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Outcomes of assisted reproduction treatment after dopamine agonist -cabergoline- for prevention of ovarian hyper stimulation syndrome

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Abstract

Background: Release of vascular endothelial growth factor (VEGF) by ovaries in response to HCG administration is one of the main mechanisms of ovarian hyper stimulation syndrome. Since Dopamine/dopamine receptor2 (Dp-r2) pathway activity -mediated by VEGF/ Vascular endothelial growth factor receptor 2 (VEGFR-2) signaling-, is associated with angiogenic events, dopamine agonists were used for the management of severe forms of OHSS. In order to assess the effects of Cabergoline on angiogenesis in the human endometrium, and subsequently its impacts on the implantation rate this study was conducted.

Methods: This historical cohort study was conducted based on existing data of 115 patients (20-40 years) whom underwent assisted reproductive treatment (ART) and with a high probability for developing OHSS between March 2007 and September 2008. Forty five cases received Cabergoline were compared to 70 control subjects. The statistical methods used were: Unpaired t-test for continuous variables and the chi-square test (or Fisher's exact test if required) for categorical variables.

Results: None of the patients (treatment or control group) developed OHSS. The etiologies of infertility and administration of GnRH agonist or antagonist protocols were similar in two groups ($p>0.2$). Number of transferred embryos and zygote intra-fallopian transfer (ZIFT) did not differ between the two groups ($p\geq0.06$). Implantation rate in treatment (3.1%) and control (6.6%) subjects was similar ($p=0.4$). No significant difference was observed in fertilization rate, chemical, clinical and ongoing pregnancies between the two groups ($p>0.5$).

Conclusion: Cabergoline can be safely administered in ART protocols to prevent OHSS, without compromising ART outcomes.

Keywords: Cabergoline, Ovarian Hyper stimulation Syndrome, Dopamine agonist, OHSS, Implantation rate.

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Introduction

Ovarian hyper stimulation syndrome (OHSS) is the most serious complication of ovulation induction (1). It is a result of increased vascular permeability (VP) and extravasations of fluid, which in turn causes

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hemoconcentration with reduced organ perfusion, alterations in blood coagulation with the risk of thromboembolism and leakage of fluid into the peritoneal cavity and lungs (1,2). Vascular complications are serious and potentially life-threatening iatrogenic complications (3). Its exact pathophysiology remains unknown and it has been managed empirically over the years, but it is known that the presence of Luteinizing hormone (LH)-like activity similar to human chorionic gonadotropin (HCG) plus an ovary (corpus luteum and/or antral follicles) are absolute requirements for OHSS onset. In rat study this syndrome subsided or did not develop when oophorectomy was performed (4), or once the administration of hCG was ceased during controlled ovarian hyper stimulation with gonadotropins (5). HCG does not have any vasoactive properties by itself (6), thus its function seems to be mediated by one or more angiogenic substances released by ovaries in response to HCG. Vascular endothelial growth factor (VEGF) is the main angiogenic factor released by ovaries in response to HCG (6-8).

If we antagonize or stop the production of VEGF, we would be able to prevent the onset of OHSS or reduce its severity (9). Dopamine/dopamine receptor2 (Dp-r2) pathway activity -mediated by VEGF/ Vascular endothelial growth factor receptor 2 (VEGFR-2) signaling-, is associated with angiogenic events (10). Thus, for the first time, in 2003, dopamine agonists were used for the management of severe forms of OHSS (11) and then their efficacy was confirmed in further studies (12,13). The early stages of pregnancy are highly dependent on ovarian (14) and uterine angiogenesis (15). In vivo, VEGF is strongly involved in the initiation and progression of angiogenesis in the developing embryo (16), growth and maintenance of ovarian follicles and corpus luteum (17).

Immunohistochemistry analysis has shown that the peak VEGF ligands and receptors in the human endometrium and in glandular epithelial cells occur in the mid-luteal phase of the menstrual cycle (17). This expression is regulated by ovarian steroids and HCG in different mammalian species (18). It seems that VEGF transcripts are up-regulated in all peri-implantation endometrial samples after the administration of HCG in gonadotropin-stimulated cycles and patients whom have received hormone replacement therapy (17,18).

