The questionable use of albumin for the prevention of ovarian hyperstimulation syndrome in an IVF programme: a randomized placebo-controlled trial

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BACKGROUND: The role of intravenous (IV) albumin administration in the prevention of ovarian hyperstimulation syndrome (OHSS) and in the improvement of IVF conception outcomes was evaluated in a prospective, randomized, placebo-controlled double-blind study.

METHODS: Ninety-eight women were enrolled in the study and were consecutively assigned to either a treatment group or a control group. Eleven patients were lost to follow-up after assignment. Of the remaining 87 women, 46 received albumin on the day of oocyte retrieval, and 41 received 0.9% sodium chloride solution as a placebo control. Outcome measures included OHSS incidence rates and pregnancy rates in the two trial groups.

RESULTS: Four of the 46 patients in the study group developed severe OHSS and six developed moderate OHSS. In the control group, one of the 41 developed severe OHSS and five developed moderate OHSS. The difference in OHSS incidence rates between the two groups was not statistically significant (relative risk (RR) = 1.49, 95% CI = 0.59–3.73). Fourteen patients (30%) in the intervention group conceived, compared with 16 patients (39%) in the control group. The difference in conception rates between the two groups was not statistically significant (RR = 0.78, 95% CI = 0.44–1.39).

CONCLUSIONS: Albumin appears to have no positive effect on OHSS or conception rates, while its use carries the risk of undesirable side effects, including exacerbation of ascites in OHSS, nausea, vomiting, febrile reaction, allergic reaction, anaphylactic shock and risk of virus and prion transmission. We suggest that this form of treatment should not be included in the prevention of OHSS.

Key words: albumin/IVF/OHSS

Introduction

Mild to moderate ovarian hyperstimulation syndrome (OHSS) is a common iatrogenic complication associated with ovulation induction. However, the overall incidence of clinically significant (moderate to severe) OHSS ranges from 1 to 10% of ovulation induction cycles (Navot et al., 1992). Only a small proportion (0.5–1%) of cases are severe. Severe OHSS is characterized by massive ovarian enlargement, ascites, hydrothorax, haemoconcentration, renal and liver dysfunction, and very rarely venous thrombosis. Although the pathophysiology of OHSS remains unclear, the appearance of its features and symptoms are always associated with the presence of human chorionic gonadotrophin (HCG). Therefore, pregnancy may aggravate early OHSS and may induce late OHSS. Several methods have been suggested to prevent OHSS or to reduce its severity, including the use of low doses of gonadotrophins during the follicular phase (Asch et al., 1991), partial follicular aspiration at follicular phase (Tomazevic and Meden Vrtovec, 1996), triggering of ovulation with low doses of HCG (Navot et al., 1992), natural gonadotrophin-releasing hormone (GnRH) or GnRH analogue (Casper, 1996), avoiding embryo transfer (Amso et al., 1990) and avoiding HCG administration in the luteal phase (Araujo et al., 1994). In extremely high risk cases, treatment is interrupted by avoiding any HCG administration or by GnRH antagonist injection. On reviewing the literature, we found disagreement in regard to the role of human albumin administration on the day of ovum retrieval for the prevention of OHSS. While Asch et al. (Asch et al., 1993) and, subsequently, other investigators, concluded that human albumin has importance in the prevention of OHSS (Shoham et al., 1994; Brinsden et al., 1995; Shalev et al., 1995; Isik et al., 1996), others reported that severe OHSS occurred despite prophylactic albumin infusion after ovum retrieval (Halme et al., 1995; Mukherjee et al., 1995; Ng et al., 1995; Orvieto et al., 1995; Lewit et al., 1996; Moutos et al., 1997; Ndukwe et al., 1997). In 1998 we reported our retrospective data regarding albumin administration. Only four patients of 126 who received albumin on the day of retrieval developed moderate OHSS, and all of them were pregnant (Hornreich et al., 1998). Following this encouraging result, we decided to
conduct a prospective, randomized, placebo-controlled double blind study to evaluate more precisely the role of intravenous administration of human albumin solution in the prevention of OHSS and the improvement of IVF conception outcomes.

Materials and methods

For the purpose of this study, we defined inclusion criteria, which included serum oestradiol $>10,000$ pmol/l on the day of HCG administration, or retrieval of $>20$ oocytes. Ninety-eight patients undergoing IVF treatment in the IVF Unit of the Shaare Zedek Medical Centre (Jerusalem, Israel) between April and December 1999 met these inclusion criteria, and were recruited after giving their written informed consent. Both our institutional Human Subjects Review Board and that of the Israeli Ministry of Health approved the study. Each participant underwent preliminary evaluation including medical history, physical examination, ultrasonographic ovarian evaluation, and routine laboratory testing (complete blood count, urinalysis, thyroid, liver and kidney functions, and blood prolactin levels). Patients ranged in age from 18 to 40 years, and all were in good general health.

