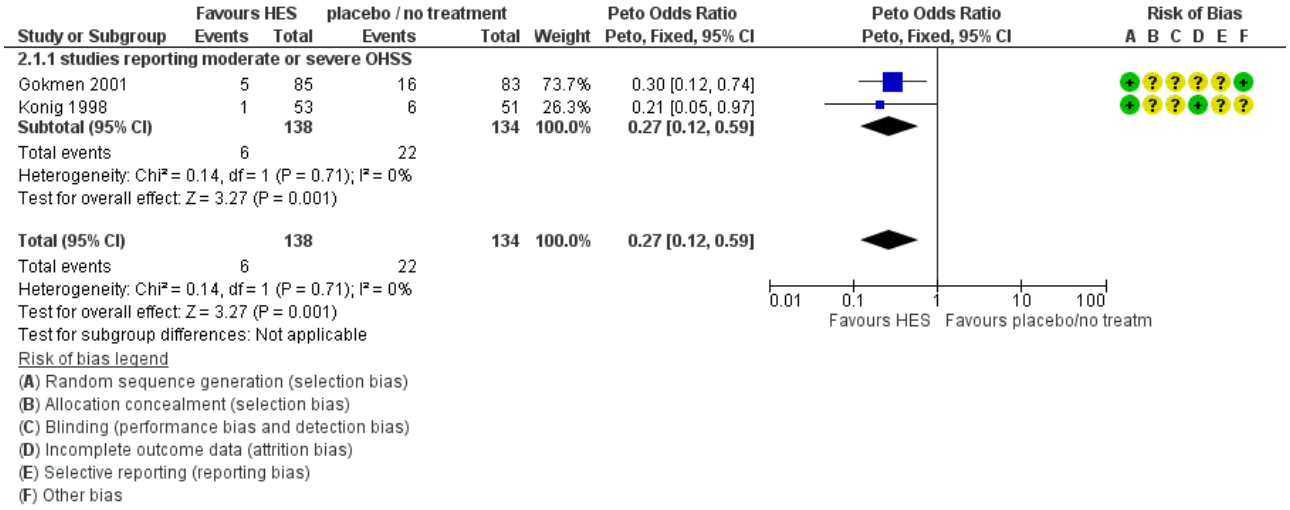
Two studies compared hydroxyethyl starch (HES) versus placebo (Gokmen 2001; Konig 1998). Both reported overall rates of moderate or severe OHSS.

Primary outcome

2.1 Moderate or severe OHSS

There was evidence of a beneficial effect of HES on OHSS (Peto OR 0.27 95% CI 0.12 to 0.59, I^2 = 0%, two studies, 272 women, very low quality evidence). This suggests that if the rate of moderate or severe OHSS with no treatment is 16%, it will be about 5% (2% to 10%) with the use of HES (Analysis 2.1; Figure 6; Summary of findings 2).

Figure 6. Forest plot of comparison: 2 HES vs placebo / no treatment, outcome: 2.1 Total OHSS.



Sensitivity analysis

Use of a risk ratio did not materially change the main findings. Sensitivity analysis by study risk of bias was not possible as neither studies was at low risk of bias in most domains.

Secondary outcomes

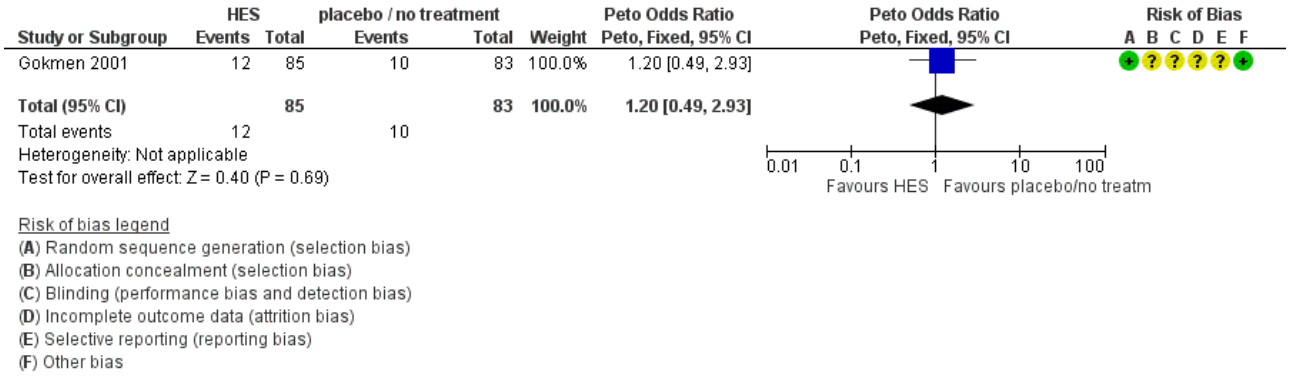
2.2 Live birth

Neither of the studies reported live birth as an outcome.

2.3 Pregnancy

There was no evidence of a difference in pregnancy rates (diagnosed by serum β-hCG level) between women receiving IV HES and those receiving placebo (Peto OR 1.20 95% CI 0.49 to 2.93, one study, 168 women, very low quality evidence) (Analysis 2.2; Figure 7; Summary of findings 2).

Figure 7. Forest plot of comparison: 2 HES vs placebo / no treatment, outcome: 2.2 Pregnancy rate.



2.4 Adverse effects

Neither of the studies explicitly mentioned 'adverse effects' as a prespecified outcome. There were two mild cases of urticaria in one study (Gokmen 2001) and one case of urticaria in the other (Konig 1998).

3. Mannitol versus placebo or no treatment

One study compared mannitol versus no treatment (Saremi 2003).This study reported overall rates of moderate or severe OHSS.

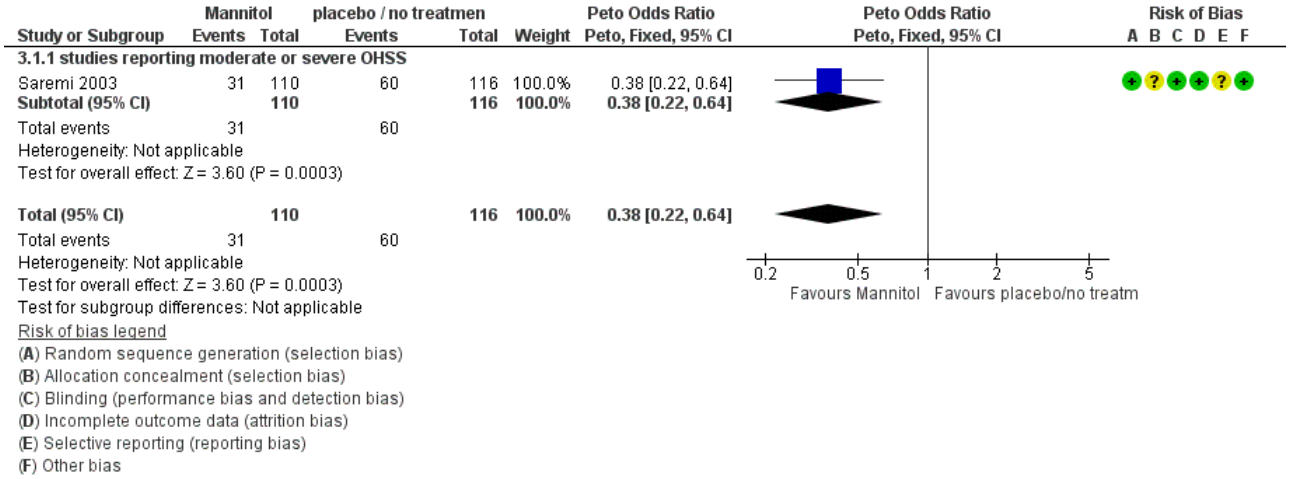
Primary outcome

3.1 Moderate or severe OHSS

There was evidence of a beneficial effect of mannitol on OHSS (Peto OR 0.38, 95% CI 0.22 to 0.64, one study, 226 women, low quality evidence).

This suggests that if the rate of OHSS with no treatment is 52%, it will be about 29% (19% to 41%) with mannitol (Analysis 3.1; Figure 8; Summary of findings 3).

Figure 8. Forest plot of comparison: 3 Mannitol vs placebo / no treatment, outcome: 3.1 Total OHSS.



Sensitivity analysis

Use of a risk ratio did not materially change the main findings.

Secondary outcomes

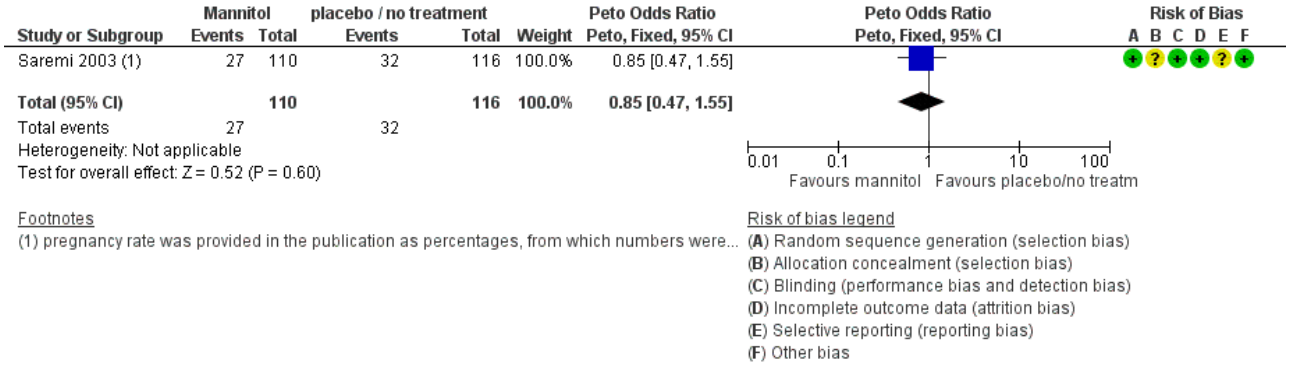
3.2 Live birth

Live birth was not reported as an outcome.

