Human Reproduction Vol.18, No.11 pp. 2283–2288, 2003 DOI: 10.1093/humrep/deg451

Intravenous albumin does not prevent moderate-severe ovarian hyperstimulation syndrome in high-risk IVF patients: a randomized controlled study

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BACKGROUND: Intravenous albumin administration has been described for many years as a debatable, but probably useful preventive measure in ovarian hyperstimulation syndrome (OHSS). The present study details the largest randomized controlled trial to date of albumin infusion versus no treatment in IVF patients with a high risk of developing moderate to severe OHSS. METHODS: Between March 1999 and February 2002, women undergoing IVF at the IVI Valencia with >20 retrieved oocytes were included. A total of 988 patients was initially enrolled. Immediately after oocyte retrieval, patients were allocated to two groups based on a computer randomization: the first group received 40 g human albumin; the second group received no treatment. Subjects were weighed and a blood analysis performed immediately after oocyte retrieval and again 7 days later. Women were monitored on an outpatient basis until menstruation, or until fetal heart activity was detected. Twelve subjects were excluded due to follow-up loss, leaving 976 women (377 of them oocyte donors), with 488 in each group. RESULTS: No difference was found between the two groups in terms of patient characteristics and outcome. Moderate-severe and severe-only OHSS rates were similar. The incidence of haemoconcentration and liver and renal dysfunction at 7 days after oocyte retrieval was similar in the two groups. In women who developed moderate/severe (n = 66) or only severe (n = 46) OHSS, there was no difference based on prior albumin administration between blood parameters or body weight on the day of oocyte retrieval, 7 days later, and even when comparing variation between both measurements. Moreover, the number of patients with paracentesis, hospital admissions, complications and days of OHSS until resolution did not differ. CONCLUSIONS: Albumin infusion on the day of oocyte retrieval is not a useful means of preventing the development of moderate-severe OHSS.

Key words: albumin/ovarian hyperstimulation syndrome/prevention/randomized

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially life-threatening iatrogenic complication of controlled ovarian hyperstimulation (COH) cycles (Whelan and Vlahos, 2000), and is usually associated with regimens of exogenous gonadotrophins. The incidence of OHSS ranges from 0.6 to 14% of IVF cycles with embryo transfer (Brinsden *et al*., 1995; Al-Ramahi, 1999; Fluker *et al*., 2000), with the severe form appearing in about 0.2–5% of cases (Navot *et al*., 1992; Al-Ramahi, 1999; Forman, 1999; Graf and Fischer, 1999).

The pathophysiology of OHSS is still not well understood, but different factors related to an increased capillary permeability have been involved (Chen *et al*., 2000; Albert *et al*., 2002; Gómez *et al*., 2002), leading to a massive extravascular exudate accumulation combined with profound intravascular volume depletion and haemoconcentration (Schenker and Weinstein, 1978; Navot *et al*., 1992). OHSS is a self-limiting condition (Whelan and Vlahos, 2000), especially when pregnancy is not achieved.

When a profile of high risk is recognized, preventive measures should be taken. Intravenous albumin administration has been described for many years as a debatable, but probably useful, measure (Asch *et al*., 1993; Shalev *et al*., 1995; Aboulghar *et al*., 2000). Albumin seems to have osmotic functions, as it contributes to around 75% of the plasma oncotic pressure, drawing extracellular fluid into the circulation, and possesses transport functions, binding and inactivating the vasoactive intermediates responsible for the pathogenesis of OHSS (McClelland, 1990; Shalev *et al*., 1995; Isik *et al*., 1996; Aboulghar *et al*., 2002). Recently, the benefits of preventive intravenous albumin administration have been discussed in a

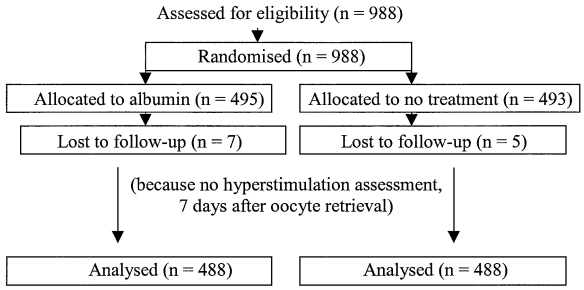

Figure 1. Patient flow through the stages of the randomized controlled trial.

