High doses of GnRH antagonists are efficient in the management of severe ovarian hyperstimulation syndrome

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Summary

Objective: To determine whether treatment of severe ovarian hyperstimulation syndrome (OHSS) with high-dose gonadotropin-releasing hormone (GnRH) antagonist, due to its luteolytic effect, is an effective method of management. *Methods:* Six infertile patients who had been scheduled for embryo transfer and developed early-onset severe OHSS with ascites and hemoconcentration were chosen for treatment with 3.0 mg of a GnRH antagonist (Cetrotide; Cetrorelix, Serono, Madrid, Spain). The response of these patients was compared with five patients with severe early-onset OHSS who received support therapy alone. All patients were evaluated clinically, echographically, and hematologically. *Results:* Estradiol (E2) levels dropped significantly a few days after treatment. Peritoneal fluid regression measured by ultrasound was faster on the study group compared with controls. Hematocrit remained comparable in both groups during follow-up. In two cases a second bolus of GnRH-antagonist was used due to clinical and biochemical findings during the four days of observation following the initial dose. None of the patients treated with GnRH antagonists required paracentesis. *Conclusions:* Treatment with high doses of GnRH antagonists seems to be effective in the management of severe OHSS.

Key words: Ovarian hyperstimulation syndrome; GnRH antagonists.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic, life-threatening disease that complicates in its most severe form 0.2-2% of *in vitro* fertilization (IVF) attempts. Characteristics of patients prone to develop OHSS are: young (< 35 years of age), thin women of short stature, women who produced multiple cysts or were high responders in previous IVF cycles, those exposed to aggressive stimulation regimens such as those using recombinant follicle stimulating hormone (r-FSH), women with hormonal and/or ultrasound (US) morphological signs of polycystic ovary syndrome, women who produce excessively high numbers of small follicles (> 15-30 in the present IVF cycle), and women who have a high E2 response (> 2000 - 6000 pg/ml) in the present IVF cycle.

Human chorionic gonadotropin (hCG) may promote ovarian secretion of vasoactive substances. Pregnancy, as a continuum of ever-increasing quantities of hCG, may aggravate early onset OHSS and may induce late onset OHSS. GnRH receptors have been shown to be present in granulosa-lutein cells [1, 2], the endometrium [3, 4], endosalpinx, and in ovarian structures [3-8]. Some studies suggest that steroidogenic activity of cultured granulosa cells may be affected by GnRH [6, 8, 9], suggesting that the ovary, the endometrium, and the embryo (3,4,7) could be targets for direct extrapituitary GnRH action in humans.

Revised manuscript accepted for publication August 14, 2008

There are reports [10, 11] on the efficacy of GnRH antagonists to induce luteolysis and elicit subsequent ovarian quiescence in IVF cycles. The purpose of our study was to determine whether high-dose GnRH antagonist treatment of patients with severe OHSS is effective after triggering ovulation with hCG.

Materials and Methods

Eleven patients who developed severe OHSS were selected for treatment with high doses of a GnRH antagonist and support therapy or for treatment with only support therapy. Six of these infertile patients scheduled for *in vitro* fertilization-embryo transfer (IVF-ET) who were afflicted with severe OHSS following ovulation induction with r-FSH and administration of 10,000 IU of hCG were treated with high doses of a GnRH antagonist and support therapy. The outcomes of these patients were compared with the outcomes of five other patients with severe OHSS who were treated only with support therapy. All patients provided written informed consent to participate in this study, which was approved by the Ethics Committee of The University of Valencia Hospital. OHSS was diagnosed as a patient having at least [12]: ovarian diameter > 10 cm; marked ascites, hematocrit > 45%; leucocytes > 15000/mm^3; serum creatinine > 1.0 mg/dl .

All patients who received GnRH antagonist treatment had ovaries greater than 10 cm in diameter, more than 25 follicles with diameters greater than 15 mm by US examination, and either E2 levels greater than 3500 pg/ml on triggering day, or greater than 25 oocytes retrieved. Embryo transfer was not performed in any of the patients. The six selected patients who fulfilled the criteria for diagnosis of early-onset severe OHSS following US examination received a subcutaneous bolus of 3.0 mg of Cetrotide® (Cetrorelix; Serono, Madrid-Spain) immedi-

ately after oocyte retrieval. All embryos (in the pronuclear stage) were subjected to freezing for transfer in subsequent cycles. Patients chosen for supportive therapy received intravenous fluids (1500 to 3000 ml saline solution or Ringer's lactate). Cases with resistant hemoconcentrations were treated with 1000 ml Voluven® 6% plasma volume expander (6% hydroxyethylstarch) in"Y" with 1500 ml physiologic serum over a 24-hour period. Fluid dose was adjusted every six hours according to hematocrit. All patients were heparinized using enoxaparin (Clexane®) at a dose of 40 mg subcutaneously every 24 hours and kept at bed rest. Patients were monitored every four days with a complete physical examination, transvaginal US examinations, and repeat endocrine studies. They remained hospitalized until there was objective evidence of clinical resolution.

