Original Article

Calcium infusion plus or minus cabergoline for prevention of ovarian hyperstimulation syndrome: Randomized double-blind placebo-controlled trial

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ABSTRACT

Aim: To evaluate the interaction of adding oral cabergoline (OC) to calcium infusion as a preventive modality for ovarian hyperstimulation syndrome (OHSS) in risky women undergoing controlled ovarian hyperstimulation (COH) in context of in- vitro fertilization (IVF) / intracytoplasmic sperm injection (ICSI).

Patients and Methods: This prospective, double-blind, randomized, placebo-controlled trial was conducted at Benha IVF center of Obstetrics and Gynecology Department of Benha University and Nour Al Hayah Fertility Center Between January 2015 and February 2016. 220 risky women for OHSS undergoing ICSI were included, they were randomized to 110 women received once daily OC for eight days, starting at HCG triggering and infusion of calcium gluconate 10 ml 10% in 200 ml 0.9% saline daily for 4 days beginning at ovum pick up (OPU), coined as calcium infusion plus group (CI+) and 110 women received only calcium infusion in the same fashion as in CI+ coined as calcium infusion minus group (CI-). The primary outcome was the overall incidence of OHSS while the secondary issues were OHSS types and grades as well as other ICSI outcomes.

Results: The incidence of overall OHSS was significantly lower in calcium infusion plus oral cabergoline (CI+) group compared to calcium infusion alone (CI-) group [8/110(7.2%) in CI+ versus 18/110 (16.3%) in CI- with difference in proportion percentage point (ΔPP)=-9.1%, 95% CI: -0.49, -17.4; *P = 0.036*]. Despite the incidence of moderate and severe OHSS was lower in CI+ than in CI-, this difference didn't reach the significance level (2.7% vs 5.4%; *p = 0.3*) and (0.9% versus 2.7%;), respectively. The other COH and ICSI outcomes didn't show any statistically significant differences.

Conclusion: Adding oral cabergoline to calcium infusion is effective than calcium infusion alone in the reduction of overall OHSS incidence as well as its severity at comparable pregnancy outcomes.

Key Words: Calcium infusion (CI), intracytoplasmic sperm injection (ICSI), oral cabergoline (OC), Ovarian hyperstimulation syndrome (OHSS), polycystic ovary syndrome (PCOS), randomized clinical trial (RCT)

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is the most potentially dangerous iatrogenic sequel of controlled ovarian hyperstimulation (COH) as well as it is associated with significant morbidity and mortality in context of assisted reproductive technology (ART) cycles [1,2,3,4]. OHSS incidence varies greatly in literatures, owning to existence of several OHSS grading systems with a vague definition of different stages, without specific cut-off values as well as incorporating of subjective and objective parameters [5,6,7]. According to Toftager *et al.*[8] depended on Golen criteria in long agonist protocol (LAP), the incidence of mild, moderate and severe OHSS was 31.9%, 15.6% and 8.9%, respectively, in broad largely unselected ART candidates (n = 495) with varying ages, infertility causes as well as OHSS risks. OHSS manifested clinically by groups of symptoms and signs related to increased vascular permeability with serous sacs fluid collection as ascites, pleural effusion, abdominal discomfort and enlarged ovaries[2]. OHSS may occur early within nine days of triggering with human chronic gonadotrophin (HCG), coined as early onest OHSS or later after ten days, where in this state the trigger is the endogenous trophoblastic HCG and coined as late onest OHSS[9].

HCG action on gonadotrophic stimulated ovaries is the triggering of OHSS where numerous proinflammatory mediators were produced including vascular endothelial growth factor (VEGF), interleukin 6 (IL6), angiotensin II (AGII), insulin-like growth factor I (IGF-I), epidermal growth factor (EGF) a and b, interleukin Ib (IL-Ib) and basic fibroblast growth factor (beta-FGF). These mediators

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increase vascular capillary permeability either directly or indirectly where the chef player is VEGF with subsequent fluid leakage in third spaces including serous sacs as well as hemoconcentration[3].