3.3 Pregnancy

There was no evidence of a difference in pregnancy rates (diagnosed by ultrasound) between the groups (Peto OR 0.85 95% CI 0.85 to 1.55; one study, 226 women, low quality evidence) (Analysis 3.2; Figure 9; Summary of findings 3).

Figure 9. Forest plot of comparison: 3 Mannitol vs placebo / no treatment, outcome: 3.2 Pregnancy rate.



3.4 Adverse effects

Adverse events were not mentioned in this study. In private correspondence the authors stated that data on adverse events were collected, but they did not specify what type or report any events.

Assessment of publication bias

There were insufficient studies to construct a funnel plot to assess the risk of publication bias.

DISCUSSION

Summary of main results

Nine randomised controlled studies compared the effectiveness of intravenous (IV) administration of the volume expanders human albumin, hydroxyethyl starch (HES), or mannitol versus placebo or no treatment for the prevention of ovarian hyperstimulation syndrome (OHSS) in women at high risk of OHSS. The overall quality of the evidence ranged from very low to moderate (Summary of findings table 1).

There was evidence that intravenous albumin administration around the time of oocyte retrieval has a beneficial effect on the incidence of moderate or severe OHSS. However, there was substantial unexplained heterogeneity between studies for this outcome (I^2 = 69%).

Our analysis suggested that HES might be associated with reduced rates of moderate or severe OHSS, but this was only based on two studies reporting only 28 events. Mannitol also appeared to have a beneficial effect on the incidence of OHSS, but this finding was based on a single study, so this moderate quality evidence remains to be confirmed in additional, large RCTs.

Live birth rate was not reported in any of the studies.There was moderate quality evidence that administration of human albumin lowered pregnancy rates in women at high risk for OHSS. For HES or mannitol there was no evidence of an effect on pregnancy rates.

Adverse effects were poorly reported and no firm conclusions could be drawn; although uncommon, clinicians should be aware that administration of IV fluids could cause severe morbidity.

Overall completeness and applicability of evidence

There were no randomised controlled studies (RCTs) that compared other volume expanders such as dextran or polygeline versus placebo or no treatment.

There was significant clinical heterogeneity between the included studies. The criteria for selecting women with a risk of OHSS varied across trials. Some used the number of oocytes at the day of hCG administration or the number of retrieved oocytes. Other studies used E2 level as a basic risk marker, but cut-off levels varied greatly amongst studies; for example, inclusion E2 level for the study matched cycle cancellation (and therefore exclusion level) in another study. The method or criteria of OHSS diagnosis also varied widely between studies. With regard to studies of human albumin, the dosage of gonadotropins used for controlled ovarian hyperstimulation was not stated in most of the studies; the dose and timing of administration of albumin or starch varied between studies, between 10 g albumin immediately after oocyte retrieval to 50 g albumin one or two hour before oocyte retrieval, whilst 52.5 g albumin is required to accomplish a normal plasma albumin level of 4.2 to 4.5 g/100 mL in a well-hydrated patient (Kissler 2001).

All of the plasma expanders were given either on the day of hCG administration or day of oocyte retrieval, therefore implicitly aiming to prevent early onset OHSS. The included studies made no distinction between early and late onset OHSS.

Quality of the evidence

All the studies were at serious risk of bias: none adequately described their method of allocation concealment, none prospectively collected comparative data on adverse events and only one clearly reported blinded outcome assessment.

The quality of the evidence was rated as very low to moderate for all comparisons. The main limitations in the evidence were risk of bias, statistical heterogeneity, imprecision, and lack of data for most comparisons. (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

Potential biases in the review process

Previous versions of the review included both Gokmen 2001 and a subsequent study by the same group (Gokmen 2005). We understand from personal communication with Christos Venetis (first author of Venetis 2011) that these two studies overlap and so we have removed the data for Gokmen 2005 from this updated version of the review. However, we have been unable to contact the study authors directly. No other potential biases were identified in the review process.

Agreements and disagreements with other studies or reviews

Two older systematic reviews of human albumin for the prevention of OHSS reached slightly different conclusions, but both focused on severe OHSS only. Both reviews reported no difference in the occurrence of severe OHSS between those who received intravenous albumin and those who did not (Venetis 2011: odds ratio (OR) 0.80; 95% confidence interval (CI), 0.52 to 1.22, eight RCTs, 1199 women; Jee 2010: risk ratio (RR) 0.80, 95% CI 0.57 to1.12, 9 RCTs, 1613 women). These reviews however included quasi-randomised studies which were not eligible for the current review (for Jee 2010 this was Panay 1999; for Venetis 2011 this was Ben-Chetrit 2001) and Venetis 2011 also included data from Gokmen 2005, that we considered possibly biased. The slightly deleterious effect of albumin on pregnancy rate reported by Jee 2010 was confirmed in our review.

We have not identified any other systematic reviews comparing HES or mannitol with placebo or no treatment for prevention of OHSS.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence suggests that the plasma expanders assessed in this review (human albumin, HES and mannitol) reduce rates of moderate and severe OHSS in women at high risk. Adverse events appear to be uncommon, but were too poorly reported to reach any firm conclusions, and there were no data on live birth. However, there was evidence that human albumin reduces pregnancy rates. While there was no evidence that HES, or mannitol had any influence on pregnancy rates, the evidence of effectiveness was based on very few trials which need to be confirmed in additional, larger randomised controlled trials (RCTs) before they should be considered for routine use in clinical practice.

.

Implications for research

- High-quality, well-designed and adequately powered RCTs are needed to assess the effectiveness of volume expanders in women at high risk of developing OHSS.
- Future studies should take into consideration the cost-effectiveness and psychological impact of treatment with volume expanders and should systematically report on adverse events.

ACKNOWLEDGEMENTS

Dr Saremi is acknowledged for providing additional information on his publication. Special thanks also to the highly supportive team at the Cochrane office in Auckland, especially editor Jane Marjoribanks and the Information Specialist Marian Showell for designing and running the search strategies.

We thank Professor Johannes Evers, Professor Hesham Al-Inany and Professor Mohamed Aboulghar for their contributions to previous versions of this review. Professor Al-Inany took the lead in writing the protocol and the first version of the full review. Prof Aboulghar screened studies and extracted and interpreted data in the first version of the full review.

REFERENCES

References to studies included in this review

Bellver 2003 *{published data only}*

Bellver J, Munoz EA, Ballesteros A, Soares SR, Bosch E, Simon C, et al. Intravenous albumin does not prevent moderate–severe ovarian hyperstimulation syndrome in high-risk IVF patients: a randomized controlled study. *Human Reproduction* 2003;**18**(11):2283–8.

Gokmen 2001 *{published data only}*

Gokmen O, Ugur M, Ekin M, Keles G, Turan C, Oral H. Intravenous albumin versus hydroxyethyl starch for the prevention of ovarian hyperstimulation in an in-vitro fertilization programme: a prospective randomised placebo controlled study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2001;**96**(2):187-92.

Isik 1996 *{published data only}*

Isik AZ, Gokmen O, Zeyneloglu HB, Kara S, Keles G, Gulekli B. Intravenous albumin prevents moderate-severe ovarian hyperstimulation in in vitro fertilisation patients: a prospective randomized and controlled study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 1996;**70**:170-83.

Isikoglu 2007 *{published data only}*

Isikoglu M, Berkkanoglu M, Senturk Z, Ozgur K. Human albumin does not prevent ovarian hyperstimulation syndrome in assisted reproductive technology program: a prospective randomized placebo-controlled double blind study. *Fertility and Sterility* 2007;**88**(4):982-5.

Koike 1999 *{published data only}*

Koike E, Araki S, Ogawa S, Minakami H, Sato I. Does i.v albumin prevent ovarian hyperstimulation syndrome?. *Human Reproduction* 1999;**14**(7):1920.

Konig 1998 *{published data only}*

Konig E, Bussen S, Sütterlin M, Steck T. Prophylactic intravenous hydroxyethyle starch solution prevents moderate-severe ovarian hyperstimulation in in-vitro fertilization patients: a prospective, randomized, double-blind and placebo-controlled study. *Human Reproduction* 1998;**13**(9):2421-4.

Saremi 2003 *{published and unpublished data}*

Saremi A, Alam M, Motaghi M. Administration of mannitol to prevent severe ovarian hyperstimulation syndrome: A randomized controlled trial. *Middle East Fertility Society Journal* 2003;**8**(2):159-163.

Shalev 1995 *{published data only}*

Shalev E, Giladi Y, Matilsky M, Ben-Ami M. Decreased incidence of severe ovarian hyperstimulation syndrome in high risk in-vitro fertilisation patients receiving intravenous albumin: a prospective study. *Human Reproduction* 1995;**10**:1373-6.

Shoham 1994 *{published data only}*

Shoham Z, Weissman A, Barash A, Borenstein R, Schachter M, Insler V. Intravenous albumin for the prevention of severe ovarian hyperstimulation syndrome in an invitro fertilisation program: a prospective, randomised, placebo-controlled study. *Fertility and Sterility* 1994;**62**:137-42.

References to studies excluded from this review

Abramov 2001 *{published data only}*

* Abramov Y, Fatum M, Abrahamove D, Schenker JC. Hydroxyethyl starch versus human albumin for the treatment of severe ovarian hyperstimulation syndrome: a preliminary report. *Fertility and Sterility* 2001;**75**:1228-30.

Abramov Y, Fatum M, Fasouliotis S, Abrahamov D, Schenker JC. Hydroxyethylstarch versus human albumin for the treatment of severe ovarian hyperstimulation syndrome. *Fertility and Sterility. Abstracts of the 17th Annual meeting of the ESHRE* 2001;**16**(1):121.

Abuzeid 2010 *{published data only}*

Abuzeid M, Abed S, Salem W, Joseph S, Ashraf M, Rizk P.B. The effectiveness of 6% hydroxyethyle starch solution in reducing the incidence of severe hyperstimulation syndrome in polycystic ovarian disease patients: A prospective cohort clinical trial. *Journal of Reproductive Medicine and Endocrinology,* IFFS 2010 September 12-16 Munich;**7**(4):240-383.

