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RESEARCH ARTICLE

Efficacy of Cabergoline in the Prevention of Ovarian Hyperstimulation Syndrome: A Randomized, Double-blind and Placebo-controlled Trial

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ABSTRACT

Introduction: Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication that arises due to assisted reproductive technologies (ARTs) during infertility treatment. Recently, the use of selective dopamine receptor agonists on D2 receptors (e.g., cabergoline) has been suggested in the prevention of OHSS. The aim of this study was to evaluate the effect of cabergoline in the prevention of OHSS in high-risk patients undergoing ART.

Materials and methods: This was a randomized, double-blind, parallel group (cabergoline group and placebo) study. A total of 110 women undergoing *in vitro* fertilization (IVF)–intracytoplasmic sperm injection procedure using a long agonist protocol with high risk for OHSS were recruited for the study on the day of final trigger. All the patients were followed up every 48 hours for 10 days from the day of the final trigger and clinically assessed with ultrasound and blood tests. The size of ovaries and fluid collection in the pouch of Douglas (POD) was measured with ultrasound. A sample size of 92 subjects was calculated for the study to be powered at 80%. Assuming a drop-out rate of 10%, 110 subjects were enrolled for the study.

Results: There was no significant difference observed in the size of right and left ovary, POD fluid volume, total leukocyte count (TLC), and serum estradiol level (E2 level) between both the groups from day 0 to day 8, except packed cell volume. No significant difference was observed in the incidence rate of moderate OHSS between both groups (p = 0.728). The differences in clinical pregnancy rate, implantation rate, and live birth rate were also insignificant.

Conclusion: Cabergoline does not reduce the incidence of moderate OHSS when compared with placebo. Large, well-designed studies are needed to evaluate the effectiveness of cabergoline when used for the prevention of OHSS.

Keywords: Endometrial receptivity, Fetal, Infertility, Ultrasonography.

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INTRODUCTION

Ovarian hyperstimulation syndrome is characterized by enlargement of ovaries, increase in vascular permeability, and shifting of fluid into the extracellular compartment under human chorionic gonadotropin (hCG) stimulation. This in turn may cause the development of hemoconcentration, oligo-perfusion, and thromboembolism.[1-3] It is an iatrogenic complication that arises during ART due to ovarian stimulation by gonadotropins; though it occurs mainly in women who are undergoing ovarian stimulation for IVF but sometimes it develops in women undergoing ovulation induction and intrauterine insemination (IUI). Moreover, OHSS is associated with various signs and symptoms, including abdominal distension, ascites, pleural effusion, shortness of breath, and edema of the extremities.[3,4] Generally, major symptoms of OHSS do not appear instantly after the trigger, but in the luteal phase.[5] The incidence rate of moderate and severe OHSS has been estimated between 3 to 6% and 0.1 to 3% respectively.[6]

Various treatment options aim at controlling ovarian response, i.e., primary prevention, such as discontinuing gonadotropin therapy, withholding hCG and intravenous (IV) albumin administration.[7] Additionally, interventions aim at reducing inflammation with steroids and aspirin, increasing plasma oncotic pressure with the use of IV albumin and hydroxyl ethyl starch (HES), and reducing membrane permeability with agents like calcium gluconate and dopamine agonists. But, these treatments have shown varying success.[8-13] Embryo cryopreservation is another option useful in the prevention of late form of

OHSS due to endogenous hCG production, but does not prevent early OHSS development due to exogenous hCG administration.

Till date, no effective treatment is available for OHSS that would not show negative effects on pregnancy, as well as prevent the reproductive losses. Ovarian hyperstimulation syndrome enforces a psychological, heavy physical, and economic burden on the patients as a result of hospitalization, fear of infertility, and miscarriage. Thus, there is a need for pharmacotherapy that can prevent OHSS.[14]

Recent studies have reported that vascular endothelial growth factor (VEGF) is the major molecule responsible for increased vascular permeability, and VEGF receptor type II (VEGF R2) exists in ovarian tissue, namely in granulosa cells and corpus luteum.[3] The production of VEGF in ovarian follicles increases during the stimulation period and results in a rapid increase in vascular permeability upon binding to type II VEGF receptors.[15] With the better understanding of pathophysiology and an important role of VEGF in OHSS, the use of selective dopamine receptor agonists on D2 receptors (e.g., cabergoline) has been suggested.[3] Cabergoline decreases the risk of development and progression of OHSS due to its ability to bind with VEGF R2 and thus blocks the interaction of VEGF with VEGF R2. The blockage of VEGF shows a reduction in vascular permeability, which helps to eliminate the trigger level in the pathogenesis of clinical manifestations of OHSS.[16]

Different studies have evaluated the effect of cabergoline in the prevention and reduction of incidence of OHSS using different doses and regimens.[17] However, there is a paucity of data available from India. The present study aimed to assess the efficacy of cabergoline as a preventive measure for OHSS in high-risk polycystic ovarian syndrome patients.

