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Embryo freezing for preventing ovarian hyperstimulation syndrome (Review)

D'Angelo A, Amso NN

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Embryo freezing for preventing ovarian hyperstimulation syndrome.
Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD002806.
DOI: 10.1002/14651858.CD002806.pub2.

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TABLE OF CONTENTS

[Intervention Review]

Embryo freezing for preventing ovarian hyperstimulation syndrome

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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 2, 2012.

Citation: D'Angelo A, Amso NN. Embryo freezing for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD002806. DOI: 10.1002/14651858.CD002806.pub2.

ABSTRACT

Background

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic potentially life threatening condition resulting from an excessive ovarian stimulation. Its reported incidence varies from one percent to ten percent of in vitro fertilization (IVF) cycles. It seems likely that the release of vasoactive substances, secreted by the ovaries under human chorionic gonadotropin (hCG) stimulation plays a key role in triggering this syndrome. The hallmark of this condition, is a massive shift of fluid from the intra-vascular compartment to the third space resulting in profound intra-vascular depletion and haemoconcentration.

Objectives

To evaluate
(i) the effectiveness of cryopreservation (embryo freezing) for the prevention of OHSS when compared with human intra-venous albumin infusion
(ii) the effectiveness of the elective cryopreservation (embryo freezing) of all embryos for the prevention of OHSS when compared with fresh embryo transfer.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Review Group specialised register of controlled trials up to April 2007. In addition, MEDLINE (PUBMED 1985 to March 2007), EMBASE (1985 to April 2007), CINAHL (1985 to March 2007) and the National Research Register (April 2007) were searched.

Selection criteria

Randomised controlled trials (RCTs) in which either human intra-venous albumin or cryopreservation of all embryos were used as a therapeutic approach to OHSS were included.

Data collection and analysis

The interventions compared were cryopreservation (embryo freezing) versus intra-venous human albumin administration and elective cryopreservation of all embryos versus fresh embryo transfer. The primary outcomes were: incidence of moderate and severe OHSS versus nil and or mild OHSS, clinical pregnancies and or woman. The secondary outcomes were: number of oocytes retrieved, number of oocytes fertilized, number of embryos transferred, number of embryos frozen, multiple pregnancy rate, live birth rate, number of women admitted to the hospital as inpatient or outpatient and time to the next menstrual period (resolution time). Statistical analysis was performed in accordance with the Cochrane Menstrual Disorders and Subfertility Group guidelines.

Main results

No new studies found for inclusion in the update of this review, the results from the original review published Issue 2 , 2002 (which identified seventeen studies) remain unchanged. It therefore remains that two studies of which met our inclusion criteria one study was included where cryopreservation (embryo freezing) was compared with intra-venous human albumin administration (Shaker 1996) and one study was included where elective cryopreservation of all embryos was compared with fresh embryo transfer (Ferraretti 1999). When cryopreservation was compared with intra-venous human albumin administration no difference was found in all the outcomes examined between the two groups. When elective cryopreservation of all embryos was compared with fresh embryo transfer no difference was found in all the outcomes examined between the two groups.

Authors' conclusions

This updated of the review (D'Angelo 2002) has showed that there is insufficient evidence to support routine cryopreservation and insufficient evidence for the relative merits of intra-venous albumin versus cryopreservation.

PLAIN LANGUAGE SUMMARY

Embryo freezing for preventing ovarian hyperstimulation syndrome

More research is needed to determine whether using frozen embryos and or intravenous albumin can reduce the rate of severe ovarian hyperstimulation syndrome in IVF. Ovarian hyperstimulation syndrome (OHSS) is a complication of using hormones to induce ovulation (stimulate the release of eggs) in IVF (in vitro fertilisation). The drugs can sometimes over-stimulate ovaries. Severe OHSS can be life-threatening. Fewer hormones are needed if frozen embryos are transferred in a subsequent cycle, although this lowers pregnancy rates. However, this update the review first published in 2002 (D'Angelo 2002) found there is not enough evidence to show whether using frozen embryos and or intravenous albumin infusion (artificial fluid to increase the woman's blood volume) can reduce OHSS in women who are at high risk. More research is needed on effects on pregnancy rates.

Summary of findings for the main comparison. Cryopreservation compared to fresh embryos transfer for preventing ovarian hyperstimulation syndrome

Cryopreservation compared to fresh embryos transfer for preventing ovarian hyperstimulation syndrome

Patient or population: patients with risk of ovarian hyperstimulation syndrome
Settings:
Intervention: Cryopreservation
Comparison: Fresh embryo transfer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Fresh embryo transfer	Cryopreservation				
Moderate and or severe OHSS	**60 per 1000**	**8 per 1000** (1 to 128)	**OR 0.12** (0.01 to 2.29)	125 (1 study)	⊕⊕⊝⊝ **low** [1,2]	
Clinical pregnancies	**463 per 1000**	**482 per 1000** (318 to 654)	**OR 1.08** (0.54 to 2.19)	125 (1 study)	⊕⊕⊝⊝ **low** [1,2]	
Number of live-births (livebirth rate)	**373 per 1000**	**380 per 1000** (229 to 558)	**OR 1.03** (0.5 to 2.12)	125 (1 study)	⊕⊕⊝⊝ **low** [1,2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Not enough information given about methods of allocation concealment, and study was not blinded.
[2] The summary effect included both the line of no effect and appreciable benefit and harm.

Summary of findings 2. Cryopreservation compared to intra-venous albumin for preventing ovarian hyperstimulation syndrome

Cryopreservation compared to intra-venous albumin for preventing ovarian hyperstimulation syndrome

Patient or population: patients with risk of ovarian hyperstimulation syndrome
Settings:
Intervention: Cryopreservation
Comparison: Intra-venous albumin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Intra-venous albumin	Cryopreservation				
Moderate and or severe OHSS	**77 per 1000**	**308 per 1000** (41 to 824)	**OR 5.33** (0.51 to 56.24)	26 (1 study)	⊕⊝⊝⊝ **very low** [1,2]	
Nil and or mild OHSS	**538 per 1000**	**307 per 1000** (85 to 689)	**OR 0.38** (0.08 to 1.9)	26 (1 study)	⊕⊕⊝⊝ **low** [1,3]	
Clinical pregnancies	**385 per 1000**	**36 per 1000** (0 to 423)	**OR 0.06** (0 to 1.17)	26 (1 study)	⊕⊕⊝⊝ **low** [1,4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Study was not blinded.
[2] Very large confidence interval that included the line of no effect.
[3] The summary effect included both the line of no effect and apprciable benefit and harm.
[4] Very wide confidence interval.

BACKGROUND

The mechanism of action of albumin in the treatment of women at high risk for OHSS may relate both to increasing the carrier protein capacity and its oncotic properties as albumin is responsible for 75% of the plasma oncotic pressure. Both factors could prevent leakage of fluid from the intra-vascular space into the peritoneal cavity (Asch 1993). It could be speculated that human albumin binds an undefined factor (ovarian renin-angiotensin, VEGF) at a specific and critical time of the cycle and thus helps to prevent the development of OHSS (Shoham 1994). Timely administration of albumin, during oocyte recovery or immediately following, may serve to bind and inactivate this factor. However, Doldi 1999 contradicted the above hypothesis and demonstrated that human albumin increases VEGF gene expression in human luteinizing granulosa cells with maximum expression present in cultured granulosa cells when obtained from women with serum oestradiol concentration >2000 pg and or ml on the day of hCG injection.