Ahmadi 2010 *{published data only}*

Ahmadi Sh, Rahmani E, Oskouian H. Cabergoline versus human albumin in prophylaxis ovarian hyperstimulation syndrome. *Reproductive BioMedicine Online* 2010;**Suppl. 3**:S41–S42.

Asch 1993 *{published data only}*

Asch R, Ivery G, Goldsman M. The use of intravenous albumin in patients at high risk for severe ovarian hyperstimulation syndrome. *Human Reproduction* 1993;**8**:1015-20.

Ben-Chetrit 2001 *{published data only}*

Ben Chetrit A, Eldar-Geva T, Gal M, Huerta M, Mimon T, Algur N, et al. The questionable use of albumin for the prevention of ovarian hyperstimulation syndrome in an IVF programme: a randomized placebo-controlled trial. *Human Reproduction* 2001;**16**(9):1880-4.

Ben-Rafael 1995 *{published data only}*

Ben-Rafael Z, Orvieto R, Dekel A, Peleg D, Gruzman C. Intravenous albumin and the prevention of severe ovarian hyperstimulation syndrome. *Human Reproduction* 1995;**10**(10):2750-2.

Cambiaghi 2005 *{published data only}*

Cambiaghi AS, Castellotti DS. Oral whey protein for preventing ovarian hyperstimulation syndrome. *Fertility and Sterility. Abstracts from the annual meeting of ASRM* 84 Suppl 1;**84**(1):315.

Chen 1997 *{published data only}*

Chen C, Chen S, Wu M, Ho H, Yang J, Yang Y. Intravenous albumin does not prevent the development of severe ovarian hyperstimulation syndrome. *Fertility and Sterility* 1997;**68**:287-91.

Chen 2003 *{published data only}*

Chen CD, Chao KH, Yang JH, Chen SU, Ho HN, Yang YS. Comparison of coasting and intravenous albumin in the prevention of ovarian hyperstimulation syndrome. *Fertility and Sterility* 2003;**80**(1):86-90.

Costabile 2000 *{published data only}*

Costabile L, Unfer V, Manna C, Gerli S, Rossetti D, Di Renzo GC. Use of intramuscular progesterone versus intravenous albumin for the prevention of ovarian hyperstimulation syndrome. *Gynecologic and Obstetric Investigation* 2000;**50**(3):182-5.

Dmitrieva 2010 *{published data only}*

Dmitrieva NV, Yakovenko SA, Zorina IV, Voznesenskaya YV, Apryshko VP. Comparison of calcium gluconate and starch solution in the treatment of ovarian hyperstimulation syndrome. *Reproductive BioMedicine Online* 2010;**3**:S41–S42.

Egbase 1997 *{published data only}*

Egbase PE, Makhseed M, Al Sharhan M, Grdzinskas JG. Timed unilateral ovarian follicular aspiration prior to administration of human chorionic gonadotrophin for the prevention of severe ovarian hyperstimulation syndrome in invitro fertilisation: a prospective randomised study. *Human Reproduction* 1997;**12**:2603-6.

El-Khayat 2015 *{published data only}*

El-Khayat W, Elsadek M. Calcium infusion for the prevention of ovarian hyperstimulation syndrome: a double-blind randomized controlled trial. *Fertility and Sterility* 2015;**103**(1):101-5.

Endo 2004 *{published data only}*

Endo T, Kitajima Y, Hayashi T, Fujii M, Hata H, Azumaguchi A. Low-molecular-weight dextran infusion is more effective for the treatment of hemoconcentration due to severe ovarian hyperstimulation syndrome than human albumin infusion. *Fertility and Sterility* 2004;**82**(5):1449-51.

Fan 2006 *{published data only}*

Fan YH, Qiao J, Chen XN, Wang HY, Ma CH, Liu P. Assisted reproductive Intravenous hydroxyethyl starch versus human albumin for prevention of the ovarian hyperstimulation syndrome. *VIII FIGO World Congress of Gynecology and Obstetrics* 2006;**2**:34.

Fan YH, Qiao J, Chen XN, Wang HY, Ma CH, Liu P. Intravenous hydroxyethyl starch versus human albumin for prevention of the ovarian hyperstimulation syndrome. *Fertility and Sterility* 2006;**86 Suppl 2**:136.

Fluker 2000 *{published data only}*

Fluker MR, Copeland JE, Yuzpe AA. An ounce of prevention: outpatient management of the ovarian hyperstimulation syndrome. *Fertility and Sterility* 2000;**73**(4):821-4.

Gamzu 2002 *{published data only}*

Gamzu R, Almog B, Levin Y, Avni A, Lessing BJ, Baram A. Comparative efficacy of hydroxyethyl starch and Haemaccel for the treatment of severe ovarian hyperstimulation syndrome. *Fertility and Sterility* 2002;**77**(6):1302-3.

Gokmen 2005 *{published data only}*

Gokmen O, Ozcan S, Erman Akar M, Ugur M. A randomized prospective placebo-controlled study of intravenous albumin vs. hydroxyethyl starch for the prevention of ovarian hyperstimulation in an in-vitro fertilization programme. *Fertility and Sterility: Abstracts of ASRM* 2005;**84**(Suppl 1):308.

Graf 1997 *{published data only}*

Graf AM, Fischer R, Naether ONJ, Baukloh V, Tafel J, Nuckel M. Reduced incidence of ovarian hyperstimulation syndrome by prophylactic infusion of hydroxyethyl starch solution in an in-vitro fertilization programme. *Human Reproduction* 1997;**12**(12):2599-602.

Halme 1995 *{published data only}*

Halme J, Toma SK, Talbert LM. A case of severe ovarian hyperstimulation in a healthy oocyte donor. *Fertility and Sterility* 1995;**64**(4):857-9.

Isik 1997 *{published data only}*

Isik AZ, Ozgun OD, Kahraman S, Polat G, Vicdan K, Biberoglu K, et al. Intravenous albumin combined with low dose human chorionic gonadotrophin and late step-down administration of menotropins are effective in prevention of severe ovarian hyperstimulation syndrome in high-risk patients in an in vitro fertilisation program. *Middle East Fertility Society Journal* 1997;**2/3**:238-42.

Isik 2001 *{published data only}*

Isik AZ, Vicdan K. Combined approach as an effective method in the prevention of severe ovarian hyperstimulation syndrome. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2001;**97**(2):208-12.

Kissler 2001 *{published data only}*

Kissler S, Neidhardt B, Siebzehnrübl E, Schmitt H, Tschaikowsky K, Wildt L. The detrimental role of colloidal volume substitutes in severe ovarian hyperstimulation syndrome: a case report. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2001;**99**(1):131-4.

Koike 2000 *{published data only}*

Koike E, Araki S, Ogawa S, Minakami H, Sayama H, Shibahara H, et al. Clinical efficacy of peritoneovenous shunting for the treatment of sever ovarian hyperstimulation syndrome. *Human Reproduction* 2000;**15**(1):113-7.

Kumbak 2005 *{published data only}*

Kumbak B, Kahraman S, Karlikaya G, Karagozoglu H, Sen T, Hatirnaz S. Intravenous albumin prophylaxis in high risk patients for moderate to severe ovarian hyperstimulation syndrome. *Fertility and Sterility* 2005;**84 Suppl**(1):264.

Lewit 1996 *{published data only}*

Lewit N, Kol S, Ronen N, Itskovitz-Eldor J. Does intravenous administration of human albumin prevent severe ovarian hyperstimulation syndrome?. *Fertility and Sterility* 1996;**66**(4):654-6.

Lincolin 2002 *{published data only}*

Lincoln SR, Opsahl MS, Blauer KL, Black SH, Schulman JD. Aggressive outpatient treatment of ovarian hyperstimulation syndrome with ascites using transvaginal culdocentesis and intravenous albumin minimizes hospitalization. *Journal of Assisted Reproduction and Genetics* 2002;**19**:159-63.

Matorras 2013 *{published and unpublished data}*

Matorras R, Andrés M, Mendoza R, Prieto B, Pijoan JI, Expósito A. Prevention of ovarian hyperstimulation syndrome in GnRH agonist IVF cycles in moderate risk patients: randomized study comparing hydroxyethyl starch versus cabergoline and hydroxyethyl starch. *European Journal of Obstetrics Gynecology and Reproductive Biology* 2013;**170**(2):439-43.

Milacic 1996 *{published data only}*

Milacic D, Radonjic G, Matijasevic S, Kontic O. Prevention of ovarian hyperstimulation syndrome with iv albumin. *Human Reproduction* 1996;**11**(1):216.

Mukherjee 1995 *{published data only}*

Mukherjee T, Copperman AB, Sandler B, Bustillo M, Grunfeld L. Severe ovarian hyperstimulation despite prophylactic albumin at the time of oocyte retrieval for in vitro fertilization and embryo transfer. *Fertility and Sterility* 1995;**64**(3):641-3.

Naredi 2013 *{published and unpublished data}*

Naredi N, Karunakaran S. Calcium gluconate infusion is as effective as the vascular endothelial growth factor antagonist cabergoline for the prevention of ovarian hyperstimulation syndrome. *Journal of Human Reproductive Sciences* 2013;**6**(4):248-52.

Ndukwe 1997 *{published data only}*

Ndukwe G, Thornton S, Fishel S, Dowell K, Aloum M. Severe ovarian hyperstimulation syndrome: is it really preventable by prophylactic intravenous albumin?. *Fertility and Sterility* 1997;**68**(5):851-4.

Ng 1995 *{published data only}*

Ng E, Leader A, Claman P, Domingo M, Spence JEH. Intravenous albumin does not prevent the development of severe ovarian hyperstimulation syndrome in an in-vitro fertilization programme. *Human Reproduction* 1995;**10**(4):807-10.

Panay 1999 *{published data only}*

Iammarone E, Panay N, ZosmerA, TozerA, Hussain S, Wilson C, et al. Does the prophylactic use of intravenous albumin prevent ovarian hyperstimulation syndrome? A randomised prospective study. *Human Fertility* 1999;**2**(2):179-180.

