Original Paper

Gynecologic and Obstetric Investigation

Gynecol Obstet Invest 2000;50:182–185

Received: December 2, 1999
Accepted after revision: May 10, 2000

Use of Intramuscular Progesterone versus Intravenous Albumin for the Prevention of Ovarian Hyperstimulation Syndrome

Loredana Costabile[a] Vittorio Unfer[a] Claudio Manna[a] Sandro Gerli[b]
Dario Rossetti[b] Gian Carlo Di Renzo[b]

[a]Center for Reproductive Medicine and Infertility Therapy, Rome, and [b]Department of Obstetrics and Gynecology, University of Perugia, Italy

Key Words
Ovarian hyperstimulation syndrome (OHSS) · Intramuscular progesterone · Intravenous albumin

Abstract
This study was designed to compare the effectiveness of intramuscular progesterone with that of intravenous albumin in the prevention of ovarian hyperstimulation syndrome (OHSS). Ninety-six patients at high risk to develop OHSS (estradiol concentration >9,000 pmol/l on the day of hCG administration and over 20 follicles of a diameter larger than 14 mm observed by transvaginal ultrasonography) and undergoing in vitro fertilization-embryo transfer were enrolled. They were randomly treated with intramuscular progesterone (200 mg/day) or 100 ml of 20% intravenous albumin in order to estimate the difference in the incidence of OHSS. A significant difference in the incidence of moderate OHSS and no cases of severe OHSS were observed between the groups. Our data show the effectiveness in preventing OHSS with high doses of progesterone.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious complication associated with ovulation induction. The prevalence of severe forms varies between 0.3 and 5% [1]. Understanding the pathophysiology of OHSS is essential to develop rational preventive strategies. However, the underlying mechanism of OHSS is currently not yet well understood. It is known that OHSS does not appear unless LH or hCG has been administered to induce ovulation [2]. Symptoms increase in severity during the luteal phase but vanish rapidly with the onset of menstrual bleeding [3].

However, when pregnancy has been achieved, there is a further worsening of symptoms, which persist for some weeks [2, 4, 5].

The clinical picture of this syndrome includes a large number of symptoms that show different associations in relation to the grading of OHSS: ovarian enlargement, ascites, nausea, headache, vomiting, diarrhea, generalized edema, oliguria, hemoconcentration, pleural effusion and coagulation disorders [3, 6, 7].

Several systems to classify OHSS have been proposed [3, 6, 8]. The most widely accepted system describes three

KARGER
Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0378–7346/00/0503–0182$17.50/0

Accessible online at:
www.karger.com/journals/goi

Dr. Loredana Costabile
Via Nomentana, 531
I–00141 Rome (Italy)
Tel. +39 06 3240650, Fax +39 06 3241284
E-Mail cdigerl@box2.tin.it

levels of the syndrome: mild, moderate and severe [9–11]. The mild form is characterized by enlarged ovaries (greater than 5 cm in diameter), plasma 17β-estradiol greater than 1,200 pg/ml and abdominal discomfort. Ovaries with diameters of about 12 cm, abdominal pain, ascites, nausea, vomiting and/or diarrhea mark the moderate form. The severe form is marked by ovaries enlarged more than 12 cm in diameter, ascites, hydrothorax, hemoconcentration, coagulation abnormalities, renal failure, weight gain greater than 5 kg and electrolyte imbalance.

Asch et al. [12] were the first to suggest that intravenous human albumin may help to prevent the development of the OHSS, and supportive studies have subsequently been reported [13]. Nevertheless, the use of albumin is still controversial and other authors have not substantiated these findings [14].

Other treatments, such as cortisone, antihistamine and antiprostaglandin agents, have been suggested [8, 15].

It is possible to hypothesize at least three different mechanisms of action of the prophylactic use of progesterone for preventing OHSS, either acting alone or working with other factors: (1) a general antiestrogenic effect of progesterone mediated by a downregulation of estrogen receptors, especially on the vascular endothelium; (2) an effect on the endocrine ovarian tissue, with an inhibition of hormone secretion, such as prostanoids and prorenin; (3) an antagonistic effect against the action of aldosterone, which is raised in the plasma of patients suffering from OHSS, due to increased renin activity, derived from the prorenin production by ovarian follicles.