MATERIALS AND METHODS

Study Design

The present study was a double-blinded, prospective, randomized, and placebo-controlled trial. It was conducted at Craft Hospital and Research Center, a tertiary care hospital in Kerala, India. The study was conducted in accordance with the newly revised Consolidated Standards of Reporting Trials (CONSORT 2010) statement.[18] The Institutional Ethical Committee of Craft Hospital approved the study. All participants were counselled in detail about the course of the study and a written informed consent was obtained from all the participants prior to the study.

Study Characteristics

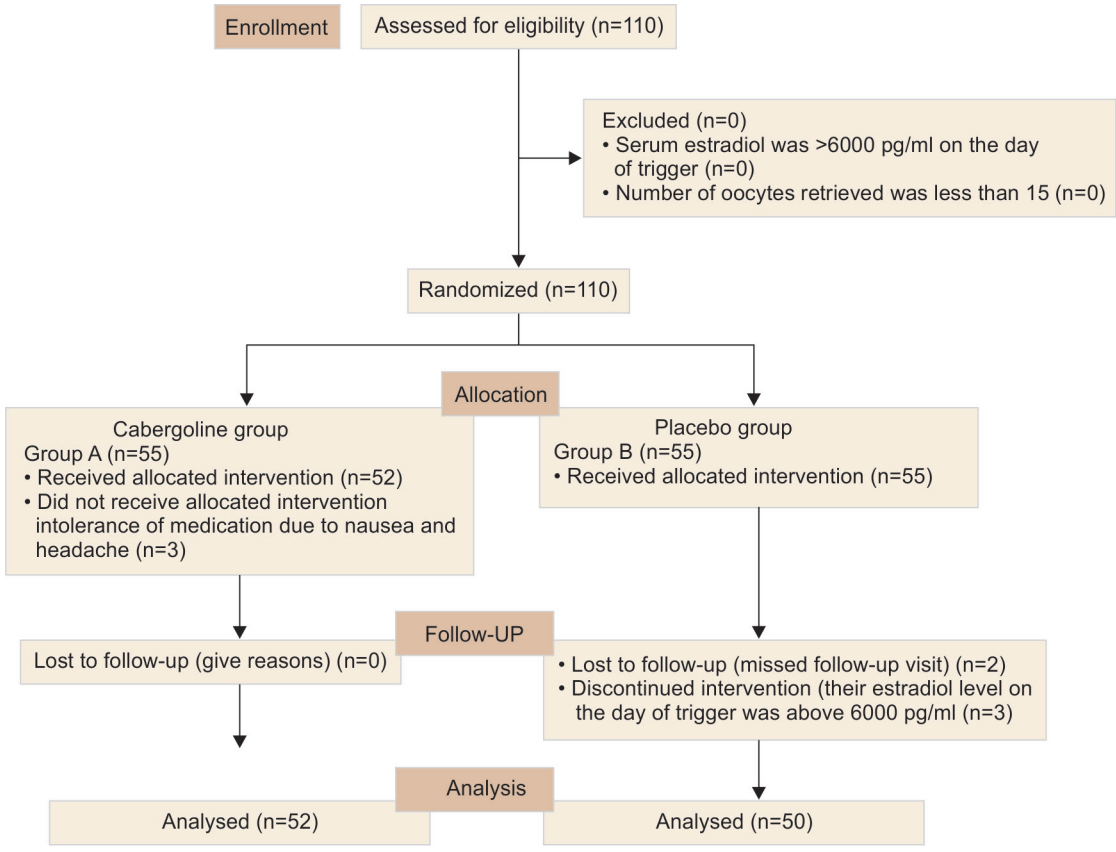
Women undergoing *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) procedure using a long gonadotropin-releasing hormone (GnRH) agonist protocol with high risk for OHSS were included in the study. A patient with ≥13 follicles of ≥11 mm on the day of hCG trigger was considered to be at high risk for OHSS as it was shown to have 85.5% sensitivity and 69% specificity for prediction of severe OHSS.[19] Patients having baseline follicle-stimulating hormone (FSH) <12 IU/L, body mass index (BMI) of >18 and <30 kg/m^2, presence of bilateral ovaries and absence of uterine abnormalities like fibroids, adenomyosis, and mullerian anomalies were included in the study. Patients who would have less than 15 oocytes retrieved were decided to be excluded from the study to have a proper representation of high-risk group. The study population was randomized into two parallel groups: Cabergoline group and placebo control group using the computer-generated model by an independent doctor who was not involved in the study. All the patients were followed up for 10 days from the recruitment (Flow Chart 1).