A lot of preventive strategies have been accessed targeting different points in OHSS pathophysiologic cascade to lower the incidence and the severity of OHSS including cycle cancellation[10], coasting[11], freeze all[10, 15], intravenous fluids infusion as calcium infusion[12], albumin[13], hydroxyethyl starch[14], replacing HCG triggering by GnRH agonist in antagonist protocol[15], utilizing antagonist protocol in risky ART population of OHSS instead of classic agonist protocol[8] as well as replacing against by antagonist during COH if there is anticipated hyper-response[16] and dopamine agonist as cabergoline[9, 17, 18]. However, all these evaluated strategies did not wholly eliminate OHSS especially after HCG administration in the course of COH in context of ART cycles. There were trials assessing clinical usefulness of cabergoline and calcium infusion against placebo[9,13,14] as well as trials comparing cabergoline versus albumin infusion[20,21], coasting[22], calcium infusion[23], however, the study could not found trials evaluating the interaction effect of adding cabergoline to calcium infusion in preventing OHSS. This trial aimed at exploring the value of adding oral cabergoline to calcium infusion to avoid OHSS in context of ART cycles in women at high risk for OHSS development.

PATIENTS AND METHODS

This prospective randomized, parallel group, concealed allocation, double-blinded, placebo-controlled trial was conducted at Benha University IVF center, Obstetrics and Gynecology Department, Benha University Hospital, Al Kalubia, Egypt and Nour Al Hayah Fertility Center, Nasr city, Cairo, Egypt from January 2015 to February 2016. An approval of the study protocol was obtained from Benha Faculty of Medicine Ethics Committee and all participants in the study signed written informed consent.

All ICSI scheduled women who were at high risk for occurrence of OHSS in the period between January 2015 and February 2016 were counseled to participate with aids of written and verbal information describing the trial. Women were considered risky to OHSS if they had one of the following : Polycystic ovaries (PCOS) (i.e., 24 antral follicles present in basal transvaginal ultrasound (TVS)), prior episodes of OHSS, more than 20 follicles of 8-12 mm seen in TVS earlier during COH, high serum estradiol (SE_2) at HCG trigger ($SE_2 \geq 3000$ pg/ml or rapidly rising SE_2) or more than 20 retrieved oocytes. All included women underwent complete fertility workup including history taking, physical examination, TVS, hormonal profile and preinclusion assessment of cardiac status to detect women at risk for the possible toxic effect of calcium infusion as women with arrhythmia and those on digitalis. The exclusion criteria included all women who had either endocrinopathies as congenital adrenal hyperplasia, diabetes mellitus or hyperprolactinemia as well as women with systemic illness as hypertension, bronchial asthma, bleeding disorders or whom at risk from calcium infusion.

Women were enrolled sequentially and randomly assigned to calcium infusion alone (CI-) or calcium infusion plus oral cabergoline (CI+) at 1: 1 ratio. A different sized blocked randomized treatment allocation was created by the trial statistician with aids of a random computer generator and stored by the trial investigator (A.S.E). Women were assigned to either CI- or CI+ when they return to investigators with results of pretrigger SE_2. Patients and staff who followed up them were double-blinded after randomization.

In calcium infusion plus oral cabergoline group (CI+) one tablet 0.5 mg oral cabergoline taken daily for eight days starting at night of HCG triggering [9,17,18] (cabergamoun 0.5 mg, AMON pharmaceutical Co, SAE, El-Obur City, Cairo, Egypt) and 10 ml IV 10% calcium gluconate in 200 ml, 0.9% saline solution were given on day of ovum pick up (OPU) over 30 minutes and this is repeated on day 1, 2 and 3 after OPU[12,19,23]. In calcium infusion alone group (CI-), Dummy tablets are taken at night of HCG administration and continuing for eight days as well as starting calcium infusion in the same fashion as stated in (CI+) group.

