http://www.ijwhr.net
doi 10.15296/ijwhr.2024.6013
Open Access Original Article
IJWHR
International Journal of Women's Health and Reproduction Sciences
Vol. 13, No. 2, April 2024, 57–62
ISSN 2330-4456

The Early Versus Standard Administration of Cabergoline to Prevent Ovarian Hyperstimulation Syndrome in Patients With Polycystic Ovary Syndrome Undergoing ICSI Cycles: A Randomized Clinical Trial

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Abstract

Objectives: The effect of cabergoline on reducing the incidence rate of ovarian hyperstimulation syndrome (OHSS) has been confirmed by several studies. Currently, what is discussed in this regard is when cabergoline should be started to be most effective in reducing the occurrence and developing rates of OHSS.

Materials and Methods: A clinical trial conducted at Arash Women's Hospital from March to November 2023 included 200 infertile women with polycystic ovary syndrome (PCOS) at risk of OHSS during in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment. Participants were divided into two groups: the experimental group received cabergoline from the start of GnRH antagonist administration for 15 days, and the control group received cabergoline for eight days after oocyte trigger. Measurements of hematocrit (Hct) percentage, serum creatinine (Cr), sodium (Na), and potassium (K) levels, and abdominal circumference were taken three days after ovum pick-up. The study monitored patients until menstruation and focused on the occurrence and severity of OHSS as primary outcomes.

Results: The data analysis showed that the two groups were comparable regarding basic characteristics. In the following, the OHSS rate in the early administration group was significantly lower than the control group (14% vs. 47%, $P<0.001$). In the study group, the severity of all OHSS cases was mild, while the control group reported a moderate severity of OHSS ($P<0.001$).

Conclusions: Earlier initiation of cabergoline from the time of administration of the GnRH antagonist compared to its initiation from the day of oocyte triggering has more effectively reduced the rate and severity of OHSS and improved patient satisfaction.

Trial Registration: The study was registered in the Iranian Registry of Clinical Trials on 2023-05-30 (identifier: IRCT20090526001952N16, https://www.irct.ir) during the recruitment phase.

Keywords: Cabergoline, Polycystic ovary syndrome, Ovarian hyperstimulation syndrome, Drug administration schedule

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder, affecting 4-20% of women worldwide (1), 50% of women with PCOS experience infertility, and 15%-20% of them require assisted-reproductive technology (ART) (2). The main challenge for these patients after controlled ovarian stimulation (COS) is ovarian hyperstimulation syndrome (OHSS), a situation that has been achieved notwithstanding a large number of oocytes; however, their quality is still low. OHSS is an unpleasant and potentially life-threatening disease process that may occur in otherwise healthy young women undergoing COS for ART. OHSS occurs when the ovaries are primed with follicle-stimulating hormone (FSH)/luteinizing hormone (LH) and then exposed to human chorionic gonadotropin (hCG) (3). Severe complications of this syndrome include thrombophilia, renal and pulmonary failure, ovarian torsion, ovarian cyst rupture, and hemorrhagic cysts (4). Since treatment is empirical to a great extent, it can be managed with prevention (5).

Numerous preventive strategies have been utilized for OHSS prevention, including using antagonists rather than agonists for COS, final oocyte triggering with an agonist, metformin therapy, intravenous albumin, cabergoline, corticosteroids, coasting, the freeze-all strategy, and others. However, the reports are controversial, and numerous have not been fundamentally assessed (6,7). Cabergoline, a dopamine-2 receptor agonist used in treating human hyperprolactinemia (category B) in pregnancy, has been proposed to prevent OHSS in ovarian stimulation by inhibiting VEGFR-2 phosphorylation (8). The side effects of this drug include nausea and vomiting, constipation, low blood pressure, dry mouth, and headache (9). In the last Cochrane review published in this field, it was concluded that dopamine agonists reduce moderate to severe OHSS without compromising IVF outcomes. However, more

Received 21 December 2023, **Accepted** 26 March 2024, **Available online** 30 August 2024

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Key Messages

- The early administration of cabergoline in patients with PCOS undergoing COS with the GnRH-antagonist protocol has been associated with a decrease in the severity of OHSS and an increase in patients satisfaction with the treatment.

research is essential to clarify the optimal dose (10).

