Role of intravenous albumin in the prevention of severe ovarian hyperstimulation syndrome

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication of ovulation induction, with an overall incidence of 23.3% (Golan et al., 1989). Despite many years of clinical experience, there is no reliable test which predicts patients who will subsequently develop OHSS, the pathophysiology of this syndrome is not well understood, and no specific treatment is currently available. Many therapeutic options have been suggested in attempts to ameliorate and reduce the risk of severe OHSS (Orvieto and Ben-Rafael, 1997). These include: reduction of the ovulatory dose of human chorionic gonadotrophin (HCG) or withholding of HCG with cycle cancellation; substitution of HCG with gonadotrophin-releasing hormone or its agonist; conversion to in-vitro fertilization (IVF) cycle; use of progesterone for luteal support instead of HCG; cryopreservation of all embryos to avoid endogenous pregnancy-derived HCG; and repeated aspiration of ovarian follicles and early corpus luteum.

In 1993, Asch et al. proposed the use of i.v. administration of human albumin solution during and immediately after oocyte retrieval as a safe, effective, and economical treatment for the prevention of severe OHSS in high-risk patients. Since that time, several contradictory reports have emerged. The aim of the present study was to comprehensively review the data on the role of i.v. albumin in the prevention of severe OHSS.

Prevention of a disease

Terminology

The term ‘prevention’ refers to the acts of averting the occurrence of disease (primary prevention) and of reversing or retarding the disease process before it has become clinically apparent (secondary prevention). Minimizing the effects of an already clinically apparent disease is considered treatment (tertiary prevention) (Orvieto et al., 1993).

Intravenous albumin in the prevention of severe OHSS

Supportive studies (Table I)

Asch et al. (1993) administered 50 g of human albumin i.v. to 36 women considered at risk of severe OHSS by oestradiol concentrations >6000 pg/ml on day of HCG administration and >30 retrieved oocytes (Asch et al., 1991), during and immediately after oocyte retrieval. In no case did severe OHSS develop. However, they noted small amounts of peritoneal fluid (12–74 ml), with no major changes in body weight (>5%) or haematocrit concentrations (>10%) that might otherwise reflect the development of less severe forms of early OHSS (onset 3–7 days after HCG administration). Furthermore, 21 of the 36 patients did not undergo embryo transfer, eliminating the possibility of late OHSS (onset 12–17 days after HCG administration) thereby artefactually reducing the incidence of severe OHSS. The authors explained albumin’s mechanism of action by its role as a carrier protein, which enables it to bind and inactivate the vasoactive intermediate released in OHSS patients (secondary prevention) and by its oncotic properties, which serve to maintain intravascular volume and prevent the ensuing effects of hypovolaemia, ascites and haemoconcentration (secondary or tertiary prevention).

Subsequently, Shahata et al. (1994) compared in patients at high risk of severe OHSS (serum oestradiol concentration >2997 pg/ml on the day of HCG administration and/or >20 oocytes retrieved), cycles with and without the use of albumin. None of the 41 cycles in which albumin was administered were associated with severe OHSS compared to seven of the 96 cycles (7.3%) without albumin. It is noteworthy, though, that only 17 patients of the control group (17.8%) had oestradiol concentrations >2997 pg/ml.

Shoham et al. (1994) used a prospective, randomized, placebo-controlled design. A high risk of severe OHSS was defined as a serum oestradiol concentration of >1906 pg/ml on the day of HCG administration. Despite a mean oestradiol concentration of 2355 and 2520 pg/ml and mean number of oocytes retrieved of 12.6 and 13.4 in the control and study group, respectively, none of the 16 albumin-treated patients had severe OHSS compared to four of the 15 (26%) control patients. Conclusions are limited by the absence of information on the possible development of milder forms of OHSS despite a past medical history of severe OHSS in three women in the albumin group.

Shalev et al. (1995) prospectively randomized 40 high-risk patients into albumin treatment and no treatment groups for the prevention of severe OHSS. Inclusion criteria were young age, normal body weight, and oestradiol concentration >2500 pg/ml on the day of HCG administration, and transvaginal sonography findings of >20 follicles >14 mm in circumference. These patients were randomized, and 10 patients (20%) in the control group had severe OHSS whereas only 1 (4.8%) in the albumin group had severe OHSS.