All ART cycles in this trial were ICSI cycles through long luteal agonist protocol (LAP), in which the patients intake combined oral contraceptive pills (COCs) on day 4 of preceding cycle then on day 20 of the cycle subcutaneous GnRh agonist triptorelin (0.1 mg Decapepthyl; ferring, Germany) injection were continued till documented down regulation (TVS endometrial thickness < 5 mm or/and SE2 < 50 pg/ml) at day two of next cycle, where GnRh agonist dose reduced to half and COH started with intramuscular HMG injection (Merional; IBSA, Switzerland) at 150300- in daily according to women's age, antral follicle count, basal FSH level, and previous ovarian response, follow up usually started on day 5 of stimulation with TVS folliculometery and SE_2 measurements where if necessary gonadotrophin (Gn) dose was adjusted. When at least three follicles ≥ 18 mm, ovulation triggered with 10,000 IU HCG (Choriomon; IBSA, Switzerland). OPU has scheduled 3436- hours Post HCG injection with aids of TVS and OPU suction machine. Day 3 good quality maximally three embryos were transferred under transabdominal ultrasound (AUS) guidance usually with labotect embryo transfer catheter (Labor-technical, USA). Luteal support started one day after OPU with vaginal progesterone suppositories (400 mg prontogest; IBSA, Macryl, Egypt). All included women were monitored on an outpatient basis at OPU day, embryo transfer day, then biweekly via phone contact until menstruation occurred or until detected fetal heart activity in pregnant women.

Women were accessed clinically, laboratory as well as with AUS and TVS to detect the occurrence of OHSS. Also, all women were instructed to contact a member of infertility unit where OPU was done if they were complaining of breathing difficulty, reduced urine output, excessive vomiting, abdominal discomfort or enlargement and rapid weight gain to be accessed as needed.

In this trial, Humaidan *et al.*[7] criteria for diagnosis and classification of OHSS was followed. Mild OHSS was coined in the presence of abdominal distension, pelvic discomfort and evidence of ascites in Douglas pouch and enlarged ovaries in AUS or TVS. Moderate OHSS was diagnosed in the presence of abdominal enlargement, pelvic discomfort, ultrasonic evidence of pelvic and pouch of Douglas ascites, enlarged ovaries and hemoconcentration (hematocrit > 45%). Severe OHSS was stated in the presence of both subjective (pelvic pain, abdominal enlargement, breathing difficulty, ovarian enlargement, and pregnancy occurrence) and objective (pelvic and pouch of Douglas ascites, fluid around intestinal loops, hematocrit > 45%, low urine output < 600 ml /24h, white blood cells > 15.000 / ml) criteria. OHSS was defined as early if "onest" with nine days of HCG administration and as "late" if occurred after ten days of OPU according to Carizza *et al.*[9]. Mild and moderate OHSS cases were managed symptomatically, on an outpatient basis, while severe OHSS was admitted to high-risk unit of Obstetrics and Gynecology Department at Benha University Hospital. Clinical pregnancy was considered when a gestation sac with positive fetal heart activity was detected on either TVS or AUS, while implantation rate was defined as the number of gestational sacs in relation to the number of transferred embryos.

The main outcome measure was the total OHSS rate while the secondary outcomes were OHSS types as mild, moderate, severe and early onest or late onest OHSS in addition to fertilization rate, implantation rate, chemical pregnancy, clinical pregnancy, ongoing pregnancy, first-trimester miscarriage, live birth rate.

A sample size of 110 women per arm was needed at two sided 5% significance level (type 1 (a) error = 0.05), and efficacy (power) of 80% (type II (B) error = 0.02) and anticipated dropout rate of 10%, after conducting internal pilot study on 30 patients in each group and the study found that the incidence of total OHSS in calcium infusion plus cabergoline (CI+) (26.6% ,30/) while in calcium infusion alone CI- (620% ,30/).