Cochrane review of five randomized controlled trials of albumin infusion versus placebo/no treatment for women at high risk of developing severe OHSS after COH (Aboulghar *et al*., 2002). In those studies, in which the albumin doses ranged from 10 to 50 g and were administered 1–2 h before or immediately after oocyte retrieval, only 463 patients were considered. Since the prevention of OHSS is so important in assisted reproductive technologies, a broad prospective randomized controlled trial was designed to compare albumin infusion with no treatment in patients at high risk of moderate to severe OHSS after COH, in order to ascertain the actual preventive role of this protein.

Materials and methods

Between March 1999 and February 2002, all women undergoing IVF treatment at the Instituto Valenciano de Infertilidad (Valencia, Spain) and considered at risk of developing moderate or severe OHSS entered into the study. The inclusion criterion was the collection of >20 oocytes during oocyte retrieval. A total of 988 women was initially accepted, all of whom provided their oral consent. The study protocol was approved by the institution's Ethical Committee. Each participant underwent a complete evaluation protocol prior to COH, including clinical history, physical and ultrasound examination and hormonal profile.

Stimulation protocol

The protocol for COH consisted of pituitary desensitization with daily subcutaneous administration of 0.1 mg triptorelin (Decapeptyl 0.1; Lasa S.A., Barcelona, Spain) or 1 mg leuprolide acetate (Procrin; Abbott S.A., Madrid, Spain) beginning in the luteal phase of the previous menstrual cycle. This dose was continued until ovarian quiescence was demonstrated by vaginal ultrasound following menstruation. The standard protocol consisted of 225 IU/day highly purified or recombinant FSH (Neofertinorm or Gonal; Serono Laboratories, Madrid; or Puregon; Organon Española, S.A, Barcelona, Spain) plus 75 IU/day hMG (Lepori; Farma Laboratories, Barcelona, Spain) administered on days 1 and 2 of ovarian stimulation. This protocol was modified when the patient presented risk factors of hyperstimulation or poor response in her clinical history, ultrasound examination or hormonal assessment. Polycystic ovary syndrome (PCOS), defined as oligomenorrhoea and hyperandrogenism, was especially considered for COH. From day 3 of stimulation onwards, gonadotrophins were individualized according to serum estradiol levels and ultrasonographic ovarian response. hCG (10 000 IU; Profasi; Serono Laboratories, Madrid, Spain) was administered i.m. when at least two leading follicles reached a mean follicular diameter of 18 mm. GnRH agonist and gonadotrophin injections were discontinued on the day of hCG administration. Transvaginal oocyte retrieval was scheduled 36 h after hCG injection, at which time the treatment terminated for oocyte donors. In the remaining women, a luteal phase support of 400 mg/day micronized intravaginal progesterone (Progeffik; Laboratories Effik S.A., Madrid, Spain) was started the day after oocyte retrieval and maintained until a pregnancy test was performed, or until day 80 of pregnancy if the patient tested positive. Embryos were transferred on day 2–3 or 5–6 of development, according to the case, and always that cryopreservation was discarded because of the risk of OHSS. Serum β-hCG levels were monitored 14 days after oocyte retrieval.

Study protocol and randomization

The study was both prospective and randomized in nature. A computer-based randomization (Sigmastat for Windows, version 2.0; Jandel Scientific Corporation, San Rafael, CA, USA) was used to allocate the patients to two groups immediately after confirmation of retrieval of >20 oocytes. The first group received 40 g human albumin (Albúmina humana Grifols 20%; Grifols, Barcelona, Spain), infused i.v. at a slow rate during 30 min, immediately after oocyte retrieval. The second group did not receive any albumin treatment. All patients allocated by randomization to the albumin group received this protein, whereas in those of the control group albumin was always avoided. Randomization was strictly followed over the study period.

The incidence in the studied groups (albumin versus no treatment) of moderate and severe OHSS and biochemical serum changes were the primary outcome measures considered to assess the preventive role of albumin. The implantation and pregnancy rates in patients, and the clinical evolution of the hyperstimulated women were the secondary outcome measures.