Stimulation protocol

All subjects underwent controlled ovarian hyperstimulation consisting of a long GnRH agonist protocol, utilizing daily subcutaneous GnRH analogue [0.1 mg decapetyl; Ferring Ltd (A. Lapidot Ltd), Herzliya, Israel] and parenteral gonadotrophins beginning on day 5 of menstrual bleeding. The standard protocol consisted of two ampoules of human menopausal gonadotrophin (HMG, 75 IU/ampoule, Pergonal; Teva, Petah Tikva, Israel) and two ampoules of purified FSH (75 IU/amp Metrodin; Teva). The standard protocol was modified where there was a previous history of poor response or a risk of hyperstimulation based on menstrual history or prior response.

Ultrasound for follicular tracking and blood samples for measurement of serum oestradiol were performed every 2–3 days, starting on day 4 of gonadotrophin administration. Human chorionic gonadotrophin (10 000 IU; Chorigon, Teva, Petah Tikva, Israel) was administered when two or more follicles with a diameter $>18$ mm were detected on transvaginal ultrasound (TVUS), and oestradiol concentrations were $>1000$ pmol/mature follicle. TVUS guided ovum retrieval was performed 34–36 h following HCG administration. Up to three embryos, and rarely four embryos, were transferred 48–72 h following ovum retrieval. Freezing of extra-fertilized oocytes, usually at the 2-pronuclear stage, was offered to all patients. The luteal support protocol consisted of a daily injection of 100 mg progesterone in oil. Women judged to be at very high risk for OHSS (peak oestradiol $>20,000$ pmol/l and more than 35 retrieved oocytes), were excluded from the study, and their embryos frozen, thus avoiding the possibility of conception during the treatment cycle.

Study protocol and randomization

The study was prospective, randomized and double-blind. A research nurse with no direct involvement in patient care alternately randomized the patients into one of two groups. The patients in group 1 (intervention group) received 50 g of human albumin (Kamada Ltd, Beit Kama, Israel), diluted in 500 ml of 0.9% sodium chloride. The patients in group 2 (control group), received 500 ml of 0.9% sodium chloride. The solutions were administrated through sealed tubing on the day of ovum retrieval. All patients and caregivers were blinded to the type of intravenous solution administered.

Follow-up

Patients were followed during the luteal phase on days 3, 6, 10 and 14 post-embryo transfer. (Measurement on days 10 and 14 was aimed to detect late OHSS, especially among pregnant women, and to follow the resolution of early-detected OHSS.) On each visit, serum oestradiol was measured and ovarian size and ascites were evaluated by ultrasound examination. The severity of OHSS was determined according to the criteria of Schenker and Weinstein (Schenker and Weinstein, 1978). Pregnancies were detected by serum $\beta$-HCG subunit 2 weeks after embryo transfer and were included in the study records only if fetal heartbeat was present on ultrasound examination.

Study parameters

Clinical characteristics that were evaluated included patient age, infertility duration and diagnosis. Cycle characteristics included number of human menopausal gonadotrophin (HMG) ampoules used for ovarian hyperstimulation, the cycle day of HCG administration and oestradiol concentration on day of HCG administration. Serum albumin concentration was measured prior to the administration of IV albumin or saline, and again 1 h after the end of the administration (evaluators remained blinded to the results of albumin tests). Outcome parameters included number of oocytes retrieved per patient, number of embryos transferred, clinical pregnancies (fetal heartbeat identified on ultrasound) and the characteristics of ovarian hyperstimulation syndrome in severe cases.

Hormone assay

Serum oestradiol was measured by a competitive immunoassay using the Immulite Analyzer (DPC, Los Angeles, CA, USA). The intra- and inter-assay coefficients of variation were $<10\%$. Albumin was measured using the Vitro 950 system (Ortho Clinical Diagnostics, Johnson & Johnson Company), which has intra- and inter-assay coefficients of variation of $<2.4\%$.

Statistical analysis

Data were analysed using Student’s $t$, paired $t$, $\chi^2$ and Fisher’s exact tests. $P$ values were reported as two-tailed, and statistical significance was set at $P < 0.05$. Power calculations were performed to determine the probability of type II error. Statistical analysis was carried out using a PEPi$^\text{D}$ computer software (version 3.01, Brixton Books, Llanidloes, Powys, Wales).

Results

Ninety-eight patients were initially recruited to the study; 11 were lost to follow-up due to failure to present for serial examinations. Of the remaining 87 subjects, 46 were randomized to group 1 and received albumin (intervention group) and 41 were randomized to group 2 and received 0.9% sodium chloride solution (control group). Mean patient age and duration and cause of infertility were similar in both study and control groups.

