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Reduced incidence of ovarian hyperstimulation syndrome by prophylactic infusion of hydroxyaethyl starch solution in an in-vitro fertilization programme

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Prophylactic infusion of human serum albumin can reduce or mitigate severe ovarian hyperstimulation syndrome (OHSS) in patients at high risk. Recently, concern has been expressed in the lay press regarding the potential viral transmissions with blood constituents. Hence, we looked for a safe non-biological substitute with comparable physical properties in order to cope with this concern. One hundred patients of our in-vitro fertilization (IVF) programme with oestradiol serum concentrations ⩾11 010 pmol/l on the day of human chorionic gonadotrophin injection and/or ⩾20 oocytes retrieved and/or previous severe OHSS were infused with 1000 ml 6% hydroxyaethyl starch solution at the time of oocyte collection and 500 ml 48 h later. A total of 82 IVF patients at risk without prophylactic infusions during the preceding years served as controls. Both groups were identical according to patient's age, body mass index, androgen concentrations, peak oestradiol concentrations, number of retrieved oocytes, fertilization and pregnancy rates. There were seven cases of severe OHSS in untreated patients and two cases in the treatment group ($P = 0.08$). In moderate OHSS a significant difference became obvious with only ten cases in the treatment group and 32 cases in the control group ($P < 0.00001$). Hydroxyaethyl starch solution seems to be an effective and economic alternative in reducing severe and moderate OHSS during IVF treatment.

Key words: in-vitro fertilization/human serum albumin infusion/hydroxyaethyl starch infusion/ovarian hyperstimulation syndrome/prophylactic therapy

Introduction

Severe ovarian hyperstimulation syndrome (severe OHSS) can be a life-threatening complication after controlled ovarian stimulation with exogenous gonadotrophins to induce multiple ovulation in patients undergoing treatment by assisted reproductive techniques. Besides extensive cystic enlargement of ovaries the pathophysiological key factors are: angiogenesis (new capillary vessel formation) and increased capillary permeability resulting in extravascular fluid accumulation (ascites, hydrothorax), hypoalbuminaemia, haemoconcentration and electrolyte disturbances (Navot *et al.*, 1992). The risk of thromboembolic events massively rises (Mills *et al.*, 1992; Hignett *et al.*, 1995). Tense ascites with decreasing renal perfusion leads to oliguria and further degrees of renal failure. Adult respiratory distress syndrome contributes to potentially lethal complications (Zosmer *et al.*, 1987).

The pathophysiology of OHSS is not yet fully understood and remains controversial. Activation of the ovarian prorenin-renin-angiotensin system (Delbaere *et al.*, 1997), increased prostaglandin synthesis (Schenker and Polishuk, 1976) and capillary changes due to histamine, serotonin and cytokines including platelet-derived growth factor and vascular endothelial growth factor were mentioned in this regard. The latter is expressed in increasing amounts in granulosa cells stimulated by human chorionic gonadotrophin (HCG; Neulen *et al.*, 1995). Recently a significant correlation was found between plasma vascular endothelial growth factor concentrations and certain biological characteristics of OHSS and of capillary leakage such as leukocytosis and increased haematocrit (Abramov *et al.*, 1997). In addition, interleukin (IL)-2 concentrations in follicular fluid were demonstrated to be higher in patients subsequently developing severe OHSS (Orvieto *et al.*, 1995a).

Lacking causal therapy, prevention of severe OHSS in patients at high risk is most important. Asch *et al.* (1993) were the first to introduce the use of intravenous human albumin solution prior to and immediately after oocyte retrieval to prevent severe OHSS in women at risk. In only two of their first 100 cases of albumin administration was hospitalization required due to hyperstimulation syndrome (Asch, 1994). Since then two Israeli groups have demonstrated a preventive effect of albumin solution in prospective studies (Shoham *et al.*, 1994; Shalev *et al.*, 1995). On the other hand intravenous albumin does not prevent severe OHSS in absolute terms (Morris and Paulson, 1994; Mukherjee *et al.*, 1995; Orvieto *et al.*, 1995b) and recently other authors could not confirm the beneficial effects on in-vitro fertilization (IVF) patients at high risk for severe OHSS (Ng *et al.*, 1995; Lewit *et al.*, 1996a).

Since the first report on prophylactic albumin in 1993 we have tested the effectiveness and mechanism of action of this treatment in our IVF programme and could confirm a distinct reduction of severe OHSS but not a prevention in all cases (unpublished data). Although literature documents the clinical safety of human albumin (Asch *et al.*, 1993), a number of patients raised questions of potential viral transmissions because of its human origin. Uncertainty was supported by articles in the lay press. Therefore we looked for a safe non-biological substitute for human albumin with comparable physical properties able to avoid severe OHSS. In this study the results of our first 100 cases of prophylactic hydroxyaethyl starch solution are evaluated by retrospective case-series.

