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Randomized trial of combined cabergoline and coasting in preventing ovarian hyperstimulation syndrome during in vitro fertilization/intracytoplasmic sperm injection cycles

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Abstract

Objective: To assess the efficacy of coasting alone, cabergoline alone, or combining both interventions for preventing ovarian hyperstimulation syndrome (OHSS) among high-risk patients undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment cycles.

Methods: The present randomized controlled trial was conducted at the IVF unit of a university hospital in Cairo between October 28, 2013, and July 31, 2015. Patients undergoing IVF/ICSI considered at risk of OHSS were randomly allocated to coasting, cabergoline, or combined coasting and cabergoline. The primary outcome was the rate and degree of symptomatically assessed OHSS. Data were analyzed on a per-protocol basis.

Results: There were 100 patients recruited to each group. The occurrence of early OHSS was lowest in the combination group compared with the other groups (P=0.002).

Conclusion: Combining coasting and cabergoline was associated with a lower OHSS rate compared with either therapy alone.

ClinicalTrials.gov: NCT01984320

KEYWORDS

Dopamine agonist; IVF/ICSI; Long luteal agonist protocol; OHSS; Withholding gonadotropins

1 | INTRODUCTION

The most troublesome iatrogenic adverse event associated with assisted reproductive techniques, as well as simple ovulation induction, is ovarian hyperstimulation syndrome (OHSS).

An important aim of fertility treatment is to prevent OHSS from happening. Many methods have been adopted with this objective, and the oldest is coasting. The technique was first described by Rabinovici et al.[1] and was first applied during in vitro fertilization (IVF) by Sher et al.[2] In coasting, gonadotropin-releasing hormone (GnRH) agonist treatment is continued and gonadotrophins are stopped until estradiol (E2) levels drop to a safe level for the initiation of human chorionic gonadotrophin (hCG) triggering.[1,2]

Although coasting has many advantages, including not cancelling cycles, and not requiring any additional procedures or medical therapies, it has also been thought to be associated with lower pregnancy rates compared with other preventive measures. It has been suggested that it lowers the quantity of oocytes retrieved through reducing external gonadotrophins for a variable amount of time.[3,4]

The vascular permeability associated with OHSS has been suggested to result from vascular endothelial growth factor use and the use of cabergoline—a dopamine agonist—has been identified to reduce this permeability and aid pregnancy outcomes.[5–7] Consequently, cabergoline has been evaluated in several studies for the prevention of moderate and severe OHSS.[8,9]

The aim of the present study was to assess the effect of coasting alone, cabergoline alone, or combining both interventions to prevent OHSS among patients considered at high risk of developing OHSS.

2 | MATERIALS AND METHODS

The present randomized trial was performed at Kasr AlAini IVF Center, Cairo University, Egypt, between October 28, 2013, and July 31, 2015. Patients who were considered at high risk of developing OHSS were evaluated for eligibility. Eligible patients were aged 20–35 years, had a body mass index (calculated as weight in kilograms divided by the square of height in meters) of up to 30, had long GnRH agonist protocol treatment cycles, had E2 levels of at least 3500 pg/mL on the day of hCG administration, and had more than 15 oocytes collected on ovum pickup day. Patients who were experiencing infertility that was due to male and uterine factors were excluded. The institutional review board of Cairo University approved the study prior to enrolment. At enrolment, all couples with eligible patients had the study clearly described and provided informed consent to participate.

Quickcalcs (Graphpad, La Jolla, CA, USA) was used to perform a block randomization, with a block size of four, to generate group assignments to three groups: coasting, cabergoline, and coasting with cabergoline. Assignments were concealed in sealed opaque envelopes until enrolment. Both patients and investigators were unmasked to group assignments at enrolment.

Patients in all three groups began the same long GnRH agonist protocol; they received 0.1 mg of subcutaneous triptorelin (Decapeptyl, Ferring, Kiel, Germany), a GnRH agonist, from day 21 of a cycle before receiving a 225-IU/day injection of human menopausal gonadotropin (hMG) (Merional; Institut Biochimque SA, Pambio Noranco, Switzerland) on day 3 of the following cycle once down regulation was confirmed (endometrial thickness below 5 mm and/or an E2 level below 50 pg/mL); this was accompanied by a reduction in GnRH agonist dose to 0.05 mg daily. On day 6, hMG folliculometry began using transvaginal ultrasonography, and E2 levels were recorded on days 8, 10, and 12.

