ADMINISTRATION OF CORTICOSTEROIDS TO PREVENT SEVERE OVARIAN HYPERSTIMULATION SYNDROME IN PATIENTS UNDERGOING GnRH AGONIST DOWN REGULATED ICSI CYCLES

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ABSTRACT

Objectives : To test if Corticosteroids (methylpredniosolone) reduces and prevents OHSS in women undergoing IVF-ICSI cycles.

Design : Prospective, randomized study.

Setting : Shatby hospital for women and Elmadina IVF-ICSI center.

Patients : 67 women undergoing IVF-ICSI from May 2006 to April 2007.

Intervention : Corticosteroid (Methylpredinsolone), was given at the day of oocyte recovery till the day of pregnancy test then the dose was tapered.

Main Outcome Measure(s) : Occurrence of OHSS and pregnancy.

Results : A significantly lower proportion of methylprednisolone recipients than untreated participants developed OHSS (20% vs. 43%). Treatment recipients had more oocytes retrieved and moe embryos fertilized than did untreated participants.

Conclusions : Given the corticosteroid (methylprednisolone) is a well established and safe medication. This study provides evidence that the use of methylprednisolone in the prevention of OHSS in women undergoing assisted reproduction, is successful and without affection of the pregnancy rate.

Key words : Ovarian hyperstimulation syndrome, in vitro fertilization.

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovulation induction. Its cardinal features are marked ovarian enlargement and acute third-space fluid sequestration. The fluid shift from the intra- to the extravascular spaces in response to the increase in capillary permeability contributes most to the mobidity associated with OHSS [1].

The syndrome almost always presents either 3-7 days after HCG administration in susceptible patients (early onset) or during early pregnancy, 12-17 days after hCG administration (late onset). Early OHSS can to some extent be predicted by pre-ovulatory indices of ovarian response, in time to institute preventive measures such as cancellation[2]. Late OHSS does not relate strongly to pre-ovulatory ovarian response, making it difficult for clinicians to

identify the cycles in which it is likely to occur[3]. In the original description of OHSS, the late form was observed only in cycles with multiple gestations[4], with a trend toward an increase in the severity of the disease with an ienrease in the number of gestational sacs [5].

Several articles have reviewed the epidemiological, hormonal and ultrasonographic characteristics of patients susceptible to OHSS [6-12] Despite the many years of clinical experience, however, the pathophysiology of OHSS remains poorly understood, and there is no reliable test to predict which patients will develop severe OHSS[13]. When all the accepted predictive variables were combined, the prevalence of severe OHSS in the ostensibly high-risk patients was only ~20% [12,14] , an extremely low value for reliable prediction.

No definitive treatment of OHSS currently exists, which makes prediction of the risk of development and prevention exceptionally important. Patients at risk for OHSS should be identified before treatment becomes necessary. Women with the polycystic ovarian syndrome and high follicle reserve have been shown to be at particular risk for OHSS, even when endocrine test results do not suggest polycystic ovaries [15].

The ovarian hyperstimulation syndrome is associated with the necklace sign on ultrasonography and is generally associated with high preovulatory estrogen levels. Nevertheless, it sometimes occurs in the presence of normal or low E2 levels [7,16,17]. An association has also been reported between the number of follicles, particularly small and medium-sized follicles, and the occurrence of OHSS [16,18]. It is generally accepted that patients with both a large number of ovarian follicles and high preovulatory serum E_2 concentrations are at increased risk for the syndrome. It was once thought that incorporation of a GnRH agonist into ovarian stimulation regimens would reduce the incidence of OHSS. To the contrary, several studies have shown that use of GnRH agonist, in conjunction with higher doses of fertility drugs to maximize assisted reproductive technology success rates, is associated with a higher prevalence of OHSS [19-21]. Diverse mechanisms have been postulated to explain this finding, including the initial flare-up effect, inhibition of premature luteinization, and a direct action of GnRH agonist on the ovarian stroma. In addition, the use of pituitary down-regulation requires HCG to induce ovulation, which increases the risk for OHSS over endogenous LH for ovulation [18,22]. Recent studies, however, have not substantiated predictions of an increase in the incidence of OHSS [23], perhaps because preventive measures were taken[19]. Because HCG is considered the major trigger for development of OHSS, withholding HCG would be one method of avoiding OHSS. To achieve this, the IVF cycle is abandoned and a new cycle is commenced 1 or 2 months later [9]. Alternatively, gonadotropin administration can be discontinued until serum E_2 values return to safe levels (coasting). However, in a cohort study of 252 consecutive IVF cycles, the risk for severe OHSS was shown to be multifactorial and was not always prevented by withholidng HCG [24]. It has been suggested that i.v. administration of human albumin around the time of oocyte retrieval might reduce the development of OHSS in high-risk women [17]. Albumin contributes significantly to plasma colloid osmotic pressure. Other studies have suggested that i.v. administration of albumin at oocyte retrieval does not prevent severe OHSS. especially in cases associated with pregnancy [25,26]. Corticosteroids have been already used in IVF and infertility, for example, to treat recurrent abortions of autoimmune etiology and to treat endometriosis [27].

