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ORIGINAL ARTICLE

Cabergoline administration prevents development of moderate to severe ovarian hyperstimulation syndrome and it contributes to reduction in ovarian volume

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Abstract
Purpose The aim of this study was to determine the prophylactic effects of cabergoline on ovarian hyperstimulation syndrome (OHSS) after oocyte retrieval.
Methods A total of 187 women underwent controlled ovarian stimulation using gonadotropin releasing hormone (GnRH) agonist long protocol or flexible GnRH antagonist protocol for in vitro fertilization. They responded excessively to ovulation induction, and fresh embryo transfers were canceled. Sixty-one patients in the intervention group were administered oral cabergoline (0.5 mg) three times after oocyte retrieval (day 0, 2, and 4 following the oocyte retrieval). Ultrasonography and blood examination were performed on the seventh day following oocyte retrieval. The main outcomes measured were the incidence of OHSS, estimated ovarian volumes, ascites, hematocrits, and white blood cell counts.
Results The incidence of moderate to severe OHSS was lower after cabergoline administration (9.8 vs. 23.0 %, $p = 0.03$). The ovarian volumes reduced after intervention (96.2 vs. 145.5 cm^3, $p = 0.008$). The reduction was evident in the patients with agonist long protocol (92.1 vs. 167.5 cm^3, $p = 0.0005$). No significant differences were observed for other factors.
Conclusions Cabergoline has a favorable effect on the prevention of moderate to severe OHSS affiliated with ovarian volume reduction.

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a common complication in assisted reproductive technology (ART) as well as in other fertility treatments using ovulation stimulation [1]. It typically occurs when an ovary responds excessively to ovulation induction therapy, thereby exposing a large number of growing follicles to human chorionic gonadotropin (hCG). A previous study using a rodent model found that the essential characteristic of OHSS was increased vascular permeability of the capillaries of the swollen ovaries, which induces a fluid shift from the intravascular space to the third space [2]. Acceleration of this fluid shift induces hemoconcentration, renal failure, thromboembolism, and further systemic organ failure, which are common features of moderate to severe OHSS.

Dopamine agonist administration has recently emerged as a strategy to reduce the incidence of OHSS and its severity [3]. Cabergoline is a dopamine agonist that inhibits the phosphorylation of vascular endothelial growth factor (VEGF) receptor (VEGFR). Rodent OHSS models have revealed that the activation of the VEGF/VEGFR signaling pathway plays an important role in OHSS development [4]. During ovarian hyperstimulation, VEGF and VEGFR-2 mRNA expression increases in the ovaries and is accelerated by hCG administration. It has been demonstrated that both the ovarian gene expression levels and the serum VEGF levels strongly correlate with vascular permeability in an animal model [5]. VEGF/VEGFR-2 binding resulted

in increased vascular permeability, which is an essential OHSS feature, but low-dose administration of cabergoline blocked this critical step and inhibited downstream VEGF signaling in rodents and humans [6, 7]. Many studies have documented the effectiveness of cabergoline in OHSS prevention in high-risk women receiving ovarian stimulation for ART treatment [8].

In this study, we focused on objective clinical parameters from women treated with cabergoline. Because our data was collected from a single clinical facility, we only describe the extent to which cabergoline reduced the incidence or gravity of OHSS. We also analyzed the differences between the types of ovarian stimulation methods that may promote the onset of OHSS.

Materials and methods

Administration of cabergoline aiming at prevention of OHSS is out of approval in Japanese pharmaceutical situation, so informed consent was obtained from all patients for being included in this study. And all procedures followed were approved by the institutional review board of IVF Namba Clinic (Osaka, Japan).

Study population

This study was carried out during January 2010–March 2011. Patients who underwent controlled ovarian stimulation for in vitro fertilization (IVF) and had serum estradiol (E_2) levels exceeding 3500 pg/mL were included in this study. Sixty-one women who had IVF between December 2010 and March 2011 were administered 0.5 mg of cabergoline (Cabaser, Pfizer Inc. Japan) after oocyte retrieval. They started oral cabergoline administration on the day of oocyte retrieval and continued it every second day for two further doses. In contrast, 123 women who had IVF between January 2010 and November 2010 did not receive cabergoline, which formed the control group. Both groups had same treatment other than cabergoline administration.