Protocol for Controlled Ovarian Stimulation

In the present study, dual suppression protocol was used for all the patients. The combined oral contraceptive pill containing 30 µg of ethinylestradiol and 150 mg of desogestrel was started from day 3 of previous periods for 21 days. This was followed by downregulation with 0.25 mg daily subcutaneous administration of GnRH agonist (Buserelin acetate, BUSARLIN®, Intas, India), starting from day 18 to day 21 of the menstrual cycle and was maintained until the day before hCG administration. Ovarian stimulation started after confirmation of pituitary downregulation by both serum estradiol levels <50 pg/mL and the absence of ovarian follicles >10 mm in diameter on transvaginal ultrasound. After the confirmation of pituitary downregulation, dose of buserelin was reduced to 0.1 mg daily. For ovarian stimulation initial daily doses of 150 IU to 225 IU recombinant human FSH (Gonal-F®, Merck Serono, India) was used, which was determined based on taking the following parameters into account: Age, BMI, serum FSH on day 2 or day 3 of the menstrual cycle, and number of antral follicles on day 2 or 3 of the menstrual cycle after pituitary downregulation.

Ultrasound assessment on day 5 and then on day 7 or 8 of stimulation was performed to determine if gonadotropin dose adjustments were required. The dose was reduced if the prevention of ovarian hyperresponse was deemed necessary. The cycle was cancelled for the patients having a poor response to the injection. Urinary hCG 5000 IU (Sifasi, Serum Institute, India) was administered to patients when two or more ovarian follicles reached a mean diameter of 17 mm for the final maturation of oocytes. After 35 hours of administration of hCG, oocyte retrieval was performed. During oocyte aspiration procedure, all the patients in both the groups received

Flow Chart 1: Study disposition



hexaethyl starch (Pentarch, Nirma Limited, India) as it was thought to be unethical not to offer any preventive modality to the patients on high risk of OHSS.

Oocytes Retrieval and Laboratory Procedures

Transvaginal ultrasound-guided oocytes retrieval was done under paracervical block and intravenous sedation with midazolam (Mezolam, Neon Laboratories Limited, India), using 17-gauge aspiration needle (ReproMed single lumen ovum pickup needle, IM Services BV, The Netherlands). Aspiration needle was connected to a prewarmed collection tubes containing HEPES-buffered medium. Follicular fluid was examined for cumulus–corona–oocyte complexes after oocyte aspiration. One hour after aspiration, these complexes were chemically denuded with 40 IU hyaluronidase solution (Sage, USA) and then these were mechanically denuded and classified according to nuclear maturity. Oocytes were classified as mature oocytes, i.e., metaphase II, and immature oocytes as in metaphase I or germinal vesicle stage. The oocytes were maintained in the fertilization medium until sperm microinjection and into cleavage medium immediately after microinjection. Oocytes were cultured in groups of two to three in 20 µL microdroplets under oil (Sage, USA) at 37°C, under 5% O_2, and 6% CO_2. Fertilization was checked 16 to 18 hours after ICSI. Embryo development was evaluated daily. The embryos were transferred to blastocyst medium on day 3.

The suitability of the embryo transfer was assessed by calculating the risk of OHSS. Women with high risk of OHSS had their embryos cryopreserved for a freeze–thaw embryo transfer later. Those women who had low risk of OHSS had the embryo transfer on day 5 of ICSI. The embryos were placed 10 to 15 mm from the fundus of the uterine cavity under transabdominal ultrasound guidance. In both the groups, luteal phase supplementation for patients who underwent embryo transfer was done with vaginal micronized progesterone 400 µg twice a day (Susten, Sun Pharma, India) till 12 weeks, if pregnancy test was positive.

