Human Reproduction Vol.17, No.11 pp. 2787–2794, 2002

Embryo freezing for preventing ovarian hyperstimulation syndrome: a Cochrane review

A.D'Angelo[1] and N.N.Amso

Department of Obstetrics and Gynaecology, University Hospital of Wales College of Medicine, Cardiff CF14 4XN, UK

[1]To whom correspondence should be addressed. E-mail: d-angeloa@cardiff.ac.uk

This paper is based on a Cochrane review published in The Cochrane Library, issue 3, 2002 (see www.CochraneLibrary.net for information) with permission from The Cochrane Collaboration and Update Software. Cochrane reviews are regularly updated as new evidence emerges and in response to comments and criticisms, and The Cochrane Library should be consulted for the most recent version of the review.

BACKGROUND: Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic condition resulting from an excessive ovarian response to superovulation medication. The objective of this review was to evaluate the effectiveness of cryopreservation (embryo freezing) when compared with human i.v. albumin infusion and with fresh embryo transfer for the prevention of OHSS. METHODS: This was based on a Cochrane Review. Randomized controlled trials in which either human i.v. albumin or cryopreservation of all embryos was used as a therapeutic approach to OHSS were included. The participants were women down-regulated by GnRH agonist, undergoing superovulation in IVF/ICSI cycles. The interventions compared were cryopreservation versus i.v. 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/mild OHSS, and clinical pregnancies/woman. Statistical analysis was performed in accordance with the Cochrane Menstrual Disorders and Subfertility Group guidelines. RESULTS: Seventeen studies were identified, two of which met our inclusion criteria. One study was included where cryopreservation was compared with i.v. human albumin administration and another where elective cryopreservation of all embryos was compared with fresh embryo transfer. In both interventions no difference was found in all the outcomes examined between the two groups. CONCLUSIONS: This review has shown that there is insufficient evidence to support routine cryopreservation and insufficient evidence for the relative merits of i.v. albumin versus cryopreservation.

Key words: elective cryopreservation/i.v. albumin/ovarian hyperstimulation syndrome/randomized controlled trials/systematic review

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic and potentially life threatening condition resulting from an excessive ovarian response to superovulation medication. Its reported incidence varies from 1 to 10% of IVF cycles (Forman *et al.*, 1990; Wada *et al.*, 1990; MacDougall *et al.*, 1992). The incidence of the severe form of OHSS in women undergoing controlled ovarian hyperstimulation for IVF has been estimated to be ~0.5–2.0% (Forman *et al.*, 1990; Society for Assisted Reproductive Technology, the American Fertility Society, 1992) with a reported positive correlation between young age, lean appearance and OHSS (Navot *et al.*, 1992). In addition, polycystic ovarian syndrome 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, hCG supplementation of the luteal phase and high serum estradiol (E_2; >2500 pg/ml) were also reported to be associated with an increased risk of OHSS.

OHSS was originally classified as mild, moderate and severe (Rabau *et al.*, 1967; Schenker and Weinstein, 1978) and subsequently modified to incorporate ultrasonographic measurement of the stimulated ovaries (Golan *et al.*, 1989). Briefly, mild OHSS presents clinically as weight gain, thirst and abdominal discomfort; ultrasound examination shows the ovaries to be enlarged (5–10 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 10–12 cm in diameter. In severe OHSS, all of these symptoms are associated with clinical evidence of excessive third-space fluid accumulation (ascites, hydrothorax), ovaries >12 cm in diameter and in extreme cases may present with acute respiratory distress, hepato-renal failure and thrombo-

Table I. Golan classification of OHSS

	Size ovaries	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 II. Navot classification of severe OHSS

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 >50 ml/min	Creatinine clearance <50ml/min
Liver dysfunction	Renal failure
Anasarca	Tromboembolic phenomena
	Adult respiratory distress syndrome

embolic phenomena (Brinsden, 1995) (Table I). Navot *et al.* introduced further modification to the above classification by differentiating between severe and life threatening forms of OHSS (Navot *et al.*, 1992) (Table II).