Ovarian stimulation protocol

The patients received either the gonadotropin rereleasing hormone (GnRH) agonist long protocol treatment or flexible GnRH antagonist protocol treatment as controlled ovarian stimulation. Each one's stimulation protocol was basically assigned in a random manner. When a patient had undergone previous IVF treatment, different stimulation protocol was chosen. Ovarian stimulation starts with administration of recombinant follicle-stimulating hormone (FSH) (Gonal F, Serono Japan, or Follistim, MSD, Japan) intramuscularly or subcutaneously on day 3 of the treatment cycle. The initial FSH dose was based on each patient's anti-Müllerian hormone (AMH) levels, and it varied from 150 to 300 IU. Patients received additional FSH and/or human menopausal gonadotropin (hMG) (Fuji HMG, Fuji Pharma Co., Ltd. Japan, or Ferring HMG, Ferring Pharmaceuticals Co., Ltd. Japan) until two or more follicles reached 18 mm in average diameter. At this time, 5,000 IU of hCG (HCG 5,000 IU, Fuji Pharma Co., Ltd. Japan) was administered and the oocyte retrieval was performed 36 h later. In the GnRH agonist long protocol, patients received buserelin acetate (Suprecur nasal solution 0.15 %, Mochida Pharmaceutical Co., Ltd. Japan) at 0.6 mg/day beginning on the day 21 of the previous cycle to suppress the endogenous luteinizing hormone (LH) surge until the day of hCG administration. Patients on the GnRH antagonist protocol received 0.25 mg of cetrorelix acetate or ganirelix acetate (Cetrotide, Shionogi & Co. Ltd, Japan or Ganirest, Schering-Plough K.K., Japan) subcutaneously starting on the day when the diameter of the leading follicle exceeded 14 mm or when an increase in serum LH levels was detected until the day of hCG administration. No patients had fresh ETs for prevention of the development of late-onset OHSS.

Evaluation of OHSS

Patients were required to visit the clinic to undergo testing for OHSS. A diagnosis of OHSS was made as per the Japan Society of Obstetrics and Gynecology (JSOG) guidelines for diagnosis, classification, and management of OHSS (Table 1) [9]. The JSOG OHSS classification system is based on the combination of clinical features, including the

Table 1 Diagnostic criteria for OHSS based on the 2009 Japanese Society of Obstetrics and Gynecology classification system

OHSS grade	Mild	Moderate	Severe
Symptoms	Abdominal fullness	Abdominal discomfort, nausea, vomit	Severe abdominal discomfort or pain, nausea, vomit, dyspnea
Ascites	Limited to pelvic cavity	Spreading to upper abdomen	Excessive amount of ascites, pleural effusion
Maximum diameter of ovaries[a]	>6 cm	>8 cm	>12 cm
Data of complete blood count and biochemistry	Normal findings	Worsening	Ht > 45 % WBC > 15000/mm^3

When several categories overlapped, the higher grade was adopted

The original table is described in reference 9

[a] The larger ovary was chosen for evaluation

amount of ascites, ovary size, and simple blood test results. Five physicians at our clinic participated in each patient's interview process and performed transvaginal sonography. Ovarian volume was calculated using the following formula: estimated ovarian volume = 0.52 × (L1 × L2 × L2 + R1 × R2 × R2), where L1 is the major axis length of the left ovary, L2 is the minor axis length of the left ovary, R1 is the major axis length of the right ovary, and R2 is the minor axis length of the right ovary. The amount of ascites was represented as the pocket diameter of the peritoneal fluid in the Douglas pouch measured in the lithotomic position. The diagnosis of abnormalities in hematocrit and white blood cell (WBC) count was difficult because of the wide variation in individual basal data; therefore, we observed differences between values before and after oocyte retrieval. Preoperative hematocrit value and WBC were originated from the result of peripheral blood count before starting infertile treatment at our clinic. No women received intravenous injection of albumin during the IVF cycles.

Statistical analysis

The collected data was analyzed using the Chi square and Student's *t* test, where appropriate. Mann–Whitney *U* test was also adopted in the case of non-normal distribution. We considered that $p < 0.05$ is statistically significant in each analysis.

