Original Article

Cabergoline versus Coasting in the Prevention of Ovarian Hyperstimulation Syndrome and Assisted Reproductive Technologies Outcome in High Risk Patients

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Abstract

Background: Coasting is the most common method used in the prevention of ovarian hyperstimulation syndrome (OHSS) acting through vascular endothelial growth factor (VEGF) reduction. However, the pregnancy rate is reported to fall with coasting when it takes more than three days. Recently low-dose cabergoline, a selective D2 dopamine receptor agonist has been proven to selectively reduce vascular permeability without affecting angiogenesis and seems to be able to decrease the rate of OHSS without affecting pregnancy rate.

Materials and Methods: This clinical trial was performed on 60 women in assisted reproductive technologies (ART) cycles at risk of OHSS, having at least 20 follicles in their ovaries (mostly ≤14mm) and a serum estradiol level ≥3000pg/mL. Patients were divided into two equal groups. In group A, oral cabergoline 0.5 mg/day was given for seven days after hCG administration; while in group B gonadotropin administration was halted until serum estradiol levels reached less than 3000pg/mL before hCG administration. The main outcome measurements compared were rates of pregnancy and severity of OHSS.

Results: Total number of oocytes, metaphase II oocytes, fertilization and clinical pregnancy rates were higher in group A ($p<0.05$). Severe OHSS was not found in either group. Moderate OHSS was seen in one subject in the cabergoline group versus seven in the coasting group.

Conclusion: Cabergoline seems to be a safe drug for prevention of moderate-severe OHSS.

Keywords: Cabergoline, Coasting, Ovarian Hyperstimulation Syndrome, Prevention

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic condition caused by gonadotropin administration and a potential threat to life. The incidence of severe OHSS varies from 0.5%-2% (1, 2). The pathophysiology of OHSS is not clear (3) and at present only supportive therapy is available. Therefore prevention is of utmost importance in this potentially life-threatening disease (4). Coasting is the most common preventive measure taken in high-risk women with assisted reproductive technologies (ART) cycles (5). During the past decade, there have been numerous reports on the effect of this protocol on the prevention of OHSS while keeping to the specified pregnancy rate (6-9). Although many studies have been performed to determine the criteria for coasting, there is still some doubt about the best time for starting coasting or the optimum serum estradiol (E2) level for hCG administration, both of which require sonography and immediate and accurate serum estradiol level measurements. On the other hand, the pregnancy rate has been seen to fall significantly in case of prolonged coasting that is more than 3 days (10). Therefore, the need to seek for a pharmacologic agent which can be used with ease and confidence in high risk conditions, is greatly felt. Recent studies show that vascular endothelial growth factor (VEGF) plays a basic role in developing OHSS through its effect on the microvascular circulation by increasing vascular permeability which causes third space fluid shift (11). Also, it has been seen that dopamine agonists have an anti-VEGF effect which decreases VEGF receptor phosphorylation through D2 receptors (12). Even so, studies performed by Gomez et al. showed that cabergoline, which is a long-acting dopamine agonist acting via D2 receptors, is dose-dependent and at low doses it only effects vascular permeability through its VEGF effect without affecting the luteal aspect of angiogenesis (13). The use of cabergoline in the prevention (14) and treat-

Received: 5 May 2009, Accepted: 6 Jun 2009
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Royan Institue
International Journal of Fertility and Sterility
Vol 3, No 1, May-Jun 2009, Pages: 35-40

ment (15) of OHSS has recently been studied but no study has yet been performed to compare the effect of cabergoline and coasting on OHSS and especially pregnancy rates. Therefore, this prospective study was performed to compare low-dose cabergoline after hCG administration with delayed hCG administration (coasting) in high-risk patients to prevent OHSS in ART cycles.

Materials and Methods

In this clinical trial all patients who underwent ART in Vali-e-Asr Reproductive Health Research Center and a private center from April 2006 through March 2007 were studied. This study was approved by the Medical Ethics Committee of Tehran University of Medical Sciences. Among the 650 patients who were in the ART cycles in these two centers, 60 had the required inclusion criteria. Patients were divided into two equal groups. In group A, oral cabergoline 0.5 mg/day was given for seven days after hCG administration; while in group B, gonadotropin administration was ceased until serum estradiol levels reached below 3000 pg/mL before hCG administration. The patients were informed about the success probability of both methods in preventing OHSS and written consent was obtained before continuing treatment.

Inclusion criteria included presence of at least 20 follicles in both ovaries, the majority being ≤ 14 mm in diameter and serum E2 level 3000 pg/mL. Exclusion criteria included patients in whom the use of dopamine agonists were contraindicated.

All patients were visited and followed-up by a single gynecologist.