During IVF/intracytoplasmic sperm injection (ICSI) cycles, patients assigned to the coasting group stopped receiving hMG for 1–3 days until safe E2 levels were obtained; agonist injections continued. Patients assigned to the cabergoline group received 0.25 mg/day of cabergoline (Dostinex; Pfizer, Montreal, QC, Canada) during their IVF/ICSI cycle for 8 days following hCG administration. In the coasting and cabergoline group, participants stopped receiving hMG for 1 day while continuing agonist injections and received 0.25 mg/day of cabergoline for 8 days from hCG administration.

Final triggering was performed with 10 000 IU of hCG (Choriomon; Institut Biochimque SA); 36 hours later, oocyte collection was performed with transvaginal ultrasonography. Embryo transfer was performed 3 days later with abdominal ultrasonography guidance. The protocol included the transfer of a maximum of two embryos. Any surplus embryos were cryopreserved. Vaginal suppository of 400 mg of cyclogest (Alpharma, Bradford, UK) was administered twice daily for luteal phase support. Participants underwent quantitative estimation of serum β-hCG levels 14 days after embryo transfer.

On the day of embryo transfer and 7 days later, patients were examined to detect early OHSS. Late OHSS was evaluated 14 days after embryo transfer. Cycles were canceled if early OHSS was observed on embryo transfer day and all embryos were cryopreserved to be transferred during future cycles.

The primary outcome was the rate and degree of OHSS. OHSS was symptomatically assessed based on the presence of nausea, vomiting, shortness of breath, abdominal pain, abdominal distension, ovarian size, ultrasonography-assessed fluid in the Douglas pouch, hematocrit, total leucocyte count, and creatinine and E2 levels. The degree of OHSS was classified per Golan et al.[10]

Secondary outcomes included the number of oocytes collected, the number of metaphase II oocytes collected, the fertilization rate (ratio of fertilized oocytes to the number of oocytes collected), the number of embryos (number of embryos assigned for embryo transfer in each participant), the implantation rate (ratio of the number of gestational sacs to the number of embryos transferred), the chemical pregnancy rate (defined by >50 IU/L hCG followed by a drop in hCG levels and menstruation), the clinical pregnancy rate (visible intrauterine gestational sac on transvaginal ultrasonography 14 days after positive pregnancy test result, with positive fetal pulsations), the early spontaneous abortion rate (spontaneous termination of pregnancy before 12 weeks), the ongoing pregnancy rate (pregnancies beyond 12 weeks in duration), and the live delivery rate (number of achieved live deliveries). All rates were calculated per cycle started and per embryo transfer.

To prevent a type II error, the necessary sample size was calculated. Earlier data[11] demonstrated an OHSS rate among patients treated with coasting of 23.3%, and 3.3% among patients treated with cabergoline. With a type-I error rate of 0.05, a group size of 72 patients was calculated; enrolment continued until 100 patients had been recruited to each group to account for loss to follow-up.

Data were expressed as mean ± SD, or frequency and percentage where appropriate. Numerical variables were compared between the study groups using the one way analysis of variance (ANOVA) test with post-hoc multiple two-group comparisons. Categorical data were compared using the χ^2 test. Per-protocol analyses were performed using SPSS version 22 (IBM, Armonk, NY, USA) and $P<0.05$ was considered statistically significant.

3 | RESULTS

In total, 300 patients were enrolled and no patients were lost to follow-up (Fig. 1). However, several cycles in each group were cancelled owing to the occurrence of early OHSS. All patients were managed according to institutional protocols and embryos were cryopreserved for transfer during future cycles. Baseline characteristics were similar between the groups, with no difference in age, body mass index, infertility duration, and type of infertility (Table 1).