The factors leading to this syndrome have not been completely elucidated. It seems likely that the release of vasoactive substances, such as vascular endothelium growth factor (VEGF), secreted by the ovaries under hCG stimulation plays a key role in triggering this syndrome (Tsirigotis and Craft, 1994; Goldsman *et al.*, 1995). 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 E_2 level and in an as yet poorly defined manner, vasoactive substances (Agrawal *et al.*, 1998; Al-Shawaf *et al.*, 2001). The hallmark of this condition is a massive shift of fluid from the intravascular compartment to the third space resulting in profound intravascular depletion and haemoconcentration (Rabau *et al.*, 1967; Schenker and Weinstein, 1978).

The crucial event in the development of OHSS is the administration of hCG. However, some have reported the onset of OHSS after gonadotrophin in stimulation despite withholding hCG (Allegra *et al.*, 1991; Lipitz *et al.*, 1991). Moderate or severe OHSS typically presents in the luteal phase as a consequence of ovulatory hCG or in the early gestation phase in which endogenous hCG is produced. When establishment of 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 gestation, and is more often associated with multiple pregnancy (Dahl *et al.*, 1994). The elective cryopreservation of all embryos and their subsequent transfer in non-gonadotrophin stimulated cycles have been employed to avoid the endogenous hCG rise in IVF–embryo transfer programmes (Amso *et al.*, 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 and implantation rates than fresh embryo transfer (Awonuga *et al.*, 1996).

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 intravascular space into the peritoneal cavity (Asch *et al.*, 1993). It could be speculated that human albumin binds an undefined factor (ovarian renin-angiotensin and/or VEGF) at a specific and critical time of the cycle and thus helps to prevent the development of OHSS (Shoham *et al.*, 1994). Timely administration of albumin, during oocyte recovery or immediately following, may serve to bind and inactivate this factor. However, Doldi *et al.* contradicted the above hypothesis and demonstrated that human albumin increases VEGF gene expression in human luteinizing granulosa cells (Doldi *et al.*, 1999) and maximum expression was present in cultured granulosa cells obtained from women with serum E_2 concentration >2000 pg/ml on the day of hCG injection.

Other, alternative strategies have also been proposed for

IVF/ICSI patients at risk of OHSS: (i) cancellation of the treatment cycle (Forman *et al.*, 1990); (ii) gonadotrophin discontinuation prior to hCG triggering injection (coasting) (Sher *et al.*, 1993); (iii) early unilateral follicular aspiration (Egbase *et al.*, 1999); (iv) avoidance of luteal supplementation with hCG (Araujo *et al.*, 1994); and (v) 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 *et al.*, 1990; Segal and Casper, 1992). Each of these strategies may reduce but not eliminate the risk. The objectives of this review were to evaluate: (i) the effectiveness of cryopreservation (embryo freezing) for the prevention of OHSS when compared with human i.v. albumin infusion; and (ii) the effectiveness of the elective cryopreservation (embryo freezing) of all embryos for the prevention of OHSS when compared with fresh embryo transfer. A more detailed review has been published in the Cochrane Database of Systematic Reviews (Issue 2, 2002).

Materials and methods

We searched publications in the literature that described randomized controlled trials of both human i.v. albumin and elective freezing of all embryos in the management of OHSS. The Cochrane Menstrual Disorders and Subfertility Review Group (CMDSG) specialized register of controlled trials was searched, Medline (Pubmed; 1985–2001), Embase (1985–2001), Cinhal (1985–2001) and the National Research Register were searched. In addition, the authors also hand-searched specialist journals retrieving relevant articles from titles and abstracts, checked the reference lists of articles, contacted authors of conference abstracts to obtain details of any subsequent publication(s), contacted the principal journals (*Human Reproduction*, *Fertility and Sterility*, *British Journal of Obstetrics and Gynaecology* and *Lancet*) asking for any published and/or unpublished articles, and contacted authors of ongoing studies on this topic to obtain, where possible, study data and updates of any unpublished work. The authors of the included published studies were contacted twice to obtain additional information that was required for the analysis.

Two reviewers, N.N.A. and A.D.A., scanned the titles and the abstracts of the reports identified by electronic searching in order to find relevant papers. One reviewer (A.D.A.) obtained copies of the full text articles and made copies for the other reviewer (N.N.A.) in which details of authors, institution, results and discussion were removed in order to assess their eligibility for inclusion. Then, both reviewers extracted data independently using forms designed according to CMDSG guidelines. Disagreements were resolved by discussion. The unit for randomization was women fulfilling the criteria for inclusion into the study. The quality of allocation concealment was graded as adequate (A), unclear (B) or inadequate (C), following the detailed descriptions of these categories provided by the CMDSG.

