

The Effectiveness of Cabergoline for the Prevention of Ovarian Hyperstimulation Syndrome

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Abstract

Type 2 receptors for vascular endothelial growth factor are believed to be involved in the pathophysiology of ovarian hyperstimulation syndrome (OHSS). The objective of this study was to examine the preventive effects of cabergoline on OHSS and its complications. The study is a non randomized clinical trial conducted in 2006-2008 on 75 patients, which were at risk of OHSS and underwent assisted reproductive techniques. The diagnosis and severity of OHSS were determined using standard criteria. The study included an intervention and a control group. The intervention group comprised of 50 women at risk of OHSS, who were treated with cabergoline (1 mg every other day for 8 days) commencing from the day of ovum pick up. The control group comprised of 25 historical cases, which were similar to the case group. The latter group did not receive cabergoline, and their OHSS, if occurred, were managed conservatively after hospital admission. The rates of OHSS, baseline characteristics, ovarian stimulation parameters, and pregnancy occurrence were compared. There was no significant difference between baseline characteristics or ovarian stimulation parameters from the two groups. The incidence of OHSS in the cabergoline-treated group, was significantly ($P=0.01$) lower than that in the control group (12% vs 36%). Embryo freezing was significantly ($P=0.001$) lower in the control group, but cycle cancellation was significantly (0.03) lower in the cabergoline group. The findings of the study indicate that cabergoline reduces the incidence of OHSS, and is not associated with adverse effects on pregnancy.

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Keywords • Vascular endothelial growth factor • cabergoline
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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening situation, and thus regarded to be the most serious complication of assisted reproduction treatment (ART). It is characterized by the presence within the ovaries of multiple luteinized cysts, which leads to ovarian enlargement and secondary complications such as increased capillary permeability and fluid shift to the third space.¹

Recent findings have identified vascular endothelial growth factor (VEGF) as the major molecule responsible for increased capillary permeability.¹ The production of VEGF in ovarian follicles increases during stimulation period, and results in a rapid increase in vascular permeability upon binding to type 2 VEGF receptors.¹ Although, cytokines and growth factors (interleukins

IL-2, IL-6, IL-8, IL-10, and IL-18), histamine, prolactin, prostaglandins and renin-angiotensin have been proposed as participants in OHSS pathophysiology, the exact responsible factor is under debate.²

Standard treatments for OHSS are generally conservative, and potentially life-threatening complications of OHSS, which require costly long-term hospitalizations, render prophylactic measures a must.^{3,4}

Some approaches, which are based on the pathophysiology of OHSS, are now applied for its prevention. Studies show a reduced incidence of OHSS when recombinant luteinizing hormone (rLH) or a gonadotropin releasing hormone (GnRH) analogue is used to trigger the final steps of oocyte maturation. Prophylactic administration of cabergoline, a dopamine agonist, is associated with a significant reduction in the incidence of symptoms and signs of moderate to severe OHSS. This drug inhibits vascular endothelial growth factor 2 (VEGFR-2) phosphorylation and signaling. Its use is not associated with an inferior ART outcome or obstetric/neonatal complications.^{2,4-6}

In some cases, ovarian hypersensitivity to gonadotropins is the consequence of mutations in the follicular stimulating hormone (FSH) receptors.⁷ Genetic variations may cause different responses in various populations; therefore, different responses to cabergoline may be detected. The present study was conducted to determine the preventive effects of cabergoline on OHSS, especially its severe forms, in patients referring to an Iranian University Hospital.

Material and Methods

The study is a non-randomized clinical trial recruiting 75 patients, who had undergone assisted reproductive procedure and were at risk of OHSS. The study was conducted in the Infertility Department of Shariati Hospital, a teaching hospital affiliated to Tehran University of Medical Sciences during 2006-2008. The project was approved by the Ethics Committee of the Infertility Department, and was initiated after obtaining written consents of the participants.