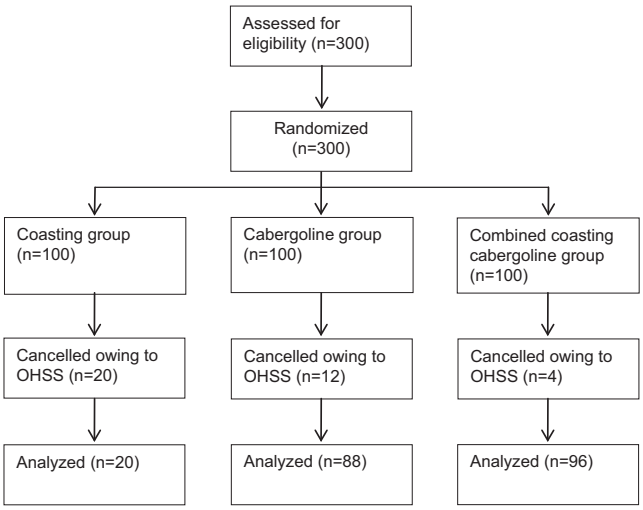

FIGURE 1 Flow chart of patient recruitment. Abbreviation: OHSS, ovarian hyperstimulation syndrome.

The total hMG dose was significantly lower among patients assigned to the coasting group compared with the other groups. Fewer follicles 15–17 mm in size and 10–14 mm in size were observed in the combination group compared with the coasting or cabergoline only groups (Table 2). The total number of oocytes collected, and the number of metaphase II oocytes collected were lower in the coasting group compared with the other groups (Table 2).

TABLE 1 Patient characteristics.[a]

Variables	Coasting group (n=100)	Cabergoline group (n=100)	Combined coasting and cabergoline group (n=100)	*P* value
Age, y	27.7 ± 3.9	27.8 ± 3.7	27.5 ± 4.1	0.796
BMI	26.1 ± 3.2	26.9 ± 2.6	26.8 ± 2.6	0.079
Duration of infertility, y	4.6 ± 2.1	4.5 ± 1.7	4.9 ± 1.6	0.302
Type of infertility				0.987
Primary	50 (50)	51 (51)	51 (51)	
Secondary	50 (50)	49 (49)	49 (49)	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).
[a]Values are given as mean ± SD or number (percentage), unless indicated otherwise.

The incidence of early OHSS was lowest in the combination coasting and cabergoline group compared with the other groups (Table 3). The incidence of early mild OHSS was also lower in the combination group. When early moderate OHSS and early severe OHSS were combined, the incidence was also lowest among patients in the combination group.

The proportion of cycles that reached embryo transfer was highest among patients in the combined group (Table 3). No differences were

TABLE 2 Cycle characteristics.[a]

Variables	Coasting group (n=100)	Cabergoline group (n=100)	Combined coasting and cabergoline group (n=100)	*P* value
Duration of hMG treatment, d	11.3 ± 1.4	10.9 ± 1.4	11.0 ± 1.3	0.202
Total hMG dose, IU	2499 ± 488	2672 ± 737	2739 ± 726	0.031
E2 levels on day 8, pg/mL	2120 ± 958	1835 ± 1361	1828 ± 1203	0.141
E2 levels on day 10, pg/mL	3916 ± 1318	3624 ± 2638	3886 ± 2279	0.147
E2 levels on hCG day, pg/mL	4850 ± 1444	4838 ± 2627	5434 ± 2990	0.146
No. of follicles >17 mm on day of hCG	12.9 ± 3.4	12.9 ± 5.7	13.8 ± 5.2	0.291
No. of follicles 15–17 mm on day of hCG	9.2 ± 2.6	9.1 ± 2.1	6.6 ± 1.4	<0.001
No. of follicles 10–14 mm on day of hCG	8.1 ± 1.6	8.0 ± 1.2	4.9 ± 1.2	<0.001
Endometrial thickness, mm	11.0 ± 1.3	11.2 ± 1.4	11.2 ± 1.2	0.495
No. of oocytes collected	16.1 ± 6.2	17.9 ± 3.8	18.1 ± 5.4	0.014
No. of MII oocytes	10.7 ± 4.4	11.6 ± 2.5	13.1 ± 4.2	<0.001
No. of fertilized oocytes per cycle started	9.8 ± 2.3	9.9 ± 3.8	10.3 ± 3.1	0.505
No. of fertilized oocytes per embryo transfer	9.1 ± 1.8	9.2 ± 2.3	9.6 ± 2.8	0.267
No. of embryos transferred per cycle started	1.6 ± 0.4	1.6 ± 0.5	1.7 ± 0.4	0.767
No. of embryos transferred per embryo transfer	1.8 ± 0.3	1.9 ± 0.2	1.9 ± 0.2	0.278
No. of frozen embryos per cycle started	3.4 ± 2.8	3.1 ± 3.2	3.1 ± 3.3	0.818
No. of frozen embryos per embryo transfer	2.6 ± 2.5	2.5 ± 2.8	2.9 ± 3.2	0.622
No. of cycles with frozen embryos per cycle started	64/100 (64)	53/100 (53)	49/100 (49)	0.087
No. of cycles with frozen embryos per embryo transfer	44/80 (55)	41/88 (47)	45/96 (47)	0.467