In both groups, subjects were weighed and haematological tests performed immediately following oocyte retrieval and again 7 days later. Haemoglobin, haematocrit and leukocyte count and renal (creatinine) and liver [transaminases: aspartate aminotransferase (AST); alanine aminotransferase (ALT)] functions were analysed. Women were monitored on a non-rigid outpatient basis via phone contact and visits until menstruation occurred or until fetal heart activity was detected in pregnant patients. Cases of OHSS were classified according to previously published criteria (Golan *et al*., 1989)

The present study followed the CONSORT guidelines for the reporting of randomized control trials (Moher *et al*., 2001)

Hormone assay

Serum estradiol was measured using microparticle enzyme immunoassay (MEIA) technology and employing the Axsym System (Abbot Laboratories, Illinois, USA). The intra- and inter-assay coefficients of variation (CVs) were <13.9%. Haemoglobin, haematocrit and leukocytes were measured using the Cell-Dine 3200 (Abbot Laboratories), with intra- and inter-assay CVs <2.1, 6.0 and 5.7% respectively. Creatinine, AST and ALT were measured using the Alcyon 300i (Abbot Laboratories), with intra- and inter-assay CVs <10.4, 7.2 and 7.7% respectively.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Science version 10.0 (SPSS Inc., Chicago, IL, USA). Categorical data were expressed as number and percentage, and numerical data as mean ± SD. Student's *t*-test, chi-square test and Fisher's exact test were used when appropriate. Statistical significance was assumed when P was < 0.05.

Table I. Women characteristics and results of treatment cycles (ITT analysis)

Parameter	Oocyte donors + patients (n = 988)		Oocyte donors (n = 383)		Patients (n = 605)	
	Albumin group (n = 495)	Control group (n = 493)	Albumin group (n = 197)	Control group (n = 186)	Albumin group (n = 298)	Control group (n = 307)
Age (years)	29.9 (5.3)	29.7 (5.1)	26.4 (4.5)	26.2 (4.9)	32.2 (4.5)	31.9 (4.0)
Body mass index (kg/m^2)	23.0 (3.5)	22.9 (3.3)	22.7 (3.4)	22.6 (3.0)	23.3 (3.5)	23.1 (3.4)
PCOS (n)[a]	67	87	12	20	55	67
Coasting (n)			0	0	5	6
Estradiol on day of hCG (pg/ml)	3804 (1615)	3617 (1337)	3645 (1483)	3444 (1272)	3910 (1692)	3726 (1366)
Oocytes retrieved (n)	28.2 (6.7)	27.8 (6.7)	28.1 (6.1)	27.8 (6.2)	28.2 (7.1)	27.9 (6.9)
IVF fertilization rate (%)	69.7 (24.0)	68.3 (29.7)	70.2 (18.5)	74.1 (8.3)	69.7 (24.2)	68.2 (29.9)
ICSI fertilization rate (%)	77.2 (15.0)	76.4 (16.5)	78.9 (16.3)	80.9 (19.2)	77.1 (15.0)	76.3 (16.5)
Embryo freezing (n)	–	–	–	–	7	9
No embryo transfer (n)	–	–	–	–	15	19
Transferred embryos (n)	–	–	–	–	2.8 (1.2)	3.0 (0.9)
Implantation rate (%)	–	–	–	–	22.5	25.1
Pregnancy rate (%)	–	–	–	–	46.4	54.0
Biochemical pregnancy rate (%)	–	–	–	–	7.0	7.1
Ectopic pregnancy rate (%)	–	–	–	–	3.1	1.3
Miscarriage rate (%)	–	–	–	–	13.2	7.1
On-going pregnancy rate (%)	–	–	–	–	76.7	84.5
Moderate+severe OHSS (%)	7.1	6.7	5.6	6.5	8.0	6.9
Severe OHSS (%)	5.0	4.7	3.6	5.4	6.0	4.2

Values are mean (SD) unless otherwise indicated.
Comparison of all parameters of the albumin and control groups showed non-significant differences ($P \geqslant 0.05$) in the three studied populations.
[a]From January 2000, PCOS women were not accepted as oocyte donors at the authors' institution, except for cases of clinical trials.
ITT = intention-to-treat; OHSS = ovarian hyperstimulation syndrome; PCOS = polycystic ovary syndrome.