Randomized controlled trials (RCTs) in which either human i.v. albumin or freezing of all embryos were used as a therapeutic approach to OHSS were included. Ovulation induction treatment without IVF/ICSI was not included in the meta-analysis. Crossover trials were excluded.

The participants were women of reproductive age, down-regulated by GnRH agonist, undergoing superovulation in IVF/ICSI cycles. Women were considered at risk of OHSS according to the serum E_2 level (>1906 pg/ml or >7000 pmol/l) on the day of hCG administration. The interventions compared were: (i) cryopreservation of all embryos versus i.v. albumin infusion; (ii) cryopreservation of all embryos versus fresh embryo transfer. The primary outcomes analysed were: incidence of moderate and/or severe OHSS versus nil or mild OHSS, subsequent to oocyte retrieval; clinical pregnancy rate/woman (after fresh or frozen embryo transfer where applicable). The secondary outcomes analysed were: number of oocytes retrieved; fertilization rate; number of embryos transferred; number of embryos frozen; multiple pregnancy rate; live birth rate; number of women admitted to the hospital as an in-patient versus out-patient; number of days to next menstrual period (resolution time).

Statistical analysis was performed in accordance with the guidelines developed by the CMDSG. 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 weighted mean differences and have been reported separately. Because of the small number of studies included, no sensitivity analysis was performed.

Results

This review identified 17 studies but only two trials met our inclusion criteria (Table III). Fifteen studies were excluded (Table IV). We have identified one randomized controlled study in which cryopreservation of all embryos was compared with i.v. albumin infusion (before/during or after oocyte recovery) and subsequent fresh embryo transfer for the prevention of moderate and severe OHSS, and one randomized controlled study in which elective cryopreservation of all embryos was compared with fresh embryo transfer for the prevention of moderate and severe OHSS.

The only study in which cryopreservation of all embryos was compared with i.v. albumin infusion and subsequent fresh embryo transfer that met our inclusion criteria was Shaker *et al.* (Shaker *et al.*, 1996). Women's age and superovulation protocols are listed in Table III. Women were considered to be at risk of hyperstimulation when E_2 was >10 000 pmol/l and >15 oocytes collected or E_2 >13 000 pmol/l. A diagnosis of moderate or severe OHSS was made according to the Schenker and Weinstein classification (Schenker and Weinstein, 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 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 a single centre, randomized study by Ferraretti *et al.* (Ferraretti *et al.*, 1999). Women undergoing superovulation for IVF/ICSI treatment (GnRH agonist down-regulation and gonadotrophin stimulation) were included in the study. They were considered to be at risk of hyperstimulation when the E_2 level was >1500 pg/ml (>5500 pmol/l) and >15 oocytes were collected. The diagnosis of moderate and severe OHSS was made according to the Golan classification (Golan *et al.*, 1989) revised by Navot (Navot *et al.*, 1992). The incidence of moderate or severe OHSS, clinical pregnancy rate per woman, number of oocytes retrieved, number of embryos transferred, live birth rate and number of women

Table III. Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Allocation concealment
Ferraretti, 1999	Randomized study; parallel prospective design; single centre; power calculation: not stated; method of randomization: not specified.	125 infertile women considered at risk of OHSS (58/125 had cryopreservation; 67/125 had fresh embryos transfer); E_2 (major risk factor for OHSS) >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), other (3 versus 4); BMI <30 kg/m^2	Study group: cryopreservation of all embryos immediately (zygotes); control group: fresh embryo transfer after 48 h of culture. Both groups received 20 g of human albumin i.v. on the day of oocyte recovery	Method of diagnosing different grades of OHSS: Golan and Navot criteria. 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%); number of embryos transferred (3.1 ± 0.8 versus 3.2 ± 1.0); multiple pregnancy rate (not stated); live birth rate (39.6 versus 38.8); number of in-patient or out-patient (4 versus 0); resolution time (12.1 ± 1.0 days in the study group).	B
Shaker, 1996	Randomized study; parallel prospective design; single centre; power calculation: not stated; intention to-treat analysis done; randomization done by drawing cards, each contained a number obtained from a table of random numbers.	26 infertile women considered at risk of OHSS (13/26 had i.v. albumin infusion; 13/26 had cryopreservation of all embryos); E_2 (major risk factor for OHSS) >3540 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).	Study group: i.v. albumin infusion (200 ml of 20% concentration) on the day of oocytes collection and repeated 5 days later + fresh embryo transfer; control group: cryopreservation of all embryos at pronucleate stage.	Method of diagnosing different grades of OHSS: Schenker and 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); no. 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); live birth rate (not stated); number of in-patient or out-patient (not stated); resolution time (not stated).	B

BMI = body mass index; PCO = polycystic ovaries.