Description of the condition

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic potentially life threatening condition resulting from an excessive ovarian stimulation. Its reported incidence varies from 1% to 10% of In Vitro Fertilization (IVF) cycles (Forman 1990; MacDougall 1992; Wada 1990). The incidence of the severe form of OHSS in women undergoing controlled ovarian hyperstimulation for IVF has been estimated to be approximately 0.5 to 2% (Forman 1990; SART 1992) with a reported positive correlation between younger age, lean appearance and OHSS (Navot 1992). In addition, polycystic ovarian syndrome (PCOS) or ultrasonographic ovarian appearance of polycystic ovaries (presence of multiple, small follicles at the periphery of the ovary with echogenic stroma 'necklace sign'), establishment of pregnancy during assisted reproduction treatment (ART), human chorionic gonadotrophin (hCG) supplementation of the luteal phase, high serum oestradiol (less than 2500 pg and or ml) were also reported to be associated with OHSS.

OHSS was originally classified as mild, moderate and severe by Rabau 1967 ; Schenker 1978 and subsequently modified by Golan 1989 to incorporate ultrasonographic measurement of the stimulated ovaries. Briefly, mild OHSS presents clinically as weight gain, thirst and abdominal discomfort; ultrasound examination shows the ovaries to be enlarged (five to ten cm in diameter) with a small amount of fluid in the pelvis. Moderate OHSS is associated with more pronounced symptoms (nausea, vomiting, abdominal distension, pain and dyspnoea), ultrasound examination of the pelvis reveals moderate amounts of ascitic fluid and the ovaries are 10 to 12 cm in diameter. In severe OHSS, all of these symptoms are associated with clinical evidence of excessive third-space fluid accumulation (ascites, hydrothorax), ovaries larger than 12 cm in diameter and in extreme cases may present with acute respiratory distress, hepato-renal failure and thromboembolic phenomena (Brinsden 1995)(Table 1). Navot 1992 introduced further modification to the above classification by differentiating between severe and life threatening form of OHSS (Table 2).

The factors leading to this syndrome have not been completely elucidated. It seems likely that the release of vasoactive substances, e.g. vascular endothelium growth factor (VEGF), secreted by the ovaries under hCG stimulation plays a key role in triggering this syndrome (Goldsman 1995 ; Tsirigotis 1994). As more follicles are recruited in response to gonadotrophin stimulation, the mass of the granulosa cells increases and at the same time the cells gain functional maturation. These two factors, acting synergistically, cause a concomitant increase in serum oestradiol level and in, as yet poorly defined, vasoactive substances (Agrawal 1998; Al-Shawaf 2001). The hallmark of this condition, is a massive shift of fluid from the intra-vascular compartment to the third space resulting in profound intra-vascular depletion and haemoconcentration (Rabau 1967; Schenker 1978).

Description of the intervention

The crucial event in the development of the OHSS is the administration of hCG. However, some have reported the onset of OHSS after gonadotrophin in stimulation despite withholding hCG (Allegra 1991 ;Lipitz 1991). Moderate or severe OHSS typically presents in the luteal phase as a consequence of ovulatory hCG or in early gestation phase in which endogenous hCG is produced. When the OHSS develops in the luteal phase and pregnancy does not take place, the syndrome rapidly resolves spontaneously with the onset of the menses, rarely progressing into its severe form. If a pregnancy is established, notable aggravation will be observed and the symptoms can persist for up to 12 weeks of gestation, this is more often associated with multiple pregnancy (Dahl 1994). The elective cryopreservation of all embryos and their subsequent transfer in non gonadotrophin stimulated cycles may be used to avoid the endogenous hCG rise in IVF-ET programmes (Amso 1990). However, the policy of elective cryopreservation of all embryos in patients at risk would reduce the chances of pregnancy, since frozen-thawed embryo replacement may be associated with lower pregnancy rate than fresh embryo transfer (Awonuga 1996).

How the intervention might work

In addition, alternative strategies have been proposed for IVF and or ICSI (intra-cytoplasmic sperm injection) patients at high risk of OHSS:
(1) cancellation of the treatment cycle (Forman 1990)
(2) gonadotrophins discontinuation prior to hCG triggering injection (coasting) (Sher 1993)
(3) early unilateral follicular aspiration (Egbase 1999); (4) avoidance of luteal supplementation with hCG (Araujo 1995); the use of a GnRH agonist instead of hCG to induce the final oocyte maturation prior to retrieval in non GnRH agonist down regulated cycles (Gonen 1990; Segal 1992). Each of these strategies may reduce but not eliminate the risk.

OBJECTIVES

To evaluate
(i) the effectiveness of cryopreservation (embryo freezing) for the prevention of OHSS when compared with human intra-venous albumin infusion
(ii) the effectiveness of the elective cryopreservation (embryo freezing) of all embryos for the prevention of OHSS when compared with fresh embryo transfer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) in which freezing of all embryos was used as a therapeutic approach to OHSS were included. Ovulation induction treatment without IVF and or ICSI was not included in the meta-analysis. Cross-over trials were excluded from this meta-analysis.

Types of participants

- Women of reproductive age;
- Women down-regulated by GnRH-a, undergoing superovulation in IVF and or ICSI cycles.

Types of interventions

- Cryopreservation of all embryos versus intra-venous albumin infusion;
- Cryopreservation of all embryos versus fresh embryo transfer.

Types of outcome measures

Primary outcomes

- Incidence of moderate and severe OHSS versus nil or mild OHSS, subsequent to oocyte retrieval;
- Clinical pregnancy rate and or woman (after fresh or frozen embryo transfer where applicable).

Secondary outcomes

- Number of oocytes retrieved
- Fertilization rate (number of oocytes fertilised divided by total oocytes inseminated x 100);
- Number of embryos transferred;
- Number of embryos frozen;
- Multiple pregnancy rate;
- Livebirth rate;
- Number of women admitted to the hospital inpatient versus outpatient;
- Number of days to next menstrual period (resolution).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Menstrual Disorders and Subfertility Review Group specialised register of controlled trials up to 22 April 2007.

See Appendix 1

Searching other resources

In addition, the review authors were also involved in hand searching of specialist journals *(Human Reproduction* Abstract Books 1999 and 2000) retrieving relevant articles from titles and abstracts, checking the reference lists of articles, contacting authors of conference abstracts to obtain details of the subsequent publication, informing the principal journals (*Human Reproduction, Fertility and Sterility, British Journal of Obstetrics and Gynaecology* and *Lancet)* asking for new published and unpublished articles, contacting authors of ongoing studies on this topic to obtain study data and update of the not already published paper. The authors of the included published studies were contacted to obtain additional information that was required for the analysis and they kindly replied.