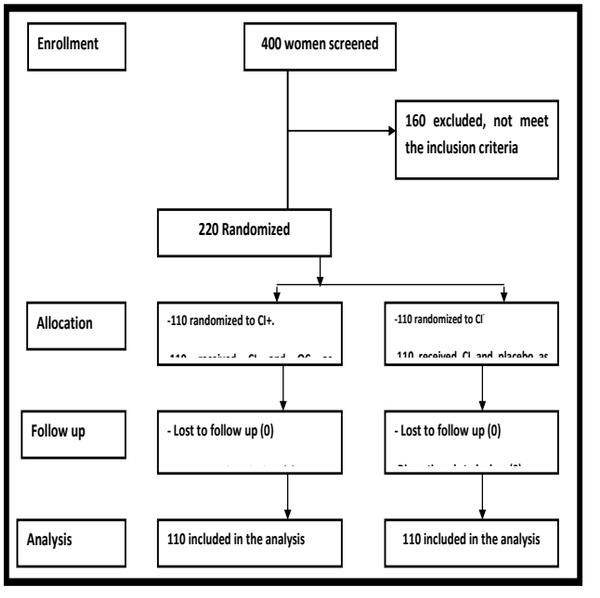
STATISTICAL ANALYSIS

Statistical analysis was done using MedCalc software (www. MedCalc.org)[24] and according to modified intention to treat analysis policy where only women who received all the trial intervention as randomized were included in the final analysis. Continuous data, including baseline demographic, clinical and laboratory criteria as age, hormone profiles, infertility causes, used HMG amount, SE_2 level on HCG administration day as well as fertilization and implantation rates were presented as means, standard deviations and ranges, then compared with independent sample Student's t-test. Categorical data, including the incidence of overall, early, late ; mild, moderate and severe OHSS as well as pregnancy rates were presented in terms of frequencies and percentages and were compared by Chi-square test. P values, as well as a point estimate difference with 95% confidence interval (CI) were used to determine the significance ; $P < 0.05$ was stated statistically significant.

RESULTS

In the current study, 400 ICSI candidate women were examined for eligibility, 220 patients were at high risk for OHSS development after COH, all of them have not any exclusion criteria. These 220 women were randomized to either receiving calcium infusion plus oral cabergoline (CI+) or calcium infusion alone (CI-) as 110 in each group. All randomized patients have received the allocated intervention as randomized and all these 220 patients were included in the final analysis as presented in Figure 1.

Fig. 1: CONSORT Participants flow chart in CI+ versus CI- in OHSS prevention study



CI+: calcium infusion plus oral cabergoline, CI: calcium infusion, OC: Oral cabergoline, CI-: calcium infusion alone, OHSS : Ovarian hyperstimulation syndrome.

The participants basic demographic, clinical and laboratory criteria were presented in table (1) and there was no significant statistical difference between groups except for duration of infertility where it was shorter in CI+ than CI- (3.2 vs. 3.8, $p = 0.018$) and basic LH level where it was higher in CI+ than CI- (5.3 vs. 4.8, $p = 0.003$) and this could be explained only on the basis of random error variability.

Table 1: Basic criteria of patients allocated to CI+ or CI- in OHSS prevention study

Variable	CI+ (n = 110)	CI- (n = 110)	Δ	95% CI	P value
Age (y)*	27.8±4.2	28.2 ±3.8	-0.4	(-0.66, 1.46)	=0.45
BMI (kg/m2)*	29.3±2.9	28.8±3.2	0.5	(-1.31, 0.31)	=0.22
Infertility Duration (y)*	3.2±1.6	3.8±2.1	-0.6	(0.103, 1.09)	=0.018***
Infertility type:** - Primary	65(59%)	68(62%)	-3%	(-9.7, 15.6)	-0.64
- Secondary	45(41%)	42(38%)	3%	(-9.7, 15.6)	-0.64
-Infertility causes:** - An ovulation	21(19%)	17(16%)	3%	(-7.1, 13.0)	=0.55
- Tubal cause	28(26%)	31(28%)	-2%	(-9.6, 130)	=0.73
- Male cause	18(16%)	19(17%)	-1%	(-8.9, 10.8)	=0.84
- Endometrosis	8(7%)	7(6%)	1%	(-6.00, 8.08)	=0.76
- Unexplained	35(32%)	36(33%)	-1%	(-11.2, 13.2)	=0.87
Basal FSH (mIU/mL)*	6.2 ± 1.5	5.8±1.6	0.4	(-0.81, 0.01)	=0.057
Basal LH (mIu/mL)*	8.3 ± 1.3	7.8±1.2	0.5	(0.83, 0.16)	0.003***
Basal E2 (pq/mL)*	45.9 ± 11.5	44.8±10.2	1.1	(-3.98, 1.78)	=0.45
Basal AMH (ng/mL)*	5.1 ± 2.9	4.9±3.1	0.2	(-0.99, 0.59)	=0.62
Basal AFC (n)*	26.6 ± 6.1	27.5±5.8	0.9	(-0.68, 2.48)	=0.2