So the aim of this study is to determine whether administration of a corticosteroid to patients at high risk for OHSS helps reduce the development of the disease.

MATERIALS & METHODS

This study included 40 female patients between May 2006 and April 2007; it was approved by our institution's Ethical Committee, and all participants signed a written consent form.

A long protocol was used for ovulation induction starting with subcutanous daily injections of buserelin acetate (Hoechst UK Limited, Hounslow, Middlesex, UK), 300 micrograms, on Day 21 of the preceding cycle. Recombinant FSH (Puregon, Organon Laboratories Ltd, UK) injections were administered after the third day of the subsequent cycle, at an initial dose of 150 IU; the doses were subsequently adjusted on the basis of responses and monitoring with transvaginal scan, and serum estradiol levels.

The duration of FSH stimulation ranged from 10 to 12 days, and serial estradiol estimations and ultrasound scans were performed on alternate days between Days 5 and 10 of the cycle and as necessary thereafater. Only patients at risk of developing OHSS, defined by the development of 20-30 follicles > 12 mm in diameter, and retrieveal of > 20 oocytes, were included. Once the decision to administer HCG was taken, patients were immediately allocated into two groups based on a computer randomization:

a) **The study group** initially consisted of 35 patients, The regimen consisted of administration of corticosteroids (bolus i.v. dose of methylprednisolone, 1g), starting on the day of egg collection and on the day of embryo transfer. Followed by daily administration of methylprednisolone, 16 mg, till the day of pregnancy test (day 13 after the embryo transfer) then the dose was tapered. Luteal support was provided by daily intravaginal administration of progesterone tables.

b) **The control group** was also initially composed of 32 women receiving a placebo tablet from the day of egg collection till the day of pregnancy test in addition to the luteal support previously mentioned in the study group.

All high-risk patients were seen 5 days after ET to determine whether they had developed clinical hyperstimulation. Ultrasonography was also performed. The patients were then examined every 2 days.

Ultrasonography and Laboratory Assays:

All ultrasonographic measurements were performed by A 6.5 MHz vaginal probe (Voluson 730 Pro V, General Electric, Madrid, Spain) .

Estradiol was measured by using the commercially available Coat-a-Count recombinant immunoassay kit (Diagnostic Products Corp., Los Angeles, CA).

To evaluate the risk of hemoconcentration, we measured hemoglobin, hematocrit, and leukocyte count. Moreover, renal (creatinine) and liver [transaminases: aspartate 6 aminotransferase (AST); alanine aminotransferase (ALT) functions, and electrolytes (Na, K) were analyzed to ascertain the severity of the syndrome. We centered our attention on analyzing the incidence of moderate and severe OHSS, which were identified according to our modified [28] classification of Golan et al [29]. Moderate OHSS was confirmed when a patient presented ultrasonographic evidence of ascites, while diagnosis of severe OHSS required clinical evidence of ascites and/or hydrothorax and breathing difficulties, or one of the following criteria:

a) increased blod viscosity: hemoglobin ≥ 15 g/dl, hematocrit ≥ 45%; or leukocyte count ≥ 20,000/mm^3;

b) coagulation abnormality;

c) diminished renal perfusion and function (serum creatinine levels > 1.2 mg/dl);

d) liver dysfunction: defined when transaminases (AST or ALT) were > 40 U/ml [28,29].

Statistical Analysis:

Statistical analysis was performed using the χ^2, or t-test as appropriate. All P-values quoted with values < 0.05 indicated statistical significance. Analyses were performed using the SPSS statistical package (SPSS, Inc, Chicago).

RESULTS

The age and duration of infertility in both high-risk groups (Table II) did not differ significantly, but the treated group had on average more previous IVF trials than did the untreated group ($P<05$). The treated group had a significantly higher E2 concentration, more oocytes retrieved, and more embryos fertilized than did the untreated group ($P<05$).

A significantly lower proportion of treated patients than untreated patients developed moderate degree of ovarian hyperstimulation syndrome (OHSS) and ascites respectively (20% vs. 43%; $P=$ 0.094), & (25% vs 59%) as shown in table I.