High doses of Cabergoline influences three processes: prolactin secretion, angiogenesis and VP (19). It also reduces VEGFR-2 density on the membrane of endothelial cells by inducing internalization. As a consequence, VEGF could not reach the receptors, resulting in the general inhibition of the VEGF/VEGFR-2 pathway which decreases VP and angiogenesis simultaneously (7). The fundamental step in mammalian embryo implantation -blastocyst implantation- is VEGF-mediated angiogenesis and pregnancy could be stopped by targeting VEGF with monoclonal antibodies (20). Thus, it would clinically so important to know if treatment of OHSS would adversely affect endometrial angiogenesis and thus pregnancy outcome in high risk women who undergoing ART. Successful implantation of a replaced embryo is the best indicator of sufficient angiogenesis in the endometrium. The purpose of current study was to evaluate implantation rate and other pregnancy outcomes in women under ART who received Cabergoline to prevent OHSS.

Methods

Subjects

This retrospective cohort study was conducted on existing data of 115 women (ages 20-40 years) who underwent ART and with a high probability for developing OHSS between March 2007 and September 2008 in the Fertility Center of Shariati Hospital, Tehran University of Medical Sciences, Iran. Participants were afflicted by either primary or secondary infertility. Patients underwent different ART protocols using gonadotropin-releasing hormone (GnRH)

agonist, GnRH antagonist, and no GnRH protocols (in patients who had hypothalamic amenorrhea). Among selected subjects, 45 cases received Cabergoline (treatment group), whereas in 70 cases with an oocyte count of 14-18, Cabergoline was not administered (control group).

ART protocol

The treatment protocol in patients undergoing GnRH agonist was performed as previously reported by our group (21). Gonadotropin or human menopausal gonadotropin (hMG) dosage were individually adjusted according to the patient's age, response in previous cycles, basal follicle-stimulating hormone (FSH) levels and body mass index (BMI). On the first day of after administration of gonadotropin or hMG, the dosage of GnRH was decreased by half. On the 7^{th} day of stimulation, ultra sonographic examination was performed to evaluate ovarian follicle sizes, and once at least 2 follicles reached 17 mm in diameter, 10000 IU intramuscular hCG (Organon Pregnyl) was administered. GnRH analog and gonadotropins were discontinued on the day of HCG administration.

In the GnRH antagonist protocol, 0.25 mg Cetrorelix (Cetrotide, Serono Laboratories, Madrid; or Ganirelix, Organon Laboratories, Barcelona, Spain) was administered by daily subcutaneous injections, beginning on day 7 of the menstrual cycle. Once the lead follicle reached 17 mm in diameter, 10000 IU of intramuscular hCG (Organon Pregnyl) was administered. GnRH-antagonists and gonadotropins were discontinued on the day of hCG administration. Transvaginal oocyte retrieval was scheduled 36 hours after the hCG injection and under general sedation. Microinjection was performed on oocytes in metaphase II, and 2-3 days after oocyte pickup 8-10 cell embryos were transferred to the uterus. On the day of oocyte pickup, based on ultra sonographic findings, patients at risk for OHSS were treated with daily 0.5 mg of Cabergoline (Dostinex 0.5 mg, Pharmacia Italia S.P.A., Italy) for 10 consecutive days. Those who developed of more than 18 follicles on the day of oocyte pickup were considered as high risk for OHSS. For patients with hypothalamic amenorrhea, none of GnRH protocols were implemented.

Primary and Secondary Outcomes

Our primary outcome was implantation rate defined as the number of gestational sacs confirmed by ultrasound examination, divided by the total number of transferred embryos). Secondary outcomes were ART outcomes including fertilization rate, chemical pregnancy, clinical pregnancy and ongoing pregnancy (defined as pregnancies lasting more than 12 weeks of LMP with the appropriate cardiac activity for the fetal gestational age when examined by ultrasonography).