Data collection and analysis

Selection of studies

For the purposes of the update of the review published in 2002 (D'Angelo 2002) two review authors, Mr N.N. Amso (NNA) and Dr A. D'Angelo (ADA) scanned the titles and the abstracts of the reports identified by electronic searching in order to find relevant papers no further trials were identified,
In the original review (D'Angelo 2002) Mr N.N. Amso (NNA) and Dr A. D'Angelo (ADA) scanned the titles and the abstracts of the reports identified by electronic searching in order to find relevant papers. One reviewer (ADA) obtained copies of the full text articles and made copies for the other review author (NNA) in which details of authors, institution, results and discussion were removed in order to assess their eligibility for inclusion.

Data extraction and management

Both review authors extracted data independently using forms designed according to Cochrane guidelines. Disagreements were resolved by discussion.

Assessment of risk of bias in included studies

The unit for randomisation was women fulfilling the criteria for inclusion into the study. The quality of allocation concealment was graded as either adequate (A), unclear (B), or inadequate (C), following the detailed descriptions of these categories provided by the Menstrual Disorders and Subfertility Review Group. Additional information on the trial methodology or data were requested by writing to the corresponding authors directly. Included trials data were processed as:

Trial characteristics

- Method of randomisation
- Number of women randomised, excluded and reasons;
- Multicentre or single centre design;
- Presence or absence of blinding to treatment allocation;
- Whether an intention-to-treat analysis was done;
- The presence of a power calculation;
- Duration, timing, and location of the study;
- Sources of any funding

Characteristic of women

- Age of the women;
- Down-regulation and superovulation in ART cycles;
- Causes of infertility: unexplained subfertility; tubal factor; endometriosis; anovulatory factor; male factor;
- Duration of infertility;
- Women at risk of developing OHSS based on serum oestradiol level (>1,906 pg and or ml or >7,000 pmol and or L) on the day of human chorionic gonadotrophin (hCG) administration

Interventions used

- Treatment:

- elective cryopreservation.

- Control:

- intra-venous human albumin infusion;
- fresh embryo transfer.

Outcomes

Primary

- Incidence of moderate and severe OHSS versus nil or mild OHSS;
- Clinical pregnancy rate and or woman (after fresh or frozen embryo transfer where applicable).

Secondary

- Number of oocytes retrieved;
- Fertilization rate;
- Number of embryos frozen;
- Number of embryos transferred;
- Multiple pregnancy rate;
- Livebirth rate;
- Number of women admitted to the hospital inpatient versus outpatient;
- Number of days to the next menstrual period (resolution).

Measures of treatment effect

Statistical analysis was performed in accordance with the guidelines developed by the Menstrual Disorders and Subfertility Group. For a dichotomous data, results for each study were expressed as an odds ratio (OR) with 95% confidence intervals (CI) and combined for meta-analysis with RevMan software using Peto-modified Mantel-Haenszel method. Continuous data were not normally distributed therefore the results for these outcomes have not been combined using WMD and have been reported separately. Because of the small number of studies included no sensitivity analysis was performed.

Unit of analysis issues

None

Dealing with missing data

The data will be analysed on an intention-to-treat basis as far as possible and attempts were made to obtain missing data from the original investigators of Shaker 1996.

Assessment of heterogeneity

Not applicable

Assessment of reporting biases

There were less than ten included studies therefore this was not assessed formally

Data synthesis

Not applicable

Subgroup analysis and investigation of heterogeneity

Not applicable

Sensitivity analysis

Because of the small number of studies included no sensitivity analysis was performed.

RESULTS

Description of studies

There were no new studies identified for inclusion or exclusion in this update.

In the original review published in 2002 (D'Angelo 2002) one randomised controlled study in which cryopreservation of all embryos was compared with intra-venous albumin infusion and subsequent fresh embryo transfer for the prevention of moderate and severe OHSS was identified and one randomised controlled study in which elective cryopreservation of all embryos was compared with fresh embryo transfer for the prevention of moderate and severe OHSS was identified.

Results of the search

In the original review published in 2002 (D'Angelo 2002) the only study in which cryopreservation of all embryos was compared with intra-venous albumin infusion and subsequent fresh embryo transfer which met our inclusion criteria was Shaker et al. (Shaker 1996).

Included studies

See Characteristics of included studies Women's age and superovulation protocols are listed in the table of included studies. Women were considered to be at risk of hyperstimulation when: E2 was less than 10,000 pmol and or L and less than 15 oocytes collected or E2 less than 13,000 p mol and or L. A diagnosis of moderate or severe OHSS was made according to the Schenker and Weinstein classification (Schenker 1978). The intervention and control groups were compared in relation to the incidence of moderate or severe versus nil or mild OHSS, the number of clinical pregnancies, number of oocytes retrieved, and the number of embryos transferred and frozen.

The only study in which elective cryopreservation of all embryos was compared with fresh embryo transfer which met our inclusion criteria was Ferraretti 1999. It was a single centre randomised study. Women undergoing superovulation for IVF and or ICSI treatment (GnRH-a down-regulation and gonadotrophin stimulation) were included in the study. They were considered to be at risk of hyperstimulation when the E2 level was >1500 pg and or ml (less than 5500 pmol and or L) and less than 15 oocytes collected. The diagnosis of moderate and severe OHSS was done according to Golan classification (Golan 1989) revised by Navot 1992. The incidence of moderate or severe OHSS, clinical pregnancy rate per woman, number of oocytes retrieved, number of embryos transferred, livebirth rate and number of women admitted as inpatient or outpatient were compared in the intervention and control groups.

Excluded studies

See Characteristics of excluded studies. A total of fifteen studies were excluded in the original review published in 2002 (D'Angelo 2002) . Six were prospective observational studies (Asch 1993; Awonuga 1996; Chen 1997; Queenam 1997; Titinem 1995 ;Wada 1993). Four were randomised controlled studies where intravenous albumin was compared with no treatment and or placebo, therefore did not meet our inclusion criteria (Isik 1996; Munoz 2000; Shalev 1995; Shoham 1994), and is the subject of an existing Cochrane review (Aboulghar 1999). Three were retrospective (Pattinson 1994; Ndukwe 1997; Wada 1993). One was prospectively randomised but on alternating basis (Panay 1999). One was a cohort study (Ng 1995).