Results

The characteristics of 187 patients are demonstrated in Table 2. Two different types of controlled ovarian stimulation for IVF are provided, and the ratio of the number of cases receiving the agonist long protocol to the antagonist protocol was approximately 2:1 in both groups. In each stimulation group, patient age, number of retrieved oocytes, peak E_2 levels, and serum AMH levels were similar between the cabergoline-treated and control groups. The main causes of infertility were PCOS (6 vs. 4 % in the cabergoline-treated group and the control group, respectively), male factor infertility (27 and 26 %), tubal factors (21 and 14 %), endometriosis (7 and 6 %), uterine abnormalities (2 and 4 %), and unexplained infertility (36 and 45 %). There were no differences between the groups with regard to cause of infertility.

Although no significant difference in the incidence of OHSS was observed after cabergoline administration ($p = 0.06$), the incidence of moderate to severe OHSS were lower in the combined analysis of both stimulation groups (long + antagonist protocol, $p = 0.030$) (Table 3). The estimated ovarian volume in the cabergoline-treated group was smaller than that in the control group. Although this difference was statistically prominent in the agonist long protocol and the long + antagonist protocol group ($p = 0.0005$ and 0.008, respectively), no difference was detected in the group receiving the flexible antagonist protocol. The data from one woman who underwent unilateral oophorectomy was eliminated from the ovarian volume analysis. The pocket diameter of the Douglas pouch, hematocrit value, and WBC count did not differ among groups according to whether or not cabergoline was administered.

A few patients receiving cabergoline complained of stomach discomfort, although all dosages were taken as per administrative instructions and their symptoms resolved spontaneously soon after cabergoline discontinuation.

Table 2 Age and in vitro fertilization outcomes of patients according to stimulation protocol

Agonist long protocol	Cabergoline ($n = 41$)	Control ($n = 82$)	p value
Age	35.1 ± 3.1	34.9 ± 3.2	NS
AMH (ng/mL)	4.13 ± 3.16	4.69 ± 2.02	NS
No. of oocytes	18.7 ± 6.10	19.2 ± 6.43	NS
Peak E_2 (pg/mL)	5590.2 ± 2082.4	5331.4 ± 1847.3	NS
Total gonadotropins (IU)	2015 ± 535	1996 ± 583	NS
Antagonist protocol	Cabergoline ($n = 20$)	Control ($n = 44$)	p value
Age	36.3 ± 3.4	36.0 ± 3.4	NS
AMH (ng/mL)	4.79 ± 1.47	5.14 ± 2.76	NS
No. of oocytes	19.2 ± 8.48	19.2 ± 8.83	NS
Peak E_2 (pg/mL)	4884.1 ± 1971.8	4914.3 ± 1740.5	NS
Total gonadotropins (IU)	2348 ± 933	2390 ± 960	NS

AMH anti-Müllerian hormone, *NS* not significant

Table 3 OHSS incidence and its parameters in patients with each stimulation protocol

Long + antagonist protocol (in total)	Cabergoline ($n = 61$)	Control ($n = 126$)	p value
Incidence of OHSS	40/61 (65.6 %)	98/126 (77.8 %)	NS
Moderate to severe OHSS	6/61 (9.8 %)	29/126 (23.0 %)	0.030[a]
Ovarian volume (cm^3)	96.166 ± 52.618	145.451 ± 82.883	0.008[a]
Pocket diameter in Douglas pouch (mm)	11.9 ± 12.7	14.3 ± 12.8	NS
Change in hematocrit (%)	−0.20 ± 2.57	−0.58 ± 2.72	NS
Change in WBC (count/mm^3)	2285.2 ± 1891.8	2411.9 ± 2020.5	NS
Agonist long protocol	**Cabergoline ($n = 41$)**	**Control ($n = 81$)**	**p value**
Incidence of OHSS	28/41 (68.3 %)	68/82 (82.9 %)	NS
Moderate to severe OHSS	6/41 (14.6 %)	23/82 (28.0 %)	NS
Ovarian volume (cm^3)	92.057 ± 51.592	167.466 ± 82.396	0.0005[a]
Pocket diameter in Douglas pouch (mm)	12.8 ± 13.7	15.7 ± 13.4	NS
Change in hematocrit (%)	−0.10 ± 2.68	−0.59 ± 4.27	NS
Change in WBC (count/mm^3)	2531.1 ± 1670.7	2907.3 ± 2033.5	NS
Antagonist protocol	**Cabergoline ($n = 20$)**	**Control ($n = 44$)**	**p value**
Incidence of OHSS	12/20 (60.0 %)	33/44 (75.0 %)	NS
Moderate to severe OHSS	0/20 (0 %)	6/44 (13.6 %)	NS
Ovarian volume (cm^3)	103.152 ± 53.649	104.174 ± 66.379	NS
Pocket diameter in Douglas pouch (mm)	10.2 ± 10.6	11.8 ± 11.4	NS
Change in hematocrit (%)	−0.39 ± 2.41	−0.95 ± 2.16	NS
Change in WBC (count/mm^3)	1780.0 ± 2241.8	1488.6 ± 1654.6	NS