* Panay NA, Iammorrone E, Zosmer A, Tozer A, Hussain S. Does the prophylactic use of intravenous albumin prevent ovarian hyperstimulation syndrome? A randomized prospective study. *Abstracts from the 15th Annual Meeting of the ESHRE, Tours, France* 1999;**14**:105.

Shaker 1996 *{published data only}*

Shaker AG, Zosmer A, Dean N, Berik JS, Jacob HS, Tan SL. Comparison of intravenous albumin and transfer of fresh embryos with cryopreservation of all embryos for subsequent transfer in prevention of ovarian of ovarian hyperstimulation syndrome. *Fertility and Sterility* 1996;**65**:992-6.

Tan 1992 *{published data only}*

Tan Sl, Balen A, El Hussein E, Campbell S, Jacobs HS. The administration of glucocorticoids for the prevention of ovarian hyperstimulation syndrome in invitro fertilisation: a prospective randomised study. *Fertility and Sterility* 1992;**58**:378-83.

Tehraninejad 2012 *{published and unpublished data}*

Tehraninejad E, Hafezi M, Arabipoor A, Aziminekoo E, Chehrazi M, Bahmanabadi A. Comparison of cabergoline and intravenous albumin in the prevention of ovarian hyperstimulation syndrome: a randomized clinical trial.. *Journal of Assisted Reproduction & Genetics.* 2012;**29**(3):259-64.

Torabizadeh 2013 *{published and unpublished data}*

Torabizadeh A, Vahidroodsari F, Ghorbanpour Z. Comparison of albumin and cabergoline in the prevention of ovarian hyperstimulation syndrome: A clinical trial study.. *Iranian Journal of Reproductive Medicine* 2013;**11**(10):837-42.

Yakovenko 2009 *{published and unpublished data}*

Yakovenko SA, Zorina IV, Dmitrieva NV, Troshina MN, Apryshko VP, Voznesenskaya JV. Intravenous administration of calcium in ovarian hyperstimulation syndrome (OHSS) prevention. *European Journal of Obstetrics Gynecology and Reproductive Biology* 2011;**1**:s20.

Additional references

Aboulghar 2003

Aboulghar MA, Mansour RT. Ovarian hyperstimulation syndrome: classifications and critical analysis of preventive measures. *Human Reproduction Update* 2003;**9**(3):275-89.

Cerrilo 2009

Cerrillo M, Pacheco A, Rodríguez S, Mayoral M, Ruiz M, García Velasco JA. Differential regulation of VEGF, Cadherin, and Angiopietin 2 by trigger oocyte maturation with GnRHa vs hCG in donors: try to explain the lower OHSS incidence. *Abstracts of the 25th annual meeting of the ESHRE* 2009;**24**(1):i60.

Chen 2003a

Chen D, Burmeister L, Goldschlag D, Rosenwaks Z. Ovarian hyperstimulation syndrome: strategies for prevention. *Reproductive Biomedicine Online* 2003;**7**(1):43-9.

D'Angelo 2007

D'Angelo A, Amso NN. Embryo freezing for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD002806.pub2]

D'Angelo 2011

D'Angelo A, Brown J, Amso NN. Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 6. [DOI: 10.1002/14651858.CD002811.pub3]

Delvigne 2002

Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. *Human Reproduction Update* 2002;**8**:559-77.

Edwards 2007

Edwards RG. IVF, IVM, natural cycle IVF, minimal stimulation IVF - time for a rethink. *Reproductive Biomedicine Online* 2007;**15**:106-19.

Egbase 2000

Egbase PE. Severe OHSS: how many cases are preventable?. *Human Reproduction* 2000;**15**:8-10.

Engmann 2008

Engmann L, DiLugie A, Schmidt D, Nulsen J, Maier D, Benavida C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomised controlled study. *Fertility and Sterility* 2008;**89**(1):84-91.

Enskog 2001

Enskog A, Nilsson L, Brännström M. Plasma levels of free vascular endothelial growth factor(165) (VEGF(165)) are not elevated during gonadotropin stimulation in in vitro fertilization (IVF) patients developing ovarian hyperstimulation syndrome (OHSS): results of a prospective cohort study with matched controls. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2001;**96**:196-201.

Foong 2006

Foong LC, Bhagavath BA, Kumar J, Ng SC. Ovarian hyperstimulation syndrome is associated with reversible impairment of vascular reactivity. *Fertility and Sterility* 2002;**78**(6):1159-63.

Garcia-Velasco 2003

Garcia-Velasco JA, Pellicer A. New concepts in the understanding of the ovarian hyperstimulation syndrome. *Current Opinion in Obstetrics and Gynecology* 2003;**15**(3):251-6.

Golan 1989

Golan A, Ron-el R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. *Obstetrical & Gynecological Survey* 1989;**44**(6):430-40.

Higgins 2011

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011; Vol. Available from www.cochrane-handbook.org..

Humaidan 2010

Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: guidance for the clinician. *Fertility and Sterility* 2010;**94**(2):389–400.

Jee 2010

Jee BC, Suh CS, Kim YB, Kim SH, Choi YM, Kim JG, et al. Administration of intravenous albumin around the time of oocyte retrieval reduces pregnancy rate without preventing ovarian hyperstimulation syndrome: a systematic review and meta-analysis. *Gynecologic and Obstetric Investigation* 2010;**70**(1):47-54. Epub 2010 Feb 19.

Kol 2008

Kol S, Solt I. GnRH agonist for triggering final oocyte maturation in patients at risk of ovarian hyperstimulation syndrome: still a controversy?. *Journal of Assisted Reproduction and Genetics* 2008;**25**:63-6.

Loutradis 2006

Loutradis D, Kiapekou E, Zapanti E, Antsaklis A. Oocyte maturation in assisted reproductive techniques. *Annals of the New York Academy of Sciences* 2006;**1092**:235-46.

Mathur 2000

Mathur RS, Jenkins JM. Is ovarian hyperstimulation syndrome associated with a poor obstetric outcome?. *BJOG* 2000;**107**:943-6.

McClelland 1990

McClelland DB. Human albumin solutions. *BMJ* 1990;**300**:35-57.

Navot 1988

Navot D, Relou A, Birkenfeld A, Rabinowitz R, Brzezinski A, Margalioth EJ. Risk factors and prognostic variables in the ovarian hyperstimulation syndrome. *American Journal of Obstetrics and Gynecology* 1988;**159**:210-5.

Navot 1992

Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies:prevention and treatment. *Fertility & Sterility* 1992;**58**:249-61.

Rizk 1997

Rizk B, Aboulghar M, Smitz J, Ron-El R. The role of vascular endothelial growth factor and interleukins in the pathogenesis of severe ovarian hyperstimulation syndrome. *Human Reproduction Update* 1997;**3**:255-6.

Rizk 1999

Rizk B, Aboulghar MA. Classification, pathophysiology and management of ovarian hyperstimulation syndrome. In: Brinsden P editor(s). In-Vitro Fertilization and Assisted Reproduction. New York, London: The Parthenon Publishing Group, 1999:131-55.

Schenker 1978

Schenker JG, Weinstein D. Ovarian hyperstimulation syndrome: a current survey. *Fertility and Sterility* 1978;**30**:225-68.

Shawkat 2012

Shawkat H, Westwood M, Mortimer A. Mannitol: a review of its clinical uses. *Continuing Education in Anaesthesia, Critical Care & Pain* 2012;**12**(2):82-5.

Tang 2012

Tang H, Hunter T, Hu Y, Zhai SD, Sheng X, Hart RJ. Cabergoline for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2012, Issue 2. [DOI: 10.1002/14651858.CD008605.pub2]

Venetis 2011

Venetis CA, Kolibianakis EM, Toulis KA, Goulis DG, Papadimas I, Tarlatzis BC. Intravenous albumin administration for the prevention of severe ovarian hyperstimulation syndrome: a systematic review and metaanalysis. *Fertility and Sterilility* 2011;**95**(1):188-96.

Vloeberghs 2009

Vloeberghs V, Peeraer K, Pexsters A, D'Hooghe T. Ovarianhyperstimulation syndrome and complications of ART. *Best Practice & Research. Clinical Obstetrics & Gynaecology* 2009;**23**(5):691-709.

WHO 1973

WHO. Agents stimulating gonadal function in human. World Health Organization Technical Report Series 1973:514-20.

Yan 1993

Yan Z, Weich HA, Bernart W, Breckwoldt M, Neulen J. Ascular endothelial growth factor (VEGF) messenger ribonucleic acid (mRNA) expression in luteinized human granulosa cells in vitro. *Journal of Clinical Endocrinology and Metabolism* 1993;**77**:1723-5.