We performed a randomized prospective study to determine whether there was any benefit using progesterone to prevent OHSS in our population.

Materials and Methods

Patients

A total of 96 patients, undergoing in vitro fertilization-embryo transfer in our centers, were enrolled in this study. The indications for an assisted reproduction technique were the tubal factor (61%), polycystic ovarian syndrome (4%), endometriosis (12%), unexplained (14%) and the male factor (9%). Inclusion criteria were estradiol concentration >2,500 pg/ml on the day of hCG administration and over 20 follicles of a diameter larger than 14 mm observed by transvaginal ultrasonography.

No patient had a history of bleeding disorders or coagulation abnormalities. Routine evaluation of coagulation factors before in vitro fertilization-embryo transfer was normal in all patients.

Criteria for OHSS

According to Rabau et al. [10], OHSS was classified into mild (ovarian enlargement less than 5 cm, no ascites and abdominal pain), moderate (ovaries less than 10 cm, nausea, vomiting and ascites) and severe (ovaries greater than 10 cm, ascites, hydrothorax, dehydration, nausea, vomiting and weight gain).

Treatment Protocol

The Institutional Board of Research approved the protocol, and all patients gave their written informed consent before entering the study.

All ovarian stimulations for patients were performed with a combination of GnRH agonist (400 μg administered subcutaneously twice a day from day +20 of the previous menstrual cycle until the injection of hCG) and pure FSH. Patients were monitored by measuring the plasma concentration of 17β-estradiol and by ultrasonographic determinations of follicular size and number on days +5, +7 and +12 of stimulation.

The dosage of gonadotropins was adjusted according to the individual response.

All patients received 10,000 IU of hCG intramuscularly when the serum concentration exceeded 200 pg/follicle and when there were at least 3 follicles with a diameter of 18 mm. Oocytes were retrieved 34–36 h after hCG administration under vaginal ultrasound control (day 0).

On the day of hCG administration, all patients whose characteristics came under the inclusion criteria were randomly enrolled in one of the following two groups: group A (including 42 patients) received 100 ml of 20% albumin intravenously, and starting on day +3 all patients received an intramuscular administration of 50 mg progesterone daily until the βhCG test evaluation; group B (including 54 patients) had been receiving 200 mg/day progesterone i.m. for 14 days starting immediately after the oocyte retrieval day, when the βhCG test was performed.

The embryo transfer was performed at the 2- to 4-cell stage. A maximum of 2 embryos was placed.

Laboratory Determinations and Ultrasound Scans

The plasmatic concentration of estradiol was determined by radioimmunoassay, of blood samples on day +1, +5, +9 and +12 of the menstrual cycle, on the day of hCG administration and then every other day.

Ultrasound monitoring was performed daily from the 5th day of the cycle until oocyte retrieval, and afterwards on the 4th, 8th, 11th and 14th days after ovulation. It included ovarian morphology, ovarian volume, number of follicles and their dimension. Ovarian volume was calculated according to the formula 4/3 (1/2 diameter), where the diameter was considered as the mean of the length, width and depth of the ovary [16]. Monitoring was performed by transvaginal ultrasound with a 7.5-MHz transducer.

Statistical Analysis

Statistics were performed with the SPSS® statistical package. The χ^2 and Fisher's t tests were used. Significance was defined as a p value <0.05.

Results

In table 1, the characteristics of the two groups of patients are reported. No statistical differences were observed between the two groups of patients in estradiol lev-

Table 1. Characteristics of patients who received albumin (group A) or progesterone (group B)

Characteristics	Albumin	Progesterone	p value
Patients	42	54	n.s.
Age, years	29.6 ± 4.2	30.4 ± 4.0	n.s.
BMI	25.2 ± 3.8	26.1 ± 5.9	n.s.
Incidence of polycystic ovaries	21 (50%)	25 (46.3%)	n.s.
History of OHSS in previous cycles	4 (9.5%)	5 (9.2%)	n.s.
Baseline FSH, IU	5.8 (IQR 4.7–6.7)	6.3 (IQR 5.1–7.3)	n.s.
Days of stimulation	11.4 ± 1.1	11.5 ± 1.6	n.s.
FSH ampoules	22.5 (IQR 18–35.8)	24 (IQR 20–32.8)	n.s.
Estradiol levels on the day of hCG administration, pmol/l	9,872 ± 478	9,920 ± 501	n.s.
Follicles (before retrieval) >14 mm	25 ± 2	23 ± 1	n.s.
Oocytes retrieved	13.8 ± 6.1	10.3 ± 6.4	<0.05
Embryos	8.5 ± 1	8 ± 2	n.s.
Pregnancy rates	22 (52.3%)	37 (68.5%)	<0.05
Incidence of mild OHSS	4 (8.6%)	4 (8.6%)	n.s.
Incidence of moderate OHSS	4 (8.6%)	0 (0%)	<0.05
Incidence of severe OHSS	0	0	–