Table IV. Characteristics of excluded studies

Study	Reason for exclusion
Asch *et al.*, 1993	Observational study
Awonuga *et al.*, 1996	Prospective observational study
Chen *et al.*, 1997	Prospective observational study
Isik *et al.*, 1996	Randomized controlled study comparing i.v. albumin infusion with no treatment
Munoz *et al.*, 2000	Randomized controlled study comparing i.v. albumin infusion with placebo
Ndukwe *et al.*, 1997	Retrospective review and data analysis
Ng *et al.*, 1995	Cohort study not randomized
Panay *et al.*, 1999	Randomization based on alternating basis
Pattinson *et al.*, 1994	Retrospective review
Queenam *et al.*, 1997	Prospective observational longitudinal study
Shalev *et al.*, 1995	Randomized controlled study comparing i.v. albumin infusion with no treatment
Shoham *et al.*, 1994	Randomized controlled study comparing i.v. albumin infusion with placebo
Titinem *et al.*, 1995	Observational study
Wada *et al.*, 1992	Prospective observational study
Wada *et al.*, 1993	Retrospective review

Table V. List of comparisons

Comparison	Outcome	No. of studies	No. of participants	Statistical method	Effect size
Cryopreservation versus fresh embryo transfer	Moderate/severe OHSS	1	125	OR (fixed) (95% CI)	0.12 (0.01, 2.29)
	Clinical pregnancies				1.08 (0.54, 2.19)
	Live birth rate				1.03 (0.50, 2.12)
	No. of women admitted				0.12 (0.01, 2.29)
Cryopreservation versus i.v. albumin	Moderate/severe OHSS	1	26		5.33 (0.51, 56.24)
	Nil/mild OHSS				0.38 (0.08, 1.90)
	Clinical pregnancies				0.06 (0.00, 1.17)

OR = odds ratio; CI = confidence interval.

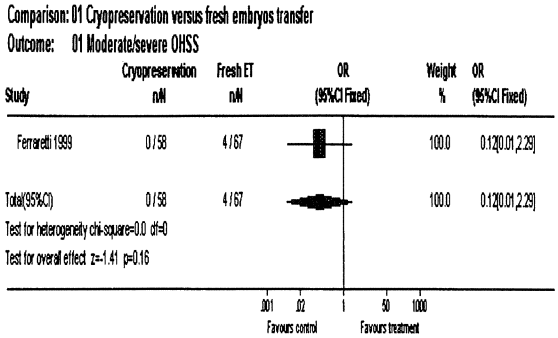
admitted as in- or out-patients were compared in the intervention and control groups. Both studies included were single centre unblinded RCTs. Women were randomized using a random card method (Shaker *et al.*, 1996) or not specified (Ferraretti *et al.*, 1999). Neither of the studies described a power of calculation, and neither described allocation concealment adequately. Both authors were contacted by letter to obtain missing data. The number of women included in these studies was small. Three women withdrew from the Shaker *et al.* study (Shaker *et al.*, 1996) requesting to have fresh embryos rather than cryopreservation. No withdrawals or loss of follow-up were mentioned in the other study.

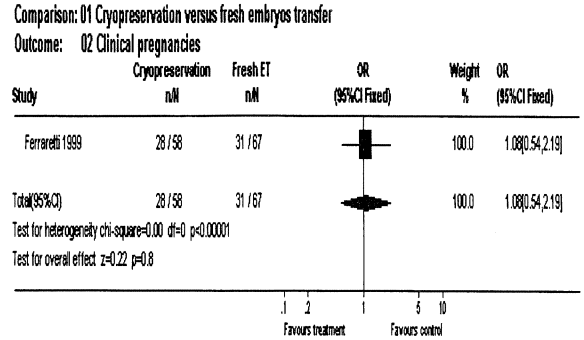
Comparisons were classified into two main categories (Table V). When cryopreservation was compared with i.v. human albumin administration no difference was found in any of the outcomes examined between the two groups. When elective cryopreservation of all embryos was compared with fresh embryo transfer no difference was found in any of the outcomes examined between the two groups (Figure 1).