Youssef 2014

Youssef MAFM, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. *Cochrane Database of Systematic Reviews* 2014, Issue 10. [DOI: 10.1002/14651858.CD008046.pub4]

References to other published versions of this review

Youssef 2002

Youssef MA, Al-Inany HG, Evers JHANSLH, Aboulghar M. Intravenous fluids preventing severe ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2002, Issue 2. [DOI: 10.1002/14651858.CD001302]

Youssef 2011

Youssef MAFM, Al-Inany HG, Evers JLH, Aboulghar M. Intra-venous fluids for the prevention of severe ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD001302.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bellver 2003

Methods	Randomised controlled trial Parallel design Single centre Not blind Power calculation: done
Participants	988 women (infertile women n = 605 and donors n = 383) who were all considered to be at risk of moderate or severe OHSS (495 albumin/493 control) > 20 retrieved oocytes was the basic risk factor of OHSS Age (29.9 versus 29.7years) Duration of infertility (not stated) No. of FSH and hMG ampoules (not stated) No. of oocytes (28.7 versus 27.8) No. of embryos (15 versus 19) No. of transferred embryos (2.8 versus 3.0)
Interventions	**Study group:** 40 g human albumin infused intravenously at a slow rate, immediately after oocyte retrieval **Duration**: during 30 min **Control group**: no treatment
Outcomes	Method of diagnosing severe OHSS: criteria for (Golan 1989) Severe OHSS: 25/495 versus 23/493

Bellver 2003 *(Continued)*

	Pregnancy: 138/298 versus 166/307 Method of diagnosing pregnancy: fetal heart rate Tolerability: yes Safety: yes Cost-benefit: stated (195 euros/patient)
Notes	Two kinds of GnRH agonist were used and only early OHSS was assessed. Placebo was not used in their control group, which eliminates the placebo effect of albumin administration. Serum E2 level, which was previously reported as an independent risk factor for severe OHSS, was not considered a high-risk factor in this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	966/988 (98%) randomised women included in analysis
Selective reporting (reporting bias)	Unclear risk	Unclear whether data on adverse events were collected prospectively as it was not a prespecified outcome, though mentioned in the discussion section
Other bias	Low risk	No other potential bias identified

Gokmen 2001

Methods	Randomised controlled trial, three-arm trial, parallel design, single centre Power calculation: not done
Participants	250 infertile women at risk of severe OHSS (82 albumin/83 control/85 HES) E2 (the basic risk factor of OHSS) was 3000 pg/mL or the presence of > 20 follicles on the day of hCG. Age: albumin 29.6 versus HES 31.2 versus placebo 32.3 years Duration of infertility (not mentioned) No. of hMG ampoules (not mentioned) No.of oocytes (albumin 12.0 versus HES 13.2 versus placebo 11.1) No.of embryos (albumin 3.3 versus HES 3.1 versus placebo 3.0)
Interventions	**Study group:** 10 g albumin immediately after oocyte retrieval, or 6% HES (200/0.5) 500 mL **Duration of infusion**: over 30 minutes **Control group:** received saline
Outcomes	Method of diagnosing severe OHSS: criteria of Schenker and Weinstein, 1978 Severe OHSS: albumin versus control 0/82 versus 4/83, and HES versus control 0/85 versus 4/83 Pregnancy: albumin versus control 11/82 versus 10/83, and HES versus control 12/85 versus 10/83 Method of diagnosing pregnancy: serum β-hCG Tolerability: yes

Gokmen 2001 *(Continued)*

	Safety: one case of anaphylactic reaction with albumin and two cases of urticaria with HES Cost-benefit: not stated
Notes	Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	250 women randomised and all included in analysis - but later unpublished report (Gokmen 2005) apparently refers to same study and includes a larger sample and two additional events. Attempts to contact the study authors were unsuccessful.
Selective reporting (reporting bias)	Unclear risk	Unclear whether data on adverse events were collected prospectively as it was not a prespecified outcome
Other bias	Low risk	No other potential bias identified

Isik 1996

Methods	Randomised controlled trial, parallel design, single centre Power calculation: done
Participants	55 infertile women who were all considered to be at risk of severe OHSS (27 albumin/28 control) E2 (the basic risk factor of OHSS) was 11010 pmol/L Age (31.2 versus 30.8 years) Duration of infertility (7.8 versus 7.3) No. of hMG ampoules (25.9 versus 26.1) No. of oocytes (15.3 versus 16.4) No. of embryos (3.2 versus 3)
Interventions	**Study group:** 10 g albumin 2 hours before oocyte retrieval **Duration of infusion**: over 1 hour **Control group**: no treatment
Outcomes	Method of diagnosing severe OHSS: criteria of Schenker and Weinstein, 1978 Severe OHSS: 0/27 versus 1/28 Pregnancy: 5/27 versus 5/28 Method of diagnosing pregnancy: serum β-hCG Tolerability: yes Safety: 2 urticaria Cost-benefit: not stated
Notes	Source of funding: not stated

Isik 1996 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random table
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women included in analysis
Selective reporting (reporting bias)	Unclear risk	Unclear whether data on adverse events were collected prospectively as it was not a prespecified outcome, though mentioned in the results section
Other bias	Low risk	No other potential bias identified

Isikoglu 2007

Methods	Randomised, placebo-controlled trial, parallel design, single centre No sample size calculation
Participants	**Study group:** 75 infertile women who were all considered to be at risk of severe OHSS (38 albumin/37control) High blood E2 level (> 4000 pg/mL) and > 20 follicles R14 mm on the day of hCG administration have been defined as the basic risk factors for severe OHSS Age (29.3 versus 29.1 years) Duration of infertility (not stated) No. of hMG ampoules (no significant difference between both groups) No. of FSH ampoules (no significant difference between both groups) No.of oocytes (22.6 versus 20.5) No.of embryos (3.4 versus 3.2)
Interventions	**Study group:** 10 g (50 cc, 20% HSA diluted in 100 mL 0.9% NaCl or 100 mL 0.9% NaCl) just after oocyte retrieval **Duration**: 1 hour **Control group**: 100 mL 0.9% NaCl
Outcomes	Method of diagnosing severe OHSS: according to Navot et al, 1992 Severe OHSS: 8/38 versus 6/37 Pregnancy: 21/38 versus 23/37 Method of diagnosing clinical pregnancy: heartbeat at ultrasound 3 weeks after ET Tolerability: yes Safety: yes Cost-benefit: not calculated
Notes	

Isikoglu 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods unclear: "Patients were randomised by third-party sealed envelope entry"
Allocation concealment (selection bias)	Unclear risk	Methods unclear: "Patients were randomised by third-party sealed envelope entry"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The outcome assessors were blind to the interventions. The patients were also blind to the infusions"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were included in analysis
Selective reporting (reporting bias)	Unclear risk	Unclear whether data on adverse events were collected prospectively as it was not a prespecified outcome, though mentioned in the results section
Other bias	Low risk	No other potential bias identified

Koike 1999

Methods	Randomised, placebo-controlled trial, single centre, unpublished
Participants	98 infertile women at risk of severe OHSS (43 albumin plus saline versus 55 saline alone) undergoing IVF/ICSI/GIFT > 20 oocytes were retrieved from patients at high risk.The estradiol in their serum was not measured Age (32.1 versus 31.0 years) Duration of infertility (not stated) No. of hMG ampoules (not stated) No. of oocytes (27 versus 26.1) No. of embryos (19 versus 17)
Interventions	**Study group**: 37.5 g albumin plus 1000 mL electrolyte solution just after oocyte retrieval **Duration**: consecutive 3 days **Control group**: 1000 mL electrolyte solution for consecutive 3 days
Outcomes	Method of diagnosing severe OHSS: marked haemoconcentration (haematocrit ≥ 45) and/or hypoproteinaemia (serum total protein < 6.0 g/dL) in addition to marked ascites on the upper abdomen at least 4 days after oocyte retrieval (Orvieto and Ben-Rafael,1998) Severe OHSS: 13/43 versus 21/55 Pregnancy: 14/43 versus 24/55 Method of diagnosing pregnancy: serum β-hCG Tolerability: not stated Safety: not stated Cost-benefit: not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Koike 1999 *(Continued)*

Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Methods not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women included in analysis
Selective reporting (reporting bias)	Unclear risk	Adverse effects not reported as an outcome
Other bias	Unclear risk	No other potential bias identified

Konig 1998

Methods	Randomised, placebo-controlled, double blind
Participants	104 infertile women at risk of severe OHSS (53 HES/51 control) E2 the basic risk factor of OHSS) was > 1500 pg/mL and more than 10 follicles on the day of hCG injection Age (HES 32.6 versus placebo 30.7 years) Duration of infertility (not mentioned) No. of hMG ampoules (not mentioned, similar in both groups) No. of oocytes (not mentioned, similar in both groups) No. of embryos (not mentioned)
Interventions	**Study group:** 1000 mL of 6% HES solution shortly after embryo transfer (48 hr after the oocyte retrieval) originally 104 pt randomised: HES 53 control 51; data presented only for 51 and 50 patients respectively. dropout 2.9% (3 women; 2 missing data, 1 allergic reaction) **Duration of infusion**: over 2 hours **Control group**: 1000 mL NaCl 0.9% solution
Outcomes	Method of diagnosing severe OHSS: criteria of WHO, 1973 Severe OHSS 0/53 versus 1/51 Pregnancy: not stated but similar between both group Method of diagnosing pregnancy: not stated (clinical pregnancy) Tolerability: yes Safety: one case of urticaria Cost-benefit: not stated
Notes	Commercially funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table

Konig 1998 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Methods not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double blinded; both patients and physicians blinded, but outcome assessors not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	101/104 (97%) randomised women were included in analysis
Selective reporting (reporting bias)	Unclear risk	Unclear whether data on adverse events were collected prospectively as it was not a prespecified outcome, though mentioned in the results section
Other bias	Unclear risk	No other potential bias identified

Saremi 2003

Methods	Randomised controlled trial; simple randomisation per random number table
Participants	226 patients with endocrine and sonographic evidence of PCOS. 110 women study group, 116 women control group E2 : no threshold for inclusion. Exclusion and cancelling when E2 > 6000 pg/mL Age (mannitol 27.5yr vs control 28.6yr)) Duration of infertility not mentioned No. of hMG ampoules not mentioned No. of oocytes (mannitol 25.5 vs control 23.6) similar in both groups No. of embryos (not mentioned)
Interventions	**Study group (A):** 3 gr/kg bodyweight mannitol (20 g mannitol/100 mL water for injection) daily starting on the day after hCG injection until third day after embryo transfer (lasting 5-7 days depending on day of transfer) **Duration of infusion:** 30-60 minutes **Control group (B):** no drugs
Outcomes	Incidence of OHSS (mild, moderate and severe), pregnancy rates (defined as heartbeat at ultrasound 3 weeks after ET), blood pressure, Hb levels, white blood cell count, vital sign per 4 hrs after administration, serum osmolality and osmolar gap, intake and output volumes before and during mannitol administration & renal functionality, serum electrolytes
Notes	Funding not stated; additional information from correspondence with author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation per random number table
Allocation concealment (selection bias)	Unclear risk	Methods not reported