Different cabergoline utilization protocols were detailed in several studies. The reported dosages were extended from 0.25 to 0.5 mg and initiated on the day of HCG injection or ovum pick-up (7,10-12). Recently, the impact of the timing of cabergoline initiation on the prevention of OHSS has been under consideration (7). On the other hand, therapeutic strategies with reduced treatment burden and reduced risk would be expected to diminish psychological distress and, consequently, the ART treatment drop-out rate (13). With preventive strategies, the rate of severe OHSS has reached zero; however, mild and moderate OHSS have been reported despite these preventive methods, which can affect patients' satisfaction with treatment and their quality of life after ovum pickup. Therefore, choosing a treatment strategy associated with the least treatment complications and the highest patient satisfaction is essential. In the present study, we have tried to minimize the OHSS rate by considering all available strategies, such as the freeze-all approach and continued use of the antagonist after the oocyte trigger. In addition, the present randomized clinical trial was outlined to investigate the effect of early onset versus standard administration of cabergoline on minimizing the OHSS rate and increasing the PCOS patients' satisfaction regarding their treatment cycle.

Materials and Methods

Study Protocol

This randomized clinical trial (RCT) was performed in the department of infertility treatment at Arash Women's Hospital from March 2023 to November 2023. The women in the age range of 18 to 45 years old with a PCOS diagnosis along with a high anti-Müllerian hormone (AMH) level (>3 ng/mL) and/or a high antral follicle count (AFC) >20 who underwent in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles were evaluated. Patients were included in the study after being examined by the infertility fellowship if they met the entry criteria and had written consent. The PCOS diagnosis was determined according to the Rotterdam criteria (16). Patients with a history of allergic reactions to dopamine inhibitor drugs or cabergoline were not included in the study. Additionally, the analysis did not include participants who failed to attend follow-up appointments or did not take their medication as prescribed by the research guidelines.

The eligible patients on the 2nd or 3rd day of the menstrual cycle were allocated into two groups randomly using the block randomization method. The random allocation list for patients was exclusively based on the authority of the epidemiologist, and a block size of four was considered. The study group type was written on 200 cards, respectively, and then placed inside sealed envelopes. Once the physician announced a patient's eligibility, the methodologist provided the doctor with the envelope. The random allocation process and type of intervention were covered by the final outcome's assessor and the data analyzer. Unfortunately, blinding the study was not feasible as both groups were administered the original drug; the only difference lay in the duration of drug usage. The individual assessing the treatment outcomes was unaware of the grouping or treatment type.

Study Groups

Participants were divided into two groups:

- Group A (n=100) (early administration group), the oral tablets of cabergoline (0.5 mg) (Cabolin®, Aburaihan Pharmaceutical Company, Iran) were prescribed daily from the starting administration day of the GnRH antagonist and then continued for 15 days after.
- Group B (n=100) (standard administration group), oral tablets of cabergoline (0.5 mg) (Cabolin®, Aburaihan Pharmaceutical Company, Iran) were administered daily, starting from the day of the oocyte trigger for eight days after.

