Human albumin does not prevent ovarian hyperstimulation syndrome in assisted reproductive technology program: a prospective randomized placebo-controlled double blind study

We aimed to clarify the efficiency of IV human albumin in the prevention of ovarian hyperstimulation syndrome (OHSS). We found that human albumin at the described strength does not seem to either prevent or reduce the incidence of severe OHSS in high risk patients undergoing intracytoplasmic sperm injection (ICSI). (Fertil Steril® 2007;88:982–5. ©2007 by American Society for Reproductive Medicine.)

Ovarian hyperstimulation syndrome (OHSS) is a purely iatrogenic condition and the most serious complication of controlled ovarian hyperstimulation (COH) with gonadotropin preparations (1). Severe forms complicate ~1% of all IVF cycles (2). The pathophysiology of the syndrome still remains obscure. Prostaglandins (3), plasma renin activity, and aldosterone levels (4), and vascular endothelial growth factor (5) have been studied to elucidate the mechanism of OHSS. Although IV human albumin (HA) seems to have some efficiency as a preventive measure, basic comparative studies have some methodological limitations. We designed a properly randomized, placebo-controlled double blind study to clarify the efficiency of IV HA in the prevention of OHSS.

Patients entering the intracytoplasmic sperm injection (ICSI) program in Antalya IVF between January 2003 and December 2004 were evaluated for high risk factors of severe OHSS. High blood E_2 level (>4,000 pg/mL) and >20 follicles ≥14 mm on the day of hCG administration have been defined as the basic risk factors for severe OHSS (6). Patients having one of these factors were included in the study. Patients were randomized by third-party sealed envelope entry to receive either a 20% HA solution or an isotonic NaCl solution intravenously.

Approval for the study was obtained from the institutional review board. Signed informed consent was also obtained from the patients before enrolling in the study.

All patients underwent a down-regulation protocol with the GnRH agonist triptorelin 0.05 mg/day (Decapeptyl Er-Kim, Istanbul, Turkey), beginning from the 21st day of the cycle. After the assessment of pituitary down-regulation on the third day of the cycle with a blood E_2 level <50 pg/mL, linear endometrium and suppressed ovaries, the dosage of triptorelin was reduced to half and gonadotropin stimulation including 75 IU FSH (Gonal F; Serono, Istanbul, Turkey) and 75 IU hMG (Pergonal; Organon, Istanbul, Turkey) was commenced. The dose was adjusted on day 6 and thereafter in accordance with the E_2 level and number of developing follicles. Gonadotropin injections continued until at least two follicles of ≥18 mm were detected. The hCG (10,000 IU) was then administered, followed 35 hours later by oocte pickup. Embryo transfers were done 50 hours after oocte pickup. Progesterone in oil (50 mg/day) was administered intramuscularly for luteal phase support until the day of β-hCG assay. Clinically determined pregnancy was defined as the detection of an embryo with fetal cardiac activity by ultrasound 3 weeks after the embryo transfer.

Immediately after oocte pickup, patients were admitted to the recovery room where they received either 20% HSA (50 cc, Human Albumin, Eczacibasi Baxter, Istanbul, Turkey) diluted in 100 mL 0.9% NaCl or 100 mL 0.9% NaCl. Solutions were infused IV during 1 hour, approximately 36 hours after the administration of hCG. Because the infusions were done in a separate location by one of the staff nurses, the outcome assessors were blind to the interventions. The patients were also blind to the infusions as both groups received the infusions as isotonic NaCl solutions. Blood was drawn on the day of hCG administration, 5 days and 12 days after embryo transfer for E_2 assays, whole blood count, creatinine, and transaminases. On days 5 and 12 after embryo transfer, ultrasound examinations for ovarian size and detection of ascites were done as well as the assessment for other symptoms of severe OHSS. Diagnosis of severe OHSS was made according to the criteria of Navot et al. (6).

Estradiol concentrations were determined from venous blood and measured by VIDAS 12 device (bioMerieux Vitek, Philadelphia, PA). Intra-assay and interassay coefficients of variation were less than 7.5% and 9.5%, respectively.

Severe OHSS rate was the main outcome parameter and clinical pregnancy rates/embryo transfer and first trimester miscarriage rates were the main secondary outcome parameters. As previously reported, OHSS occurs as two distinct

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clinical entities depending on the timing of onset (7). In accordance with this report, we classified OHSS as late onset ($\geq$10 days after oocte pickup) or early onset.