Statistical analysis

Data were analyzed with a software package for Social Sciences (SPSS) v. 13 program. Data are expressed as mean ± standard deviation and in percentages when applicable. We employed the Kruskal-Wallis non-parametric test and chi square for proportions. Sample size calculation and statistical significance were not applicable due to the small number of patients.

Results

Patient characteristics did not differ significantly between groups (age, BMI, total dosage of rFSH, follicular size, estradiol levels, the triggering of ovulation, and number of oocytes retrieved). The average age of the case patients was 28.8 ± 1.7 years and of the control patients 30.4 ± 3.6 years. The BMI was 21.4 ± 1.7 for cases and 23.0 ± 2.3 for controls (Table 1).

Table 1. — *General data.*

	Study group	Controls
No. of patients	6	5
Age	28.8 ± 1.7	30.4 ± 3.6
Total dose of FSH (IU)	1420 ± 585	1200 ± 396
Follicles > 15 mm	42.2 ± 9.7	28.4 ± 10.1
E2 triggering day	3694 ± 334	4871.2 ± 1196
Oocytes retrieved	30.6 ± 6,2	36.2 ± 10.4
BMI	21.4 ± 1.7	23.0 ± 2.3

Values are means ± SD unless otherwise stated.

Estradiol concentration

On retrieval day E2 levels were comparable in both groups. Four days after treatment there was a lowering in E2 levels in cases compared to the levels in controls (Figure 1). However, two patients in the study group needed a second dose of the antagonist because of persistently high estradiol levels and persistent symptoms of ovarian hyperstimulation after four days of initiation of treatment. The decrease in estradiol levels in cases became significant on subsequent control dates and was associated with clinical recovery.

Hematocrit

Although there was a hematocrit improvement trend in cases following treatment (Figure 2), the difference with controls was not statistically significant.

Peritoneal fluid estimation

Ascites was evident in patients in the treatment group at the first control evaluation (fourth day after oocyte retrieval). Two patients in the study group had a large amount of peritoneal fluid. This finding along with the presence of high estradiol levels was the reason for the administration of a second dose of GnRH antagonist four days after the initial antagonist administration. During subsequent evaluations better improvement was noticed in the cases, but the difference with controls was not statistically significant (Figure 3). Paracentesis, however, was not performed in any of the cases, while two patients among the controls required paracentesis. The physicians who decided whether paracentesis was necessary were not aware whether these patients were in the antagonist treatment group or in the control group.

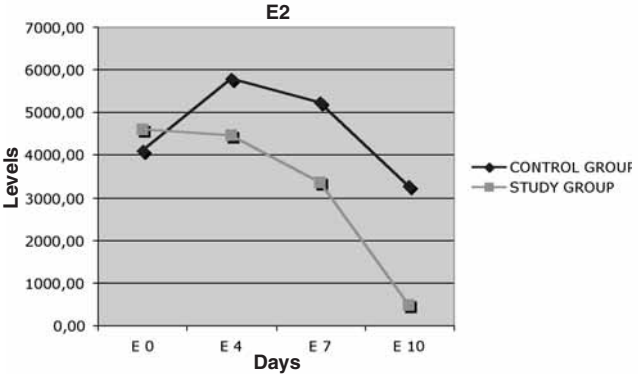
Two patients in the treatment group who were discharged after evaluation on day 4 required hospital readmission on day 8 due to US and clinical evidence of serious hyperstimulation (ascites, hemoconcentration, hypoproteinemia, hyperocoagulability, and weight gain). These two patients had a history of severe hyperstimulation in two previous ovulation induction cycles. They were treated on those occasions with paracentesis with retrieval of five to seven liters of fluid each time, and required hospitalization for 15 and 21 days, respectively. One of these patients also had pleural effusion (data not shown). Two other patients in the treatment group were discharged following the second scheduled evaluation. Ovarian enlargement was the only remaining abnormality. The ovaries of these patients were completely normal when examined one month later.

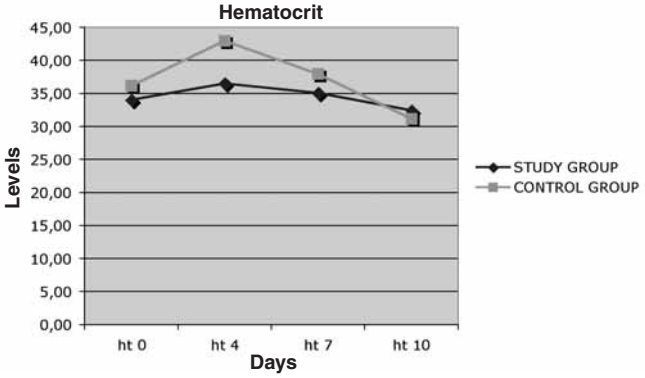
Patients in the treatment group needed a mean of nine days hospitalization. Two patients in the control group needed 21 days hospitalization. The mean hospitalisation time for the control group was 12.3 days (data not shown). One month after discharge all the patients had resumed menstruation and their ovarian sizes were of approximately 5 cm. Three patients from the treatment group have already received transfer of frozen embryos. One of these transfers was unsuccessful.