Ovarian Stimulation Protocol

The same COS protocol (a flexible GnRH-antagonist regimen) was used for all the studied populations. The ovarian quiescence was detected by observing the absence of an ovarian cyst or lead follicle >10 mm and serum E_2 concentrations <50 pg/mL through baseline ultrasounds and hormonal evaluation, which were performed on the 2nd or 3rd day of the menstrual cycle, and then the starting dose of 150 IU of recombinant human FSH (Cinnal-f, Cinagen Company, Iran) was administered daily for five days. The follicular growth monitoring was done through serial vaginal ultrasound assessments, and the dosage of gonadotropins was tailored based on the ovarian response in each patient. When follicle(s) ≥13 mm in average diameter were observed, the administration of a GnRH antagonist (Cetronax®, Ronak Pharmaceutical Company, Iran) (0.25 mg/d subcutaneously) was started, and it was continued until the day of the final oocyte triggering. The final stage of oocyte maturation was triggered by a GnRH agonist (0.2 mg Decapeptyl®, Ferring Pharmaceuticals, Australia) once at least two follicles measuring ≥18 mm in diameter were noted. On the day of oocyte triggering, the serum estradiol was checked, and if it was above 5000, the antagonist ampule was administered for five days after pick-up; otherwise, it was prescribed for three days. After final oocyte triggering, transvaginal ultrasound-guided oocyte retrieval was performed in 35–36 hours. IVF/ICSI was performed with ejaculated sperm into metaphase II

(MII) oocytes through standard procedure. In this study, a "freeze-all" strategy was used.

Examination and Follow-Up Protocol

Clinical and ultrasound assessments were carried out on the day of ovum pick-up and then weekly to detect the occurrence of OHSS. The severity of OHSS was determined based on Golan and co-workers' classification system. The patients who had experienced abdominal distention and discomfort, nausea and vomiting, and/or diarrhea and enlargement of the ovaries (5-12cm) were considered grade 2 (mild OHSS) cases. In moderate forms, ultrasound evidence of ascites has been observed, and severe OHSS has been defined with clinical signs of ascites, hydrothorax, breathing disorders, hemoconcentration (hematocrit [Hct] level >45%), coagulopathy, and renal perfusion decreases. Three days after ovum pick-up day, Hct percentage, serum creatinine (Cr), sodium (Na), and potassium (K) levels, as well as abdominal circumference, were measured in all patients. Women were followed on an outpatient basis via phone contact and visits until menstruation occurred. During the phone calls, the regularity of taking medicines, the side effects of the drugs, and the level of satisfaction of the patients with the type of treatment were followed up.

Statistical Analysis

The primary outcomes in the present study were the occurrence rates of OHSS and its severity. The secondary outcomes included clinical laboratory tests (Hct, Cr, Na, and k) and abdominal circumference three days after ovum pick-up (OPU) day. The Statistical Package for the Social Sciences, version 22, SPSS Inc., Chicago, Illinois, USA (SPSS) was utilized for the data analysis. The Kolmogorov–Smirnov test was used to distinguish the normality of quantitative variables, and it was detected that all of the studied quantitative variables had a normal distribution. The independent student t-test and chi-square test were utilized to compare the quantitative and qualitative variables between groups. The data were presented as mean ± standard deviation (SD) or number (percent) according to the type of variables. A P value < 0.05 was considered a statistical significance level.

The sample size in this research is determined as 100 patients in each group based on the Rubenfeld and Dahan study (14) and by using the following formula, taking into consideration the type 1 error of 5% and the power of 80%, along with P_1 equal to 24% for the early-onset cabergoline group and P_2 equal to 36% for the standard intake of cabergoline group.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times [P_1(1-P_1) + P_2(1-P_2)]}{(P_1-P_2)^2}$$

Results

According to the sampling flowchart, after examining 257 patients, 200 eligible patients who had written consent to participate in the study were randomly included in the study (Figure 1). In Table 1, the basic characteristics of the patients, including age, body mass index (BMI), and the serum level of AMH and the AFC, were compared between two groups, and no significant differences were