Monitoring for Ovarian Hyperstimulation Syndrome

Following the randomization on the day of final trigger, patients were clinically assessed with ultrasound and blood tests on the day of aspiration and then every 48 hours interval till day 8 post trigger. The ultrasound test was performed to measure the size of ovaries and volume of fluid in POD. The ultrasound was performed by a single consultant Dr Ambujakshy K Raman with patient in dorsal lithotomy position with head end elevated to 45° to allow the intraabdominal fluid to get accumulated into POD. The maximum fluid pocket in the POD was measured

in anteroposterior and transverse plane. Also, as per previous research of Alvarez *et al*,[16] 3.5 ± 2.8 cm^2 of fluid in the POD after pick-up was seen as a routine finding. Thus, as per their recommendation, we defined ascites as the presence of fluid pocket more than 9 cm^2. The size of both the ovaries was noted on all the follow-up days by measuring the size on two perpendicular planes with one being the maximal. The mean of the two measurements was taken to compare two groups. Blood test of all the patients was performed to check the hemoglobin, TLC, and hematocrit level to monitor the development of hemoconcentration. Liver and renal function test was also done if indicated by clinical, serological, or above-mentioned tests of the patient. The OHSS severity grading was performed using Mathur's classification.[5]

Outcome Measures

Both the groups were analyzed for primary and secondary outcomes to evaluate the effect of cabergoline on OHSS. Rate of moderate OHSS was the primary outcome measure, whereas the number of aspirated oocytes, number of embryos transferred, implantation rate (IR, defined as the number of fetal sacs per embryos transferred), clinical pregnancy rate (CPR, a gestational sac with an embryo showing cardiac activity on ultrasound at weeks 5–7), and live birth rate (LBR, defined as the number of deliveries that resulted in a liveborn neonate, expressed per 100 embryo transfer procedures) were the secondary outcome measures. Biochemical pregnancy was determined by measuring serum β-hCG level 15 days after egg retrieval. The miscarriage was considered when nonviable clinical pregnancy was noted on ultrasound follow-up to the 20 weeks of gestation.

STATISTICAL ANALYSIS

Sample Size

Considering a type I error rate of 5% and an allocation ratio of 1, a sample size of 92 subjects was calculated for the study to be powered at 80%. Assuming a drop-out rate of 10%, 110 subjects were planned to be recruited for the study.[16]

Quantitative data are presented as mean ± standard deviation (SD) and categorical as percentage (%). Statistical analyses were performed using Statistical Package for the Social Sciences, version 16.0 (IBM Corporation, 2009). Categorical data were compared using a t-test and chi-square test, depending on the data meeting assumptions. A p-value < 0.05 was considered to be statistically significant.

RESULTS

Study Population

A total of 110 patients (21–41 years) were randomly allocated (1:1) to the cabergoline-treated group and the placebo group. Three patients from the cabergoline group were withdrawn due to an intolerance of medication due to nausea and headache. From the placebo group, five patients were excluded from the study; of these, two patients missed a follow-up visit and three patients had an estradiol level above 6000 pg/mL on the day of trigger. On completion of the study, cabergoline and placebo groups had 52 patients and 50 patients respectively. On comparison of the cabergoline and placebo group, mean age of the patients (29.6 ± 3.6 *vs* 30.8 ± 4.3 years), BMI (23.8 ± 3.7 *vs* 24.7 ± 4.8 kg/m^2), the total amount of gonadotropins used (1701.5 ± 638.1 *vs* 1904.5 ± 739.6 IU), days of stimulation (7.9 ± 1.5 *vs* 8.2 ± 1.5), and the number of oocytes aspirated (17.5 ± 3.5 *vs* 18.34 ± 3.8) were not different significantly.

The baseline characteristics of all the patients are represented in Table 1.

Treatment Outcomes

Changes in Ovary Size in the Cabergoline- and Placebo-treated Groups

The data for changes in ovarian volume are presented in Table 2. No significant difference was observed in both the groups in right ovary volume [day 2 (p = 0.401), day 4 (p = 0.648), day 6 (p = 0.212), and day 8 (p = 0.900)] and the left ovary volume [day 2 (p = 0.186), day 4 (p = 0.604), day 6 (p = 0.221), and day 8 (p = 0.966)].