Statistical Analysis

Results were reported as mean ± SD for quantitative variables and percentages for categorical variables. Data obtained in treatment and control groups were compared using the unpaired t-test for continuous variables and the chi-square test (or Fisher's exact test if required) for categorical variables. Statistical significance was based on two-sided design-based tests evaluated at α=0.05. Statistical analysis was performed using SPSS 21 (SPSS Inc, Chicago, IL, USA).

Results

Mean age in subjects with (30 ± 4 years, N=45) and without (30 ± 5 years, N=70) Cabergoline was similar (p=0.9). Demographic data of each group is summarized in Table 1. The rate of primary infertility was significantly lower in treatment than in control subjects (p=0.02), but the rate of secondary infertility was similar between two groups (p=0.1). No difference was observed in the etiology of infertility between groups, except for mixed factor which was significantly higher in control group (p=0.005).

Data of controlled ovarian hyper stimulation (COH) and ART protocol in each

Table 1. Demographic data of groups

Characteristic	Without Cabergoline	With Cabergoline	Total	p
	(n=70)	(n=45)	(115)	
Age (year)	30.54±4.97	30.60± 4.51	30.57±4.78	0.9
BMI (kg/m2)	26.14±3.87	26.64±3.37	26.33±3.67	0.5
FSH	6.71±3.58	6.26±1.78	6.54±2.99	0.4
Duration of infertility(year)	8.36±5.23	8.56±5.13	8.43±5.17	0.8
Type of infertility				
Primary	61(87.1%)	31(68.9%)	92(80%)	
Secondary	5(7.1%)	7(15.6%)	12(10.4%)	0.05
Primary and secondary	4(5.7%)	7(15.6%)	11(9.6%)	
Etiology of infertility				
Male factor	31(44.3%)	25(55.6%)	56(48.7%)	0.2
Tubal factor	6(8.6)	1(2.2%)	7(6.1%)	0.2
Ovulatory factor	12(17.1%)	10(22.2%)	22(19.1%)	0.4
Unexplained	7(10%)	7(15.6%)	14(12.2%)	0.2
Mixed	11(15.7%)	0	11(9.6%)	0.00
Endometriosis	3(4.3%)	2(4.4%)	5(4.4%)	1.0

BMI: Body Mass Index. FSH: follicular Stimulating Hormone

Table 2. Information of COH and ART in each group

Characteristic	Without Cabergoline	With Cabergoline	Total	p
	(n=70)	(n=45)	(115)	
GnRH agonist	60(87%)	37(82.2%)	97(85.1%)	
GnRH antagonist	7(10.1%)	7(15.6%)	14(12.3%)	0.7
Without GnRH	2(2.9%)	1(2.2%)	3(2.6%)	
Number of retrieved oocytes	16.20±3.06	20.47±3.67	17.87±3.91	0.00
Rout of transfer				
ET	31(44.3%)	28(62.2%)	59(51.3%)	0.08
ZIFT	39(55.7%)	17(37.8%)	56(48.7%)	
Number of embryo transferred	3.97±0.96	4.79±4.08	4.34±2.84	0.26
Number of injected oocyte transferred in ZIFT procedure	5.09±0.62	5.24±0.43	5.14±0.56	0.38

COH: controlled ovarian hyper stimulation. ART: assisted Reproduction Treatment. GnRH: gonadotropin releasing hormone. ET: embryo transfer. ZIFT: zygote in fallopian tube.

Table 3. Outcomes of Assisted Reproduction Treatment each group

Characteristic	Without Cabergoline	With Cabergoline	p
	(n=70)	(n=45)	
Fertilization rate	58.37±16.24	65.12±18.31	0.20
Implantation rate	3.13±12.29	6.64±18.30	0.10
Chemical pregnancy	18(25.7%)	13(28.9%)	0.8
Clinical pregnancy	15(21.7%)	10(22.2%)	1.0
Ongoing pregnancy	13(19.1%)	7(15.6%)	0.8

group is listed in Table 2. None of patients in two groups developed OHSS. The number of retrieved oocytes was significantly greater in women whom received Cabergoline than who did not receive ($p<0.001$). The number of embryos transferred and the number of ZIFT was similar between two groups ($p=0.06$).