Table II. Comparison of abnormal haematological parameters of albumin and control groups 7 days after oocyte retrieval

Parameter	Oocyte donors + patients (n = 976)		Oocyte donors (n = 377)		Patients (n = 599)	
	Albumin group (n = 488)	Control group (n = 488)	Albumin group (n = 195)	Control group (n = 182)	Albumin group (n = 293)	Control group (n = 306)
Haemoglobin $\geqslant$15 g/dl (n)	29	19	8	2	21	17
Haematocrit $\geqslant$45 % (n)	16	13	5	3	11	10
Leukocytes $\geqslant$20 000/mm^3 (n)	1	3	0	2	1	1
Creatinine >1.2 mg/dl (n)	1	1	0	0	1	1
AST >40 IU/ml (n)	10	13	1	3	9	10
ALT >40 IU/ml (n)	27	29	10	11	17	18

Comparison of all parameters of the albumin and control groups showed non-significant differences ($P \geqslant 0.05$) in the three studied populations.
ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Results

In total, 988 women were recruited during the study period based on the retrieval of >20 oocytes, and randomized to either the albumin group (n = 495) or control group (n = 493). Twelve were later excluded due to follow-up loss. A complete biochemical and clinical assessment was carried out in the remaining 976 women (n = 488 in each group; Figure 1). Among 976 women, 66 developed OHSS (20 in a moderate form, 46 in a severe form). The women's characteristics in relation to OHSS risk factors as age, body mass index, incidence of PCOS, estradiol levels on the day of hCG and number of retrieved oocytes were similar in the two groups, both in terms of the group as a whole and patients and oocyte donors separately (Table I). There was no difference in the number of oocyte donors included in each group. The incidence of coasting, embryo freezing and absence of embryo transfer in patients did not differ between the albumin and control groups. Similarly, the results of treatment cycles in patients did not show any significant difference (Table I). The incidence of moderate-severe and severe-only OHSS was identical in both groups [6.8% (n = 33) and 4.7% (n = 23) respectively]; neither was any difference detected in patients and oocyte donors when these were studied separately.

In order to determine the beneficial impact of albumin administration on biochemical parameters 7 days after oocyte retrieval, cases of increased haemoconcentration or renal or liver dysfunction were compared. Severe haemoconcentration was defined as haemoglobin $\geqslant$15 g/dl, haematocrit $\geqslant$45% or leukocyte count $\geqslant$20 000/mm^3. Renal dysfunction was considered when creatinine levels were >1.2 mg/dl, and liver dysfunction when transaminases (AST or ALT) were >40 U/ml. No significant differences were seen in these parameters according to prior albumin administration (Table II).

Table III. Comparison of body weight and blood parameters of albumin and control groups in severe ovarian hyperstimulation syndrome cases