Saremi 2003 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Physicians were blinded to the allocated groups, nurse performed protocol
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women included in analysis, no drop-outs
Selective reporting (reporting bias)	Unclear risk	Data on adverse events were collected though not explicitly mentioned what kind of events. "mannitol protocol, all of the lab tests and patient's signs and symptoms were recorded; including vital sign Q4h, serum osmolality and osmolar gap, intake and output volumes before and during mannitol administration & renal functionality, serum electrolytes and etc… " (private correspondence)
Other bias	Low risk	No other potential bias detected

Shalev 1995

Methods	Randomised, placebo-controlled trial, parallel design, single centre No power of calculation
Participants	40 infertile women who were all considered to be at risk of severe OHSS (22 albumin/18control) E2 (the basic risk factor of OHSS) was 9200 pmol/L Age (29.7 versus 28.3 years) Duration of infertility (not stated) No. of hMG ampoules (not stated) No. of oocytes (21 versus 19.3) No. of embryos (19 versus 17)
Interventions	**Study group:** 20 g albumin just after oocyte retrieval **Duration**: not stated **Control group**: no treatment
Outcomes	Method of diagnosing severe OHSS: according to Navot et al, 1992 Severe OHSS: 0/22 versus 4/18 Pregnancy: 6/22 versus 2/18 Method of diagnosing pregnancy: serum β-hCG Tolerability: yes Safety: yes Cost-benefit: not stated
Notes	Source of funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Methods not reported

Shalev 1995 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women were included in analysis
Selective reporting (reporting bias)	Unclear risk	Unclear whether data on adverse events were collected prospectively as it was not a prespecified outcome, though mentioned in the results section
Other bias	Low risk	No other potential bias identified

Shoham 1994

Methods	Randomised, placebo-controlled trial, parallel design, single centre
Participants	31 infertile women who were all considered to be at risk of severe OHSS (16 albumin/15control) E2 (the basic risk factor of OHSS was 7000 pmol/L) Age (32.5 versus 29.7 years) Duration of infertility (6.9 versus 7) No. of hMG ampoules: (23.3 versus 22.7) No. of oocytes: (13.4 versus 12.6) No. of embryos: (3.4 versus 3.2)
Interventions	**Study group:** 50 g albumin 2 hours before oocyte retrieval **Duration**: over 1 hour **Control group**: 500 mL of 9% NaCl
Outcomes	Method of diagnosing severe OHSS: criteria for Schenker and Weinstein, 1978 Severe OHSS (0/16 versus 4/15) Pregnancy: (4/16 versus 2/15) Method of diagnosing pregnancy: serum β-hCG Tolerability: yes Safety: yes Cost-benefit: not stated
Notes	Source of funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not reported
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not reported
Incomplete outcome data (attrition bias)	Low risk	All randomised women included in analysis

Shoham 1994 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Unclear whether data on adverse events were collected prospectively as it was not a prespecified outcome, though mentioned in the results section
Other bias	Low risk	No other potential bias identified

ET: embryo transfer
FSH: follicle-stimulating hormone
GIFT: gamete intra-fallopian transfer
GnRH: gonadotropin-releasing hormone
Hb: haemoglobin
hCG: human chorionic gonadotrophin
HES: hydroxyethyl starch
hMG: human menopausal gonadotropin
ICSI: intracytoplasmic sperm injection
IVF: in vitro fertilisation
NaCl: sodium chloride
OHSS: ovarian hyperstimulation syndrome
PCOS: polycystic ovary syndrome

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abramov 2001	Case control study
Abuzeid 2010	Prospective cohort clinical trial
Ahmadi 2010	RCT, compared human albumin with cabergoline as prophylaxis of OHSS
Asch 1993	Case series
Ben-Chetrit 2001	Quasi-randomised study
Ben-Rafael 1995	Case series
Cambiaghi 2005	RCT compared oral whey protein versus albumin
Chen 1997	Prospective non-randomised trial with historical control
Chen 2003	Retrospective study, compared coasting versus intravenous albumin
Costabile 2000	Albumin infusion versus intra-muscular progesterone
Dmitrieva 2010	RCT, compared starch solution versus calcium gluconate in prevention of OHSS
Egbase 1997	Non-controlled randomised study
El-Khayat 2015	RCT, excluded because calcium gluconate is not a volume expander
Endo 2004	Quasi-randomised study, comparing human albumin versus dextran
Fan 2006	Randomised, placebo-controlled trial comparing human albumin versus hydroxyethyl starch versus placebo. Abstract and the data were not reported clearly

Study	Reason for exclusion
Fluker 2000	Prospective cohort study
Gamzu 2002	Non-randomised study, comparing hydroxyethyl starch versus Haemaccel
Gokmen 2005	Data appear to overlap with Gokmen 2001. Attempts to obtain clarification from author were unsuccessful
Graf 1997	Cohort study
Halme 1995	Case report
Isik 1997	Non-controlled randomised study
Isik 2001	Non-randomised study, used combined approach for OHSS prevention
Kissler 2001	Case report
Koike 2000	Randomised controlled trial comparing human albumin versus continuous autotransfusion system of ascites (CASTA)
Kumbak 2005	Retrospective study
Lewit 1996	Retrospective case series
Lincolin 2002	Retrospective study
Matorras 2013	comparison of HES vs cabergoline and HES
Milacic 1996	Method of randomisation was unclear
Mukherjee 1995	Case reports
Naredi 2013	Quasi-randomised study (patients appointed to groups by odd/ even registration numbers)
Ndukwe 1997	Retrospective review and data analysis
Ng 1995	Cohort study
Panay 1999	RCT, quasi-randomised
Shaker 1996	Compared albumin infusion versus embryo cryopreservation
Tan 1992	The trial did not study the relevant intervention, instead it studied the use of glucocorticoids
Tehraninejad 2012	Comparison of cabergoline with albumin
Torabizadeh 2013	Comparison of cabergoline versus albumin
Yakovenko 2009	Comparison of calcium gluconate versus HES

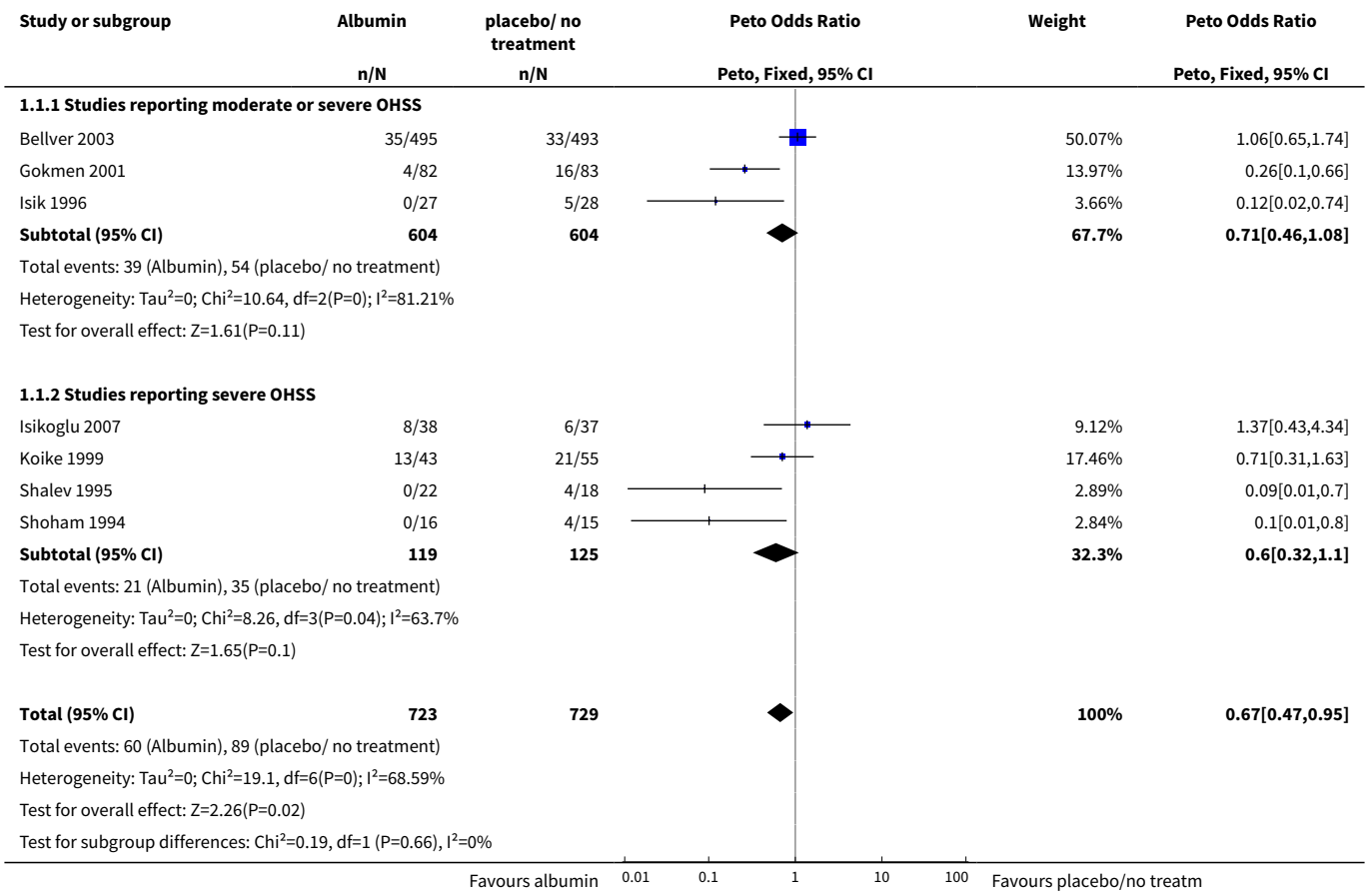
HES: hydroxyethyl starch
OHSS: ovarian hyperstimulation syndrome
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Human Albumin vs placebo / no treatment

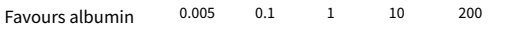
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total OHSS	7	1452	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.47, 0.95]
1.1 Studies reporting moderate or severe OHSS	3	1208	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.46, 1.08]
1.2 Studies reporting severe OHSS	4	244	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.32, 1.10]
2 Pregnancy rate	7	1069	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.55, 0.94]

Analysis 1.1. Comparison 1 Human Albumin vs placebo / no treatment, Outcome 1 Total OHSS.