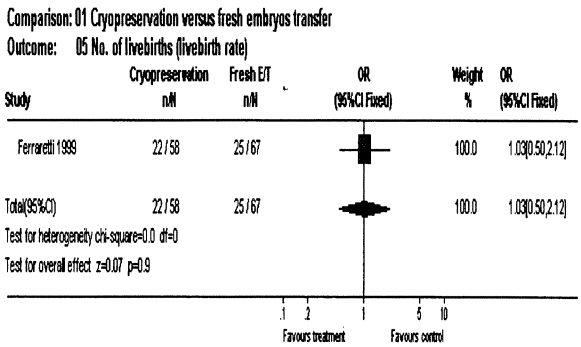
Discussion

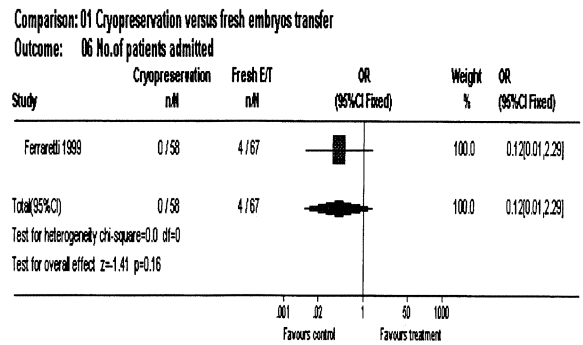
This systematic review showed that there was no statistically significant difference in the incidence of moderate and/or severe OHSS when cryopreservation of all embryos was employed compared with i.v. albumin infusion and fresh embryo transfer in women at risk of OHSS. These results have to be interpreted with caution because of the small number of women in the individual studies and because they were based on an experimental treatment (i.e. i.v. 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. However, there are a number of methodological concerns which may have affected the results, such as the administration of i.v. albumin to all participants (Ferraretti *et al.*, 1999) and its possible influence on the incidence of severe OHSS. Although there were four cases of severe OHSS in the fresh embryo transfer group and none in the cryopreservation group, this was not signifcantly different. According to this review and to a previous meta-analysis conducted by Aboulghar *et al.* which has demonstrated a statistically significant difference in the incidence of severe OHSS between i.v. albumin infusion and placebo/no treatment (Aboulghar *et al.*, 1999), there is a need for a larger multicentre RCT of these interventions with sufficient power to show a statistically significant difference in the occurrence of moderate and/or severe OHSS.

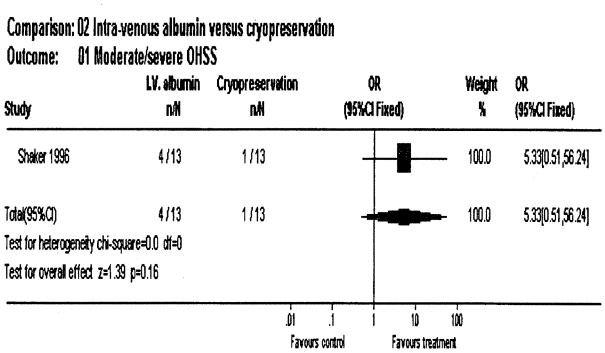
On the basis of the studies included in both reviews, power calculations were carried out which indicated that to demonstrate a difference of 25% between experimental (i.v. albumin infusion) and control (elective cryopreservation of all embryos) groups at a power of 80%, with a statistical significance level of 0.05, 185 women are needed in each