The two groups were also similar in terms of quantity of menotrophins (HMG) used, treatment duration (as reflected by the day of HCG administration), endometrial thickness and oestradiol concentration on HCG day, number of oocytes retrieved and number of embryos transferred (Table I).

The mean pretreatment serum albumin concentration in the intervention group was $3.96 \pm 0.39$ g/dl, and increased to $4.22 \pm 0.49$ g/dl, 1 h following albumin infusion ($P < 0.001$). The mean pretreatment serum albumin concentration in the control group was $3.9 \pm 0.41$ g/dl, and remained unchanged ($3.9 \pm 0.39$ g/dl), 1 h following saline infusion.

Mean ovarian size and mean serum oestradiol concentrations on days 3 and 10 after embryo transfer were similar in both
Table I. Patient characteristics and treatment cycle results

<table>
<thead>
<tr>
<th></th>
<th>Albumin group</th>
<th>Control group</th>
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<tbody>
<tr>
<td></td>
<td>(n = 46)</td>
<td>(n = 41)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.1 ± 5.7</td>
<td>30.1 ± 7.6</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>5.9 ± 2.2</td>
<td>5.3 ± 1.8</td>
</tr>
<tr>
<td>Number of HMG ampoules used</td>
<td>41.1 ± 19.4</td>
<td>37.1 ± 12.2</td>
</tr>
<tr>
<td>Day of HCG administration</td>
<td>18.2 ± 4.6</td>
<td>16.6 ± 3.3</td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>12.6 ± 2.7</td>
<td>13.1 ± 2.8</td>
</tr>
<tr>
<td>Serum oestradiol concentration (pmol/l)</td>
<td>10,660 ± 3250</td>
<td>9,459 ± 3,060</td>
</tr>
<tr>
<td>Number of retrieved oocytes</td>
<td>23.8 ± 9.1</td>
<td>23.8 ± 6.3</td>
</tr>
<tr>
<td>Number of embryos transferred</td>
<td>3.4 ± 1.6</td>
<td>2.9 ± 0.9</td>
</tr>
</tbody>
</table>

No significant differences between albumin and control groups were observed.

Table II. Ovarian response to treatment protocols

<table>
<thead>
<tr>
<th></th>
<th>Albumin group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 46)</td>
<td>(n = 41)</td>
</tr>
<tr>
<td>Day 3 post-embryo transfer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>5592.7 ± 3875.0</td>
<td>5873.4 ± 3233.6</td>
</tr>
<tr>
<td>Right ovary (mm)</td>
<td>64.1 ± 17.9</td>
<td>61.1 ± 17.6</td>
</tr>
<tr>
<td>Left ovary (mm)</td>
<td>66.5 ± 20.7</td>
<td>59.6 ± 18.3</td>
</tr>
<tr>
<td>Day 10 post-embryo transfer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>2050.9 ± 3609.4</td>
<td>1552.8 ± 1498.2</td>
</tr>
<tr>
<td>Right ovary (mm)</td>
<td>48.2 ± 16.0</td>
<td>44.7 ± 10.5</td>
</tr>
<tr>
<td>Left ovary (mm)</td>
<td>45.6 ± 16.5</td>
<td>41.3 ± 11.0</td>
</tr>
</tbody>
</table>

No significant differences between albumin and control groups were observed.

Table III. OHSS incidence rates and rate ratios, by disease severity and group assignment

<table>
<thead>
<tr>
<th>OHSS severity</th>
<th>Albumin group</th>
<th>Control group</th>
<th>Rate ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 46)</td>
<td>(n = 41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>36</td>
<td>35</td>
<td>0.92</td>
<td>0.75–1.12</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>10</td>
<td>6</td>
<td>1.49</td>
<td>0.59–3.73</td>
</tr>
<tr>
<td>Moderate</td>
<td>6</td>
<td>5</td>
<td>1.07</td>
<td>0.35–3.24</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
<td>1</td>
<td>3.57</td>
<td>0.42–30.62</td>
</tr>
</tbody>
</table>

No significant differences between albumin and control groups were observed.

groups (Table II). Four of the 46 patients in the intervention group developed severe OHSS and six developed moderate OHSS. In the control group, one of 41 developed severe OHSS and five developed moderate OHSS. The difference in the incidence rates between the two groups was not significant (RR = 1.49, 95% CI = 0.59–3.73) (Table III). The overall conception rate was 34.5%. Fourteen patients of 46 in the study group conceived (30%), compared with 16 of 41 in the control group (39%). The difference in conception rates between the two groups was not statistically significant (RR = 0.78, 95% CI = 0.44–1.39).