High risk patients were defined as young females, who had antral follicle counts of more than 15, poly cystic ovaries on ultrasound scan and/or polycystic ovarian syndrome (PCOS), serum estradiol of more than 3500 pg/ml and/or multiple follicular recruitments in both ovaries during ultrasound monitoring in controlled ovarian hyperstimulation (COH). The inclusion criteria were an age of less than 33 years, high risk of developing OHSS in the

absence of taking antipsychotic medications, no known allergy to cabergoline or ergot alkaloids, and absence of hepatic dysfunction or hypertension. Polycystic ovarian syndrome was diagnosed according to Rotterdam criteria.⁸ According to the Rotterdam criteria, patients with two of the three characteristics including: 1) oligomenorrhea/amenorrhea, 2) clinical (hirsutism) finding of hyperandrogenism, or 3) polycystic ovaries on transvaginal sonography, were included in the study. Metabolic features of PCOS patients were not of concern in this study; therefore, insulin resistance and androgen index were not measured. The oligomenorrhea/amenorrhea and polycystic appearance of ovaries were seen in more than two third of the PCOS patients. All PCOS patients were treated with metformin (1500 mg/day). Few of the patients had positive history of OHSS, regardless of its severity.

All of the participants underwent controlled ovarian hyperstimulation (COH) with Gonadotropin/GnRH-agonist long protocol. All of them received folic acid (one mg/day) before initiating the induction cycle, low dose oral contraceptive pills (on the third of the previous cycle) and doxycycline (100 mg twice a day) for the first 10 days of the previous cycle. Long term desensitization protocol using subcutaneous GnRH agonist Buserelin (500 µg) was started on the day 21 of the previous cycle. After complete desensitization, ovarian stimulation using recombinant-FSH (Gonal F, Serono, Switzerland) was commenced on day 3 of the next cycle at a daily dose 150 IU. Transvaginal ultrasound (Siemens, Sonoline G20) was done every 3-5 days for the examination of follicular development, and serum estradiol levels were measured every 2-3 days using radioimmunoassay method. When at least two follicles with diameter of at least 17 mm were observed, final oocyte maturation was triggered with 10,000 IU human chorionic gonadotropin (HCG, Ferring, Germany) administered as a single intramuscular injection. Oocytes were collected 36-38 hours later under general anesthesia using transvaginal guided follicle aspiration. After fertilization through intracytoplasmic sperm injection (the routine ART practiced at our center), three good quality embryos were transferred transcervically three days later. Luteal phase support was started the day after ovum pick up by the administration of progesterone suppository Cyclogest (Actavis, UK) at 800 mg/day.

The participants were divided in two groups. The first group (intervention or case group) comprised 50 women treated with 1 mg

of Cabergoline (Dostinex®, Pharmacia Italia S.P.A, Italy) every other day for eight days commencing on the day of ovum pick up. If OHSS occurred, the standard conservative and supportive management for OHSS was employed. The second group (historical control group) was comprised of 25 women, who were similar to the former group with respect to age as well as the number and quality of the retrieved oocytes, number and quality of the transferred embryos, embryonic stage at transfer, and the sperm quality. The latter group did not receive Cabergoline; however, their OHSS (if occurred) were managed conservatively according to our standard protocols after hospital admission. All OHSS patients were admitted to the hospital, and the diagnosis of OHSS as well as its severity was performed according to a standard definition.⁹ The standard classification categorizes the disease based on its severity to mild, moderate, and severe OHSS. In mild OHSS, patients often report mild abdominal distention and soreness, nausea, vomiting, and ovarian enlargement between 5 to 12 cm. Moderate diseases were characterized by the presence of abdominal ascites on ultrasound examination. Severe diseases were diagnosed when there are clinical signs of tense ascites, hydrothorax, shortness of breath, hemoconcentration, hypercoagulability, or any complications of OHSS such as renal failure, thromboembolism, or acute respiratory distress syndrome (ARDS).⁹

The investigators filled out a standard questionnaire for each participant. Data were collected from the questionnaires, clinical, laboratory notes and ultrasound reports. Age, body mass index (BMI), number of retrieved oocytes, number of metaphase II oocytes, number and days of gonadotropin injections, estradiol level on the day of HCG administration

were recorded. Chemical pregnancy was detected by the measurement of serum beta-HCG 14 days after the embryo transfer. The existence of clinical pregnancy was confirmed using transvaginal ultrasound scan, which was scheduled two weeks later to detect the gestational sac of pregnancy. Patients were followed until the detection of fetal heart rate. Abortion, early OHSS (mild, moderate, severe), cycle cancellation, frozen embryos and multifetal pregnancy were also recorded. Early OHSS was defined as the onset of the syndrome during the first 9 days after HCG administration. Cycle cancellation was defined as receiving HCG and transvaginal guided follicle aspiration followed by fertilization through intracytoplasmic sperm injection, and freezing the resultant embryos for future transfers. All of the patients were checked for any complaints or side effects of cabergoline, however, none of them reported any side effects.