Effect on POD Fluid Level in the Cabergoline- and Placebo-treated Groups

The data for POD fluid level are presented in Table 2. No significant difference was observed in both the cabergoline and placebo groups on day 2 (p = 0.703), day 4 (p = 0.752), day 6 (p = 0.436), and day 8 (p = 0.616).

Effect on Other Parameters in the Cabergoline- and Placebo-treated Groups

No significant difference was observed in serum estradiol level between both the groups on day 2 (p = 0.120), day 4 (p = 0.782), day 6 (p = 0.381), and day 8 (p = 0.277) (Table 2).

Table 1: Baseline characteristics of the patients

Characteristics	*Cabergoline group (n = 52)*	*Placebo group (n = 50)*	*p-value*
Age (years)	29.6 ± 3.6	30.8 ± 4.3	0.1487
BMI (kg/m^2)	23.8 ± 3.7	24.7 ± 4.8	0.2905
Total gonadotropins used (IU)	1701.5 ± 638.1	1904.5 ± 739.6	0.1462
Days of stimulation	7.9 ± 1.5	8.2 ± 1.5	0.3543
Oocytes aspirated	17.5 ± 3.5	18.34 ± 3.8	0.2340

n: Number of patients; p: Probability value (p < 0.05 = statistically significant) measured using t-test procedure

Table 2: Clinical parameters from day 0 till day 8 for patients receiving cabergoline or placebo treatment

Parameters	*Cabergoline group (n = 52)*	*Placebo group (n = 50)*	*p-value*
Right ovary size (mm, mean ± SD)			
Day 0	44.9 ± 22.8	46.5 ± 23.6	0.729
Day 2	78.6 ± 131.6	62.0 ± 33.8	0.401
Day 4	104.6 ± 54.3	109.3 ± 48.6	0.648
Day 6	121.4 ± 50.6	136.7 ± 70.0	0.212
Day 8	117.0 ± 65.4	118.6 ± 59.1	0.900
Left ovary size (mm, mean ± SD)			
Day 0	49.8 ± 40.8	39.8 ± 25.9	0.151
Day 2	63.2 ± 38.5	52.6 ± 40.8	0.186
Day 4	103.0 ± 59.5	97.1 ± 54.1	0.604
Day 6	139.5 ± 83.6	120.3 ± 70.5	0.221
Day 8	122.7 ± 70.7	122 ± 76.9	0.966
POD fluid volume (mm^3, mean ± SD)			
Day 0	3.3 ± 2.7	3.0 ± 2.4	0.480
Day 2	7.6 ± 8.4	8.3 ± 10.4	0.703
Day 4	13.1 ± 14.8	13.9 ± 13.0	0.752
Day 6	22.1 ± 23.9	18.7 ± 18.2	0.436
Day 8	16.9 ± 20.1	15.2 ± 14.1	0.616
Serum E2 (pg/mL, mean ± SD)			
Day 0	3587.3 ± 1501.1	3552.3 ± 989.8	0.892
Day 2	2520.7 ± 1010.1	2834.9 ± 988.3	0.120
Day 4	1851.8 ± 950.6	1914.2 ± 1283.0	0.782
Day 6	2275.2 ± 1079.7	2574.0 ± 2177.4	0.381
Day 8	1811.5 ± 1060.1	2040.9 ± 1034.4	0.277
PCV (%, mean ± SD)			
Day 0	34.5 ± 4.7	35.0 ± 3.2	0.614
Day 2	34.5 ± 4.0	32.8 ± 3.5	0.028
Day 4	33.9 ± 4.2	32.2 ± 3.7	0.042
Day 6	33.5 ± 4.3	31.9 ± 3.6	0.044
Day 8	32.9 ± 3.7	32.1 ± 3.2	0.267
TLC (10^3/μL, mean ± SD)			
Day 0	11.0 ± 4.0	11.0 ± 2.5	0.982
Day 2	11.3 ± 2.8	11.3 ± 2.5	0.893
Day 4	11.6 ± 3.0	11.8 ± 2.8	0.741
Day 6	11.2 ± 3.0	11.2 ± 2.8	0.925
Day 8	11.0 ± 2.8	10.6 ± 2.1	0.477

n: Number of patients; p: Probability value (p < 0.05 = statistically significant) measured using t-test procedure; serum E2 level: Serum estradiol level; PCV: Packed cell volume; SD: Standard deviation

A significant decrease was observed in the hematocrit level on day 2 (p = 0.028), day 4 (p = 0.042), and day 6 (p = 0.044) in the placebo group in comparison to the cabergoline group. The hematocrit levels did not differ significantly on day 8 (p = 0.267) (Table 2).