CI+: Calcium infusion plus oral cabergoline, CI- : Calcium infusion alone, OHSS: Ovarian hyperstimulation syndrome, Δ : difference of point estimate, FSH : Follicular stimulating hormone, LH: Luteinizing hormone, E2 : Estradiol, AMH : Antimullerian hormone, AFC: Antral follicular count, 95% CI : 95% confidence interval.

- Values were given as mean ± standard deviation* or number (percentage)**
- $P < 0.05$: statistically significant.***

There were no statistical significant differences between both study arms as regarding COH and ICSI outcomes including total amount of Gn (*P = 0.39*), length of COH in days (*P = 0.23*), SE2 peak at HCG triggering (*P = 0.22*) as well as fertilization rate, implantation rate, pregnancy including chemical and clinical, first trimester miscarriage rate, ongoing pregnancy total and live birth rate except No. of retrieved oocytes which is more in CI+ than CI- (28.6 vs 26.8, *P = 0.01*) as in table (2).

Table 2 : Difference in COH and ICSI outcomes between CI+ and CI- in OHSS prevention study

Variable	CI+ (n = 110)	CI- (n = 110)	Δ	95% CI	P value
Total used HMG (Iu)*	2.745.6±492.5	2.687.7±510.5	57.9	(-191.1, 75.3)	= 0.39
Length of COH (day)*	9.8 ± 1.8	10.1 ± 1.9	- 0.3	(-0.19, 0.79)	= 0.23
E2 Peak2 on HCG day (pg/ml)*	5233.8±870.5	5380.7±930.2	-146.9	(-92.5, 386.3)	= 0.22
Endometrial thickness on HCG day (mm)*	9.9±3.6	10.1±3.8	-0.2	(-0.78, 1.18)	= 0.68
No of retrieved oocytes (n)*	28.6±5.2	26.8±5.2	1.8	(0.41, 3.18)	=0.0109***
No of retrieved MII oocytes (n)*	19.6±5.2	20.1±4.8	- 0.5	(-0.82, 1.82)	=0.45
Fertilization rate (%)*	76.4 ± 8.2	75.6±7.2	0.8	(-2.8, 1.2)	=0.44
Implantation rate (%)*	29.2 ± 5.9	30.5±6.1	- 1.3	(-0.29, 2.8)	=0.10
Chemical pregnancy (n)**	74(67%)	71(65%)	2%	(-10.3, 14.3)	=0.75
Clinical pregnancy (n)**	56(51%)	54(49%)	2%	(-11.0, 14.9)	=0.76
Early miscarriage (n)**	13(12%)	14(13%)	-1%	(-7.9, 9.9)	=0.82
Ongoing pregnancy (n)**	43(39%)	40(36%)	3%	(-9.6, 15.5)	=0.64
Live birth rate (n)**	43(39%)	40(36%)	3%	(-9.6, 15.5)	=0.64

COH: Controlled ovarian hyperstimulation, ICSI: Intracytoplasmic sperm injection, CI+: Calcium infusion plus oral cabergoline, CI- : Calcium infusion alone, OHSS: Ovarian hyperstimulation syndrome, MII: Metaphase two oocyte, Δ : difference of point estimate, 95% CI : 95% confidence interval.
Values were given as mean ±standard deviation* or number (percentage)**
- *P < 0.05* : statistically significant.***

The occurrence of OHSS was statistically significant more in patients receiving calcium infusion alone (CI-) than whom receiving calcium infusion plus oral cabergoline (CI+) as regards the overall rate [18/110 (16.3%) in CI- versus 8/110(7.2%) in CI+, *P = 0.036*) with -9.1% difference in incidence at 95% CIS of (-0.49, -17.8) while there was no statistically significant difference as regards incidence of mild, moderate, severe as well as early and late OHSS table (3).