Optimal treatment

It is evident that the role of intravenous albumin in the prevention of severe OHSS is promising, but it is not clear how to optimize this treatment. Further studies are needed to establish optimal dosing, timing, and duration of intravenous albumin administration in the prevention of severe OHSS.
Shaker et al. (1997) assessed the effectiveness of i.v. albumin in prevention of OHSS: negative studies

Table II. Intravenous albumin in the prevention of severe ovarian hyperstimulation syndrome (OHSS): supportive studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>No. of patients with severe OHSS versus no. of patients treated with albumin</th>
<th>No. of patients with severe OHSS versus no. of controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asch et al. (1993)</td>
<td>Case series</td>
<td>Oestradiol &gt;6000 pg/ml;  &gt;30 oocytes retrieved</td>
<td>0/36</td>
<td>–</td>
</tr>
<tr>
<td>Shahata et al. (1994)</td>
<td>Retrospective analysis</td>
<td>Oestradiol &gt;2997 pg/ml;  &gt;20 oocytes retrieved and/or 30 follicles on ultrasonography and development of severe OHSS prior to oocyte retrieval</td>
<td>0/41</td>
<td>7/7</td>
</tr>
<tr>
<td>Shoam et al. (1994)</td>
<td>Prospective randomized study</td>
<td>Oestradiol &gt;1906 pg/ml</td>
<td>0/16</td>
<td>4/15</td>
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<tr>
<td>Shalev et al. (1995)</td>
<td>Prospective randomized study</td>
<td>Oestradiol &gt;2500 pg/ml;  &gt;20 follicles &gt;14 mm in diameter, young with normal body weight retrieved</td>
<td>0/22</td>
<td>4/18</td>
</tr>
<tr>
<td>Isik et al. (1996)</td>
<td>Prospective randomized study</td>
<td>Oestradiol &gt;3000 pg/ml and &gt;15 oocytes retrieved</td>
<td>0/27</td>
<td>1/28</td>
</tr>
<tr>
<td>Shaker et al. (1997)</td>
<td>Prospective randomized study</td>
<td>Oestradiol &gt;3540 pg/ml on the day of HCG administration, or oestradiol &gt;2725 pg/ml but &gt;15 oocytes collected</td>
<td>0/13</td>
<td>0/13</td>
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HCG = human chorionic gonadotrophin.

Table II. Intravenous albumin in the prevention of severe ovarian hyperstimulation syndrome (OHSS): negative studies

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<tr>
<td>Ng et al. (1995)</td>
<td>Retrospective analysis</td>
<td>Oestradiol &gt;2725 pg/ml and &gt;16 follicles &lt;16 mm in diameter at the day of HCG administration</td>
<td>2/49</td>
<td>10/158</td>
</tr>
<tr>
<td>Mukherjee et al. (1995)</td>
<td>Case reports</td>
<td>Oestradiol = 4900 and 5238 pg/ml; 22 and 38 oocytes retrieved respectively</td>
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<tr>
<td>Halme et al. (1995)</td>
<td>Case report</td>
<td>Oestradiol = 2400 pg/ml and 15 oocytes retrieved</td>
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<tr>
<td>Ben-Rafael et al. (1995)</td>
<td>Case series</td>
<td>Oestradiol &gt;2724 pg/ml and &gt;20 oocytes retrieved</td>
<td>2/30</td>
<td></td>
</tr>
<tr>
<td>Lewit et al. (1995)</td>
<td>Case reports</td>
<td>Oestradiol &gt;3600 pg/ml, history of OHSS and large number of growing follicles</td>
<td>4/5</td>
<td></td>
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<tr>
<td>Ndukwe et al. (1997)</td>
<td>Retrospective analysis</td>
<td>Oestradiol &gt;4086 pg/ml and &gt;30 follicles &gt;14 mm in diameter</td>
<td>5/60</td>
<td></td>
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HCG = human chorionic gonadotrophin.

diameter. Results showed a mean oestradiol concentration of 3830 and 4100 pg/ml and a mean number of oocytes retrieved of 19.3 and 21 in the two groups, with no cases of severe OHSS in the albumin group, compared with four out of 18 (22%) in the control group. However, one patient in the control group (5.5%) and three patients in the albumin group (13.6%) did not undergo embryo transfer, and this difference may have artefactually reduced the incidence of late severe OHSS in the albumin group. Furthermore, no details were presented regarding the type of OHSS (early or late).

Isik et al. (1996) assessed the effectiveness of i.v. albumin in prevention of OHSS by a prospective, randomized study. Patients with oestradiol concentration >3000 pg/ml on the day of HCG administration were recruited. While none of the 27 albumin-treated patients had severe OHSS, one and four of the 28 control patients developed severe and moderated OHSS, respectively.

Finally, Shaker et al. (1996) compared the efficacy of i.v. albumin in IVF patients with the standard policy of cryopreservation of all embryos for subsequent transfer. While no difference was observed in the incidence of severe OHSS in the two groups, the pregnancy rates were significantly higher in the patients in whom all embryos were cryopreserved. Despite a mean oestradiol concentration of 5060 and 5300 pg/ml and a mean number of oocytes retrieved of 17.1 and 19.6, only three patients in the cryopreservation group and four in the albumin group exhibited moderate OHSS, and no patient had severe OHSS.