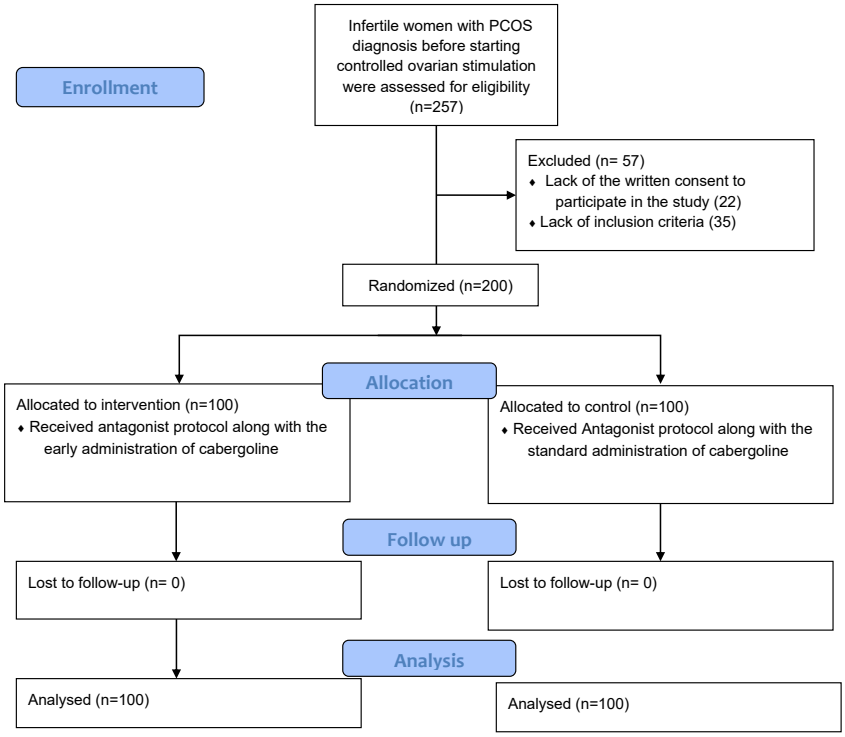

Figure 1. Flowchart of the Study Sampling.

found between groups regarding these variables.

In Table 2, the characteristics of the ovarian stimulation cycle and the results of trigger day clinical tests are compared between the two groups. There were no significant differences between groups in terms of duration of stimulation ($P=0.735$), trigger injection day (P=0.332), serum estradiol level on trigger day ($P=0.866$), and duration of antagonist administration ($P=0.269$). In addition, in the follow-ups, no significant difference was found in the mean levels of Hct percentage ($P=0.948$), serum Cr ($P=0.343$), Na ($P=0.766$), and K ($P=0.599$), as well as the abdominal circumference three days after OPU day, between the two groups ($P=0.075$) (Table 2).

Table 3 compares the occurrence rates of OHSS between groups. The OHSS rate in the early administration group was significantly lower than the control group (14% vs. 47%, P<0.001). In the study group, the severity of all OHSS cases was mild, while in the control group, a moderate severity of OHSS was also reported (P<0.001) (Figure 2). There were no cases of severe or critical OHSS in both groups.

The patient's satisfaction was evaluated using a verbal scale of poor, satisfactory, and good. The patients' satisfaction with early administration of cabergoline was significantly noticeable, so all of them reported good (83%) and satisfactory (17%) results in comparison to the control group reporting good (30%), satisfactory (64%), and poor (6%) results (P<0.001). Patients throughout the study reported no side effects associated with cabergoline use.

Discussion

This study investigated whether the timing of cabergoline administration affects the rate of OHSS in high-risk PCOS patients with the antagonist protocol. The study results showed that the early administration of cabergoline significantly reduced the rate and severity of the syndrome compared to its late onset.

According to the latest network meta-analysis of randomized controlled trials for evaluating the effectiveness of various medicines in the prevention of OHSS, administration of cabergoline was associated with a significant reduction in the incidence of moderate-to-severe OHSS (RR: 0.43, 95% CI: 0.24, 0.71), and the quality of the evidence was ranked as moderate (15). In all previous trials, cabergoline was administered after the day of oocyte triggering.