In this trial, there were 4 cases with severe OHSS who required admission. In all these four cases, the ascetic tap was done due to severe distension and breathing difficulties. All four cases of severe OHSS were improved and discharged once be asymptomatic. Also, in this trial, no apparent complication in either of both groups could be due to calcium infusion as nausea, vomiting, hypotension, flushing, bradycardia, gastric upset, chalky tastes and tingling sensation.

Table 3 : Differences in cycle characteristics and OHSS incidence and type between CI+ and CI- in OHSS prevention study

Variable	CI+ (n = 110)	CI- (n = 110)	Δ	95% CI	P value
Previous attacks of OHSS* Absent	88(80%)	92 (84%)	-4%	(-6.23, 14.6)	=0.44
Present	22 (20%)	18 (16%)	4%	(-6.23, 14.6)	= 0.44
Cycle number* First	67 (61%)	71 (66%)	-5%	(-7.63, 17.4)	=0.44
Second or More	43 (39%)	39 (34%)	5%	(-7.63, 17.4)	=0.44
Total OHSS incidence*	8 (7.2%)	18 (16.3%)	-9.1%	(-0.49, -17.8)	=0.036***
Mild OHSS*	4 (3.6%)	9 (8.9%)	-5.3%	(-1.3, 12.4)	=0.10
Moderate OHSS*	3 (2.7%)	6 (5.4%)	-2.7%	(-2.06, 8.8)	=0.31
Severe OHSS*	1 (0.9%)	3 (2.7%)	-1.8%	(-2.63, 6.82)	=0.31
Early Onset OHSS*	6 (5.4%)	12 (10.9%)	-5.5%	(-1.9, 13.2)	=0.13
Late Onset OHSS*	2 (1.8)	6 (5.4%)	-3.6%	(-1.8, 9.6)	0.15

CI+: Calcium infusion plus oral cabergoline, CI- : Calcium infusion alone, OHSS: Ovarian hyperstimulation syndrome, Δ : difference of point estimate, 95% CI : 95% confidence interval.
- Values were given as number (percentage)*
- $\geq\geq$ *0.05* : statistically significant.***

DISCUSSION

Severe OHSS takes maximal concern of infertility clinicians as it may complicate up to 8.9% of crude IVF/ICSI women who were stimulated by long agonist protocol (LAP) and ovulation was triggered with conventional HCG regimen[8] as well as if not timely and efficiently treated, may be associated with severe morbidity and even mortality[1,2,3,4]. All tried preventive modalities, for OHSS occurrence, up till now didn't achieve complete prevention rather than reduce the incidence of overall all as well as severe OHSS[25].

The present study demonstrated that the use of calcium gluconate 10ml of 10% solution added to 200 ml saline over 30 min. from OPU day for 4 days in combination with oral cabergoline 0.5 mg from the day of HCG triggering is superior to calcium infusion alone. The OHSS protective effect of antagonists protocol (AP) was recently demonstrated in adequately powered randomized clinical trial[8] (RCT) in crude IVF/ICSI population, where the incidence of severe OHSS in AP versus LAP 5.1% vs 8.9% with $p = 0.02$; while moderate OHSS was 10.2 vs. 15.6% with $p = 0.01$ and rate of hospital admission due to OHSS was lower in AP when compared with LAP (1.7% vs 3.6%, $P = 0.06$) as well as there is no ascetic tap in AP compared to 2% in LAP ($P < 0.01$). In analysis of subgroup with irregular anovulatory cycle PCOS, authors reported a development of more severe OHSS when compared to less risk, women with regular ovulatory cycles[8], so there is a need for adequate powered RCT to explore the antagonist protocol OHSS sparing effect in women at high risk for OHSS development; namely, with high basal Antimullerian hormone (AMH), Antral follicular count (AFC) and high SE2 at ovulation triggering. GnRh agonist ovulation triggering instead of HCG as OHSS protective strategy, despite it is only possible in non-agonist based protocols as antagonist

protocols as well as recently introduced progesterone primed ovarian stimulation protocol (PPOS),[30, 31, 32, 33] was less effective than HCG triggering as regards of ongoing pregnancy rate and live birth rate[26] as well as infertility clinician still preferred HCG over GnRh agonist in antagonist protocol[28] and that recent review of utilization of GnRh agonist as ovulation triggering instead of HCG stated that this issue still needs more research[29].