Parameter	Oocyte donors + patients (n = 46)		Oocyte donors (n = 17)		Patients (n = 29)	
	Albumin group (n = 23)	Control group (n = 23)	Albumin group (n = 7)	Control group (n = 10)	Albumin group (n = 16)	Control group (n = 13)
Day of oocyte retrieval						
Haemoglobin (g/dl)	12.3 (1.9)	12.6 (1.3)	12.2 (1.9)	12.9 (0.9)	12.4 (1.9)	12.4 (1.5)
Haematocrit (%)	35.0 (5.3)	36.7 (3.5)	33.8 (4.7)	36.6 (3.3)	35.5 (5.6)	36.9 (3.8)
Leukocytes (n/mm^3)	8815.2 (3054.8)	9684.8 (3499.2)	7100.0 (1694.1)	9725.0 (3320.1)	9565.6 (3250.3)	9653.8 (3679.9)
Creatinine (mg/dl)	0.6 (0.1)	0.7 (0.1)	0.5 (0.1)	0.6 (0.1)	0.7 (0.1)	0.7 (0.2)
AST (IU/ml)	15.1 (4.8)	17.1 (4.8)	13.5 (5.7)	16.7 (5.5)	15.8 (4.4)	17.3 (4.5)
ALT (IU/ml)	14.3 (6.5)	15.1 (7.9)	12.3 (5.1)	15.5 (10.7)	15.2 (7.0)	14.7 (5.3)
Body weight (kg)	57.3 (8.0)	56.5 (7.2)	57.0 (10.2)	57.0 (6.5)	57.6 (6.6)	56.1 (8.2)
7 days after oocyte retrieval						
Haemoglobin (g/dl)	13.4 (1.4)	13.3 (1.5)	13.3 (0.9)	13.2 (1.8)	13.5 (1.6)	13.4 (1.4)
Haematocrit (%)	37.8 (3.9)	38.5 (4.1)	36.6 (2.9)	37.3 (5.2)	38.4 (4.3)	39.5 (3.0)
Leukocytes (n/mm^3)	10326.1 (3303.9)	10969.6 (3020.7)	9257.1 (2237.4)	11440.0 (1811.8)	10793.7 (3638.8)	10607.7 (3733.7)
Creatinine (mg/dl)	0.7 (0.1)	0.7 (0.1)	0.6 (0.2)	0.7 (0.2)	0.8 (0.1)	0.7 (0.1)
AST (IU/ml)	21.2 (8.4)	21.3 (10.5)	19.3 (6.9)	23.6 (14.8)	22.1 (9.1)	19.5 (5.5)
ALT (IU/ml	21.2 (11.5)	20.5 (11.2)	17.1 (6.0)	23.3 (15.7)	23.1 (12.9)	18.4 (6.0)
Body weight (kg)	59.5 (11.4)	59.0 (10.6)	62.3 (11.7)	58.1 (10.6)	56.8 (12.0)	60.1 (12.2)
Variation between both days						
Haemoglobin (g/dl)	1.1 (1.6)	0.7 (1.7)	1.1 (1.7)	0.4 (2.2)	1.1 (1.6)	1.1 (1.3)
Haematocrit (%)	2.8 (4.3)	1.8 (4.7)	2.8 (4.5)	0.8 (5.5)	2.8 (4.4)	2.6 (4.1)
Leukocytes (n/mm^3)	1510.9 (2139.0)	1284.8 (2977.9)	2157.1 (2012.3)	1715.0 (4435.3)	1228.1 (2193.2)	953.8 (1109.2)
Creatinine (mg/dl)	0.1 (0.1)	0.1 (0.1	0.1 (0.1)	0.0 (0.2)	0.1 (0.1)	0.1 (0.2)
AST (IU/ml)	6.1 (5.6)	4.2 (9.1)	5.8 (5.5)	6.9 (13.1)	6.3 (9.8)	2.2 (3.7)
ALT (IU/ml)	6.9 (12.3)	5.5 (8.2)	4.7 (8.7)	7.8 (11.4)	7.9 (13.8)	3.7 (4.5)
Body weight (kg)	0.7 (1.7)	0.1 (2.6)	0.5 (0.6)	0.3 (3.4)	1.0 (2.4)	0.6 (1.3)

Values are mean (SD).
Comparison of all parameters of the albumin and control groups showed non-significant differences ($P \geqslant 0.05$) in the three studied populations
ALT = alanine aminotransferase; AST = aspartate aminotransferase.

In cases where OHSS developed, weight and blood parameters were compared at oocyte retrieval (baseline assessment) and 7 days later (hyperstimulation assessment) in the albumin and control groups. First, the cases of moderate-severe OHSS (n = 66) were analysed together, and then only the cases of severe OHSS (n = 46). Variation of each parameter between the baseline and the hyperstimulation state was compared, as was the clinical evolution of the subjects, including incidence and number of paracentesis cases, hospital admissions, complications and duration of OHSS. No significant difference was detected in any of the parameters studied, neither among the moderate and severe OHSS cases when these were considered together, nor among the severe OHSS patients when they were studied separately (Tables III and IV).