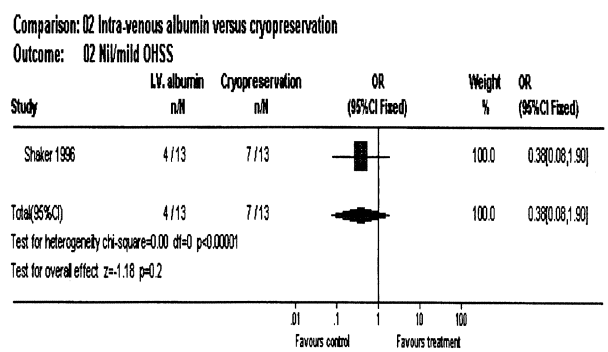












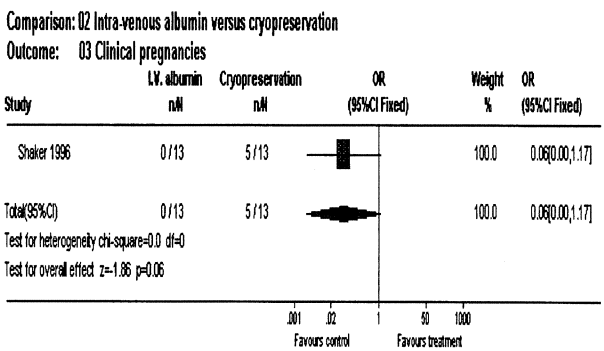


Figure 1. Meta-analysis of different interventions for prevention of OHSS.

group (a total of 370 participants). To achieve a power of 90%, 235 women are needed in each group (470 participants).

As far as the clinical pregnancy rate per woman is concerned, none of the studies reached statistical significance. However, in one study (Shaker *et al.*, 1996) there was a trend towards a 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 randomized (13 in each arm) and three participants withdrawn from the cryopreservation group; (ii) was not blinded; and (iii) the authors tried to justify the discrepancy in pregnancy rate with the fact that the second dose of i.v. albumin, administered 5

days after the fresh embryos transfer, might have affected the implantation phase.

This review has showed that there is insufficient evidence to support routine cryopreservation and insufficient evidence for the relative merits of i.v. albumin versus cryopreservation. There is a need to clearly define women at risk of OHSS, based on endocrinological/ultrasonographic/clinical criteria, and a need for a large RCT looking at (i) severe OHSS for i.v. albumin with fresh embryo transfer versus cryopreservation and (ii) pregnancy outcome for i.v. albumin with fresh embryo transfer versus cryopreservation. Randomization should take place when risk is determined (i.e. during the stimulation phase or immediately prior to oocyte collection) according to serum E_2 level (>1906 pg/ml or >7000 pmol/l) on the day of hCG administration.

Acknowledgements

The authors would like to thank the Menstrual Disorders and Subfertility Group editorial office staff, in particular Ms Sarah Hetrick and Mrs Michelle Proctor for their advice and support through the review process.

References

Aboulghar, M., Evers, J.H. and Al-Inany, H. (1999) Intra-venous albumin for preventing severe ovarian hyperstimulation syndrome (Cochrane Review). In *The Cochrane library*, Issue 4. Update Software, Oxford, UK.

Agrawal, R, Conway, G., Sladkevicius, P. *et al.* (1998) Serum vascular endothelial growth factor and Doppler blood flow velocities in *in vitro* fertilization: relevance to ovarian hyperstimulation syndrome and policystic ovaries. *Fertil. Steril.*, **70**, 651–658.

Allegra, A., Termine, N., Raineri, L. *et al.* (1991) Iperstimolazione ovarica e gravidanza gemellare in una paziente in trattamento con analogo del GnRH e gonadotropine senza somministrazione di midcycle hCG. *Riv. Ostet. Ginecol. Perinat.*, **2**, 209–211.

Al-Shawaf, T., Zosmer, A., Hussain, S. *et al.* (2001) Prevention of severe ovarian hyperstimulation syndrome in IVF with or without ICSI and embryo transfer: a modified 'coasting' strategy based on ultrasound identification of high-risk patients. *Hum. Reprod.*, **1**, 24–30.

Amso, N.N., Ahuja, K.K., Morris, N. *et al.* (1990) The management of predicted ovarian hyperstimulation involving gonadotropin-releasing hormone analog with elective cryopreservation of all pre-embryos. *Fertil. Steril.*, **53**, 1087–1090.

Araujo, E., Bernardini, L., Frederick, J.L. *et al.* (1994) Prospective randomized human chorionic gonadotropin versus intramuscular progesterone for luteal-phase support in assisted reproduction. *J. Assist. Reprod. Genet.*, **11**, 74–78.