Values are expressed as mean ± SD

AMH anti-Müllerian hormone, *NS* not significant, *WBC* white blood cell

Estimated ovarian volume (cm^3) = 0.52 × (L1 × L2 × L2 + R1 × R2 × R2)

L1 = major axis in the left ovary, L2 = minor axis in the left ovary, R1 = major axis in the right ovary, R2 = minor axis in the right ovary

Changes in hematocrit (%) = Ht (after oocyte retrieval) − Ht (before oocyte retrieval)

Changes in WBC (count/mm^3) = WBC (after oocyte retrieval) − WBC (before oocyte retrieval)

[a] Analyzed by *u*-test

During the study period, two women in the control group were hospitalized for treatment of severe OHSS, but none required hospitalization in the cabergoline-treated group.

Discussion

The overall OHSS incidence during controlled ovarian stimulation for IVF is reportedly 1–14 % [10]. The incidence of OHSS in this study was much higher. More than three quarters of the patients not receiving cabergoline administration met the JSOG's OHSS criteria and a considerable number of women were diagnosed with OHSS even after cabergoline administration. This discrepancy may be mainly due to differences in the definitions of OHSS. Compared to major classification systems proposed by Golan et al. and Navot et al. [11, 12], the JSOG classification system which emphasizes the size of swollen ovaries tends to assign more patients to a higher OHSS stage. The timing of evaluation is an additional factor contributing to the high incidence among our patient group. We evaluated the condition of patients only 7 days after oocyte retrieval, when many patients had persistently enlarged ovaries resulting from ovarian stimulation. Most patients satisfied only the single criterion of ovarian size and displayed no other symptoms. This suggests that this study assessed cabergoline effects at a very early stage of the pathophysiological process toward OHSS development.

Although we found no improvement in the incidence of all types of OHSS after cabergoline administration, the incidence of moderate to severe OHSS was significantly lower in the intervention group. This result was only obtained when the data of the two types of controlled ovarian stimulation were analyzed together. Our conclusion contradicts the previous systematic review and meta-analysis of controlled studies regarding the prophylactic

effect of cabergoline, which concluded that the OHSS overall incidence decreased by 12 % without apparent evidence of a reduction in severe OHSS incidence [8]. We believe that more studies are warranted for further clarification.

While current diagnostic procedures for OHSS usually depend on subjective patient complaints, we attempted to evaluate the gravity of the disease using more objective markers. Recently, ovarian volume has caught the attention of many physicians for the purpose of recognizing ovarian reserve before starting ovarian stimulation for ART treatment [13]. Following the technological improvements in transvaginal sonography using high-resolution probes, scanning of the ovaries has become a simple and informative examination in fertility clinics worldwide. With the help of transvaginal scanning, we recognized that the estimated mean ovarian volume significantly decreased after cabergoline administration. Analysis of ovarian size in patients receiving agonist long protocol showed an average reduction in ovarian volume of almost 75 cm^3. In contrast, the mean ovarian volume of the antagonist protocol group remained unchanged after cabergoline administration. Previous studies have shown that ovarian stimulation using GnRH antagonist instead of GnRH agonist is preferable for the prevention of OHSS in high-responder patients [14]. Our study supports the finding that the GnRH antagonist protocol is more appropriate than the GnRH agonist protocol for ovarian stimulation in OHSS high risk patients. The ovarian volume after cabergoline administration in the agonist long group was almost the same as that in the antagonist administration group. However, we need further investigation to determine whether cabergoline administration cancels out the OHSS effects due to the agonist protocol.