Currently, the effect of cabergoline on reducing the incidence rate of OHSS has been confirmed by several studies, so recent studies compare the use of cabergoline

Table 1. Demographic and Clinical Characteristics of Study Participants in Two Groups

Variables	Early Administration (n=100)	Standard Administration (n=100)	*P* Value
Female age (y)	30.95±4.86	31.36±5.74	0.587
Body mass index (kg/m²)	27.14±3.04	27.91±4.06	0.128
Serum level of anti-Müllerian hormone (ng/mL)	6.23±3.60	5.81±3.46	0.400
Antral follicle count	25.58±3.06	24.86±2.80	0.085

Descriptive data were compared using the independent student's t-test and presented as Mean ± SD. *P* value ≤ 0.05 was considered statistically significant.

Table 2. Comparison of COS Cycle Outcomes in the Two Study Groups

Variables	Early Administration (n=100)	Standard Administration (n=100)	*P* Value
Duration of stimulation (day)	10.79±1.24	10.86±1.63	0.735
Total number of injected antagonist ampules	5.54±1.91	5.28±1.34	0.269
Estradiol level on trigger day (pg/mL)	3269.1±862.8	3295.6±1306.3	0.866
Serum creatinine on 3 days after OPU day (mg/dL)	0.78±0.12	0.80±0.13	0.343
Hematocrit on 3 days after OPU day (%)	39.67±2.50	39.65±2.83	0.948
Serum Na on 3 days after OPU day (mEq/L)	140.13±1.59	140.06±1.72	0.766
Serum K on 3 days after OPU day (mEq/L)	4.58±0.12	4.57±0.12	0.599
Abdominal circumference (cm) on ovum pick-up day	86.87±5.74	88.20±4.75	0.075

Descriptive data were compared using the independent student's t-test and presented as Mean ± SD. *P* value ≤ 0.05 was considered statistically significant.

Table 3. Comparison of Occurrence Rate of OHSS and its Severity in the Studied Groups

Variables		Early Administration (n=100)	Standard Administration (n=100)	*P* Value
OHSS	No	86 (86%)	53 (53%)	<0.001
	Mild	14 (14%)	36 (36%)	
	Moderate	0 (0%)	11 (11%)	

P value ≤ 0.05 was considered statistically significant.

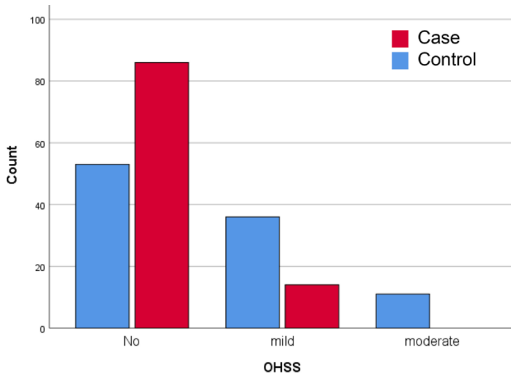

Figure 2. The Incidence and Severity of OHSS in Two Studied Groups.

as a routine method against newer experimental methods (16). What is discussed in this regard is when cabergoline should be started to be most effective in reducing the occurrence and developing rates of OHSS. To our knowledge, a few studies have investigated the effect of using cabergoline during ovarian stimulation to prevent OHSS. In the first report, Seow and co-workers investigated the effect of starting cabergoline at the time of oocyte triggering on COS outcome and OHSS rate in high-risk patients (17). They concluded that starting cabergoline at the time of triggering does not negatively impact IVF outcomes; however, they found no difference in the incidence of OHSS between groups (17). Later, Rubenfeld and Dahan, in a retrospective study, reported that starting cabergoline administration at the time of triggering has a significant impact on the rate of mild and moderate OHSS in comparison to its administration at the time of OPU (24% vs. 36%; $P=0.045$). Therefore, they recommended more prospective studies to support their findings (14). Elsewhere, Gaafar and colleagues, in a case series study, evaluated 126 high-risk patients prepared for ICSI using the fixed antagonist protocol; when the size of the leading follicle reached 15 mm, cabergoline was prescribed (0.5 mg/d) for eight days. They reported that severe and moderate OHSS incidences were 0.9% and 9.5%, respectively. They concluded that the early onset of cabergoline is a safe and potentially more effective method for preventing OHSS in high-risk cases (18).