Discussion

Albumin is the main protein of the plasma, representing 52–65% of all plasma protein. Its molecular weight is 69 kDa and its primary structure includes 610 amino acids arranged in a single peptide chain (Harper, 1977). When administered intravenously, it has a circulation half-life of ~19 days (Rappaport, 1985). Although widely used in the prevention of OHSS in high-risk patients, the precise mechanism by which it prevents OHSS remains unclear (Jenkins et al., 1995). The possible mechanisms of action include its capability to bind and inactivate vasoactive factors (such as vascular endothelial cell growth factor or factors from the renin–angiotensin system), which contribute to the development of OHSS (Asch et al., 1993; Shoham et al., 1994). Albumin also contributes to the plasma colloid oncotic pressure, which draws fluid from the third space into the vascular compartment (Asch et al., 1993).

Asch et al. were the first to administer intravenous human albumin (50 g) on the day of ovum retrieval in order to prevent OHSS in high-risk patients (Asch et al., 1993). None of the 36 treated women developed severe OHSS. However, 21 of these women did not undergo embryo transfer, and thus incurred a lower risk of severe OHSS. Three previously
published prospective studies (Shoham et al., 1994; Shalev et al., 1995; Isik et al., 1996) have assessed the effectiveness of intravenous albumin in the prevention of OHSS. In all three, the authors found albumin effective in preventing severe OHSS. Shaker et al. compared the effectiveness of cryopreserving all generated embryos with that of IV albumin administration in the reduction of risk for OHSS (Shaker et al., 1996). They found that both methods had similar effectiveness in preventing OHSS, but that the albumin group had lower pregnancy rates.

Subsequent case reports were published documenting severe OHSS despite prophylactic administration of intravenous albumin (Halme et al., 1995; Mukherjee et al., 1995; Orvieto et al., 1995; Lewit et al., 1996; Moutos et al., 1997). Moreover, Ng and Ndukwe showed in their retrospective studies no favourable effect of albumin on high-risk patients (Ng et al., 1995; Ndukwe et al., 1997). Chen showed in a prospective study that albumin could prevent OHSS in patients who did not conceive or who carried singletons, but not in patients with high-order pregnancies (Chen et al., 1997).

The ongoing controversy regarding the possible benefit of intravenous albumin in the prevention of OHSS urged us to investigate the issue in a prospective, randomized double blind placebo-controlled study. To the best of our knowledge, we have conducted the largest prospective study to date, comparing a study group of 46 patients with a control group of 41 patients. We measured parameters of ovarian hyperstimulation on days 3 and 10 post-embryo transfer to detect any early or late OHSS. Moreover, in order to control for any possible confounding effect of embryo transfer on OHSS rates, and to observe the true net effect of albumin, we excluded from our study high-risk patients who had had their embryos frozen. Had these women been included, this may have artificially reduced the risk of OHSS in our study population.

The dose of albumin which was infused to the patients in our study was similar to that used in previous studies (Asch et al., 1993; Shoham et al., 1994; Shalev et al., 1995). Unlike previous studies, however, we measured serum albumin concentrations both before and 1 h following the albumin infusion. We were thus able to demonstrate that the mean albumin level after infusion was significantly higher than before the infusion. Nevertheless, we did not observe any favourable effects of albumin on early or late ovarian response (Table II) or OHSS incidence rates (Table III).

The pregnancy rate (PR) in the intervention group was 30%, which was slightly lower but not significantly different than that of the control group (39%), which suggests that albumin does not affect PR. When analysing a possible association between pregnancy and OHSS, we found that six of the 30 pregnant patients experienced moderate to severe OHSS (20%) compared to eight of the 57 non-pregnant patients (14%). This observed excess of OHSS among pregnant patients was not statistically significant (RR = 1.43, 95% CI = 0.54–3.73).

One limitation of this study is its low power, which nears 30% for severe OHSS. Given the event rates in each group and the relatively small number of patients available for study, the possibility of type II error, namely failure to identify a true association between albumin administration and OHSS outcomes, is real. The infrequency of the clinical problem under study, however, limited our ability to enrol a larger study population at our single study site within a reasonable time frame. Based on our observed results, we calculated that increasing the study power to 80% would require the enrolment of nearly 900 additional patients, a task practically impossible for a single IVF unit to complete in a reasonable period of time. It is clear that our results require further validation through a multi-centre trial or by means of a meta-analysis of studies similar to ours in design.

Despite the power limitations of our study, and in agreement with the results of others, we conclude that albumin is ineffective both in the prevention of early and late OHSS and in improving pregnancy rates. Well-documented risks of albumin use include exacerbation of ascites in OHSS, nausea, vomiting, febrile reaction, allergic reaction, anaphylactic shock and risk of virus and prion transmission. After weighing the lack of evidence in favour of albumin use against these serious risks, we suggest that this form of treatment not be included in the regimen of OHSS prevention.

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References
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