Analysis 1.2. Comparison 1 Human Albumin vs placebo / no treatment, Outcome 2 Pregnancy rate.

Study or subgroup	Favours albumin n/N	placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bellver 2003	138/298	166/307		71.16%	0.73[0.53,1.01]
Gokmen 2001	11/82	10/83		8.66%	1.13[0.45,2.82]
Isik 1996	0/27	1/28		0.47%	0.14[0,7.07]
Isikoglu 2007	8/38	6/37		5.42%	1.37[0.43,4.34]
Koike 1999	14/43	24/55		10.88%	0.63[0.28,1.42]
Shalev 1995	0/22	4/18		1.72%	0.09[0.01,0.7]
Shoham 1994	0/16	4/15		1.69%	0.1[0.01,0.8]
Total (95% CI)	**526**	**543**		**100%**	**0.72[0.55,0.94]**
Total events: 171 (Favours albumin), 215 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=10.34, df=6(P=0.11); I^2=41.99%					
Test for overall effect: Z=2.43(P=0.02)					



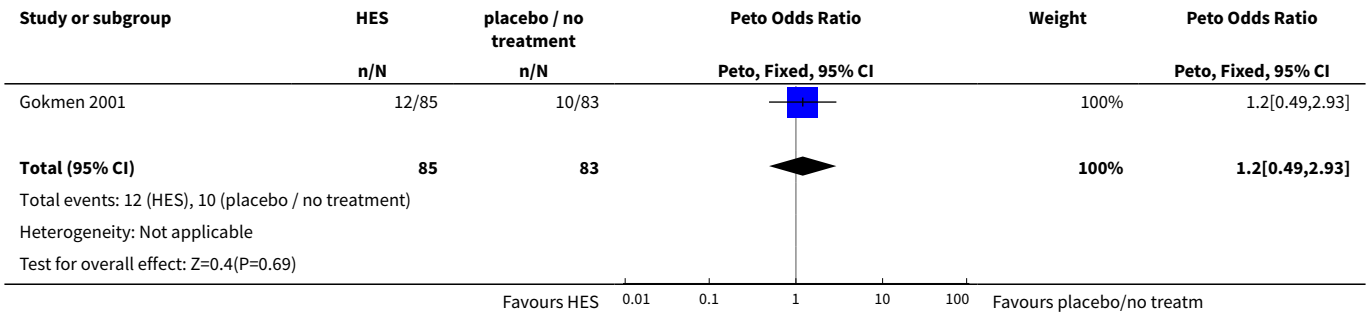
Comparison 2. HES vs placebo / no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total OHSS	2	272	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.12, 0.59]
1.1 studies reporting moderate or severe OHSS	2	272	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.12, 0.59]
2 Pregnancy rate	1	168	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.49, 2.93]

Analysis 2.1. Comparison 2 HES vs placebo / no treatment, Outcome 1 Total OHSS.

Study or subgroup	Favours HES n/N	placebo / no treatment n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.1.1 studies reporting moderate or severe OHSS					
Gokmen 2001	5/85	16/83		73.72%	0.3[0.12,0.74]
Konig 1998	1/53	6/51		26.28%	0.21[0.05,0.97]
Subtotal (95% CI)	**138**	**134**		**100%**	**0.27[0.12,0.59]**
Total events: 6 (Favours HES), 22 (placebo / no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%					
Test for overall effect: Z=3.27(P=0)					
Total (95% CI)	**138**	**134**		**100%**	**0.27[0.12,0.59]**
Total events: 6 (Favours HES), 22 (placebo / no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%					
Test for overall effect: Z=3.27(P=0)					

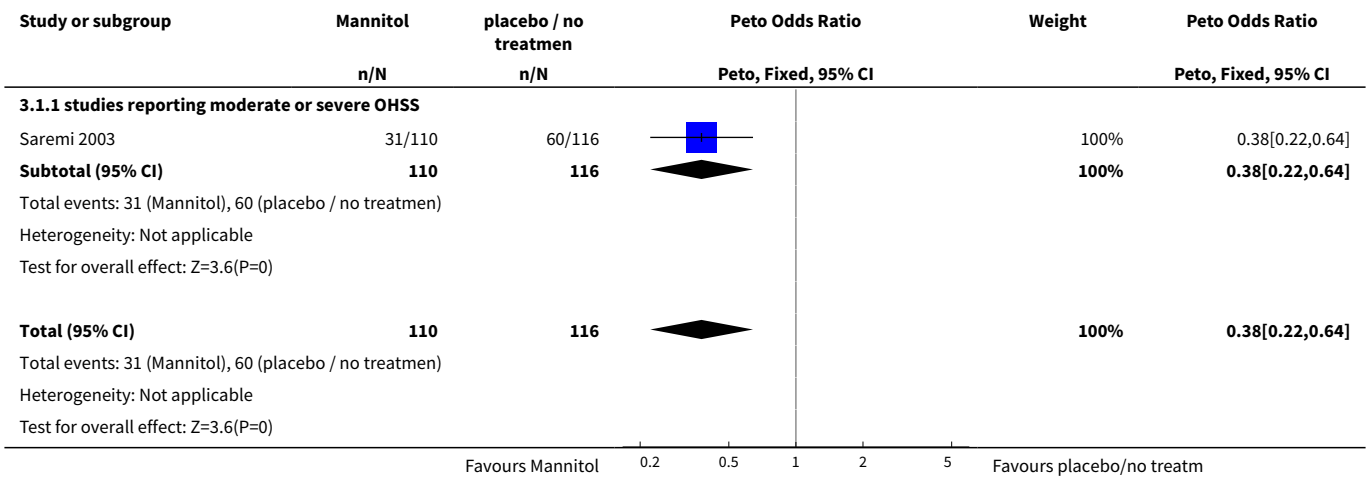
Analysis 2.2. Comparison 2 HES vs placebo / no treatment, Outcome 2 Pregnancy rate.



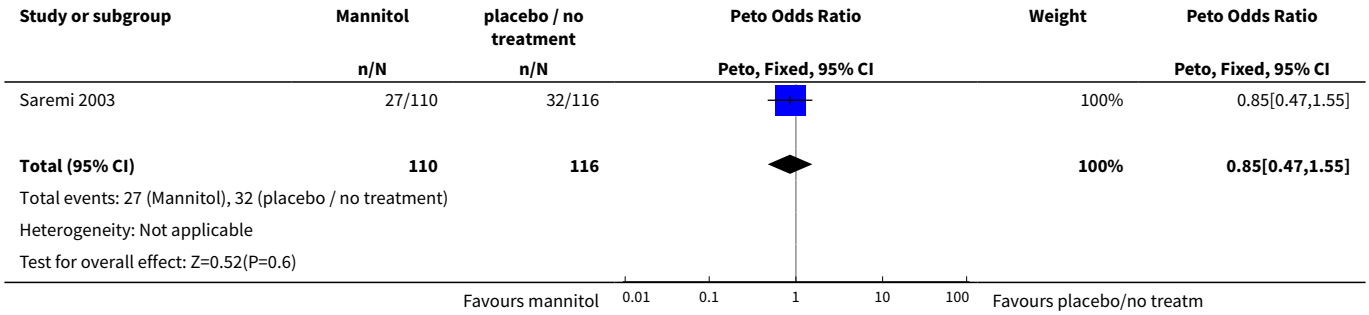
Comparison 3. Mannitol vs placebo / no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total OHSS	1	226	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.22, 0.64]
1.1 studies reporting moderate or severe OHSS	1	226	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.22, 0.64]
2 Pregnancy rate	1	226	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.47, 1.55]

Analysis 3.1. Comparison 3 Mannitol vs placebo / no treatment, Outcome 1 Total OHSS.



Analysis 3.2. Comparison 3 Mannitol vs placebo / no treatment, Outcome 2 Pregnancy rate.



APPENDICES

Appendix 1. CGF database search (formerly MDSG)

MDSG search strategy iv fluids for OHSS 15.09.15

Keywords CONTAINS "ovarian hyperstimulation" or "ovarian hyperstimulation syndrome " or "OHSS" or Title CONTAINS" ovarian hyperstimulation" or "ovarian hyperstimulation syndrome " or "OHSS"

AND

Keywords CONTAINS "human albumin" or "human serum albumin" or "human sera" or "albumin" or "hydroxyethyl starch" or "hydroxyethyle starch" or "intravenous albumin" or "intravenous fluids" or "intravenous" or "Calcium" or "calcium gluconate" or "starch solution" or "mannitol" or Title CONTAINS "human albumin" or "human serum albumin" or "human sera" or "albumin" or "hydroxyethyl starch" or "hydroxyethyle starch" or "intravenous albumin" or "intravenous fluids" or "intravenous" or "Calcium" or "calcium gluconate" or "starch solution" or "mannitol"

Appendix 2. Cochrane Central Register of Controlled Trials

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <02.09.2015>
Search Strategy:
---
1 exp Ovarian Hyperstimulation Syndrome/ (143)
2 Ovarian Hyperstimulation Syndrome.tw. (309)
3 OHSS.tw. (227)
4 or/1-3 (408)
5 exp Serum Albumin/ (1044)
6 Albumin$.tw. (6084)
7 human sera.tw. (24)
8 colloid$.tw. (1276)
9 exp starch/ or exp hetastarch/ (1018)
10 hydroxyethyl$.tw. (1018)
11 (starch or hetastarch).tw. (1567)
12 HES.tw. (583)
13 haemacel.tw. (1)
14 Haemaccel.tw. (52)
15 exp Calcium Gluconate/ (43)
16 Calcium.tw. (13188)
17 intravenous fluid$.tw. (533)
18 iv fluid$.tw. (204)
19 exp Infusions, Intravenous/ (8755)
20 exp Fluid Therapy/ (1127)
21 exp mannitol/ (375)
22 mannitol.tw. (782)
23 (osmitrol or osmofundin).tw. (0)
24 or/5-23 (32416)