Table I. Comparison of risk factors for developing severe ovarian hyperstimulation syndrome

	Treatment group HAES	Control group	Level of significance
No. of patients (cycles)	100	82	
Peak oestradiol (pmol/l)	13190 ± 3314[a]	12988 ± 2954[a]	NS[b]
(range)	(7395–25389)	(8001–27525)	
No. of oocytes	18.8 ± 6.1[a]	19.8 ± 3.8[a]	NS[b]
(range)	(8–35)	(13–30)	
Embryo transfer rate (%)	93	92.7	NS[c]
Age (years)	32.7 ± 4.2[a]	32.0 ± 3.4[a]	NS[b]
(range)	(21.4–41.5)	(24.0–38.8)	
BMI (kg/m^2)	23.3 ± 5.2[a]	22.3 ± 3.4[a]	NS[b]
(range)	(17.6–65.2)	(16.2–37.0)	
Testosterone (nmol/l)	1.94 ± 1.01[a]	2.05 ± 1.04[a]	NS[b]
(range)	(0.35–6.28)	(0.35–5.24)	
DHEAS (μmol/l)	5.91 ± 2.76[a]	6.04 ± 3.46[a]	NS[b]
(range)	(1.28–13.31)	(1.28–18.69)	

NS = not significant; BMI = body mass index; HAES = hydroxyaethyl starch solution; DHEAS = dihydroepiandrosterone sulphate.
[a]Mean ± SD.
[b]Student's *t*-test or Mann–Whitney *U*-test, two-tailed.
[c]Fisher's exact test, two-tailed.

Materials and methods

In a cohort study from January 1994 to December 1994 patients at high risk of developing severe OHSS received 6% hydroxyaethyl starch infusion (HAES; Plasmasteril, Fresenius, Germany) during 100 IVF treatment cycles: 1000 ml at the time of oocyte retrieval 36 h after injection of 10 000 IU HCG (Choragon 5000®; Ferring, Kiel, Germany) plus 500 ml at the time of embryo transfer 48 h later. Risk of developing severe OHSS was defined as follows:

- oestradiol serum concentration on the day of HCG of ⩾11 010 pmol/l or
- retrieval of ⩾20 oocytes or
- development of severe OHSS in a previous stimulation cycle.

A total of 82 patients at risk of severe OHSS, who underwent IVF in 1992 and 1993 and received neither HAES nor human albumin solution served as controls. The patient group and the controls were similar with regard to age, body mass index (BMI), serum testosterone and dehydroepiandrosterone sulphate (DHEAS) concentrations, peak oestradiol concentrations on the day of HCG, number of oocytes retrieved at follicular puncture and fertilization and pregnancy rates (Table I).

In both groups ovarian stimulation was performed according to a long protocol gonadotrophin-releasing hormone analogue (GnRHa) formulation combining Triptorelin (Decapeptyl®; Ferring) and human menopausal gonadotrophins (HMG, Menogon®; Ferring). Progesterone by vaginal route was used for luteal support in all groups. Observation of the luteal phase and diagnosis of moderate or severe OHSS were performed by us or by the referring gynaecologist at the patient's home town. The detailed classification proposed by Schenker and Weinstein (1978) based on the original classification of Rabau *et al.* (1967) was used to determine the grade of OHSS (i.e. moderate, severe).

Oestradiol concentrations were measured by radioimmunoassay using a double antibody procedure (ICN Biomedicals, Costa Mesa, USA). Testosterone and DHEAS were determined by radioimmunoassay using reagent kits obtained from ICN Biomedicals and Diagnostic Products Corporation (Bad Nauheim, Germany). Standard intra-assay coefficients of variation (CV) at 50% binding were 5.7% for oestradiol, 4.6% for testosterone and 7.2% for DHEAS.

For statistical analysis, differences between patient and control groups for the occurrence of moderate and severe OHSS as well as differences in embryo transfer rates and pregnancy rates were assessed by Fisher's exact test. Student's *t*-test or Mann–Whitney *U*-test were used to compare the other parameters between patients and controls. The concentration of statistical significance was defined as $P < 0.05$.

Table II. Results of IVF treatment cycles in patients at high risk (for details see Table I) receiving prophylactic HAES to prevent severe ovarian hyperstimulation syndrome (OHSS)

	Treatment group HAES	Control group	Level of significance
No. of patients (cycles)	100	82	
No. of pregnancies	28	24	NS[c]
Pregnancy rate/embryo transfer (%)	30.1	31.6	NS[c]
Moderate OHSS[a] (no. of cases)	10	32	$P < 0.00001$[c]
Severe OHSS[b] (no. of cases)	2	7	NS[c]

NS = not significant; HAES = hydroxyaethyl starch solution.
[a]Grades 3 and 4 according to Schenker and Weinstein (1978).
[b]Grades 5 and 6 according to Schenker and Weinstein (1978).
[c]Fisher's exact test, two-tailed.

Results

The peak estradiol concentrations at time of HCG administration did not differ between patients receiving HAES ($n = 100$; 13 190 ± 3314 pmol/l) and those who did not ($n = 82$; 12 988 ± 2954 pmol/l). The number of oocytes retrieved, embryo transfer rates and pregnancy rates per cycle also did not vary significantly between HAES treatment cycles and control cycles. Both groups were similar in terms of patient's age and body weight. Mean androgen concentrations were also comparable (Table I).