In order to suppress the pituitary gland a gonadotropin releasing hormone GnRH agonist (Buserelin, Suprefact®, Hoechst, Germany) was administered at a subcutaneous dose of 0.5mL/day on day 21 of the menstrual cycle. .Vaginal ultrasonography was done on day 2 or 3 of the next menstrual cycle to confirm absence of any functional ovarian cyst larger than 10 mm.

Gonadotropin stimulation consisted of 1-2 ampoules per day of FSH (r-hFSH, Gonal-F®, 75 UI, Serono, Switzerland) for the first 5-7 days. Dose adjustment (increase of 37.5 - 75 UI of r FSH) depended on the individual response to treatment.

In group A, when the number of follicles exceeded 20 with at least two being 18 mm in size, 10000 U of hCG (Pregnyl®, Iran, under Technical cooperation with Organon) was administered intramuscularly and oral cabergoline 0.5 mg/day was started immediately and continued for seven days. Egg retrieval was performed 36 - 38 hours after hCG administration.

In group B, when the number of follicles were 20 or more and the mean leading follicle diameter was16-mm, gonadotropin administration was ceased and Suprefact was continued according to protocol. Serum estradiol level was checked every 48 hours until it became <3000 pg/mL, after which 10000 units of hCG was administered intramuscularly and oocyte pick-up was performed after 36-38 hours.

After oocyte retrieval and intra cytoplasmic sperm injection (ICSI) procedure, embryo transfer was done trans-cervically 48-72 hours after egg retrieval for both groups. About 2-3 embryos were transferred depending on the patient's age and the quality of the embryos. In the case, clinical signs such as abdominal pain, nausea, vomiting or distinctly enlarged ovaries (>12 cm) were seen during the days of hCG administration or egg retrieval, or if the serum estradiol level was higher than specified (>6000 pg/mL), either the cycle was cancelled or the embryos were frozen, according to the physician's opinion and patient's will. After embryo transfer, all patients were given luteal phase support using progesterone vaginal pessaries 400 mg twice a day (Cyclogest®, Alpharma, Actover, UK). βhCG level was checked two weeks after embryo transfer and clinical pregnancy was confirmed two weeks later by sonographic detection of the gestational sac. Three and seven days after embryo transfer, all patients were evaluated for clinical and sonographic signs of OHSS. The criteria set by Golan et al. was used to categorize the patients into three groups of mild, moderate and severe forms of OHSS (16). The mild form was characterized by signs of abdominal pain, nausea and vomiting; moderate by sonographic detection of abdominal ascites; and severe OHSS by severe ascites, hydrothorax, dyspnea, or complications of OHSS such as renal failure, thrombocytopenia and ARDS.

Serum estradiol was measured by the ELISA method at a single laboratory using a commercial kit (IBL, Hamburg, Germany, cat no. 42 k 027-3); the dynamic range of which was (0-2000 pg/ml). Estradiol concentrations above this range were measured in dilution. The within and between- assay coefficients of variation were 4 and 5.0% respectively.

Fisher exact test, chi-square and student's T-test were used when suitable (SPSS version 15) and p 0.05 was considered as statistically significant.

Results

From April 2006 through March 2007, in 650 cycles, 60 women at risk of OHSS entered the study with moderate OHSS and total pregnancy rates of 13.8% and 36% respectively. The patients in both groups were not significantly different in regards to major demographic variables or characteristics such as age, type of infertility, menstrual cycle pattern, body mass index (BMI) and duration of infertility (Table 1).

Table 1: Clinical and hormonal characteristics of patients in the two groups

	Group A (CAB) (n=30)	Group B (Coasting) (n=30)	P value
Age (years) Mean (±SD)	29.9 ± 3.6	29.2 ± 3.5	NS
BMI	26.4 ± 3.8	27.8 ± 3.2	NS
Type of infertility [N.(%)]			
Primary	20(67)	21(70)	NS
Secondary	10 (33)	9(30)	
Cause of infertility [N.(%)]			
PCOS	9(30)	10(33.3)	NS
Tubal disease	2(6.6)	1(3.3)	
Tubal + PCOS	3(10)	2(6.6)	
Male factor	11(36.6)	10(33.3)	
Both (Male +PCOS)	4(13.3)	5(16.6)	
Unexplained	1(3.3)	2(6.6)	
PRL (ng/ml)	11.2 ± 1.9	12.34 ± 3.5	NS
FSH (IU/L)	7.2 ± 11.01	5.3 ± 1.5	NS
LH (IU/L)	14 ± 27.7	9.9 ± 5.2	NS

BMI= body mass index ; CAB=cabergoline; PCOS=polycystic ovarian syndrome; PRL=prolactin; FSH=follicular stimulating hormone; LH=luteinizing hormone.