Quantitative data are presented as mean±SD. Quantitative and qualitative data were analyzed using Student's t test, and Chi-square or Fisher's exact test, respectively. The data were analyzed using Statistical Package for Social Sciences (SPSS version 14, (SPSS Inc., Chicago, IL). A P value of less than 0.05 was considered statistically significant.

Results

The mean age of the patients in the cabergoline-treated and control groups were 28.24±4.93 and 28.80±4.63 years, respectively. There was no significant (P=0.637) difference between the ages of the two groups. Also, there was no significant difference between the two groups in terms of body mass index (BMI), infertility duration, type and cause of infertility, serum levels of FSH and LH,

Table 1: Baseline characteristics of patients in cabergoline-treated and control groups

Baseline characteristics	Cabergoline n=50	Control n=25	P value
Age (year)	28.24±4.93	28.80±4.63	0.637
BMI (kg/m ²)	24.86±6.83	24.08±3.65	0.596
Type of infertility			
Primary	38 (76%)	19 (76%)	1
Secondary	12 (24%)	6 (24%)	1
Cause of infertility			
Male factors	27 (54%)	8 (32%)	0.062
Female factors	8 (16%)	11 (44%)	0.055
Male and female factors	10 (20%)	5 (20%)	0.058
Unexplained factors	5 (10%)	1(4%)	
PCOS	25 (50.0%)	15 (60.0%)	0.413
History of OHSS	2 (4.0%)	1 (4.0%)	1
FSH (IU/L)	5.88±1.5	5.54±1.6	0.90
LH (IU/L)	7.28±2.1	5.21±1.9	0.78

Values are presented as mean±SD or frequency (percent). BMI; body mass index, PCOS; polycystic ovarian syndrome, OHSS; ovarian hyperstimulation syndrome, FSH; follicle stimulation hormone, LH; leutinizing hormone

POCS or history of previous OHSS (table 1). Moreover, there was no significant difference between the method of ART (embryo transfer or rapid zygote intrafallopian transfer), serum estradiol levels on the day of HCG administration, fertilization rate, and the number of retrieved oocytes, mature oocytes, days of gonadotropin injections, pregnancy, or abortion of the two groups (table 2). The incidence of OHSS in cabergoline-treated group was significantly ($P=0.001$) lower than that in the control group (12% vs. 36%). Embryo freezing (surplus embryos) was significantly ($P=0.001$) lower in the latter group. Cycle cancellation in the cabergoline-treated group was significantly ($P=0.03$) lower than that in the control group (table 2). The incidences of mild, moderate and severe OHSS in cabergoline-treated groups were 4%, 6% and 2%, and in the control group were 24%, 10%, 4%, respectively. Although the incidence of mild OHSS was considerably lower in the cabergoline group, there was no significant difference between the incidence of moderate or severe OHSS in cabergoline and control groups (table 2).

Discussion

Cabergoline, a dopamine agonist inhibiting VEGFR-2 phosphorylation and signalling, effectively reduced the incidence of OHSS and cycle cancellation without any adverse effects on pregnancy. The findings of the present study are in agreement with those of previous studies.^{3,5,6,10} Ovarian hyperstimulation syndrome, as a potentially life-threatening situation and the most serious complication of assisted reproduction treatment, is regarded as

an iatrogenic complication which must be avoided, and in case of occurrence its severity must be reduced. Considering the physical and psychological consequences along with medical costs like hospitalization, every intervention to decrease VEGF expression or antagonizing its effects would be valuable.

The ovary is the main source of cytokines and VEGF, which are mediators that cause increased capillary permeability and ascites. It has been suggested that parameters of ovarian activity during stimulation such as serum levels of estradiol and number of oocytes retrieved correlate closely with VEGF gene expression.¹ Cabergoline decreases the phosphorylation of VEGFR2.¹⁰ Animal studies have demonstrated that the expression of gene for tyrosine hydroxylase enzyme, which is the rate-limiting enzyme in dopamine synthesis, is significantly lower in rats with overstimulated ovaries.¹¹ High VEGF expression and activity in OHSS seem to be associated with reduced dopamine production. Cabergoline significantly reduced VEGFR2-dependent vascular permeability in rats with OHSS. Moreover, serum levels of progesterone and rates of luteal apoptosis remained unchanged, suggesting the absence of a luteolytic effect of cabergoline.¹²