Results indicate means ± SD. IQR = Interquartile range; BMI = body mass index (weight/height^2); n.s. = not significant.

el or in the number of follicles <14 mm on the day of hCG administration.

Significantly, a greater number of oocytes was retrieved in the albumin group (group A: 13.8 ± 6.1 vs group B: 10.3 ± 6.4;$p < 0.05$); despite this there was no significant difference in the number of embryos (group A: 8.5 + 1 vs group B: 8 ± 2; $p = 0.080$).

Pregnancy rates were significantly higher in group B [group A: 22 (52.3%) vs. group B: 37 (68.5%); $p < 0.05$].

No cases of severe OHSS occurred in the two groups. A significant difference in the incidence of moderate OHSS was observed between the groups [group A: 4 (8.6%) vs. group B: 0 (0%); $p < 0.05$]. Cases were not related to the occurrence of multiple pregnancy.

Discussion

The pathogenesis of OHSS is still unclear. It is believed that in overstimulation of the ovary, the renin-angiotensin system may play an important role [17]. It has also been suggested that increased capillary permeability and new capillary formation (possibly secondary to activation of the prorenin system), increased prostaglandin synthesis, histamine and serotonin are the main physiological features of OHSS [17, 18]. More recently, interleukin 6 and vascular endothelial growth factor have been implicated as etiological factors of OHSS [19].

Asch et al. [12] were the first to suggest that intravenous human albumin may help to prevent the development of OHSS. After the initial encouraging reports, several studies suggest that there is no advantage in the prophylactic use of albumin for preventing OHSS [20–23]. In accordance with this, our study shows that using albumin in order to prevent OHSS in women with an excessive ovarian response does not only produce no benefit, but it may also reduce pregnancy rates.

Furthermore, the recent concern in bovine spongiform encephalopathy and similar diseases in humans, such as Creutzfeldt-Jakob disease, have led the health authorities in many countries to increase the precautions taken in the collection of human blood and plasma, and in the use of blood-derived products for therapeutic applications. A recent result of these increased precautions has been the withdrawal of several batches of therapeutic human serum albumin from use and distribution by the major companies supplying this product in the USA. The available epidemiological data do not support the transmission of Creutzfeldt-Jakob disease via blood transfusion in humans up to now, and no transmission by intravenous infusion of whole blood in subhuman primates has been demonstrated.

Our data suggest the effectiveness of high doses of progesterone in the prevention of OHSS. As our study reports, the capacity of progesterone to prevent OHSS was superior to all the other regimens described in the literature, especially considering that we did not suppress any cycles.

The effectiveness of progesterone in preventing OHSS, although it needs to be confirmed by further studies, may help to avoid the severe complications of induction superovulation.

References

1 Navot D, Bergh PA, Laufer N: The ovarian hyperstimulation syndrome; in Adashi EY, Rock JA, Rosenwaks Z (eds): Reproductive Endocrinology, Surgery and Technology. Philadelphia, Lippincott-Raven, 1995, vol 2, pp 2215–2232.

2 Schenker JG, Weinstein D: Ovarian hyperstimulation syndrome: A current survey. Fertil Steril 1978;30:255–268.

3 Schwartz M, Jewelewiez R: The use of gonadotropins for induction of ovulation. Fertil Steril 1981;35:3–12.

4 Chotiner HC: Nonsurgical management of ectopic pregnancy associated with severe hyperstimulation syndrome. Obstet Gynecol 1985; 66:740–743.

5 Pride SM, Yuen BH, Moon YS, Leyung PCS: Relationship of gonadotropin-releasing hormone, danazol and prostaglandin blockade to ovarian enlargement and ascites formation of the ovarian hyperstimulation syndrome in the rabbit. Am J Obstet Gynecol 1986;154:1155–1160.