Abbreviations: hMG, human menopausal gonadotropin; E2, estradiol; hCG, human chorionic gonadotropin; MII, metaphase II.
[a]Values are given as mean ± SD or number/number (percentage), unless indicated otherwise.

TABLE 3 Reproductive outcomes.[a]

Variables	Coasting group (n=100)	Cabergoline group (n=100)	Combined coasting and cabergoline group (n=100)	*P* value
Cycles reaching embryo transfer	80/100 (80)	88/100 (88)	96/100 (96)	0.002
Fertilization rate per cycle start, %	55.2	55.8	56.6	0.242
Fertilization rate per embryo transfer, %	55.2	57.4	56.1	0.102
Implantation rate per cycle started, %	36.5	42.1	46.1	0.323
Implantation rate per embryo transfer, %	45.6	47.7	47.9	0.935
Chemical pregnancies per cycle started	57/100 (57)	59/100 (59)	65/100 (65)	0.485
Chemical pregnancies per embryo transfer	57/80 (71)	59/88 (67)	65/96 (68)	0.821
Clinical pregnancies per cycle started	46/100 (46)	49/100 (49)	56/100 (56)	0.349
Clinical pregnancies per embryo transfer	46/80 (58)	49/88 (56)	56/96 (58)	0.934
Single intrauterine sac	32/46 (70)	34/49 (69)	38/56 (68)	0.779
Double intrauterine sacs	14/46 (30)	15/49 (31)	18/56 (32)	0.779
Early spontaneous abortions per cycle started	6/100 (6)	8/100 (8)	8/100 (8)	0.822
Early spontaneous abortions per embryo transfer	6/80 (8)	8/88 (9)	8/96 (8)	0.933
Ongoing pregnancies per cycle started	40/100 (40)	41/100 (41)	48/100 (48)	0.813
Ongoing pregnancies per embryo transfer	40/80 (50)	41/88 (47)	48/96 (50)	0.990
Live deliveries per cycle started	40/100 (40)	41/100 (41)	48/100 (48)	0.813
Live deliveries per embryo transfer	40/80 (50)	41/88 (47)	48/96 (50)	0.990
Early OHSS	20/100 (20)	12/100 (12)	4/100 (4)	0.002
Mild	11/100 (11)	9/100 (9)	2/100 (2)	0.037
Moderate	6/100 (6)	2/100 (2)	1/100 (1)	0.090
Severe	3/100 (3)	1/100 (1)	1/100 (1)	0.443
Moderate or severe	9/100 (9)	3/100 (3)	2/100 (2)	0.039
Late OHSS	0	1/100 (1)	0	0.367

Abbreviation: OHSS, ovarian hyperstimulation syndrome.
[a]Values are given as number/number (percentage) unless indicated otherwise.

recorded in the fertilization rate, embryo transfer number, cryopreserved embryo number, implantation rate, chemical pregnancy rate, clinical pregnancy rate, early spontaneous abortion rate, ongoing pregnancy rate, and live delivery rate between the groups, both when outcomes were considered per cycle started or per embryo transfer (Table 3).

It was not possible to assess the total number of live deliveries from all the fresh and cryopreserved embryo transfer cycles owing to only some patients having embryos replaced.

Exploratory follow-up was performed for patients who had their cycles cancelled. Among patients from the coasting group, there were 126 embryos cryopreserved from 20 cancelled cycles; in the cabergoline group, 91 embryos were cryopreserved from 12 cancelled cycles; and 28 embryos were cryopreserved from the four cycles cancelled in the combination group. These patients all had embryo transfers during future cycles that resulted in nine live deliveries in the coasting group (including one twin pregnancy), five live deliveries in the cabergoline group, and one live delivery in the combination group; there was no difference between these groups (P=0.824).