There were seven cases of severe OHSS (marked ascites and ovarian enlargement, partly dyspnoea) in the group of IVF patients without prophylactic HAES in comparison to two cases in the treatment group (Table II). This difference was not significant ($P = 0.08$). However, for the incidence of moderate OHSS (large ovarian cysts with abdominal pain, swelling of the lower abdomen, nausea, vomiting) a clear distinction between the two groups became obvious, with 39% in untreated patients but only 10% after HAES ($P < 0.00001$). Treatment with HAES was well tolerated with negligible side effects. In only three cases mild pruritus and slight skin reactions with urticaria were observed.

Discussion

The aetiology of severe OHSS is still a matter for debate and causal therapy is not available so far. Therefore in patients undergoing treatment by assisted reproductive techniques it is important to recognize predisposing factors including young age, low body weight, hyperandrogenaemic chronic anovulation and especially ultrasound diagnosis of polycystic ovaries. Furthermore, in IVF patients occurrence of severe OHSS correlates with the number of oocytes retrieved by follicular puncture and concentrations of serum oestradiol at the time of HCG injection (Asch *et al.*, 1991). Within the last few years a number of preventive strategies have been evaluated for

patients at high risk. As HCG plays a crucial role in the development of OHSS, lower doses for ovulation induction and, more effectively, replacement of the longer half-life HCG (>24 h) by a single injection of a gonadotrophin-releasing hormone analogue stimulating the release of endogenous luteinizing hormone (LH) with its shorter half-life (fastest half-life 20 min) for ovulation induction have been proposed (Lewit *et al.*, 1996b).

In a different prophylactic attempt by other groups human serum albumin (HSA; 5–20% solution, 20–75g) was given intravenously at the time of follicular puncture and shortly post-retrieval to minimize OHSS. Whereas the first reports were encouraging with no cases of severe OHSS at all (Asch *et al.*, 1993; Shoham *et al.*, 1994; Shalev *et al.*, 1995) it has become obvious by now that intravenous HSA cannot prevent severe OHSS in all patients (Morris and Paulson, 1994; Mukherjee *et al.*, 1995; Orvieto *et al.*, 1995b; Ng *et al.*, 1995; Lewit *et al.*, 1996a). Nevertheless, prophylactic HSA could blunt the severity of OHSS even in the later studies (*Ng et al.*, 1995). In our own experiences HSA solution given on the day of oocyte retrieval did not abolish severe OHSS but did reduce the number of severe and moderate OHSS (29 cases out of 141 treated IVF cycles versus 64 cases out of 141 untreated IVF cycles at high risk; unpublished data). Lacking a more effective strategy we supplied every patient at high risk in our IVF programme with prophylactic HSA (50 g in 1000 ml of lactated Ringer's solution) at the time of oocyte retrieval after obtaining required consent.

Startled at some articles in the lay press a number of patients raised the question of potential viral transmissions by HSA because of its human origin. Although viral safety should be guaranteed by pasteurization and additional steps of purification, for psychological reasons we looked for a non-biological alternative with comparable physical properties able to avoid severe OHSS or at least to blunt the severity of OHSS. High molecular weight hydroxyaethyl starch solution (molecular weight 450 000) represents a colloid volume substitute capable of increasing plasma oncotic pressure similar to albumin. Because of its synthetical origin no viral transmission is possible. Anaphylactoid reactions have been reported in <1/1000 cases but more often than after HSA (Ring and Messmer, 1977). Otherwise side effects equal those of HSA infusion.

The results of our first 100 cases with prophylactic HAES solution are encouraging. Severe OHSS could not be prevented in absolute terms, but taken together the percentage of moderate and severe OHSS cases decreased in treated patients. Because of its shorter half-life of approximately 10 h compared with 10–15 days for HSA a second infusion was carried out at the time of embryo transfer. Despite its shorter half-life high molecular weight HAES led to comparable results in minimizing severe and moderate OHSS in patients at risk. HAES was well tolerated and in only three cases smaller anaphylactoid reactions (pruritus, skin symptoms like urticaria at the trunk and at arms and legs) appeared. Increase in intravascular colloid osmotic pressure and water binding capacity on the one hand and putatively binding and inactivating of vasoactive substances on the other hand are probable mechanisms in preventing OHSS.

To our knowledge this is the first demonstration that HAES is an effective tool in reducing the incidence of moderate and severe OHSS in patients undergoing assisted reproductive technologies. Courses of OHSS seemed to be mitigated. In contrast to some observations in HSA treatment (Shaker *et al.*, 1996) the pregnancy rate was not negatively influenced by HAES. Costs are less in comparison with HSA (in our study 143 DM versus 684 DM). A randomized, prospective study should be performed to assure the role of HAES as substitute for HSA. Because both procedures do not prevent severe OHSS in every case, additional precaution should be taken. There is good evidence that combination with prolonged coasting (Sher *et al.*, 1995) can further reduce severe and moderate OHSS to a minimal level.

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