The χ^2 test, Fisher's exact test, Mann Whitney U test, and Student's *t*-test were used for statistical analyses of the data. An α value <0.05 was considered significant.

A total of 75 patients with high risk factors for severe OHSS were enrolled in the study on day of hCG administration. Group 1 patients (n = 38) received HA and group 2 patients (n = 37) received isotonic NaCl. Both groups were similar with regard to age of the women, the incidence of polycystic ovary syndrome (PCOS), and the number of patients with a history of severe OHSS (Table 1). The distribution of the etiology of infertility of the two groups was not different. Total units of gonadotropins used, length of stimulation, peak E_2 levels, E_2 levels on days 5 and 12 after embryo transfer, number of follicles $\geq$14 mm on the day of hCG administration, number of MII oocytes, and number of embryos replaced did not show any statistically significant difference (Table 1). The outcome variables are also shown in Table 1. Severe OHSS developed in eight women from group 1 and in six women from group 2. All patients with late onset severe OHSS (n = 4) and both early and late onset severe OHSS (n = 6) had clinical pregnancies. Only one women with early onset severe OHSS had a negative pregnancy test result. Clinical pregnancy rates/embryo transfer and rates of miscarriage during the first trimester were similar for both groups. One patient in group 2 had an ectopic pregnancy and underwent laparoscopic salpingectomy.

None of the patients with severe OHSS had renal failure or any other life-threatening complications. Only one patient in the albumin group underwent paracentesis. All of the patients in the albumin group tolerated the infusions and we did not encounter any hypersensitivity reactions.

Although the key to controlling severe OHSS is in its prophylaxis, complete prevention is not as yet possible. Various preventive measures have been suggested for avoiding severe OHSS in assisted reproductive technology (ART) cycles, most of which have had debatable success. One of the first measures used, other than merely cancelling the

TABLE 1

Demographic characteristics, stimulation, and outcome data.

	Albumin	Placebo	*P* value
No. of cycles	38	37	NA
Age of the patients (mean ± SD)	29.3 ± 3.9	29.1 ± 4.1	.87[a]
PCOS	15/38 (39.5%)	8/37 (21.6%)	.09[b]
History of severe OHSS	4/38 (10.5%)	4/37 (10.8%)	.96[b]
FSH (IU) (mean ± SD)	1,055 ± 1,100	885 ± 1,081	.50[a]
hMG (IU) (mean ± SD)	1,117 ± 793	1,597 ± 1,232	.12[c]
Total gonadotropin (IU) (mean ± SD)	2,124 ± 851	2,462 ± 1,069	.20[c]
Length of stimulation (mean ± SD)	9.5 ± 0.8	9.5 ± 1.5	.54[c]
Peak E_2 level (pg/mL) (mean ± SD)	5,622 ± 1,326	5,431 ± 1,363	.54[a]
E_2 on day 5 after embryo transfer (pg/mL) (mean ± SD)	2,447 ± 1,683	2,274 ± 1,729	.69[a]
E_2 on day 12 after embryo transfer (pg/mL) (mean ± SD)	2,848 ± 2,569	2,013 ± 2,594	.23[a]
No. of follicles $\geq$14 mm (mean ± SD)	20.5 ± 5.2	19.3 ± 3.6	.30[a]
No. of MII oocytes (mean ± SD)	22.6 ± 7.3	20.5 ± 6.3	.17[a]
No. of embryos transferred (mean ± SD)	3.4 ± 0.8	3.2 ± 0.8	.34[a]
Severe OHSS	8/38 (21.1%)	6/37 (16.2%)	.59[b]
Early severe OHSS	3 (7.9%)	1 (2.7%)	.61[d]
Late severe OHSS	2 (5.3%)	2 (5.4%)	1.0[d]
Combined severe OHSS	3 (7.9%)	3 (8.1%)	1.0[d]
Clinical pregnancy/embryo transfer	21/38 (55.3%)	23/37 (62.2%)	.54[b]
Multiple pregnancy rate	7/21 (33.3%)	7/23 (30.4%)	.90[b]
First trimester miscarriage rate	1/20 (5%)	4/23 (17.3%)	.35[d]

Note: NA = not applicable; OHSS = ovarian hyperstimulation syndrome; PCOS = polycystic ovary syndrome.
[a] Student's *t*-test.
[b] χ^2 test.
[c] Mann Whitney U test.
[d] Fisher's exact test.