No significant difference was observed in the white blood cells count in the cabergoline and placebo-treated groups on day 2 (p = 0.893), day 4 (p = 0.741), day 6 (p = 0.925), and day 8 (p = 0.477) (Table 2).

Appearance of Moderate and Severe OHSS in the Cabergoline and Placebo-treated Groups

After the treatment, it was observed that the appearance of moderate and severe OHSS was almost similar in both the groups. In the cabergoline-treated group (n = 52), nine patients showed moderate OHSS (17.3%) and one patient (1.9%) showed severe OHSS. In the placebo group (n = 50), eight patients showed moderate OHSS (16%) and one patient showed severe OHSS (2%) (Table 3).

Table 3: Incidence and severity of OHSS in cabergoline- and placebo-treated groups

Degree of OHSS	*Cabergoline group (n = 52)*	*Placebo group (n = 50)*	*Total (N = 102)*	*p-value*
Mild; n (%)	20 (38.5)	20 (40)	40 (39.21)	0.728
Moderate; n (%)	9 (17.3)	8 (16)	17 (16.7)	
Severe; n (%)	1 (1.92)	1 (2)	1 (1.0)	

n: Number of patients; N: Total number of patients; p: Probability value (p < 0.05 = statistically significant) measured using chi-square test

Table 4: Assisted reproduction treatment outcomes

Parameters	*Cabergoline group (n = 52)*	*Placebo group (n = 50)*	*p-value*
Total number of ETs	43	42	1.00
Biochemical pregnancy rate (n)	44.2% (19)	54.8% (23)	0.421
Clinical pregnancy rate (n)	32.6% (14)	38.1% (16)	0.665
Implantation rate (n)	21.8% (21)	25% (24)	0.55
Live birth rate (n)	23.3% (10)	28.6% (12)	0.633

n: Number of patients; N: Total number of patients; p: Probability value (p < 0.05 = statistically significant) measured using chi-square test

Effect of Cabergoline and Placebo Treatment on ART Outcomes

The data of all the outcomes measured after ART for both the groups are presented in Table 4.

In the cabergoline group 43 patients (82.6%) and in the placebo group 42 patients (84%) underwent fresh embryo transfer. The CPR showed a higher trend in the placebo group as compared with the cabergoline group (38.1 *vs* 32.6% respectively); but this did not achieve a statistical significance (p = 0.665). The IR and LBR were also higher in the placebo group (25 and 28.6% respectively) as compared with the cabergoline group (21.8 and 23.3% respectively), but the difference was not significant.

DISCUSSION

For ART, OHSS is a major complication of controlled ovarian stimulation (COS). It has a wide range of signs and symptoms that includes enlarged ovaries, increased vascular permeability, ascites, abdominal distention, and discomfort.[20] The pathophysiology of OHSS remains unclear, but the increased capillary permeability and loss of fluid into the third space are the main pathophysiological features.[21] The hCG mediates the release of VEGF-A, which

through its interactions with VEGF R-2 stimulates vascular hyperpermeability, which is observed in OHSS.[14,22] It has been reported that the concentration of VEGF-A is elevated after hCG administration and in patients at risk or with OHSS.[23] Gómez et al,[24] in a mouse OHSS model, reported that after hCG injection there is increased expression of VEGF/VEGF R-2 mRNAs in ovaries which correlated well with increase in vascular permeability, and both reached peak level after 48 hours of hCG injection. Additionally, they observed that the ovary was the main organ producing VEGF, as expression of VEGF mRNA was upregulated in ovary but unchanged in the mesentery.

The prevention of OHSS is necessary at early stage, because it is an iatrogenic and potentially life-threatening condition that affects young healthy women. In addition, OHSS may represent a significant burden, and prevention of OHSS is still a major challenge that reproduction specialists must confront. Special care must be provided aiming at primary prevention for the patients who are under risk. Coasting in a long agonist protocol, cancellation of cycle, elective cryopreservation of embryos, GnRH agonists trigger in an antagonist protocol, using GnRH antagonists rather than GnRH agonist for pituitary suppression, are few of the treatment options that can benefit but do not completely prevent the early and late forms of OHSS and cannot be useful to every patient.