Asch, R.H., Ivery, G., Goldsman, M. *et al.* (1993) The use of intravenous albumin in patients at high risk for severe ovarian hyperstimulation syndrome. *Hum. Reprod.*, **8**, 1015–1020.

Awonuga, A.D., Pittrof, R.J., Zaidi, J. *et al.* (1996) Elective cryopreservation of all embryos in women at risk of developing ovarian hyperstimulation syndrome may not prevent the condition but reduces the live birth rate. *J. Assist. Reprod. Genet.*, **13**, 401–406.

Brinsden, P.R., Wada, I., Tan, S.L. *et al.* (1995) Diagnosis, prevention and management of OHSS: review. *Br. J. Obstet. Gynaecol.*, **102**, 767–772.

Chen, C., Wu, M., Yang, J. *et al.* (1997) Intravenous albumin does not prevent the development of severe ovarian hyperstimulation syndrome. *Fertil. Steril.*, **68**, 287–291.

Dahl Lyons, C.A., Wheeler, C.A., Frishman, G.N. *et al.* (1994) Early and late presentation of ovarian hyperstimulation syndrome: two distinct entities with different risk factors. *Hum. Reprod.*, **9**, 792–799.

Doldi, N., Destefani, A., Gessi, A. *et al.* (1999) Human albumin enhances expression of vascular endothelial growth factor in cultured human luteinizing granulosa cells: importance in ovarian hyperstimulation syndrome. *Hum. Reprod.*, **14**, 1157–1159.

Egbase, P.E., Al Sharhan, M. and Grudzinskas, J.G. (1999) Early unilateral follicular aspiration compared with coasting for the prevention of severe ovarian hyperstimulation syndrome: a prospective randomzed study. *Hum. Reprod.*, **14**, 1421–1425.

Ferraretti, A.P., Gianaroli, L., Magli, C. *et al.* (1999) Elective cryopreservation of all pronucleate embryos in women at risk of ovarian hyperstimulation syndrome: efficiency and safety. *Hum. Reprod.*, **14**, 1457–1460.

Forman, R.G., Frydman, R., Egan, D. *et al.* (1990) Severe ovarian hyperstimulation syndrome using agonists of gonadotrophin releasing hormone for *in vitro* fertilization:a European series and a proposal for prevention. *Fertil. Steril.*, **53**, 502–509.

Golan, A., Ron-El, R., Herman, A. *et al.* (1989) Ovarian hyperstimulation syndrome: an update review. *Obstet. Gynaecol. Surv.*, **44**, 430–440.

Goldsman, M.P., Pedram, A., Dominiguez, C.E., *et al.* (1995) Increased capillary permeability induced by human follicular fluid: a hypothesis for an ovarian origin of the hyperstimulation syndrome. *Fertil. Steril.*, **63**, 268–272.

Gonen, Y., Balakier, H., Powell, W. *et al.* (1990) Use of GnRH agonist to trigger follicular maturation for *in vitro* fertilization. *J. Clinical Endocrinol. Metab.*, **71**, 918–923.

Isik, A.Z., Gokmen, O., Zeyneloglu, H.B. *et al.* (1996) Intravenous albumin prevents moderate–severe ovarian hyperstimulation in in-vitro fertilization patients: a prospective, randomized and controlled study. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **70**, 179–183.

Lipitz, S., Zion, B.R., Bider, D. *et al.* (1991) Quintuplet pregnancy and third degree ovarian hyperstimulation despite withholding human chorionic gonadotropin. *Hum. Reprod.*, **6**, 1478–1479.

MacDougall, M.J., Tan, S.L. and Jacobs, H.S. (1992) *In vitro* fertilization and the ovarian hyperstimulation syndrome. *Hum. Reprod.*, **7**, 579–600.

Munoz, E., Cuneo, S., Ferro, J. *et al.* (2000) Intravenous albumin in the prevention of ovarian hyperstimulation syndrome. *Hum. Reprod.*, **15** (Abst. Book), P-102, p. 139.

Navot, D., Bergh, P.A. and Laufer, N. (1992) Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. *Fertil. Steril.*, **58**, 249–261.

Ndukwe, G., Thornton, S., Fishel, S. *et al.* (1997) Severe ovarian hyperstimulation syndrome: is it really preventable by prophylactic intravenous albumin? *Fertil. Steril.*, **68**, 851–854.