Discussion

Consensus about the management strategy for OHSS is lacking due to the imperfect understanding of pathogenesis of this disease. Today it is thought that OHSS results from an acute change in vascular (especially intraovarian) permeability secondary to arteriolar dilatation and extravasation or leakage of protein-rich intravascular fluid into the peritoneal, pleural, and pericardial cavities and a consequent reduction in circulating volume. All these changes seem to be influenced (or induced) by several local ovarian vasoactive mediators such as vascular endothelial growth factor (VEGF) and many others.

Severe OHSS lacks reliable predictive criteria. Although as has been described, stimulated patients presenting a large number of small-sized follicles, especially





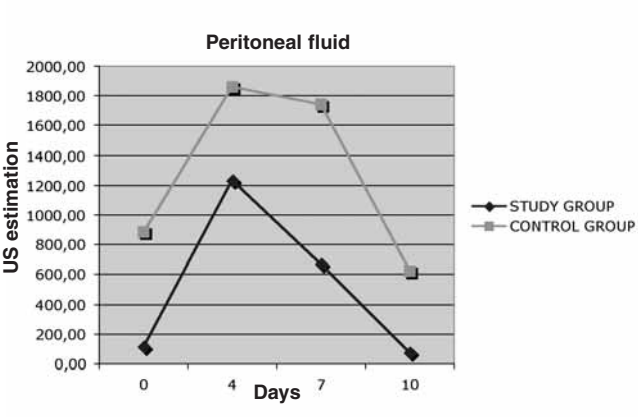


Figure 1. — Comparative graphic showing estradiol levels in OHSS patients after treatment with a bolus of GnRH antagonists (study group) versus support therapy alone (historical controls).

Figure 2. — Comparative graphic showing hematocrit levels in OHSS patients after treatment with a bolus of GnRH antagonists (study group) versus support therapy alone (historical controls).

Figure 3. Comparative graphic showing peritoneal fluid estimation by ultrasound (ml) in OHSS patients.

with a high degree of perifollicular and medullary vascularization [13], are more prone to develop the syndrome, neither of these findings are a guarantee thereof. Elevated E2 values on the day of hCG administration are not a reliable criterion. Although there is an 80% risk of developing severe OHSS when there are elevated estradiol levels on the day of hCG administration, this severe syndrome has also been observed in patients who have conceived spontaneously, as well as in patients with low serum E2 levels on the day of hCG administration. It is well known in practice that high E2 levels do not always lead to ovarian hyperstimulation [12, 14, 15].

In contrast to GnRH agonists, GnRH antagonists elicit an immediate effect by competitive blockage of GnRH receptors. Since late follicular phase growth of follicles and subsequent estradiol production are dependent on stimulation by both LH and FSH, prolonged use of high-doses of GnRH antagonists may effectively arrest further development of follicles through pronounced suppression of pituitary gonadotropin release in cases of imminent OHSS [16, 17]. GnRX (embryonic GnRH) plays a fundamental role in the development of neoangiogenesis in terms of the maternal decidua necessary for correct implantation and subsequent development of a gestation. This is carried out via modulation of VEGF and KDR, FLT-1 and sFLT-1 receptors [6, 7]. It probably produces a similar effect in the ovary in order to maintain vascularization of the corpus luteum. Once again, this process is blocked by GnRH antagonists [4]. It has yet to be determined whether GnRH antagonists act solely at the ovarian level. The optimal dose and length of treatment is not yet established.

In view of the increased risk of OHSS associated with pregnancy, it may be wise to have cryopreservation of all embryos and plan for transfer during a subsequent natural cycle. One may also consider avoidance of hCG administration in the luteal phase and substitution thereof with progesterone, coasting, GnRH agonist for triggering ovulation, and administration of anti-VEGF antibodies as other methods of prevention. However, effective preventive measures remain controversial [14].

To the best of our knowledge there is only one other recently published article focusing on this protocol [18]. In this study the antagonist was reintroduced in small doses of 0.25 mg three days after oocyte pickup showing a decline in OHSS symptoms. Surprisingly none of the patients needed hospitalization. Beside the differences between these protocols the results were positive in both trials showing that the use of GnRH antagonist combined with cryopreservation of embryos is associated to clinical recovery of severe cases of OHSS.

In conclusion, clinical, ultrasonographic, and hormonal results with our small group of patients suggests that treatment with high doses of GnRH antagonists shows promise as an effective regimen for the treatment of severe OHSS [13]. It is worth highlighting that despite

serious symptoms (severe ascites), none of the patients in the treatment group required paracentesis. The principal weakness of this study is the small number of patients included. Although the results suggest that OHSS treatment with high doses of GnRH antagonists seems to be effective, a larger double-blinded study is needed to determine whether this impression is valid.

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