Risk of bias in included studies

See Figure 1 and Figure 2. Women were randomised using drawing cards (Shaker 1996) or not specified (Ferraretti 1999).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

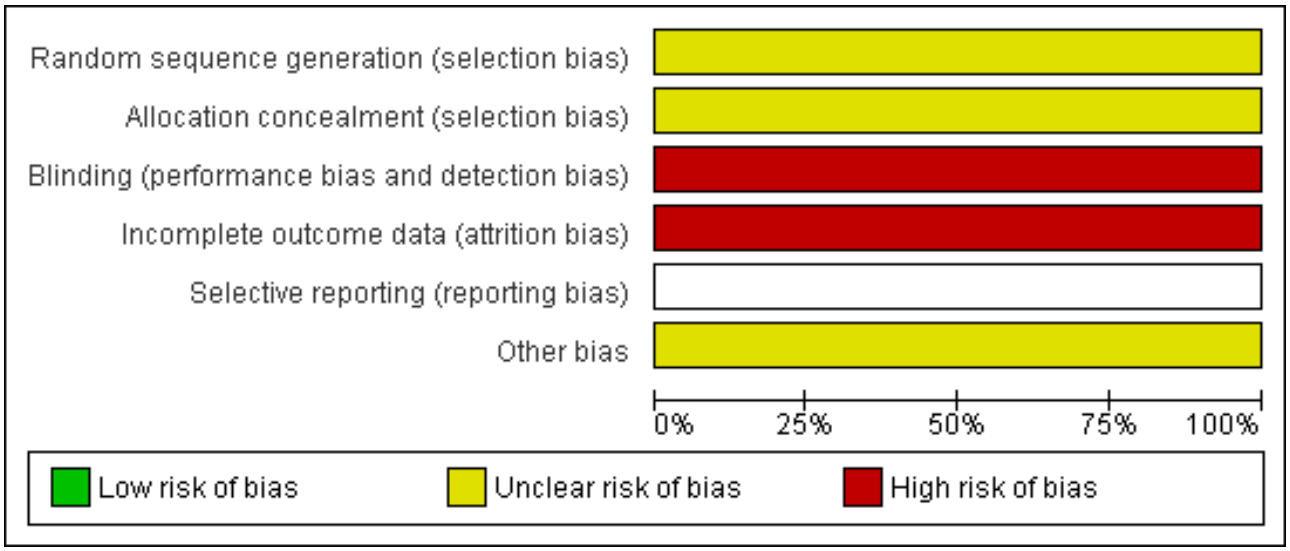
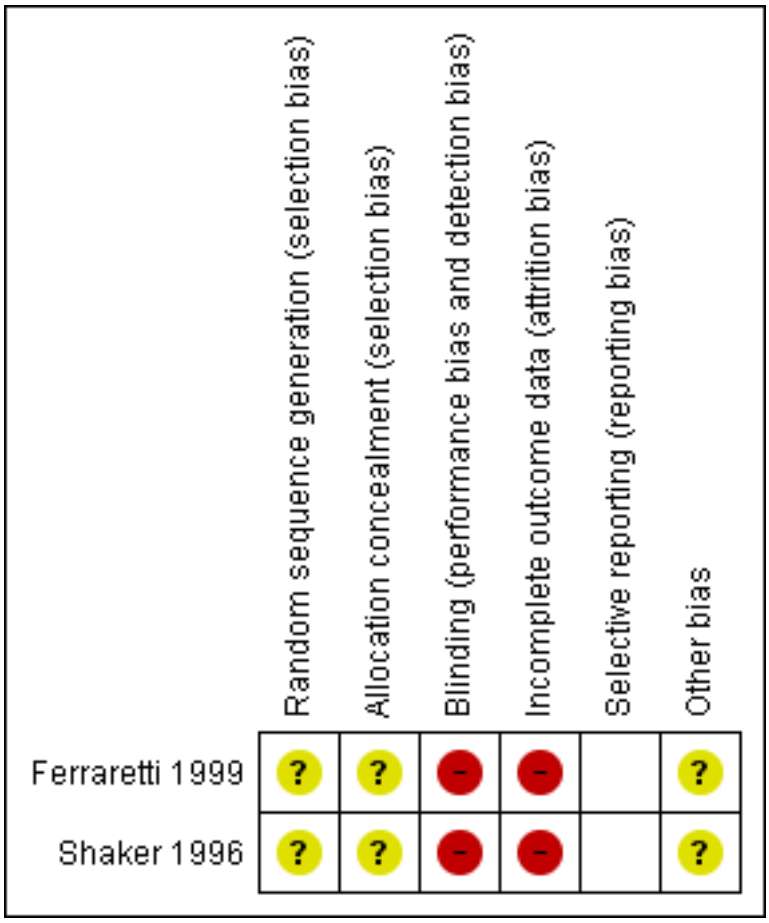


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

None of the studies described allocation concealment adequately.

Blinding

In the original review published in 2002 (D'Angelo 2002) both studies included were single centre unblinded randomised controlled trials.

Incomplete outcome data

Both authors Ferraretti 1999 and Shaker 1996 were contacted by letter to obtain missing data. The number of women included in these studies was small. Three women withdrew from Shaker 1996 requesting to have fresh embryos rather than cryopreservation. No withdrawals or loss of follow up were mentioned in the other study.

Other potential sources of bias

None of the studies described a power of calculation.

Effects of interventions

See: **Summary of findings for the main comparison** Cryopreservation compared to fresh embryos transfer for preventing ovarian hyperstimulation syndrome; **Summary of findings 2** Cryopreservation compared to intra-venous albumin for preventing ovarian hyperstimulation syndrome

Because there were no new studies found for inclusion in the update of this review the results from the original review published Issue 2 , 2002 which identified seventeen studies remains unchanged. Two trials met our inclusion criteria in 2002. Comparisons were classified into two categories:

(1) Cryopreservation versus intra-venous albumin infusion

- Incidence of moderate and or severe OHSS: there was no difference between the two groups in the incidence of moderate and or severe OHSS (n=26, OR 5.33, 95% CI 0.51 to 56.24). No cases of severe OHSS were diagnosed in both groups but one case of moderate OHSS were diagnosed in the treatment group (cryopreservation) and four cases in the control group (intra-venous albumin).
- Incidence of nil or mild OHSS: there was no difference between the two groups in the incidence of nil or mild OHSS (n=26, OR 0.38, 95% CI 0.08 to 1.90). Four cases of mild OHSS were diagnosed in the treatment group and seven cases in the control group.
- Clinical pregnancy and or woman: there was no difference between the two groups in the number of clinical pregnancies and or women (n=26, OR 0.06, 95% CI 0.00 to 1.17). There were 13 (38%) pregnancies observed in the treatment group and 13 pregnancies in the control group.
- There was no mention of multiple pregnancy rate or livebirth rate

Data for number of oocytes retrieved, oocytes fertilized and for embryos transferred were not normally distributed therefore the results for these outcomes have not been combined using WMD and have been reported separately.

- Number of oocytes retrieved: the mean (SD) number of oocytes retrieved was 17.15+and or- 7.77 in the intra-venous albumin group and 19.62+and or- 5.87 in the cryopreservation group.
- Number of oocytes fertilized: the mean (SD) number of oocytes fertilized was 6.0+and or-3.42 in the intra-venous albumin group and 7.46+and or-3.91 in the cryopreservation group.
- Number of embryos transferred: the mean (SD) number of embryos transferred was 2.31+and or- 0.84 in the intra-venous albumin group and 1.69+and or-1.32 in the cryopreservation group.