25 4 and 24 (41)

Appendix 3. Ovid MEDLINE®

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>02.09.2015
Search Strategy:
---
1 exp Ovarian Hyperstimulation Syndrome/ (1881)
2 Ovarian Hyperstimulation Syndrome.tw. (2167)
3 OHSS.tw. (1288)
4 or/1-3 (2789)
5 exp Serum Albumin/ (71943)
6 Albumin$.tw. (126452)
7 human sera.tw. (6398)
8 colloid$.tw. (41622)
9 exp starch/ or exp hetastarch/ (33340)
10 hydroxyethyl$.tw. (12274)
11 (starch or hetastarch).tw. (27745)
12 HES.tw. (4360)
13 haemacel.tw. (6)
14 Haemaccel.tw. (249)
15 exp Calcium Gluconate/ (937)
16 Calcium.tw. (311984)
17 intravenous fluid$.tw. (4082)
18 iv fluid$.tw. (1017)
19 exp Infusions, Intravenous/ (49843)
20 exp Fluid Therapy/ (15810)
21 exp mannitol/ (11611)
22 mannitol.tw. (15517)
23 (osmitrol or osmofundin).tw. (1)
24 or/5-23 (649695)
25 4 and 24 (178)
26 randomized controlled trial.pt. (411031)
27 controlled clinical trial.pt. (91630)
28 randomized.ab. (334732)
29 placebo.tw. (173207)
30 clinical trials as topic.sh. (178556)
31 randomly.ab. (241080)
32 trial.ti. (147726)
33 (crossover or cross-over or cross over).tw. (66041)
34 or/26-33 (1021994)
35 exp animals/ not humans.sh. (4113129)
36 34 not 35 (941700)
37 25 and 36 (36)

Appendix 4. EMBASE

Database: Embase <1980 to 2015 Week 37> 02.09.2015
Search Strategy:
---
1 exp ovary hyperstimulation/ (6927)
2 Ovarian Hyperstimulation.tw. (5643)
3 OHSS.tw. (2090)
4 or/1-3 (8564)
5 exp Serum Albumin/ (28111)
6 Albumin$.tw. (147231)
7 colloid$.tw. (42324)
8 exp starch/ or exp hetastarch/ (25916)
9 exp starch/ (20467)
10 exp hetastarch/ (5626)
11 hydroxyethyl.tw. (10802)
12 (starch or hetastarch).tw. (31085)

13 HES.tw. (6162)
14 haemacel.tw. (32)
15 Haemaccel.tw. (436)
16 exp gluconate calcium/ (4508)
17 calcium.tw. (353894)
18 intravenous fluid$.tw. (5388)
19 iv fluid$.tw. (2002)
20 exp infusion fluid/ (22326)
21 exp mannitol/ (25703)
22 mannitol.tw. (17118)
23 (osmitrol or osmofundin).tw. (63)
24 or/5-23 (647541)
25 4 and 24 (270)
26 Clinical Trial/ (850170)
27 Randomized Controlled Trial/ (382698)
28 exp randomization/ (67925)
29 Single Blind Procedure/ (20923)
30 Double Blind Procedure/ (123268)
31 Crossover Procedure/ (44330)
32 Placebo/ (262629)
33 Randomi?ed controlled trial$.tw. (123047)
34 Rct.tw. (18107)
35 random allocation.tw. (1447)
36 randomly allocated.tw. (23181)
37 allocated randomly.tw. (2054)
38 (allocated adj2 random).tw. (736)
39 Single blind$.tw. (16320)
40 Double blind$.tw. (154326)
41 ((treble or triple) adj blind$).tw. (482)
42 placebo$.tw. (220002)
43 prospective study/ (305847)
44 or/26-43 (1499732)
45 case study/ (33720)
46 case report.tw. (290494)
47 abstract report/ or letter/ (936759)
48 or/45-47 (1254488)
49 44 not 48 (1459953)
50 49 and 25 (76)

Appendix 5. Ovid PsycINFO

Database: PsycINFO <1806 to September Week 1 2015> 02.09.2015
Search Strategy:
---
1 Ovarian Hyperstimulation Syndrome.tw. (4)
2 OHSS.tw. (6)
3 or/1-2 (8)
4 exp Serum Albumin/ (210)
5 Albumin$.tw. (1205)
6 colloid$.tw. (193)
7 (starch or hetastarch).tw. (286)
8 hydroxyethyl.tw. (47)
9 HES.tw. (436)
10 haemacel.tw. (0)
11 Haemaccel.tw. (0)
12 calcium/ or calcium.tw. (11395)
13 intravenous fluid$.tw. (103)
14 iv fluid$.tw. (35)
15 Intravenous Infusion$.tw. (531)
16 mannitol.tw. (127)
17 or/4-16 (14271)
18 3 and 17 (0)

Appendix 6. CINAHL

CINAHL search strategy for PMA481 02.09.15

#	Query	Results
S22	S4 AND S21	10
S21	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	45,131
S20	TX Fluid* N2 Therap*	4,743
S19	(MM "Infusions, Intravenous")	1,111
S18	TX iv fluid*	291
S17	TX intravenous fluid*	1,060
S16	TX Calcium or (MM "mannitol")or TX mannitol	26,628
S15	(MM "Calcium")	3,739
S14	TX Haemaccel	22
S13	TX haemacel	1
S12	TX hetastarch	73
S11	TX starch	1,393
S10	TX hydroxyethyl	696
S9	(MM "Hydroxyethyl Starch")	388
S8	TX colloid*	1,185
S7	TX human sera	89
S6	TX Albumin*	10,636
S5	(MM "Serum Albumin")	836
S4	S1 OR S2 OR S3	278
S3	TX OHSS	79
S2	TX Ovarian Hyperstimulation Syndrome	265
S1	(MM "Ovarian Hyperstimulation Syndrome")	140

Appendix 7. Pubmed

search up to 29.07.2015

ohss and albumin (16 hits)

ohss and calcium (5 hits)

ohss and intravenous (18 hits)

ohss and starch (4 hits)

Appendix 8. ICTRP

search up to 29.07.2015

ohss and albumin (4 hits)

ohss and calcium (3 hits)

ohss and mannitol (0 hits)

ohss and intravenous (1 hits)

ohss and starch (2 hits)

ohss and fluid* (1 hits)

Appendix 9. Clinicaltrials.gov

search up to 29.07.2015

ohss and albumin (4 hits)

ohss and mannitol (0 hits)

ohss and calcium (3hits)

ohss and intravenous (2 hits)

ohss and starch (1 hits)

ohss and fluid* (13 hits)

WHAT'S NEW

Date	Event	Description
4 November 2016	Review declared as stable	Further evidence is unlikely to change the conclusions of this review.

HISTORY

Protocol first published: Issue 4, 1998
Review first published: Issue 4, 1999

Date	Event	Description
29 August 2016	New search has been performed	The revision of evidence and addition of a new comparison have led to a change in the conclusions of this review.
9 September 2015	New citation required and conclusions have changed	New search. The title has been amended to reflect differences in the inclusion criteria and change to moderate or severe OHSS as the primary outcome (previously just severe OHSS). One study added for one new comparison (mannitol versus no treatment;

Date	Event	Description
		Saremi 2003). Exclusion of suspected duplicate data. Extra author added. 'Summary of findings' table added.
2 November 2010	New citation required and conclusions have changed	Substantive amendment
24 September 2009	Amended	The title was changed from Intra-venous albumin for preventing severe ovarian hyperstimulation syndrome to Intra-venous fluids for the prevention of severe ovarian hyperstimulation syndrome
1 August 2009	New search has been performed	Five RCTs were added New comparisons 1- Between hydroxyethyl starch versus placebo 2- Overall comparison of IV fluid stratified by the nature of intervention
1 August 2009	New citation required and conclusions have changed	The conclusion has changed and a new author was added with change of authors' order
7 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Mohamed AFM Youssef: performed searches of databases for new trials for the first review update, was involved in selecting trials for inclusion, performed independent data extraction and quality assessment of the included trials, was involved in writing the review, statistical analysis and interpretation of the data.

Selma Mourad: contributed to the 2016 update. Performed searches of databases for new trials, selecting trials for inclusion, corresponding with authors of primary studies, performed independent data extraction and quality assessment of the included trials, was responsible for interpretation of the data, adding the summary of findings tables and updating the main review text.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None specified by review author, Other.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original plan for the review was to only study the preventive effect of human albumin administration on OHSS. During the 2010 update process it was decided that the review should be broadened to include all kinds of intravenous fluids being used in the prevention of OHSS. The only other intravenous fluid for which randomised controlled trials with a placebo or 'no treatment' control group could be found at that time, was hydroxyethyl starch (HES).

For the 2016 update, there were two new comparisons found, i.e. calcium gluconate and mannitol. However, calcium gluconate has a very different pathophysiological mechanism than the other fluids used, which all are volume expanders. A discussion on this topic took place between the authors and led to a decision to maintain a focus on volume expanders only. Therefore, we amended the protocol and changed the title accordingly.

The 2016 update also is the first version of the review to include 'moderate OHSS' as part of the primary outcome measure, as this is a clinically relevant degree of OHSS that could easily proceed to severe OHSS. Moreover, other interventional Cochrane reviews on the prevention of OHSS also use 'moderate OHSS' as an outcome.

Also in 2016 we added a subgroup analysis for the outcome clinical pregnancy, to explore whether the effect of the intervention on pregnancy rates was different in studies that diagnosed pregnancy by ultrasonic visualisation of fetal heart beat rather than by pregnancy test.

INDEX TERMS

Medical Subject Headings (MeSH)

Fertilization in Vitro; Hydroxyethyl Starch Derivatives [*administration & dosage]; Injections, Intravenous; Ovarian Hyperstimulation Syndrome [*prevention & control]; Plasma Substitutes [*administration & dosage]; Pregnancy Rate; Randomized Controlled Trials as Topic; Serum Albumin [*administration & dosage]; Sperm Injections, Intracytoplasmic

MeSH check words

Female; Humans; Pregnancy