Ng, E., Leader, A., Claman, P. *et al.* (1995) Intravenous albumin does not prevent the development of severe ovarian hyperstimulation syndrome in an in-vitro fertilization programme. *Hum. Reprod.*, **10**, 807–810.

Panay, N., Iammarrone, E., Zosmer, A. *et al.* (1999) Does the prophylactic use of intravenous albumin prevent ovarian hyperstimulaton syndrome? A randomized prospective study. *Hum. Reprod.*, **14**, 105.

Pattinson, H.A., Hignett, M., Dunphy, B.C. *et al.* (1994) Outcome of thaw embryo transfer after cryopreservation of all embryos in patients at risk of ovarian hyperstimulation syndrome. *Fertil. Steril.*, **62**, 1192–1196.

Queenam, J.T. Jr, Veeck, L.L., Toner, J.P. *et al.* (1997). Cryopreservation of all prezygotes in patients at risk of severe hyperstimulation does not eliminate the syndrome, but the chances of pregnancy are excellent with subsequent frozen–thaw transfers. *Hum. Reprod.*, **12**, 1573–1576.

Rabau, E., Serr, D.M., David, A. *et al.* (1967) Human menopausal gonadotropins for anovulation and sterility. *Am. J. Obstet. Gynaecol.*, **98**, 92–98.

Schenker, J.G. and Weinstein, D. (1978) Ovarian hyperstimulation syndrome: a current survey. *Fertil. Steril.*, **30**, 255–268.

Segal, S. and Casper, RF. (1992) Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin for triggering follicular maturation in *in vitro* fertilization. *Fertil. Steril.*, **57**, 1254–1258.

Shaker, A.G., Zosmer, A., Dean, N. *et al.* (1996) Comparison of intravenous albumin and transfer of fresh embryos with cryopreservation of all embryos for subsequent transfer in prevention of ovarian hyperstimulation syndrome. *Fertil. Steril.*, **65**, 992–996.

Shalev, E., Giladi,Y., Matilsky, M. *et al.* (1995). Decreased incidence of severe ovarian hyperstimulation syndrome in high-risk in-vitro fertilization patients receiving intravenous albumin: a prospective study. *Hum. Reprod.*, **10**, 1373–1376.

Sher, G., Zouves, C., Feinman, M. *et al.* (1993) Eliminating the risk of life-endangering complications following overstimulation with menotropin fertility agents: a report on women undergoing *in vitro* fertilization and embryo transfer. *Obstet. Gynaecol.*, **81**, 1009–1011.

Shoham, Z., Weissman, A., Barash, A. *et al.* (1994) Intravenous albumin for the prevention of severe ovarian hyperstimulation syndrome in an *in vitro* fertilization program: a prospective, randomized, placebo-controlled study. *Fertil. Steril.*, **62**, 137–142.

Society for Assisted Reproductive Technology, the American Fertility Society (1992) *In vitro* fertilization–embryo transfer (IVF–ET) in the United States: 1990 results from the IVF–ET registry. *Fertil. Steril.*, **57**, 15–24.

Titinem, A., Husa, L., Tulppala, M. *et al.* (1995) The effect of cryopreservation in prevention of ovarian hyperstimulation syndrome. *Br. J. Obstet. Gynaecol.*, **10**, 326–329.

Tsirigotis, M. and Craft, I. (1994) Ovarian Hyperstimuation Syndrome (OHSS): how much do we really know about it? *Eur. J. Obstet. Gynaecol.*, **55**, 151–155.

Wada, I., Matson, P.L., Troup, S.A. *et al.* (1990) Ovarian hyperstimulation syndrome in GnRH-a/hMG cycles for IVF and GIFT. *J. Obstet. Gynaecol.*, **11**, 88–89.

Wada, I., Matson, P.L., Troup, S.A. *et al.* (1992) Outcome of treatment subsequent to the elective preservation of all embryos from women at risk of ovarian hyperstimulation syndrome. *Hum. Reprod.*, **7**, 962–966.

Wada, I., Matson, P.L., Troup, S.A. *et al.* (1993) Does elective cryopreservation of all embryos from women at risk of ovarian hyperstimulation syndrome reduce the incidence of the condition? *Br. J. Obstet. Gynaecol.*, **100**, 265–269.