6 Jewelewicz R, Vande Wiele RL: Acute hydrothorax as the only symptom of ovarian hyperstimulation syndrome. Am J Obstet Gynecol 1975;121:1121.

7 Moses M, Bogowsky H, Anteby E: Thromboembolic phenomena after ovarian stimulation with human menopausal gonadotrophins. Lancet 1965;ii:1213–1214.

8 Golan A, Ron El R, Herman A, Soffer Y, Weinraub Z, Capsi E: Ovarian hyperstimulation syndrome: An update review. Obstet Gynecol 1989;44:430–440.

9 Blankstein J, Shalev J, Saadon T: Ovarian hyperstimulation syndrome: Prediction by number and size of preovulatory ovarian follicles. Fertil Steril 1987;47:597–602.

10 Rabau E, Serr DM, David A, Mashiach S, Lunenfeld B: Human menopausal gonadotrophins for anovulation and sterility. Am J Obstet Gynecol 1967;98:92–98.

11 McArdle C, Seibel M, Hann LE, Weinstein F, Taymor M: The diagnosis of ovarian hyperstimulation (OHS): The impact of ultrasound. Fertil Steril 1983;30:4646–4647.

12 Asch RH, Ivery G, Goldsman M, Frederick JL, Stone SC, Balmaceda JP: The use of intravenous albumin in patients at high risk for severe ovarian hyperstimulation syndrome. Hum Reprod 1993;8:1015–1020.

13 Shalev E: The role of intravenous albumin in the prevention of ovarian hyperstimulation syndrome; in Filicori M, Flamigni C (eds): Ovulation Induction Update '98. London, Parthenon, 1998, p 177.

14 Panay N, Iammarrone E, Zosmer A, Tozer A, Hussain S, Wilson C: Does the prophylactic use of intravenous albumin prevent ovarian hyperstimulation syndrome? A randomized prospective study (abstract book No 1); in Edwards RG, Beard HK, Hansen R (eds): Abstracts of the 15th Annual Meeting of the European Society of Human Reproduction and Embryology. Tours, Oxford University Press, 1999, p 105.

15 Borestein R, Elhalah U, Lunenfeld B, Schwartz ZS: Severe ovarian hyperstimulation syndrome: A reevaluated therapeutic approach. Fertil Steril 1989;51:791–795.

16 Campbell S, Goswamy R, Goessens L, Withead M: Real-time ultrasonography for determination of ovarian morphology and volume. Lancet 1982;i:425–426.

17 Ong AC, Eisen V, Rennie DP: The pathogenesis of the ovarian hyperstimulation syndrome (OHS): A possible role for ovarian renin. Clin Endocrinol 1991;34:43–49.

18 Navot D, Margalioth EJ, Laufer N, Birkenfeld A, Relou A, Rosler A, Schenker JG: Direct correlation between plasma renin activity and severity of the ovarian hyperstimulation syndrome. Fertil Steril 1987;48:57–61.

19 McClure N, Healy DL, Rogers PA, Sullivan J, Beaton L, Haning RV Jr, Connoly DT, Robertson DM: Vascular endothelial growth factor as capillary permeability agent in ovarian hyperstimulation syndrome. Lancet 1994;344:235–236.

20 Shaker AG, Zosmer A, Dean N, Bekir JS, Jacobs HS, Tan SL: Comparison of intravenous albumin and transfer of fresh embryos with cryopreservation of all embryos for subsequent transfer in prevention of ovarian hyperstimulation syndrome. Fertil Steril 1996;65: 992–996.

21 Mukherjee T, Copperman AB, Sandler B, Bustillo M, Grunfeld L: Severe ovarian hyperstimulation despite prophylactic albumin at the time of oocyte retrieval for in vitro fertilization and embryo transfer. Fertil Steril 1995;64:641–643.

22 Orvieto R, Dekel A, Dicker D, Bar-Hava I, Ben-Rafael Z: A severe case of ovarian hyperstimulation syndrome despite the prophylactic administration of intravenous albumin. Fertil Steril 1995;64:860–862.

23 Lewit N, Kol S, Ronen N, Itskovitz-Eldor J: Does intravenous administration of human albumin prevent severe ovarian hyperstimulation syndrome? Fertil Steril 1996;66:654–656.