(2) Cryopreservation versus fresh embryo transfer

- Incidence of moderate and or severe OHSS: there was no statistically significant difference between the two groups in the incidence of moderate and or severe OHSS (n=125, OR 0.12, 95% CI 0.01 to 2.29). No cases of moderate and or severe OHSS were diagnosed in the treatment group (cryopreservation of all embryos) versus four cases in the control group (fresh embryo transfer).
- Clinical pregnancy and or woman: there was no difference between the two groups (n=125, OR 1.08, 95% CI 0.54 to 2.19). There were 28 and or 58 (48.2%) pregnancies observed in the treatment group and 31 and or 67 (46.3%) in the control group.
- Multiple pregnancy rate was overall 30%.
- Livebirth rate: there was no difference between the two groups (n=125, OR 1.03, 95% CI 0.50 to 2.12). There were 22 babies born in the treatment group and 25 in the control group.
- Number of women admitted as inpatient or outpatient: there was no difference between the two groups (n=125, OR 0.12, 95% CI 0.01 to 2.29). No one was admitted as an inpatient in the treatment group and 4 and or 125 in the control group.

Data for number of oocytes retrieved, embryos transferred and resolution time were not normally distributed therefore the results for these outcomes have not been combined using WMD and have been reported separately.

- Number of oocytes retrieved: the mean (SD) number of oocytes retrieved was 20.80+and or- 5.50 in the cryopreservation of all embryos group and 19.80 +and or- 4.30 in the fresh embryo transfer group.
- Number of embryos transferred: the mean (SD) number of embryos transferred was 3.10+and or-0.80 in the cryopreservation of all embryos group and 3.20+and or-1.00 in the fresh embryo transfer group.
- Resolution time: the mean (SD) time to the next menstrual period was 12.1+and or-1.0 days in the cryopreservation of all embryos group

DISCUSSION

Summary of main results

This updated systematic review (and its original published issue 2, 2002) D'Angelo 2002 ,showed that there was no statistically significant difference in the incidence of moderate and or severe OHSS when cryopreservation of all embryos was employed compared to intra-venous albumin infusion and fresh embryos transfer in women at risk of OHSS.

Overall completeness and applicability of evidence

These results have to be interpreted with caution because of (i) the small number of women in the individual studies and (ii) they were based on an experimental treatment (i.e. Intra-venous albumin) which has not been validated in large studies. Comparisons of the two different management options for OHSS did not show any significant difference in the incidence of OHSS.

Quality of the evidence

There are a number of methodological concerns which may have affected the results such as the administration of intra-venous albumin to all women (Ferraretti 1999) and its possible influence on the incidence of severe OHSS. Although there were four cases of severe OHSS in the fresh embryos transfer group and none in the cryopreservation group, this did not reach a statistically significant difference between cryopreservation and fresh embryos transfer group. According to this review and to a previous meta-analysis done by Aboulghar 1999, which has demonstrated a statistically significant difference in the incidence of severe OHSS between intra-venous albumin infusion and placebo and or no treatment , there is a need for a larger multi centre RCT of these interventions with sufficient power to show a statistically significant difference in the occurrence of moderate and or severe OHSS.

On the basis of the studies included in both reviews, were carried out power calculations which indicated that to demonstrate a difference of 25% between experimental (intra-venous albumin infusion) and control (elective cryopreservation of all embryos) groups at a power of 80%, with a statistical significance level of 0.05, we need 185 women in each group (a total of 370 women). To achieve a power of 90%, 235 women are needed in each group (a total of 470 women).

Potential biases in the review process

As far as the clinical pregnancy rate per woman is concerned, none of the studies reached statistical significance. However, in one study (Shaker 1996) there was a trend for higher clinical pregnancy rate in the cryopreservation arm (P = 0.06). It should be noted that this study (i) has a low power because of the small number of women randomised (13 in each arm) and three women withdrawn from the cryopreservation group; (ii) was not blinded and (iii) the authors tried to justify such discrepancy in pregnancy rate with the fact that the second dose of intra-venous albumin, administered five days after the fresh embryos transfer, might have affected the implantation phase.

AUTHORS' CONCLUSIONS

Implications for practice

This updated review has showed that there is insufficient evidence to support routine cryopreservation and insufficient evidence for the relative merits of intra-venous albumin versus cryopreservation.

Implications for research

There is

(1) a need to have clear definition of women at risk of OHSS, based on endocrinological and or ultrasonographic and or clinical criteria (2) a need for a large RCT looking at (i) severe OHSS for intra-venous albumin with fresh embryo transfer versus cryopreservation and (ii) pregnancy outcome for intra-venous albumin with fresh embryo transfer versus cryopreservation. Randomisation should take place when risk is determined (i.e. during the stimulation phase or immediately prior to egg collection) according to serum oestradiol level (less than 1,906 pg and or ml or less than 7,000 pmol and or L) on the day of human chorionic gonadotrophin (hCG) administration.

ACKNOWLEDGEMENTS

Authors would like to thank the MDSG editorial office staff,for their advice and support throughout the review process.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ferraretti 1999

Methods	Randomised study; parallel prospective design; single centre; power calculation: not stated; method of randomisation: not specified.
Participants	125 infertile women considered at risk of OHSS (58/125 had cryopreservation;67/125 had fresh embryos transfer); E2 (major risk factor for OHSS) was >1500 pg/ml; Age (31.6 versus 31.4 years); Duration of infertility (3.9 versus 4.1 years); Causes of infertility (%): tubal factor (27 versus 30), male factor (28 versus 33), PCO (8 versus 7), others (3 versus 4) BMI (<30)
Interventions	Study group: cryopreservation of all embryos immediately (zygotes); control group: fresh embryo transfer after 48 hours of culture. Both groups received 20 gr. of human albumin intravenously on the day of oocytes recovery.
Outcomes	Method of diagnosing different grades of OHSS: Golan (1989) and Navot criteria, (1992). Severe OHSS (0/58 versus 4/67); • clinical pregnancy/woman (28/58 versus 31/67); • number of oocytes retrieved (20.8+/-5.5 versus 19.8+/-4.3); • fertilization rate (61% versus 68%);

Ferraretti 1999 *(Continued)*

- number of embryos transferred (3.1+/-0.8 versus 3.2+/-1.0);
- multiple pregnancy rate (not stated);
- livebirth rate (39.6 versus 38.8);
- number of inpatient or outpatient (4 versus 0); resolution time (12.1+/-1.0 days in the study group).

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocation concealment not described adequately
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No losses
Other bias	Unclear risk	No power calculation.

Shaker 1996

Methods	Randomised study; parallel prospective design; single centre; power calculation: not stated; intention-to-treat analysis done; randomisation done by drawing cards, each contained a number obtained from a table of random numbers.
Participants	26 infertile women considered at risk of OHSS (13/26 had intra-venous albumin infusion; 13/26 had cryopreservation of all embryos); E2 (major risk factor for OHSS) was >3,540 pg/ml; Age (33.8 versus 34.0 years); Duration of infertility (4.4 versus. 4.6 years); Causes of infertility: tubal factor (not stated), male factor (not stated), PCO (2 versus 6); BMI (not calculated).
Interventions	Study group: intra-venous albumin infusion (200 ml of 20% concentration) on the day of eggs collection and repeated 5 days later + fresh embryos transfer; control group: cryopreservation of all embryos at pronucleate stage.
Outcomes	Method of diagnosing different grades of OHSS: Schenker & Weinstein (1978). Severe OHSS (0/13 versus 0/13); moderate OHSS (4/13 versus 1/13); mild OHSS (4/13 versus 7/13); • clinical pregnancy/woman (0/13 versus 5/13); • number of oocytes retrieved (17.15+/-7.77 versus 19.62+/-5.87); • number of oocytes fertilized (6.0+/-3.42 versus 7.46+/-3.91); • number of embryos transferred (2.31+/-0.84 versus 1.69+/-1.32); number of embryos frozen (0.69+/-1.8 versus 6.69+/-3.97); • multiple pregnancy rate (not stated); • livebirth rate (not stated);

Shaker 1996 *(Continued)*

- number of inpatient or outpatient (not stated); resolution time (not stated).