Embryo transfer was not performed for one patient in the cabergoline group for whom all 20 retrieved embryos were frozen and also cancelled for one in the coasting group due to a no-egg state on the ovum pick-up day. Mean total of rFSH dose (75 IU/ampoule) and duration of gonadotropin administration were similar in groups A and B (17.5 ± 2.5 and 15.8 ± 3.4 ampoules; 9.6 ± 2.2 and 9 ± 1.4 days, respectively).

Also the mean serum estradiol levels (3503 ± 413 pg/ml versus 3766 ± 588 pg/ml) and total numbers of follicles (28.5 vs. 27.10) in both ovaries were not significantly different at the onset of intervention. Mean serum estradiol level was lower on the day of hCG administration after coasting as compared to the cabergoline group (2885 ± 502 versus 3477 ± 402; $p<0.001$; Table 2).

Table 2: Outcome of ovarian stimulation between cabergoline and coasting group

	Group A (CAB) (n=30)	Group B (Coasting) (n=30)	P value
No. of recombinant hFSH (75 IU/ampoule)	17.5 ± 2.5	15.8 ± 3.4	NS
Duration of rFSH administration (days)	9.6 ± 2.2	9 ± 1.4	NS
No. of follicles in both ovaries on day 0	27.10 ± 6.5	28.5 ± 8	NS
E2 on day 0 (pg/ml)	3503 ± 413	3766 ± 588	NS
E2 on day of hCG(pg/ml)	3477 ± 402	2885 ± 502	<0.001*
Duration of coasting (days)	-----	1.9 ± 0.8(1-4)	-----
No. of oocytes retrieved	18.3 ± 5.1	14 ± 8.6	<0.001*
No. of MII oocytes	13 ± 4.8	8.8 ± 6.0	<0.000*
No. of oocytes fertilized	10.4 ± 5.4	5.4 ± 4.2	<0.000*
Fertilization rate (%)	53 ± 21	42 ± 16	<0. 02*
No. of ETs	1.9 ± 0.5	1.8 ± 0.6	NS
No. of frozen embryos	7.5 ± 4.8	2.3 ± 3.5	<0.000*
Clinical pregnancy rate per transfer [N.(%)]	14(48.2)	7 (24.1)	<0.04**
Mild OHSS [N. (%)]	11(37)	12(40)	NS
Moderate OHSS [N. (%)]	1(3)	7(23)	<0.004**

OHSS=ovarian hyperstimulation syndrome; ET=embryo transfer; MII oocytes= metaphase II oocytes; hCG= human chorionic gonadotropin; E2=serum estradiol; CAB=cabergoline
Unpaired t test; ** χ^2 - test
Values are Mean ± SD

Total number of oocytes and metaphase II oocytes in group A were more than group B (18.3 ± 5.1 and versus 14.0 ± 8.6; p <0.001, 13.0 ± 4.8 versus 8.8 ± 6.0; p<0.000).
Fertilization rate was higher in group A than group B (53% vs. 42%, p <0.02). The number of frozen embryos in group A were more than group B (7.5 ± 4.8 vs. 2.3± 3.5, p <0.000). High quality embryos were more frequent in the cabergoline group but this difference was not statistically significant. Clinical pregnancy rate was higher in group A than group B (48.2% vs. 24.1%; p <0.04; Table 2). Severe OHSS was not seen in either of these two groups. Moderate OHSS was observed in one subject in group A and seven in group B, three of whom were pregnant (Table 2). Gonadotropin administration was discontinued for more than three days in two subjects in the coasting group. Total number of oocytes was 3 and 4 in these patients and neither became pregnant.

Discussion

Various methods have been recommended to help decrease the incidence of ovarian hyperstimulation in high-risk patients with coasting being the most popular one (6- 8, 17), although opinions vary about its effect on ART outcome. Studies show that VEGF plays a fundamental role in the pathogenesis of OHSS by acting on the microvascular system, increasing vascular permeability and third space fluid shift. In addition, dopamine agonists produce anti-VEGF action which can help decrease VEGF receptor phosphorylation through D2 receptors (12). Thus, it may be possible to prevent OHSS by using dopamine, especially D2 dopamine agonists.