Discussion

Albumin has been widely used in the prevention of OHSS in high-risk IVF patients, yet there is a lack of consensus regarding the benefits of its use and how its preventive mechanism acts. In addition, there is some concern about the potential transmission of prions and viral infections (Gokmen *et al*., 2001) such as Creutzfeldt–Jakob disease (CJD), hepatitis B and C and human immunodeficiency virus (HIV). Albumin constitutes 52–65% of all plasma proteins and, when administered intravenously, has a circulation half-life of approximately 19 days (Shoham *et al*., 1994; Ben-Chetrit *et al*., 2001). It may act by binding and inactivating vasoactive factors implicated in the pathophysiology of OHSS (Asch *et al*., 1993; Shoham *et al*., 1994) and/or drawing fluid from the third space into the vascular compartment because of its contribution to the plasma colloid oncotic pressure (Asch *et al*., 1993).

Several non-randomized trials were initially performed to determine the preventive role of albumin in high-risk patients. The prevention of severe OHSS with human albumin administration was first demonstrated during the early 1990s (Asch *et al*., 1993). None of the 36 women who received 50 g albumin on the day of oocyte retrieval developed severe OHSS; however, embryo transfer was not carried out in 58% of the women, thereby reducing the risk of severe OHSS. In the same year, others (Ng *et al*., 1993) found no statistical difference in the incidence of OHSS between a group of high-risk IVF patients who received 50 g albumin on the day of oocyte retrieval and another group that was not administered this protein. Further case reports (Orvieto *et al*., 1995; Moutos *et al*., 1997) and retrospective studies (Ng *et al*., 1995; Ndukwe *et al*., 1997) have described the ineffectiveness of prophylactic albumin in the prevention of severe OHSS.

Until now, there have existed only seven published randomized controlled trials exploring the intravenous use of albumin in preventing severe OHSS (Shoham *et al*., 1994; Shalev *et al*., 1995; Isik *et al*., 1996; Shaker *et al*., 1996; Costabile *et al*., 2000; Ben-Chetrit *et al*., 2001; Gokmen *et al*., 2001). One of these groups (Shaker *et al*., 1996) compared the

Table IV. Comparison of clinical evolution of albumin and control groups in severe ovarian hyperstimulation syndrome (OHSS) cases (n = 46)

Parameter	Albumin group (n = 23)	Control group (n = 23)	P
Paracentesis (n)	21	20	NS
No. of paracenteses per patient	1.3 (0.8)	1.9 (1.8)	NS
Hospital admission (n)	7	5	NS
Complications (n)	3[a]	2[b]	NS
Days from oocyte retrieval to beginning of OHSS	4.4 (4.0)	4.5 (3.3)	NS
Duration of OHSS (days)	8.4 (5.8)	10 (6.9)	NS

Values are mean (SD) unless otherwise indicated.
[a]Two adult respiratory distress syndromes and one pleural effusion.
[b]One thromboembolic event and one cerebrovascular accident.

efficacy of i.v. infusion of albumin for preventing OHSS in high-risk patients with a standard policy of cryopreservation of all embryos, including 26 patients as a whole (13 in each group). The albumin group did not show any advantage in preventing OHSS, but presented lower pregnancy rates. Others (Costabile *et al*., 2000) compared the effectiveness of i.m. progesterone with that of i.v. albumin in the prevention of OHSS in 96 high-risk patients, and showed a clear benefit of high-dose progesterone. A recent Cochrane review analysed the remaining five randomized controlled trials of the effect of albumin infusion versus placebo or no treatment in the prevention of severe OHSS after ovarian hyperstimulation (Shoham *et al*., 1994; Shalev *et al*., 1995; Isik *et al*., 1996; Ben-Chetrit *et al*., 2001; Gokmen *et al*., 2001). These trials, all of which were single-centre, each involved between 31 and 250 participants (n = 463 in total). The preventive therapy consisted of doses of i.v. albumin ranging from 10 to 50 g, administered 1–2 h before or just after oocyte retrieval, and infused for periods of 30–60 min. In three studies the control group received a saline infusion (Shoham *et al*., 1994; Ben-Chetrit *et al*., 2001; Gokmen *et al*., 2001), while in the other two trials the controls received no treatment (Shalev *et al*., 1995; Isik *et al*., 1996). One group (Gokmen *et al*., 2001) administered a hydroxyethyl starch solution to a third patient group. Four out of these five studies suggested a preventive role for albumin in OHSS. The Cochrane review highlighted a clear benefit of administration of i.v. albumin at the time of oocyte retrieval for preventing severe OHSS in high-risk cases, with an absolute risk reduction of 5.5%, and one case saved due to albumin infusion for every 18 women at risk of severe OHSS. Moreover, there was no evidence of an increase in the pregnancy rate (Aboulghar *et al*., 2002).