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Allocation concealment not described adequately
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Three women withdrew they requested to have fresh embryos rather than cryopreservation
Other bias	Unclear risk	No power calculation.

OHSS: Ovarian hyperstimulation syndrome
E2: oestradiol
PCO: Policystic ovaries
BMI: Body mass index

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

Study	Reason for exclusion
Asch 1993	Observational study
Awonuga 1996	Prospective observational study
Chen 1997	Prospective observational study
Isik 1996	Randomised controlled study comparing intra-venous albumin infusion with no treatment
Munoz 2000	Randomised controlled study comparing intra-venous albumin infusion with placebo
Ndukwe 1997	Retrospective review and data analysis
Ng 1995	Cohort study not randomised
Panay 1999	Randomisation based on alternating basis
Pattinson 1994	Retrospective review
Queenam 1997	Prospective observational longitudinal study
Shalev 1995	Randomised controlled study comparing intra-venous albumin infusion with no treatment

Study	Reason for exclusion
Shoham 1994	Randomised controlled study comparing intra-venous albumin infusion with placebo
Titinem 1995	Observational study
Wada 1992	Prospective observational study
Wada 1993	Retrospective review

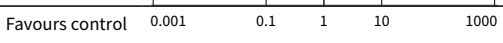
DATA AND ANALYSES

Comparison 1. Cryopreservation versus fresh embryos transfer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Moderate and or severe OHSS	1	125	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 2.29]
2 Clinical pregnancies	1	125	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.54, 2.19]
3 Number of livebirths (livebirth rate)	1	125	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.50, 2.12]
4 Number of patients admitted	1	125	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 2.29]

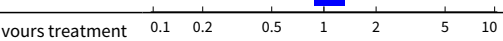
Analysis 1.1. Comparison 1 Cryopreservation versus fresh embryos transfer, Outcome 1 Moderate and or severe OHSS.

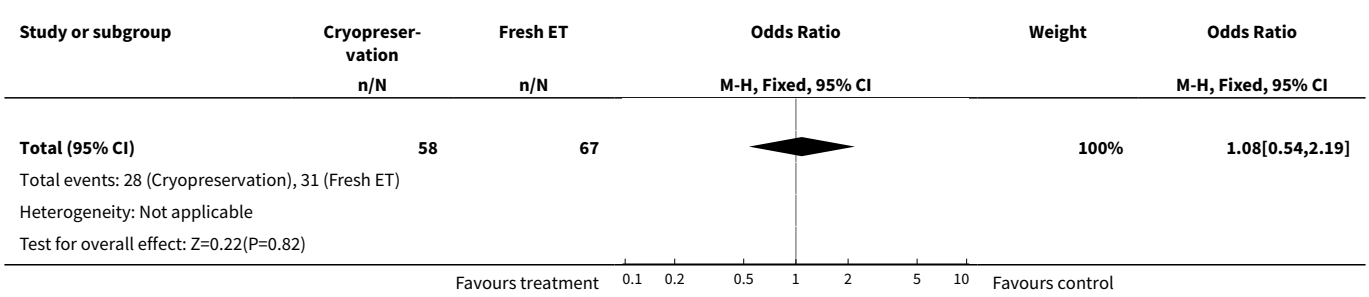
Study or subgroup	Cryopreservation n/N	Fresh ET n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Ferraretti 1999	0/58	4/67		100%	0.12[0.01,2.29]
Total (95% CI)	**58**	**67**		**100%**	**0.12[0.01,2.29]**
Total events: 0 (Cryopreservation), 4 (Fresh ET)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.41(P=0.16)					



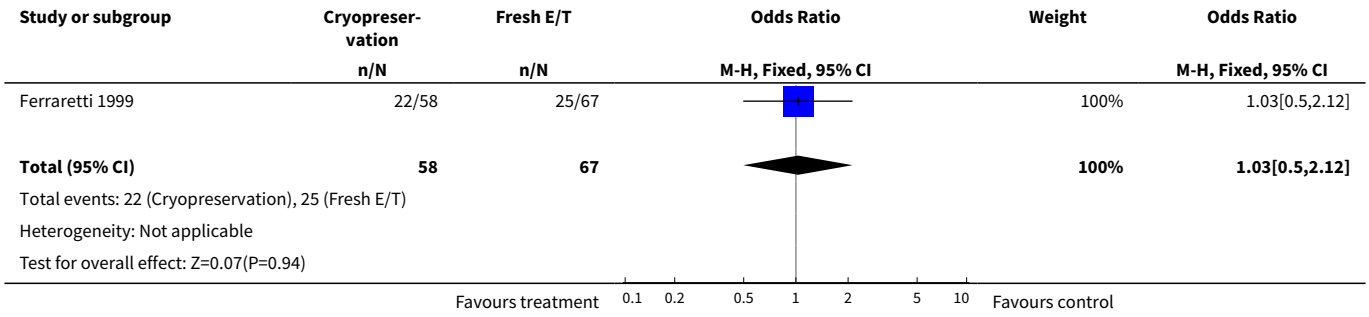
Analysis 1.2. Comparison 1 Cryopreservation versus fresh embryos transfer, Outcome 2 Clinical pregnancies.

Study or subgroup	Cryopreservation n/N	Fresh ET n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Ferraretti 1999	28/58	31/67		100%	1.08[0.54,2.19]

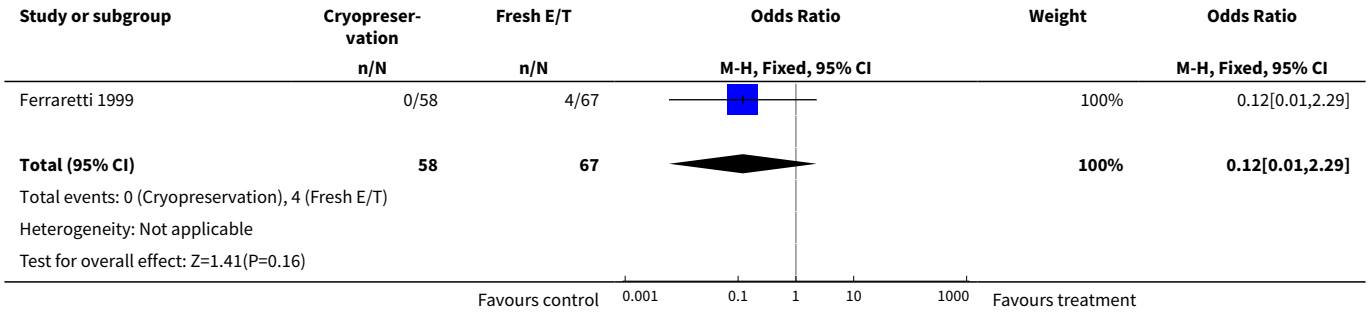




Analysis 1.3. Comparison 1 Cryopreservation versus fresh embryos transfer, Outcome 3 Number of livebirths (livebirth rate).