This prospective study was performed to assess and compare coasting with low-dose cabergoline administration in prevention of OHSS in high-risk patients.
In a big cohort study performed by Mansour et al. (10) to determine the exact criteria for coasting, this protocol was regarded to be effective in reducing the incidence of OHSS to 16 out of 1223 (1.3%) in high risk patients. None of our patients experienced severe OHSS which may be due to low-dose gonadotropin ovarian stimulation, and by selecting a 3000 pg/mL cut-off serum estradiol level for intervention. However, seven patients in group B experienced moderate OHSS while only one patient in group A experienced such complication.
The time of ceasing gonadotropin therapy and starting coasting is of much importance. A study performed by Delvign and Rozenberg showed that the duration of coasting has no effect on the outcome of *in vitro* fertilization (IVF) (5). Also it was seen that the rate of serum E2 fall during coasting is not important (18). However a study performed by Mansour et al. (10) showed that ICSI outcome is related to the number of days of coasting. When coasting is continued for more than three days the number of retrieved oocytes, implantation and clinical pregnancy rate will clearly fall and the frequency of adverse effects rises in direct proportion to the duration of coasting. Although the mean duration of coasting was short in our study 1.9 ± 0.8 (1-4), but serum estradiol levels showed significant change on the day of hCG administration and only two patients required more than three days of coasting with no pregnancy.
The study performed by Egbase et al. which compared coasting and early unilateral follicular aspiration (EUFA) showed that the total number of retrieved oocytes was lower in the coasting group, which was attributed to atresia of smaller follicles (19). In the present study the total number and metaphase II oocytes were clearly more in patients in group A than group B. In addition, the fertilization rate was markedly lower in group B and total number of high quality embryos was more in group A. Although this difference was not statistically significant, but clinically it is of importance because this finding is contrary to previous studies which show that coasting does not affect fertilization and embryo quality (8,19).
Some studies show that coasting and the associated decrease in estradiol level does not affect clinical pregnancy rate (8,19). Clinical pregnancy rate in our study was clearly higher in group A (48.2%) than group B (24.1 %).

The mechanism of coasting has recently been described by Garcia Velasco et al. who showed that coasting causes apoptosis in moderate or small sized follicles (20). They also showed that coasting decreases VEGF protein secretion and gene expression in granulosa cells, especially in smaller follicles. However, Ajonuma et al. believed that this effect is secondary to the fall in serum estradiol levels and that VEGF may indirectly affect OHSS (21). In another study, the role of dopamine on angiogenesis was found to be brought about by factors such as the vascular permeability factor/ vascular endothelial growth factor (VPF/VEGF) and they showed that dopamine acts at a non-toxic level and specifically withholds angiogenecity and permeability through VPF/VEGF (12). Dopamine acts through D2 receptors and it causes VEGF-2 receptor endocytosis. This action of dopamine is specific for VPF/VEGF and does not affect other

factors causing microscopic permeability or endothelial cell proliferation. These researchers concluded that dopamine and other D2 receptors may have clinical anti-angiogenic properties in some cases. However, Gomez et al. showed that low-dose cabergoline does not affect the angiogenic property of VEGF and the incidence of OHSS is decreased only by controlling vascular permeability (13). Therefore by comparing the mechanisms of these two methods, it seems that in contrast to low-dose cabergoline administration which controls VEGF secretion selectively, coasting controls this mediator non-selectively. This hypothesis is confirmable regarding to the fall in pregnancy rate, especially when coasting is continued for more than three days.

Recent reports have shown the benefits of using dopamine and its agonists in the treatment of OHSS. In a study performed by Manno et al. cabergoline was given to 20 high-risk patients with ovarian hyperstimulation on an out-patient basis in the afternoon of pick-up as well as to 10 patients with severe OHSS, 24-48 hours after dopamine infusion (1mg/48h) no cases of hyperstimulation occurred in high-risk patients under prophylactic treatment but a rapid increase in diuresis, decrease in weight, abdominal pain, creatinine and hematocrit levels were seen. A similar study was performed at our center in 2006 on 15 patients hospitalized with severe OHSS who were resistant to therapy (15). After receiving cabergoline, clinical signs and ascites significantly improved in 12 /15 (86.4%) patients. It is worthwhile to mention that cabergoline initiates a massive diuresis which is its major beneficial effect in the pathophysiology of OHSS.

It is noteworthy that studies performed on women who have become pregnant after using cabergoline (22- 24) or bromocriptine (24, 25) have not shown a rise in abortion or congenital malformation rates. The safety of cabergoline in patients with hyperprolactinemia was studied by Robert et al. (26). In this study, 205 pregnancies were followed in 220 women. The dose used in humans leaves a large safety margin. The results of this study did not show any increase in the rate of congenital malformations as compared to the overall population.

OHSS is the most dangerous complication of ART. Since it has a large spectrum of clinical signs, preventive measures must be chosen individually for each patient.

Conclusion

Overall, regarding the selective property of low-dose cabergoline on VEGF control, it seems to be an effective, convenient and safe drug which can be used together with other methods used in the prevention of OHSS. However more widespread studies are required in this field.

Acknowledgements

There is no conflict of interest to declare.

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