To the best of the present authors' knowledge, herein is presented the largest prospective and single-centre study to date of the effects of prophylactic albumin in high-risk IVF patients. The sample size of the present study allowed the detection of a 50% decrease in the incidence of severe OHSS, with 95% confidence and a type II error of ±2.4%. Several known risk factors for severe OHSS, previous to and during COH, were considered including young age (Navot *et al*., 1988; Enskog *et al*., 1999), body mass index (Navot *et al*., 1988), serum estradiol level (Haning *et al*., 1983; Navot *et al*., 1992), number of retrieved oocytes (Enskog *et al*., 1999) and evidence of PCOS (Buyalos and Lee, 1996; Al-Ramahi, 1999). More than 20 retrieved oocytes was chosen as inclusion criterion for the study, as this parameter was considered the best predictor for moderate and/or severe OHSS development. This would serve as an end-point of the other risk factors, and has been considered for the same purpose in previous studies (Ben-Chetrit *et al*., 2001). Participants were studied first as a whole group, and then as patient and oocyte donor groups separately.

No difference was detected between the risk parameters of the albumin and control groups, and no predisposition of either of the groups to the development of OHSS was demonstrated. On the other hand, the cycle evolution did not vary, with similar implantation, pregnancy and on-going pregnancy rates and similar numbers of moderate and severe hyperstimulated cases (Table I). Hence, in agreement with the recent Cochrane review (Aboulghar *et al*., 2002) and other authors (Ben-Chetrit *et al*., 2001), but in contrast to the suggestions of other authors (Shaker *et al*., 1996), the outcome of the IVF cycle does not appear to be influenced by albumin administration. Therefore, the decision to use prophylactic albumin only must rest on the balance of benefits (prevention of OHSS) and risks (cost, undesirable side effects). In the present study, the cost of treatment (195 euros per patient) was the only drawback, as no side effects were detected. However, other authors have described the potential side effects of albumin infusion, such as nausea, vomiting, febrile reaction, allergic reaction, anaphylactic shock and risk of virus and prion transmission (Isik *et al*., 1996; Ben-Chetrit *et al*., 2001; Gokmen *et al*., 2001).

When serum biochemical markers of haemoconcentration and renal or liver dysfunction were assessed at oocyte retrieval (baseline assessment) and 7 days later (hyperstimulated assessment), no significant difference was noted between the albumin and control groups (Table II). Hence, albumin did not improve the evolution of high-risk cases.

Blood samples were taken on the seventh day after oocyte retrieval because the early form of OHSS, related to the magnitude of the preceding ovarian response, is usually detected 3–7 days after the ovulatory dose of hCG (Lyons *et al*., 1994; Mathur *et al*., 2000). Baseline blood samples were used to determine the predisposition of the studied groups to ovarian stimulation. Thus, when cases of moderate and severe OHSS were considered as a whole (n = 66), and when severe OHSS cases (n = 46) were evaluated separately, neither the baseline nor the hyperstimulated assessment showed differences between the albumin and the control groups. Moreover, variation of weight and blood parameters (Table III), and clinical evolution (Table IV) were similar in both groups. Therefore, no clinical or biochemical differences appeared in OHSS patients based on prior albumin administration.

In the experience of the present authors, albumin infusion does not have a preventive role in moderate and/or severe OHSS. It is an expensive drug, with minimal but potential risks and side effects, and does not seem to affect the IVF outcome; hence, its use as preventive therapy in OHSS should be discouraged.

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Submitted on February 14, 2003; resubmitted on May 13, 2003; accepted on July 15, 2003