The relative risk for OHSS by not using methylprednisolone but having high risk was 2.3 (95% CI, 1.6-3.4). Taking into account all participants, the percentage of high-risk women who developed OHSS decreased from 3.5% to 1.0% with use of methylprednisolone. In this case, the relative risk for OHSS by not using methylprednisolone is 3.5 (95% CI, 1.1-5.0). No woman who was not at high risk for OHSS developed the disease before or after use of methylprednisolone.

The proportion of treated high-risk women who had an ongoing pregnancy was slightly but not significantly higher than the corresponding proportion of untreated women (60.0% vs. 51.2%). In the untreated group, the incidence of OHSS was equally divided between women with and without established clinical pregnancy. In contrast, four of the five women treated with methylprednisolone who developed OHSS had an ongoing pregnancy. The difference in the incidence of OHSS between the two groups statistically favored the treatment group both in the presence and in the absence of an ongoing pregnancy.

Table I : Signs and symptoms of moderate and sever ovarian hyperstimulation in both groups.

	Study (n = 35)	Control (n = 32)	P value
* Hemoconcentration	2	5	NS
** Renal dysfunction	0	0	-
*** Liver dysfunction	2	2	NS
Thromboembolism	0	0	-
Ascites > 9 cm^2 (%)	9 (25)	19 (59)	0.005
Moderate OHSS (%)	7 (20)	14 (43)	0.04
Sever OHSS (%)	4 (11)	6 (18)	NS

* Hematocrite > 45%

** Creatinine > 1.2 mg/dl

*** ALT or AST > 40 u/ml

Table II : Study characteristics (± S.D).

	Test (n = 35)	Control(n = 32)	P value
Age	30.5 ± 3.9	30.9 ± 4.7	NS
Duration of infertility	4.6 ± 2.8	4.4 ± 2.5	NS
Day of HCG	11.6 ± 1.5	11.6 ± 1.4	NS
E2 conc (pg / ml)	4.848 ± 1.482	3.727 ± 1.329	< .01
No of oocytes retrieved	28.7 ± 8.6	24.0 ± 9.9	< .01
No of eggs fertilized	15.4 ± 64	12.1 ± 5.2	< .01
No of emb. Transf.	3.9 ± 1.2	4.0 ± 1.0	NS

DISCUSSION

The reduction in the proportion of treated women who developed OHSS ompared with untreated women was significant. Furthermore, the effectiveness of treatment with methylprednisolone was independent of the number of IVF trials and the cause of infertility, even though both of these factors affect the development of OHSS. We believe that the reduction in OHSS that we observed is largely due to administration of methylprednisolone. This corticosteroid protocol is used in diverse situations in which immunosuppressive therapy is required. The incidence of OHSS in the untreated group is similar to that which Tan et al [30] observed in their untreated patients, even though the selection criteria were applied at different periods.

Recent studies have suggested that the increased propensity of ovaries to become overstimulated is due to increased expression of the vascular endothelial growth factor in the stroma of the ovary, which itself has increased blood flow as demonstrated by color Doppler ultrasonography [31,32]. The proposed mechanism is as follows [33]. As a result of multifollicular development effected by gonadotropin stimulation and their massive luteinization induced by hCG, excessive production of vascular endothelial growth factor occurs, which leads to the desirable effect of extensive perifollicular neovascularization. This, however, is accompaied by the escape of follicular vascular endothelial growth factor into peritoneal cavity and blood stream, causing disruption of functional integrity of blood vessels and massive fluid shift into the third compartment (i.e., clinical hyperstimulation syndrome). This syndrome may lead to intravascular hypovolemia; development of edema, ascites, hydrothorax, or hydropericardium; and impairment of cardiac, renal, pulmonary, and liver functions. Reports indicate that the ability of corticosteroids to reduce edema stems in part from their ability to abolish expression of vascular endothelial growth factor [34]. The site of action of glucocorticoids is the microcirculation and inflammation [35]. These agents inhibit vasodilatation, thereby preventing the increase in blood flow. They also prevent increases in vascular permeability.

CONCLUSION

In Conclusion, by using methylprednisolone, we avoided use of coasting. We did not withhold hCG and transferred embryos in all cycles, thereby improving pregnancy rates per cycle. The etiology of OHSS and the mechansim by which methylprednisolone may have a preventive effect on its development is not yet fully clarified. However, our results indicate that early identification of high-risk patients and immediate commencement of treatment with methylprednisolone helps decrease the incidence of OHSS and therfore avoid hospitalization, reduce cycle cancellations, and improve the cost-effectiveness of IVF cycles.

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