Negative studies (Table II)

Ng et al. (1995) reported on two cases of severe OHSS in 49 high-risk women (oestradiol concentration >2724 pg/ml and/or >15 follicles on the day of HCG administration) treated with albumin, a rate similar to the 6% (10 of 158 patients) observed in their historically matched high-risk controls. OHSS presented on an average 8.9 days after oocyte retrieval in both groups, which may be defined as the late form. Orvieto and Ben-Rafael (1996) did not find it surprising that these authors failed to demonstrate an effect on late OHSS, because a dose of 15–50 g of albumin is usually retained only transiently in the circulation and needs to be repeated every 1–2 days to achieve a sustained effect (Rackow et al., 1983). This assumption was later substantiated by Chen et al. (1997) in a prospective study of 30 consecutive albumin-treated patients at risk of severe OHSS (serum oestradiol concentration >3600 pg/ml on the day of HCG administration and/or ≥20 g of albumin).
oocytes retrieved) and 42 historical high-risk controls. In non-conception cycles none of the 16 patients had severe OHSS compared with five (21.7%) of the 23 controls (probably early form); in conception cycles, severe OHSS (late form) was noted in four of 14 study patients (28.6%) and nine of the 19 controls (47.4%).

In the same year, three groups reported on five cases of severe OHSS that developed despite the administration of i.v. albumin at the time of oocyte retrieval. In the two patients of Mukherjee et al. (1995), oestradiol concentrations were 4990 and 5238 pg/ml, with 22 and 38 oocytes retrieved, respectively; the patient with the higher oestradiol concentration and more oocytes retrieved had the early and more severe form of OHSS. The single affected patient (early OHSS) of Halme et al. (1995) was an oocyte donor with a serum oestradiol concentration of 2400 pg/ml and 15 oocytes retrieved. The remaining two patients were described by our group (Orvieto et al., 1995; Ben-Rafael et al., 1995). Serum oestradiol concentration was >2293 pg/ml with >35 oocytes retrieved; both had severe early OHSS. Though the data of Ng et al. (1995) indicate that albumin may prevent early rather than late OHSS, four of these five patients had the early form. Furthermore, in the report of Mukherjee et al. (1995), the more vigorous ovarian stimulation resulted in early, rather than the late, form with a more complicated course.

Later reports continued to question the role of albumin in the prevention of severe OHSS. Lewit et al. (1996) described the occurrence of severe OHSS in four of five patients given prophylactic albumin at the time of oocyte retrieval for IVF. Oestradiol concentrations ranged from 3814 to 7404 pg/ml, and the number of oocytes retrieved from 26 to 47. In two of the four patients in whom all embryos were cryopreserved for subsequent transfer, the OHSS was of early onset.

Ndukwe et al. (1997) retrospectively reviewed 60 women at high risk of severe OHSS (serum oestradiol concentrations 4086 pg/ml on the day of HCG administration and >30 ovarian follicles measuring >14 mm in diameter) who were treated with prophylactic i.v. albumin. Five (8%) had severe OHSS, one early and four late. Like our group (Orvieto and Ben-Rafael, 1996), they speculated that i.v. albumin may be more effective in preventing early severe OHSS, which is an acute effect of proovulatory HCG administration, than late severe OHSS, which seems to be triggered by the rising serum HCG concentrations of early pregnancy. They warned physicians against the false sense of security induced by the early promising reports on prophylactic i.v. albumin.

**Conclusion**

These studies do not suggest a role for i.v. albumin in the primary prevention of OHSS. Nevertheless, though albumin was ineffective against late severe OHSS, it may be a feasible means of secondary prevention, ameliorating but not eliminating the physiological oppression of the disease. It should be emphasized that secondary prevention requires not only knowledge of the pathophysiological mechanisms of the disease, means to intervene and correct the pathophysiological changes but also the availability of early detection methods (Orvieto et al., 1993). Hence, the studies supporting the preventive role of albumin in OHSS may have been limited by the sensitivity and predictive values of the criteria used to define high risk (Levy et al., 1996).

A summary of these studies (Tables I and II) revealed that 16 of 289 patients treated with human albumin subsequently developed OHSS, as compared to 26 of 328 patients in the control group. These figures are not statistically different ($\chi^2$ test, $P = 0.2$). Furthermore, our calculations of the required sample size to allow the detection of 50% reduction in the 20% incidence of severe OHSS, with a type I error of 0.05 and 80% power, revealed that 387 patients are needed in each study group. This observation further undermines the conclusions of the role of prophylactic i.v. albumin in severe OHSS.

Further research should be directed at investigating the fundamental cause of OHSS and developing a reliable test for this complication (Orvieto and Ben Rafael, 1998).

**References**


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