With regard to the other OHSS characteristics, we found no difference in the amount of ascites, WBC count, and hematocrit value after cabergoline administration. Álvarez clarified the suggestion that cabergoline reduces hemoconcentration and ascites in women after ovarian stimulation by pharmacokinetic modeling of magnetic resonance imaging [7]. Considering the process of OHSS development, the fluid shift through the intravascular space to the third space causes an increase in the amount of ascites, and then this pathophysiology culminates in the condition known as hemoconcentration or leukocytosis. We speculate that most patients in this study remained in the initial stage of OHSS development where the fluid shift was localized in only the ovaries and did not extend to the intraperitoneal space. A multidisciplinary approach for the prevention of OHSS which includes the avoidance of ovarian stimulant overdose, the use of low-dose hCG administration, and other kinds of prophylactic efforts should be effective in addition to cabergoline administration.

The most popular dosage of cabergoline for OHSS prevention is reportedly 5–10 μg/kg/day [15]. It is approximately 5–10 fold lower than the dosage of 50 μg/kg/day administered in rodent models, and 5–10 μg/kg/day is sufficient to block excessive prolactine secretion in human. This dosage does not interfere with ovarian function in humans [16]. Higher doses of cabergoline may pose a risk of corpus luteum disruption [17], presumably by affecting luteal angiogenesis. The duration of cabergoline administration is more than 2 weeks in many reports [7, 15, 18]. Here, we adopted a common dose of cabergoline, but we prescribed it only three times after oocyte retrieval. Although the total applied dose of cabergoline was much lower than that used in many other studies, it was sufficient to induce a prophylactic effect conducive to OHSS development. It is known that the half-time of cabergoline can be as long as 43 h (Pfizer Inc., New York, NY, USA); therefore this agent is usually administered weekly for the treatment of hyperprolactinemia [19]. At first, we attempted to administer cabergoline every day after oocyte retrieval (i.e., seven times in total), but a greater number of patients complained of minor gastrointestinal discomfort, such as constipation or nausea, although the symptoms were not serious enough to discontinue treatment. A reduced dosage of cabergoline administration seems to have enough of a prophylactic effect for OHSS and better compliance.

Finally, we must consider the safety of cabergoline. A potential risk of cardiac valvulopathy was recently reported in relation to cabergoline administration in patients with Parkinson's disease [20, 21]. A randomized trial on the long-term effects of cumulative doses of cabergoline on patients with prolactinoma showed no correlation between the presence of significant heart valve abnormalities and cumulative dose, treatment duration, prior bromocriptine use, patient age, or prolactin levels [17]. For the purpose of OHSS prevention, much lower doses are adopted over a shorter period; hence, the risk of cardiac valvulopathy seems to be very low. Cabergoline is safe enough for patients with Parkinson's disease or prolactinoma, however there is no consensus about its use during pregnancy. Some researchers have reported the clinical use of cabergoline for women who underwent ET following IVF, and observed no difference in miscarriage rates after cabergoline administration, which indicates that endometrial angiogenesis is not affected by cabergoline administration [15]. Two randomized controlled trials of patients following cabergoline administration up to the end of pregnancy found no difference in the live birth rates between the treatment and the control groups [22, 23]. Several non-randomized studies on the long-term effects of cabergoline on pregnancy outcomes also support this finding [18, 24, 25] as there were no differences in miscarriage rates, live birth rates, birth

weights, disparity of sex, and malformation rates in newborns. However, now that the technology of freezing embryos is widely available, we prefer using frozen embryos instead of fresh ones when the risk of OHSS is high. This strategy eliminates the potential risk of the drug exposure to the fetus and development of late-onset of OHSS.

The results of this report and those of previous studies leave little doubt regarding the effectiveness of cabergoline to reduce the risk of OHSS; however, further studies are warranted to establish the best protocol in dosage, treatment duration, and selection of eligible patients for cabergoline administration.

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Conflict of interest Tomoko Inoue, Shu Hashimoto, Hideyuki Iwahata, Keijiro Ito, Yoshiharu Nakaoka, and Yoshiharu Morimoto declare that they have no conflict of interest.

Human rights statements and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000(5). Informed consent was obtained from all patients for being included in the study.

Animal studies This article does not contain any studies with human or animal subjects performed by any of the authors.

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