In the present study, we investigated the onset of cabergoline administration even earlier from the starting day of the GnRH antagonist than starting cabergoline administration at the time of oocyte triggering. Similarly, Abd El-Azeem et al, in a clinical trial, investigated the effect of early intake of cabergoline in the prevention of the development of OHSS in high-risk women undergoing ovulation induction using the GnRH agonist down-regulation protocol for the ICSI cycle (7). In agreement with our finding, it was found that the early administration of cabergoline has significantly reduced the incidence of OHSS compared to its routine administration method (42.5% vs. 80%, P=0.002). Furthermore, they concluded that this approach is effective in the prevention of early OHSS without compromising pregnancy rates (7). Because in various studies, the protocol of ovarian stimulation, the type of drug used for oocyte triggering, and the duration of cabergoline administrations are different, it is impossible to have a detailed comparison and discussion.

In the present study, no remarkable difference in clinical laboratory tests and abdominal circumference size three days after OPU day was found between groups, considering that there is no similar study with a completely similar protocol to ours; therefore, more studies are needed for discussions in this field. Considering that the occurrence rate of OHSS and its severity were higher in the group of patients taking cabergoline routinely, it was expected that the changes in clinical tests and abdominal circumference in these patients would also be different from the group with an early onset of cabergoline. It seems that studies with larger sample sizes are required in this regard.

In ART treatment cycles, the patient's satisfaction, experience, and well-being during the treatment process are essential; therefore, finding treatment strategies with the least complications and the highest level of patient satisfaction is one of the main goals of treatment. The present study found that the early use of cabergoline to prevent the development of OHSS and its complications, such as ascites, was associated with greater patient satisfaction.

The strength of the study was its design as a clinical trial with an appropriate sample size. It should be noted that applying a GnRH agonist trigger and a freeze-all strategy limitation allows us to conclude the impact of cabergoline timing on severe OHSS as well as on late-onset OHSS and pregnancy rate. It should be noted that the present study had potential constraints of the research design, such as the lack of blinding, limited generalizability, and possible confounding factors. It is recommended that researchers take these crucial factors into account in future studies with a more extensive sample size.

Conclusions

Based on the findings, earlier initiation of cabergoline from the time of GnRH antagonist administration compared to its initiation from the day of oocyte triggering has more effectively reduced the rate and severity of OHSS and improved patient satisfaction. Further studies are recommended to investigate the impact of earlier initiation of cabergoline on COS outcomes as well as late-onset OHSS and the pregnancy rate in non-PCOS women who are candidates for the GnRH-agonist protocol.

Directions for Future Research

It is suggested that in future double-blind, randomized clinical trials, the effects of early administration of cabergoline during other COS protocols, such as GnRH-agonists on ovarian stimulation outcomes, as well as late-onset OHSS and pregnancy rates, would be evaluated in non-PCOS patients who have other risk factors for

excessive ovarian response.

Authors' Contribution

Conceptualization: Ashraf Moini .
Data curation: Roza Shahhosseini, Farzaneh Alemohammad, Najmeh Zarei.
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Methodology: Ladan Kashani.
Project administration: Roza Shahhosseini.
Supervision: Ashraf Moini.
Visualization: Nazanin Hajizadeh.
Writing–original draft: Roza Shahhosseini.
Writing–review & editing: Ashraf Moini, Nazanin Hajizadeh, Ladan Kashani, Maryam Farid Mojtahedi, Farzaneh Alemohammad, Farah Ghasemi, Najmeh Zarei.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The Institutional Review Boards and the Ethics Committees of Tehran University of Medical Sciences approved this study (approval code: IR.TUMS.MEDICINE.REC.1401.806).

Financial Support

The study did not have any funding support.

Acknowledgments

We would like to thank all the participants and co-workers at Arash Women's Hospital for their assistance in this study.

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