Exploratory analysis of the rate of hospitalization and paracentesis indicated that this rate was similar among the three groups (P=0.443); it was only required in severe OHSS and one patient with moderate OHSS in the coasting group.

4 | DISCUSSION

The present, open-label randomized trial demonstrated a significantly lower rate of early OHSS among patients who received combined coasting and cabergoline treatment; reproductive outcomes were similar among the three groups. To the best of our knowledge, the present study was the first to combine coasting with the use of a dopamine agonist to prevent OHSS.

In a Cochrane review by Tang et al.,[9] there were three trials that drew a comparison between a dopamine agonist with co-intervention and a co-intervention; none of these studies included a combination of coasting with a dopamine agonist to reduce OHSS.

Coasting is a well-known and effective method for preventing OHSS, provided it is performed in line with proper guidelines. A recent Cochrane review[12] reported coasting to be a promising intervention for OHSS that requires further research.

A review by Aboulghar[13] asserted that coasting should involve stopping follicle-stimulating hormone treatment and following E2 levels until they drop to safe levels before introducing hCG. Apoptosis of granulosa cells is initiated; this reduces E2 and vascular endothelial growth factor levels. Consequently, large follicles will continue growing while smaller ones will arrest. Aboulghar concluded that complete

prevention of OHSS via coasting is not possible, although it does reduce its rate, and that coasting for more than 3 days would worsen pregnancy rates.[13]

Many studies[3,4,14–16] have confirmed the benefits of coasting, and that outcomes are highly depended on multiple factors; these factors include when to begin coasting, the duration of coasting, and the level of E2 to trigger at. Coasting for more than 4 days has been associated with reduced implantation and pregnancy rates. Therefore, coasting was limited to a maximum of 3 days in the present study.

In the present study, cabergoline, a dopamine agonist, was used to reduce the rate of OHSS both alone and the combination with coasting for 1 day. The daily dose of 0.25 mg for 8 days from hCG trigger was selected; this dose has been used effectively to prevent OHSS in a previous study,[17] with a 50% reduction in OHSS reported.

Different cabergoline regimens have been used across various studies, with none proving to be superior; consequently, there is no consensus on the ideal dosage.[5,18–21] A recent Cochrane review[9] concluded that, when compared with placebo or no intervention, using a dopamine agonist was associated with a lower risk of developing moderate or severe OHSS without influencing pregnancy outcomes; this contradicted data from an earlier systemic review and meta-analysis[22] that reported that dopamine agonists did not reduce moderate or severe OHSS.

Among four previous studies[11,23–25] comparing cabergoline with coasting (0.5 mg of cabergoline daily for 7 or 8 days after hCG administration vs coasting with gonadotropin administration withheld until serum E2 levels were below 3000 pg/mL or serum E2 levels started to decline before hCG administration), all concluded that there were no differences between the two interventions with regard to the incidence of severe or moderate OHSS.

In the present study, the combination group demonstrated a lower incidence of OHSS, facilitating more cycles to reach embryo transfer; this helps to avoid cancellation, which can be devastating for couples undergoing fertility treatment. Although the triggering E2 level was higher in the combination group, combining two simple effective interventions to the treatment cycle allowed for shorter coasting duration and lower OHSS rates, with similar reproductive outcomes to using either of the two interventions alone.

A major limitation to the present study was that a GnRH antagonist protocol was not used. Consequently, the use of agonist trigger in an antagonist cycle was not available to study patients and it was not possible to change the recruiting protocol.

In conclusion, both coasting and cabergoline were effective methods to reduce the rate of OHSS, but neither eliminated it. The combination of coasting and cabergoline in treatment cycles appeared to be a practical method to prevent OHSS, without affecting reproductive outcomes.

AUTHOR CONTRIBUTIONS

YAB contributed to the conception of the study, data collection, and writing and reviewing the manuscript. DMRD contributed to the conception of the study, and writing and revising the manuscript. YAB contributed to data collection and analysis, and revising the manuscript. NMS, HMG, and AAH contributed to data collections and revising the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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