The outcomes of ART are shown in Table 3. Implantation rate in both treatment and control groups was similar ($p=0.4$). There was no statistically significant difference in chemical, clinical and ongoing pregnancies between two studied groups ($p>0.05$).

Discussion

Women undergoing ART may be at risk to develop OHSS, and thus need Cabergoline to prevent this serious complication. Due to dopaminergic properties of Cabergoline and its probable anti-angiogenesis effects it is clinically important to evaluate the potential adverse effect of Cabergoline on ART outcomes. Our results showed no significant difference in implantation rate between women received Cabergoline and those without it. Also fertilization rate, chemical and clinical pregnancies, and ongoing pregnancies were similar between two studied groups. Our findings are con-

sistent with a recent retrospective study by Alvarez, et al. which showed that the administration of Cabergoline in order to prevent OHSS is safe and does not appear to affect ART outcomes (22).

The dose of Cabergoline that we used in this study (0.5mg/day) is based on the therapeutic guidelines for hyperprolactinemia, and is the same as what applied in in similar studies (22). Cabergoline in low doses (0.5mg/day), such as those administered in hyperprolactinemic cases, specifically decreases prolactin secretion, but does not affect physiologic angiogenesis that would occur later in reproductive organs, and also does not interfere with ovarian function (23). This mechanism can explain our findings and what Papaleo, et al. demonstrated in their study. They used Cabergoline as a controlling component of LH release in polycystic ovary syndrome (PCOS) patients in order to provide the better clinical control of ovarian response to rFSH. Administration of Cabergoline did not affect pregnancy rate nor did it increase the possibility of multiple pregnancies (24).

Furthermore, it seems that the administration of Cabergoline in early stages of pregnancy is not associated with the increased risk of spontaneous miscarriage, premature delivery, multiple pregnancy, congenital abnormalities, teratogenic effects (25,26) or any alteration in the distribution of birth weight and sex ratio (27). Studies of the infants born to mothers whom received Cabergoline during pregnancy have demonstrated normal neonatal physical and mental development (27,28).

The pregnancy outcomes of ART cycles with Cabergoline 0.5mg/d in this study are compatible to those of Gomez study with similar ART protocol and using Cabergoline 0.1mg/kg per day (low dose) (7). In both studies endometrial angiogenesis did not change, neither implantation nor overall ART outcome was affected. This may imply that the effects of Cabergoline on ART do not change with 0.1 to 0.5mg/kg per day.

The formation of corpora luteal or pregnancy development regulated by the physiological states of high level of VEGFR-2 dependent vascular activity are not affected by low doses of Dopamine-r2 agonists (14,23), as it does not exert antiangiogenic activity. This hypothesis is demonstrated by the Gomez, et al. study on rats in which the high dose Cabergoline (500µg/kg·d) inhibits VP two to three fold greater than the its low dose (100µg/kg·d) measured by disruption of luteal vessel proliferation. This indicates that low doses of Cabergoline specifically block the VP not the angiogenic component of VEGFR-2 (7). This evidence raised this hypothesis that the inhibition of VEGF or VEGFR-2 production in the ovary is not the same as inhibitory mechanism of low dose Cabergoline on VP. The suggested mechanism is the reduction of phosphorylation in a single or several tyrosine sites by Cabergoline which are critical for activation of VEGFR-2. This probably separates the VP and angiogenic components. At low doses of Cabergoline, only vascular hyperpermeability is impeded without affecting angiogenesis (7).

In conclusion, Cabergoline can be safely administered in ART protocols to prevent OHSS, without compromising ART outcomes; whereas more randomized clinical trials are required to reassure the safety use of Cabergoline in ART.

Conflict of interests

None of the authors have conflicts to declare.

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