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cycle, was the avoidance of hCG for luteal phase supplementation, as there has been virtually unanimous agreement that severe OHSS is strongly associated with endogenous or exogenous hCG. Other measures have focused on hCG trigger substitutes. The use of GnRH agonist as the trigger is, however, limited to gonadotrophin-only or GnRH antagonist cycles. Another substitute for the conventional hCG trigger has been recombinant LH (8). Other measures that also have only gained limited acceptance as successful measures for the prevention of OHSS are coasting, GnRH antagonist protocols (9), reducing the trigger dose, follicular reduction (10–12), and freezing all cycles. The success of the latter measure is also highly dependent on the success of the laboratory's cryopreservation program.

Histamine has been claimed to be mediator of OHSS in animal model (13). However, studies failed to show any effect of H_1 and H_2 blockage on the syndrome (14, 15).

Although, as with other measures described there has not been an absolute consensus, the IV administration of HA at the time of oocyte retrieval has been widely accepted as a measure that may facilitate the prevention of OHSS (16). It has been suggested that the binding and transport properties of HA play a major role in the prevention of severe OHSS through the ability to bind and inactivate the vasoactive intermediates responsible for the pathogenesis of the syndrome. The osmotic properties of HA may also be responsible for maintaining the intravascular volume in the event of capillary leakage (17).

Asch et al. (18) were the first to suggest that IV albumin may prevent the development of severe OHSS. This was followed by several clinical studies with conflicting results. At present there have been eight published randomized controlled trials exploring the use of HA in preventing severe OHSS (1, 19–24). A recent Cochrane review, based on five of these randomized controlled studies in which 378 patients were involved, showed definite benefit from the administration of IV albumin at the time of oocyte pickup in high risk patients (16). However, in all but one of these trials, the exception being the study by Ben-Cherit et al. (22), the outcome assessors were not blind to the intervention (19–21). A potential for outcome bias therefore exists. Bellver et al. (24) published the largest prospective single-centered study. They compared 40 g of HA with no treatment in a total of 976 patients and concluded that albumin infusion is not useful in the prevention of moderate-to-severe OHSS. In this study, similarly, the outcome assessors were not blind to the intervention. In addition, two kinds of GnRH agonist were used and only early OHSS was assessed. Placebo was not used in their control group, which eliminates the placebo effect of albumin administration. Serum E_2, level which was previously reported as an independent risk factor for severe OHSS, was not considered high risk factor in this study. In our study, both the patients and the outcome assessors were blind to the interventions and the results of our study are in accordance with those of Bellver et al. (24).

Various HA concentrations between 10 g (19, 20) and 50 g (21, 22) were also used in these randomized studies. In the present study we assessed the efficacy of 10 g of HA and found that it does not seem to either prevent or reduce the risk of severe OHSS in high risk patients.

The incidence of severe OHSS in patients undergoing ART during the study period in our center was 1.95%, which is consistent with previous reports (2, 25). The relatively high incidence of severe OHSS in our study population was mainly due to our sample selection criteria, as well as our aggressive COH policy.

In our study, patients experiencing early severe OHSS and the resolution of the symptoms thereafter were all associated with a negative pregnancy result, whereas patients experiencing late severe OHSS with or without early severe OHSS were always associated with a positive pregnancy test result. The association between the late onset of OHSS and pregnancy has been previously reported to be a result of the endogenous hCG from the initiated pregnancy (6). Late OHSS is reported as being able to complicate a nonconception cycle only if additional hCG is given during the luteal phase (25).

It has been shown that once a clinical pregnancy has been established in a patient with OHSS (both early and late OHSS), there is a normal risk of abortion (25). Our findings regarding first trimester abortion rates were consistent with previous reports.

Although albumin is generally tolerated, hypersensitivity reactions such as urticaria (19) and even life-threatening anaphylactic reactions have been reported. The incidence of urticaria, fever, chills, or hypotension ranges from 0.47%–1.53% (26) and 0.011% for the incidence of allergic reactions (27). Despite the very low rate of life-threatening risks of HA, it is mandatory to prove a definite clinical benefit that outweighs the unnecessary risks before its routine use in clinical practice.

In conclusion, the administration of 10 g of HA to high risk OHSS patients does not seem to either prevent or reduce the risk of severe OHSS. The efficacy of higher doses of HA needs to be clarified by future randomized studies with large study samples. We believe the results of the present study will assist other investigators in the decision to use HA as an OHSS preventative measure after COH for ART.

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