As regards final oocyte maturation step in COH recently Lu *et al.* introduced dual trigger with GnRH agonist and a reduced dose of HCG in non-agonist based COH protocols and they reported improved oocyte retrieval rate[34]. Prior researches illustrated that VEGF is the main mediator in the pathogenesis of OHSS[1,2,3,4]. Infertility investigator introduced oral cabergoline as VEGF receptor antagonist[17,18]and calcium infusion [35, 36, 37, 38, 39] as VEGF lowering agent, so they targeting VEGF at different points of OHSS pathogenesis cascade and comparing both drugs against placebo as well as versus each other and reporting varying degree of success of both agents. This trial tested the interaction of adding oral cabergoline as VEGF receptor antagonist with calcium infusion as VEGF lowering drug and found a significant lowering effect of this combination on overall OHSS incidence [overall OHSS 87.2%) 110/) in CI+ versus 1816.3%) 110/) in CI- with Δpp = -9.1% at 95% CI of (-0.49, -17.8), *P = 0.036*] as well non significant lowering effect on moderate (*p = 0.3*) and severe (*p = 0.3*) OHSS. These overall reduced of OHSS incidence in high risky women for OHSS was achieved without a reduction in implantation rate, pregnancy rate, live birth rate of fresh embryo transfer, similar results were reported from trials of calcium infusion compared to placebo[12,19,40] and when compared calcium with oral cabergoline[23]. Women included in this study were compared to subgroup with irregular cycles treated with LAP and triggered with HCG in Toftager *et al*. trial, where they reported an incidence of severe OHSS to be 916.7%) 54/) in comparing two women at lower risk for OHSS with the same protocol of COH which is 35/ 441(7.9%) when there is no OHSS preventive step was done. So, applying intervention like calcium could reduce OHSS in risk group from (16.7%) as reported by Toftager *et al.*[8] to 32.7%)110/). In this trial and also as reported, a more reduction to 10.9%)110/) could be achieved with the earlier introduction of oral cabergoline at HCG administration to calcium infusion that started at OPU. So, these results could be generalized to all women at higher risk for OHSS ; namely, those with high basal AFC, basal AMH, high trigger SE2 and those with high retrieved oocyte number in the context of LAP of COH and where HCG could be the only choice for final oocyte maturation.

There were a lot of strength points in this study as being prospective, interventional, randomized, placebo-controlled, double-blind, adequately powered to detect a difference in incidence of overall OHSS between the two intervention arms as well as proper definition of included women whom at high risk for OHSS where basal AMH and basal AFC were measured as well as pretrigger SE2 and shorter duration of trial (13 months) in comparison with very lengthy trial of Toflager *et al.* (10 years) as this study was conducted mainly at high volume IVF center.

Limitations included laboratory variability in AMH and SE2 as well as inter-observer variability in assessing AFC and follicular cohort number.

CONCLUSION

This is, to my knowledge, the first RCT that evaluate the interaction of adding oral cabergoline at HCG trigger to infusion of calcium gluconate 10% , 10 ml in 200 ml saline 0.9% over 30 min, starting at OPU and continued for 4 days versus calcium infusion alone in terms of OHSS parameters as main outcome and others IVF/ ICSI parameters, as secondary outcomes. This study demonstrated a significant reduction in the overall incidence of OHSS and associated sequels of higher grades OHSS when oral cabergoline was added to calcium infusion at a similar ongoing pregnancy rate and line birth rate.

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CONFLICT OF INTEREST

There are no conflict of interest.

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