Recently, the use of dopamine agonists as a first pathophysiological approach raised a new hope in the prevention of OHSS.[20,21] Basu et al[25] reported that administration of high dose of dopamine agonist blocks the tumor-related neoangiogenesis and vascular permeability by interfering with VEGF/VEGF R-2 signaling by internalization of VEGF R-2. Some investigators suggested the use of dopamine agonist cabergoline immediately after oocyte retrieval to prevent the harmful effect on follicular growth, oocyte maturation, fertilization rate, or subsequent clinical outcome due to blockage of the VEGF system too early.[26]

Different studies have compared the effect of dopamine agonists like cabergoline, quinagolide, or bromocriptine on the incidence of OHSS. Quinagolide has a much shorter half-life (17 hours) compared with cabergoline (63–69 hours), which minimizes the exposure during organogenesis when used in high doses in an IVF setting. The advantage of cabergoline over bromocriptine is less severe and fewer side effects and longer duration of action results in fewer doses and lesser patient discomfort.[27]

Various studies have evaluated the efficacy of cabergoline as a preventive measure for OHSS. Ata et al[2] reported that the higher dose of cabergoline prevents an increase in the severity of OHSS and its prolongation following the occurrence of pregnancy. Kiliç et al[28] observed the effect of cabergoline in the prevention of OHSS in women at risk undergoing IVF/ICSI treatment cycles. It was observed that prophylactic treatment with the dopamine agonist, cabergoline, significantly reduced the incidence of OHSS in women at high risk undergoing IVF/ICSI treatment.

Leitao et al[17] published a systematic review and meta-analysis of eight randomized controlled studies (n = 858 women) comparing cabergoline *vs* placebo. It was reported that cabergoline group showed a significant reduction in the incidence of severe OHSS [relative risk: 0.38, 95% confidence interval (CI): 0.29–0.51]. Shaltout et al[29] reported that cabergoline at lower doses (0.25 mg) reduces the incidence of OHSS in women at high risk undergoing IVF/ICSI treatment.

A meta-analysis performed by Tang et al[13] showed no significant difference in the CPR [odds ratio (OR): 0.94, 95% CI: 0.56–1.59; two randomized controlled trials (RCTs), 230 women], miscarriage rate (OR: 0.31, 95% CI: 0.03–3.07; 1 RCT, 163 women), or any other adverse effects of the treatment (OR: 2.07, 95% CI: 0.56–7.70; 1 RCT, 67 women) between the cabergoline group and the control group. It was reported that cabergoline appears to reduce the risk of OHSS in high-risk women, especially for moderate OHSS.

In the present study, prophylactic cabergoline did not reduce the incidence of moderate OHSS as compared with the placebo group. One patient in both the groups showed severe OHSS. The rate of incidence of moderate OHSS in the cabergoline group was 17.3% and in placebo group was 16%, which is lower than the reported incidence of moderate OHSS in the control group (43.8%) by Alvarez et al.[16] The threshold value for OHSS prediction (≥13 follicles of 11 mm or more in diameter, and excluding patients with less than 15 retrieved oocytes) was lower compared with their criteria (≥20 follicle of > 12 mm and 20 oocytes retrieved). The observed lesser rate of incidence in the placebo group needs to be explored further. This could also be attributable to the fact that HES was administered to all women in our study as well as control group. Furthermore, there was no significant difference observed between all the parameters like embryo transferred ($p = 1.00$), biochemical positive ($p = 0.421$), CPR ($p = 0.665$), IR ($p = 0.55$), and LBR ($p = 0.633$) in both the groups.

CONCLUSION

The dopamine agonist cabergoline is not an effective option for the prevention of OHSS when used by women who are at high risk for that complication while undergoing ART using long agonist protocol. Although the estimates were imprecise, it was observed that cabergoline does not have a clinically relevant impact on various outcomes, including LBR, CPR, and IR. Large, well-designed RCTs that involve more clinical outcomes are needed to evaluate the effectiveness and optimal dose and investigate the possible side effects when indicating cabergoline for the prevention of OHSS.

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