Analysis 1.4. Comparison 1 Cryopreservation versus fresh embryos transfer, Outcome 4 Number of patients admitted.

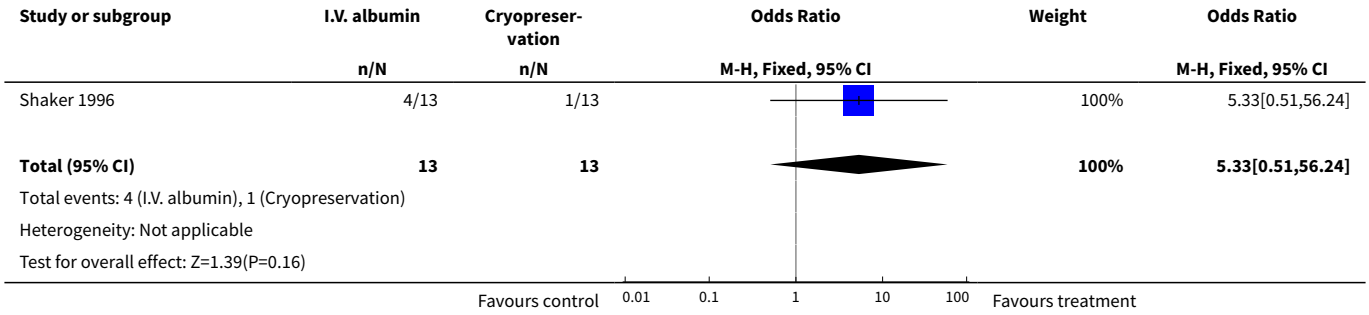


Comparison 2. Cryopreservation versus intra-venous albumin

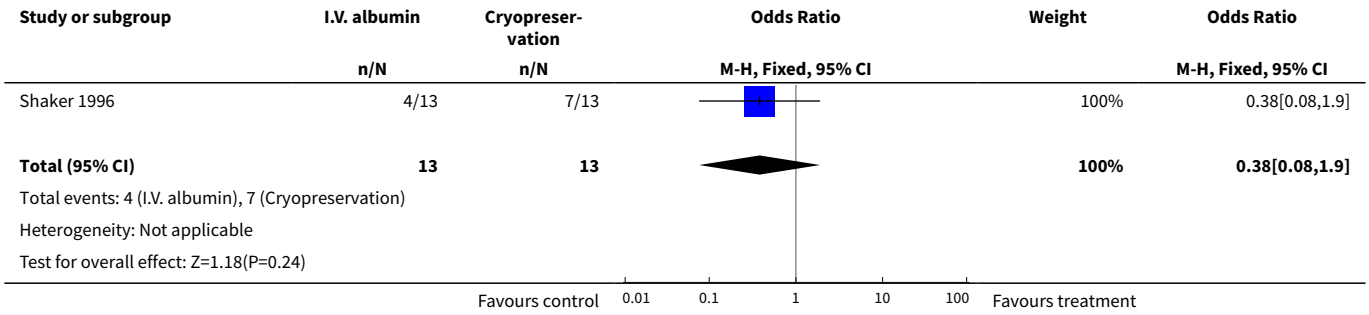
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Moderate and or severe OHSS	1	26	Odds Ratio (M-H, Fixed, 95% CI)	5.33 [0.51, 56.24]
2 Nil and or mild OHSS	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.08, 1.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Clinical pregnancies	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 1.17]

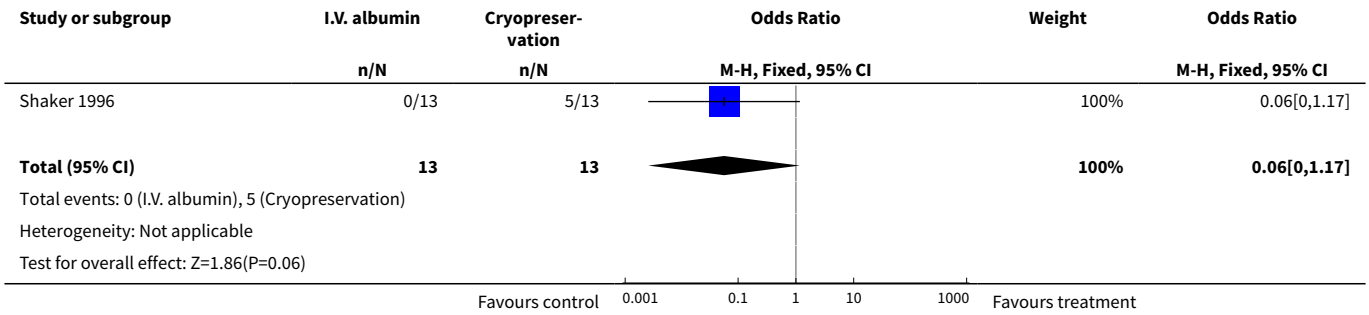
Analysis 2.1. Comparison 2 Cryopreservation versus intra-venous albumin, Outcome 1 Moderate and or severe OHSS.



Analysis 2.2. Comparison 2 Cryopreservation versus intra-venous albumin, Outcome 2 Nil and or mild OHSS.



Analysis 2.3. Comparison 2 Cryopreservation versus intra-venous albumin, Outcome 3 Clinical pregnancies.



ADDITIONAL TABLES

Table 1. Golan classification of OHSS (1989)

Classification	Size ovaries	Grade	Symptoms
MILD	5-10 cm	grade 1:	abdominal tension and discomfort
		grade 2:	grade 1 signs plus nausea, vomiting, and/or diarrhoea
MODERATE	>10 cm	grade 3:	grade 2 signs plus ultrasound evidence of ascites
SEVERE	>12 cm	grade 4:	grade 3 signs plus clinical evidence of ascites and/or pleural effusion and dyspnoea
		grade 5:	grade 4 signs plus haemoconcentration increased blood viscosity, hypovolaemia, decreased renal perfusion, oliguria

Table 2. Navot classification of severe OHSS (1992)

Severe OHSS	Critical OHSS
Variably enlarged ovary	Variably enlarged ovary
Massive ascites +/- hydrothorax	Tense ascites +/- hydrothorax
Hct >45%(30% increment over the baseline value)	Hct >55%
WBC >15,000	WBC >35,000
Oliguria	
Creatinine 1.0-1.5	Creatinine >1.6
Creatinine clearance >50mL/min	Creatinine clearance <50mL/min
Liver dysfunction	Renal failure
Anasarca	Tromboembolic phenomena
	ARDS

APPENDICES

Appendix 1. Search

MEDLINE(R) 1950 to March Week 2 2007

1 cryopreservation/ or tissue preservation/ (19871)
2 Freezing/ (16747)
3 (cryopreservat$ or cryofixation or cryonic suspension).tw. (5989)
4 thaw$.tw. (10976)
5 freez$.tw. (32035)
6 or/1-5 (59469)