Beside inhibiting VEGFR-2 phosphorylation and signalling, other theories have been suggested for the mechanism of action for cabergoline. In a study on hyperprolactinemic PCOS patients, a dopaminergic control of LH release and a support for the use of cabergoline in the management of these patients were shown. Cabergoline provided a better clinical control of ovarian response and consequently a reduction of the risk of OHSS, and did not cause a

Table 2: The outcomes of ovarian stimulation in cabergoline-treated and control groups

Outcome of ovarian stimulation	Cabergoline (n=50)	Control (n=25)	P value
Number of gonadotropin ampoules (75 IU/ampoule)	30.74±12.40	31.72±13.49	0.76
Duration of stimulation (days)	9.37±0.60	9.75±0.56	0.98
Estradiol on HCG day (pg/ml)	3890±345	3980±456	0.86
Number of retrieved oocytes	22.18±4.94	21.00±5.36	0.35
M II oocytes (%)	70	61	0.70
Fertilization rate (%)	55.41	58.91	0.67
Route of ART			
Embryo transfer	30 (60%)	13 (52%)	0.77
ZIFT	13(26%)	5 (20%)	0.45
Cycle cancellation	7 (14%)	7 (28%)	0.03
Cycle with frozen embryo (%)	65%	31%	0.001
OHSS	6 (12.0%)	9 (36.0%)	0.001
Mild	2 (4%)	6 (24%)	0.001
Moderate	3 (6%)	2 (8%)	0.001
Severe	1 (2%)	1 (4%)	0.001
Pregnancy (Chemical & Clinical)	10 (23.3%)	7 (36.0%)	0.13
Abortion	3 (6.0%)	4 (16.0%)	0.21
Multifetal pregnancy	0	0	1
Drug complication	0	0	1

Values are presented as mean±SD or frequency (percent). HCG; human chorionic gonadotropin; MII oocytes; metaphase II oocytes, ART; assisted reproduction treatment, OHSS; ovarian hyperstimulation syndrome. ZIFT; zygote intrafallopian transfer

decrease in pregnancy rate.⁵ Approximately half of the patients in each group (cabergoline and control groups) were those with PCOS, and all of them had normal serum concentrations of prolactin. The present study did not aim at evaluating the effect of cabergoline in hyperprolactinemic patients with PCOS, and further studies are in need to shed light on the issue.

Alvarez and colleagues,³ conducted a randomized, placebo-controlled double-blind clinical trial in oocyte donors at risk of OHSS, and found that the incidence of moderate or severe OHSS was significantly reduced in the cabergoline-treated group, without an adverse effect on ovarian function. In a retrospective analysis,⁶ Alvarez and colleagues showed that implantation and clinical pregnancy rates in women who received cabergoline for the prevention of OHSS was similar to those in women matched for age, embryo quality, and semen parameters.

The present study showed that BMI, patients' age, infertility duration, type and cause of infertility, serum levels of FSH and LH, PCOS, or the history of previous OHSS, estradiol level, PCOS prevalence, and number of oocytes retrieved were similar between the two groups. In spite of the small sample size, the present study has the advantages similarity of basal or background characteristics, cycle stimulation characteristics and minimal selection bias all of which make the study reliable for future practical and clinical purposes.

Another study,¹³ compared early OHSS, defined as the onset of the syndrome during the first nine days after HCG administration, and late OHSS, characterized by the onset of the syndrome after 10 days after HCG administration. Cabergoline decreased the risk of early OHSS significantly ($P < 0.001$), but the risk of late onset OHSS was not decreased. There was no significant difference between the two groups in terms of pregnancy, implantation or miscarriage rates.¹³ Though not a randomized clinical trial, the findings of our study, namely decreasing the incidence of early OHSS, are in agreement with those of such a report.¹³ Although the incidence of mild OHSS decreased, the incidence of severe form of OHSS did not change significantly. Moreover, the effects of the cabergoline found in the present study are in agreement with those of previous publications.^{3-6,10}

Conclusion

The present study showed that cabergoline did reduce the incidence of OHSS and the risk of hospitalization due to the lower occurrence of OHSS. These findings might be taken as

evidence to suggest that cabergoline might be a valuable drug for the prevention and treatment of the abnormality. However, randomized controlled trials are in need to study the efficacy as well as safety of different doses and durations of cabergoline administration for both prophylactic and therapeutic purposes.

Conflict of Interest: None declared

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