7 embryo transfer/ or fertilization in vitro/ or sperm injections, intracytoplasmic/ or exp ovulation induction/ (27399)
8 Ovarian Hyperstimulation Syndrome/ (1109)
9 (IVF or ICSI or OHSS).tw. (11422)
10 (in vitro adj5 fertili$).tw. (13045)
11 (intracytoplas$ adj5 sperm$).tw. (2894)
12 (ovar$ adj5 hyperstim$).tw. (2440)
13 (oval$ adj5 induction).tw. (112)
14 or/7-13 (32507)
15 6 and 14 (3409)
16 randomized controlled trial.pt. (231520)
17 controlled clinical trial.pt. (74401)
18 Randomized Controlled Trials/ (47478)
19 Random allocation/ (57229)
20 Double-blind method/ (90219)
21 Single-blind method/ (10694)
22 or/16-21 (392686)
23 clinical trial.pt. (433538)
24 exp clinical trials/ (187924)
25 (clin$ adj25 trial$).ti,ab,sh. (127269)
26 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh. (89503)
27 Placebos/ (25889)
28 placebo$.ti,ab,sh. (113300)
29 random$.ti,ab,sh. (482821)
30 Research design/ (46468)
31 or/23-30 (854847)
32 animal/ not (human/ and animal/) (3047680)
33 22 or 31 (861864)
34 33 not 32 (790029)
35 15 and 34 (223)
36 (2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$).ed. (3590567)
37 35 and 36 (83)
38 from 37 keep 1-83 (83)

EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2007

1 cryopreservation/ or tissue preservation/ (215)
2 Freezing/ (47)
3 (cryopreservat$ or cryofixation or cryonic suspension).tw. (129)
4 thaw$.tw. (204)
5 freez$.tw. (434)
6 or/1-5 (783)
7 embryo transfer/ or fertilization in vitro/ or sperm injections, intracytoplasmic/ or exp ovulation induction/ (1439)
8 Ovarian Hyperstimulation Syndrome/ (95)
9 (IVF or ICSI or OHSS).tw. (1695)
10 (in vitro adj5 fertili$).tw. (1130)
11 (intracytoplas$ adj5 sperm$).tw. (302)
12 (ovar$ adj5 hyperstim$).tw. (387)
13 (oval$ adj5 induction).tw. (1)
14 or/7-13 (2634)
15 6 and 14 (127)
16 from 15 keep 1-127 (127)

CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to March Week 3 2007

1 cryopreservation/ or tissue preservation/ (294)
2 Freezing/ (80)
3 (cryopreservat$ or cryofixation or cryonic suspension).tw. (61)
4 thaw$.tw. (77)
5 freez$.tw. (329)
6 or/1-5 (697)
7 embryo transfer/ or fertilization in vitro/ or sperm injections, intracytoplasmic/ or exp ovulation induction/ (766)
8 Ovarian Hyperstimulation Syndrome/ (37)
9 (IVF or ICSI or OHSS).tw. (233)

10 (in vitro adj5 fertili$).tw. (256)
11 (intracytoplas$ adj5 sperm$).tw. (46)
12 (ovar$ adj5 hyperstim$).tw. (43)
13 (oval$ adj5 induction).tw. (1)
14 or/7-13 (897)
15 6 and 14 (44)
16 exp clinical trials/ (42848)
17 Clinical trial.pt. (20246)
18 (clinic$ adj trial$1).tw. (10023)
19 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw. (6020)
20 Randomi?ed control$ trial$.tw. (8742)
21 Random assignment/ (14868)
22 Random$ allocat$.tw. (1008)
23 Placebo$.tw. (8430)
24 Placebos/ (3415)
25 Quantitative studies/ (3123)
26 Allocat$ random$.tw. (58)
27 or/16-26 (60065)
28 15 and 27 (7)
29 from 28 keep 1-7 (7)

EMBASE 1980 to 2007 Week 12

1 cryopreservation/ or tissue preservation/ (12333)
2 Freezing/ (6068)
3 (cryopreservat$ or cryofixation or cryonic suspension).tw. (4719)
4 thaw$.tw. (8017)
5 freez$.tw. (22290)
6 or/1-5 (36047)
7 embryo transfer/ or fertilization in vitro/ or sperm injections, intracytoplasmic/ or exp ovulation induction/ (25690)
8 Ovarian Hyperstimulation Syndrome/ (2905)
9 (IVF or ICSI or OHSS).tw. (11537)
10 (in vitro adj5 fertili$).tw. (11595)
11 (intracytoplas$ adj5 sperm$).tw. (2915)
12 (ovar$ adj5 hyperstim$).tw. (2541)
13 (oval$ adj5 induction).tw. (100)
14 or/7-13 (29590)
15 6 and 14 (2710)
16 Controlled study/ or randomized controlled trial/ (2374884)
17 double blind procedure/ (63195)
18 single blind procedure/ (6449)
19 crossover procedure/ (18389)
20 drug comparison/ (81250)
21 placebo/ (96088)
22 random$.ti,ab,hw,tn,mf. (362109)
23 latin square.ti,ab,hw,tn,mf. (1061)
24 crossover.ti,ab,hw,tn,mf. (32266)
25 cross-over.ti,ab,hw,tn,mf. (11194)
26 placebo$.ti,ab,hw,tn,mf. (144334)
27 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf. (105428)
28 (comparative adj5 trial$).ti,ab,hw,tn,mf. (5590)
29 (clinical adj5 trial$).ti,ab,hw,tn,mf. (476127)
30 or/16-29 (2851591)
31 nonhuman/ (2858114)
32 animal/ not (human/ and animal/) (12843)
33 or/31-32 (2861716)
34 30 not 33 (1673476)
35 15 and 34 (698)
36 (2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$).em. (2829448)
37 35 and 36 (371)
38 from 37 keep 1-371 (371)

WHAT'S NEW

Date	Event	Description
19 January 2012	Amended	Summary of findings tables added
26 November 2010	Review declared as stable	It is unlikely that any new studies will be conducted that will influence the findings of this review

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 2, 2002

Date	Event	Description
10 November 2008	Amended	Converted to new review format.
22 May 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Dr A. D'Angelo took the lead in the writing of the update for the review in 2007. The search string was modified and ran no new studies were found.
In 2002:
Dr A. D'Angelo took the lead in the writing of the review. She scanned the titles and the abstracts of the reports identified by electronic searching in order to find relevant papers she then obtained copies of the full text articles and made copies for the other reviewer (NNA). Extracted data independently using forms designed according to Cochrane guidelines. Disagreements were resolved by discussion.

N.N. Amso scanned the titles and the abstracts of the reports identified by electronic searching in order to find relevant papers. Extracted data independently using forms designed according to Cochrane guidelines. Disagreements were resolved by discussion.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, University Hospital of Wales, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

*Cryopreservation; *Embryo, Mammalian; Albumins [*administration & dosage]; Infusions, Intravenous; Ovarian Hyperstimulation Syndrome [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans