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Comparative study of cabergoline and hydroxychloroquine to prevent ovarian hyperstimulation syndrome (OHSS) in PCOS patients: a pilot randomized clinical trial

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Abstract

Background This study compared the effectiveness of cabergoline and hydroxychloroquine in preventing ovarian hyperstimulation syndrome (OHSS) in patients with polycystic ovary syndrome (PCOS) undergoing controlled ovarian stimulation.

Materials and methods This double-blind, parallel, and randomized clinical trial was performed from April to June 2024. Forty-two patients with PCOS who were candidates for assisted reproductive techniques were randomized into two groups. The first group received 0.5 mg of cabergoline, and the second group received 400 mg of hydroxychloroquine for 8 days. Then, ultrasounds were conducted on days 3 and 5 after oocyte retrieval to assess for OHSS.

Results Three and five days after oocyte retrieval, laboratory findings, and clinical outcomes were similar between the cabergoline and hydroxychloroquine groups. Key laboratory parameters, including hemoglobin, hematocrit, sodium, potassium, blood urea nitrogen, and creatinine, did not show significant differences between the groups. On day three, OHSS incidence didn't have a significant difference between the hydroxychloroquine and cabergoline groups, both for the mild (31.58% vs. 42.86%) and moderate (15.79% vs. 9.52%) groups. Mild cases were observed in one of the patients in both groups 5 days after pickup ($p=0.942$). No patients in the cabergoline group required hospitalization or treatment, compared to one in the hydroxychloroquine group ($p=0.127$).

Conclusion The incidence of OHSS was similar between cabergoline and hydroxychloroquine, with no significant differences observed in laboratory parameters or clinical outcomes after oocyte retrieval. However, given the study's sample size, further research is needed before these findings can be generalized to a larger population.

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Keywords Ovarian hyperstimulation syndrome (OHSS), Polycystic ovary syndrome (PCOS), Cabergoline, Hydroxychloroquine, Reproductive techniques, assisted (ART)

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Introduction

Ovarian hyperstimulation syndrome (OHSS), a potentially life-threatening condition, is the most severe iatrogenic side effect of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) treatment. The incidence of moderate to severe OHSS is predicted to be between 1% and 5% in all IVF cycles [1]. OHSS is characterized by ovarian hypertrophy and fluid shift from intravascular to extravascular compartments [2, 3]. OHSS has two common pathologies: (i) increased vascular permeability, and (ii) human chorionic gonadotropin (hCG) is the triggering element for this syndrome [4]. Additionally, this condition is characterized by overproduction of pro-inflammatory and vasoactive cytokines [5, 6]. Pretreatment risk factors for OHSS include young age (< 30 years), low body mass index (BMI), polycystic ovary syndrome (PCOS) or high basal antral follicle count (AFC), a history of elevated response to gonadotrophins (e.g., prior hyper-response or OHSS), and high basal anti-Müllerian hormone (AMH) concentrations [7]. During and after ovarian stimulation (OS), elevated or rapidly rising serum estradiol concentrations, a large number of small follicles (8–12 mm), the use of hCG instead of progesterone for luteal phase support after IVF, a large number of oocytes retrieved (> 20), and pregnancy following fresh embryo transfer are associated with an increased risk of OHSS [8, 9]. The clinical diagnosis of OHSS has been classified into mild, moderate, severe, and critical forms [10]. Criteria for diagnosing moderate to severe OHSS include symptoms such as nausea (with or without vomiting), clinically or ultrasound-detected ascites, hydrothorax, reduced urine output (oliguria), a hematocrit level over 45%, low protein levels (hypoproteinemia), and ovarian size greater than 8 mm [11].

As mentioned earlier, OHSS often results from an exaggerated ovarian response to hormonal stimulation, particularly in high-risk groups such as patients with PCOS. PCOS is the most common cause of anovulatory infertility and a primary reason for undergoing assisted reproductive technology (ART) [7, 12]. Patients with PCOS have larger follicles, longer follicular phases, and higher median follicular concentrations of LH, FSH, and testosterone than ovulatory women with normal ovaries [13]. During ovarian stimulation, women with PCOS respond to gonadotropins with extensive follicular development and a rapid surge in circulating estradiol. Additionally, the high sensitivity of polycystic ovaries to controlled ovarian stimulation (COS) makes controlling COS in patients with PCOS particularly challenging [7, 14]. Thus, preventing OHSS is a primary goal in reproductive therapy for these patients, necessitating individualized ovarian stimulation protocols and continuous monitoring [15]. Several approaches have been introduced to lower the risk of moderate to severe OHSS [16]. These approaches may change the stimulation protocol. These include replacing follicle-stimulating hormone (FSH) with low-dose hCG, employing GnRH antagonists instead of GnRH agonists during IVF, using a GnRH agonist instead of hCG to trigger final follicular maturation, and coasting and incorporating follitropin delta in GnRH-ant IVF cycles [17, 18]. Additionally, post-stimulation interventions, such as the administration of a GnRH antagonist after oocyte retrieval and cabergoline after the end of COS, were employed. Other strategies, such as cycle cancellation, freezing all embryos, and in vitro oocyte maturation, may also help reduce OHSS risk. However, aside from cycle cancelation, none of these interventions have been completely effective in preventing OHSS due to variations in efficacy and safety outcomes [16].

Cabergoline, a D2 dopamine receptor agonist, effectively controls vascular permeability by inhibiting VEGFR2 phosphorylation. Several studies have explored its use in OHSS prevention, employing various doses and treatment regimens [19]. This strategy is feasible for all women who are undergoing COS, with no evidence suggesting it impairs implantation [16]. Hydroxychloroquine, an antimalarial drug, is also employed to address infertility on an immunologic basis and is widely prescribed for individuals with autoimmune diseases, mainly systemic lupus erythematosus (SLE) and other rheumatic conditions [20]. Hydroxychloroquine exerts complex pleiotropic effects on multiple cell types. It reduces the production of pro-inflammatory cytokines, such as TNF-α, IFN-γ, IL-6, and IL-8, decreasing platelet aggregation. It also inhibits T follicular helper (Tfh) cells, suppresses toll-like receptor (TLR) activation, influences antigen-antibody interactions, and inhibits the release of endothelin-1 [21–23]. Hydroxychloroquine also benefits vascular compliance and helps prevent endothelial dysfunction [24, 25]. Notably, several studies highlight the involvement of various cytokines in OHSS, suggesting interactions between systemic inflammatory cytokines such as IL-2, IL-6, IL-8, IL-10, IL-18, TNF-α, and VEGF and the pathophysiology of OHSS [17, 26–29]. Due to its immunomodulatory mechanism and ability to reduce systemic inflammation [23, 30, 31], hydroxychloroquine may also have potential utility in the prevention of OHSS; however, the precise mechanism in this space is still not completely clear.

A key challenge for fertility specialists is preventing complications while striking a balance between effective ovarian stimulation for a successful outcome and minimizing the patient's risk of OHSS. As a result, doctors must carefully estimate the initial gonadotropin dose to generate the maximum number of oocytes while minimizing the risk of OHSS [32]. Based on this, we hypothesize that hydroxychloroquine, like cabergoline, may

confer beneficial effects in women at high risk of OHSS, particularly those with PCOS.

Materials and methods

Trial design and setting

This study was a double-blind, parallel, and randomized clinical trial. It was conducted from April 03, 2024, to June 21, 2024, on women with PCOS who were candidates for ART at Arash Women's Hospital, a tertiary hospital affiliated with Tehran University of Medical Sciences, Tehran, Iran.

Ethical considerations

This study followed the principles outlined in the Declaration of Helsinki. The Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran, approved the study (Ethics Code: IR.TUMS.MEDICINE.REC.1402.699; 2024 March 04). Additionally, this study was registered on the Iranian clinical trial registry (http://www.irct.ir; Registration number: IRCT20240305061171N1; Registration date: 2024 June 29). All individuals provided informed consent.

Eligibility criteria

Patients with PCOS who were undergoing ICSI and were aged 22–42 years, with BMI < 30 kg/m², AFC > 20, and AMH levels > 3.36 ng/ml [33] were included in the study. Women diagnosed with PCOS according to the Rotterdam criteria [34], including at least two of the three following criteria: oligomenorrhea or amenorrhea, hyperandrogenism biochemical or clinical evidence, and ovarian morphology.

Patients with the diagnosis of endometriosis, reduced ovarian reserve, chromosomal abnormalities, history of allergy to dopamine agonists or cabergoline, and failure to adhere to the prescribed medication regimen were excluded from the study.

Randomization, concealment, and blinding

Participants were allocated randomly into one of the two arms at a ratio of 1:1 on the trigger day. The sequence was created by generating a block size of 4. The sequence of people in the randomized list was only available to an external observer responsible for participant allocation, and the researchers were not aware of it. A nurse selected and randomized the patients using a set of sequentially numbered, sealed opaque envelopes. The study was double-blinded since the physicians prescribed the interventions, physicians assessed the participantsfor the outcomes, and participants were blinded to the group allocation of the participants in the trial.

Intervention

The standard gonadotropin-releasing hormone antagonist (GnRH-ant) protocol was utilized for all patients. On the third day of the menstrual cycle, daily administration of 150 IU of rFSH (*Cinal-F*, *Cinnagen*, *Iran*) was initiated. During the protocol, ultrasonographic monitoring was performed, and the dose of rFSH was adjusted based on the progress of follicular development and patient response. After observing at least two 13 mm follicles, GnRH antagonist (*Cetrotide 0.25 mg*, *Serpero*, *Switzerland*) was administered via subcutaneous injection daily. When the dominant follicles reached a diameter of 18 mm, the final stage of oocyte maturation was induced with 0.2 mg of Decapeptyl (*Decapeptyl 0.2 mg*, *Ferring*, *Germany*) as a trigger. Oocyte retrieval was performed 36 h later. On the trigger day, one group received 0.5 mg of cabergoline (*Caberlin*, *Iranhormone*, *Iran*), while the other group simultaneously administered 400 mg (2 × 200 mg tablets) of hydroxychloroquine (*Hydroxychloroquine sulfate*, *Rouzdarou*, *Iran*) for 8 days. In this study, the Freeze-all strategy was employed for all embryos. Clinical symptoms, laboratory tests, and ultrasounds were conducted on days 3 and 5 after the pickup procedure to assess for OHSS.

Outcome measurements

On the third and fifth days following oocyte retrieval, OHSS was diagnosed, and its severity was determined using Golan's classification [35]. Mild OHSS is defined as abdominal pain, nausea, and ovarian enlargement (8–12 cm) detected via ultrasound, with small amounts of fluid in the pelvis. Moderate OHSS is defined as more extensive ascites and nausea or vomiting requiring hospital admission. Severe OHSS is defined as significant fluid accumulation in the abdomen or thorax, shortness of breath, hematocrit > 55%, electrolyte imbalances, elevated blood urea nitrogen (BUN)/creatinine, reduced urine output, or kidney failure [35]. At each visit, the patient's vital signs and weight were taken. A transvaginal ultrasound (*Philips Affiniti 70*, *Philips*, *Netherlands*) was performed to determine the ovarian volume and estimate the volume of pelvic free fluid. Data were obtained from the checklist, clinical and laboratory notes, and ultrasound reports. All patients were evaluated for cabergoline and hydroxychloroquine-related symptoms and side effects. Patients are also instructed to report any issues from day 8 until their next menstrual cycle.

Sample size

Since this was a pilot randomized clinical trial aimed primarily at assessing feasibility and generating preliminary data rather than testing a formal hypothesis, we determined the sample size based on the commonly used rule of thumb for pilot studies (typically 12 participants per

arm) [36]. Also, no prior studies have evaluated the effect of hydroxychloroquine on OHSS, so this pilot study was designed with a sample size of 21 patients per group.

Statistical analysis

Data were analyzed using Stata version 17.0 and P-values < 0.05 were considered statistically significant differences. The normality of data distribution was evaluated using the Shapiro-Wilk test, skewness, kurtosis indices, as well as histograms and boxplots. To compare continuous variables, we used the Student's t-test (or its non-parametric alternative, the Mann-Whitney test), and for categorical variables, we used the Chi-square test (or Fisher's exact test). To evaluate the clinical effectiveness and safety of the intervention, we calculated the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) along with their corresponding 95% confidence intervals (CIs). The NNT was derived as the reciprocal of the absolute risk reduction (ARR) between the intervention and control groups for incidence of any severity of OHSS:

$$NNT = \frac{1}{Risk_{\text{cabergoline group}} - Risk_{\text{hydroxychloroquine group}}}$$

Similarly, for adverse outcomes, NNH was calculated as the reciprocal of the absolute risk increase (ARI) for incidence of any severity ofOHSS:

$$NNH = \frac{1}{Risk_{\text{hydroxychloroquine group}} - Risk_{\text{cabergoline group}}}$$

Additionally, odds ratios (ORs) and their 95% CIs were calculated using logistic regression to estimate the association between treatment group and binary outcomes. Due to the small number of outcomes, variables were analyzed as binary (presence/absence).

Results

Initially, 44 participants were screened, and 2 (4.5%) were subsequently excluded. The remaining 42 (95.4%) participants were randomly assigned to either the 50% cabergoline group ($n = 21$) or the 50% hydroxychloroquine group ($n = 21$). During the study, two participants in the hydroxychloroquine group withdrew from the trial as they failed to attend the follow-up visits after the second visit on day five post-trigger and were not considered in the final analysis (Fig. 1).

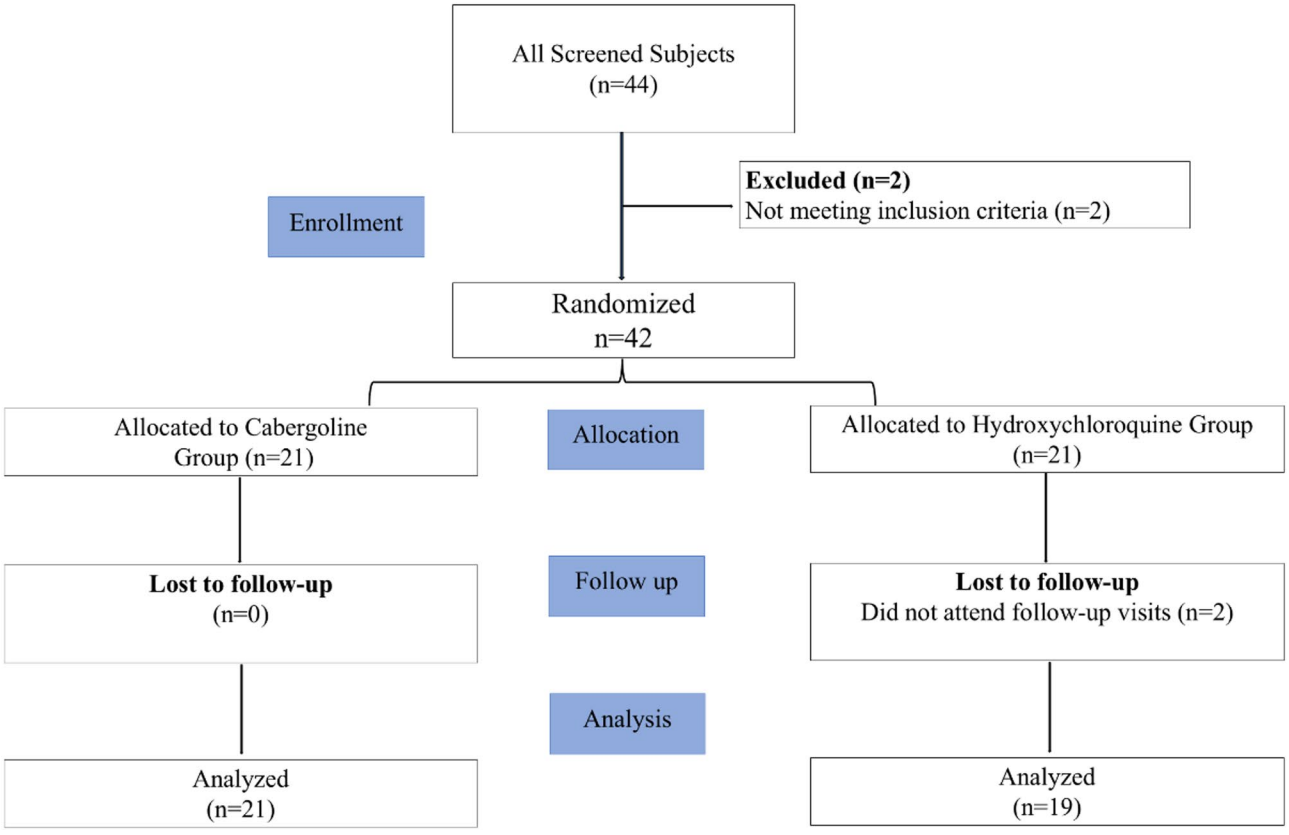

Fig. 1 Participant enrollment, randomization, and follow-up

Recruitment and baseline assessment

All the participants were recruited from patients referred to Arash Women's Hospital. We recruited participants via conversations, and interested patients received detailed information about the study. After checking the eligibility criteria, the baseline assessment involved demographic characteristics (age, BMI, menstrual cycle regularity, and infertility type and factors) and hormonal profiles of patients (including serum levels of FSH, luteinizing hormone (LH), prolactin (PRL), progesterone, estradiol, testosterone, vitamin D, and anti-Müllerian hormone (AMH)), and ultrasounds were evaluated.

Baseline characteristics

The baseline demographic, clinical, and laboratory characteristics of participants in the cabergoline ($n=21$) and hydroxychloroquine ($n=19$) groups were comparable (Table 1). The mean age was 32.09 ± 4.10 years in the cabergoline group and 29.58 ± 4.78 years in the hydroxychloroquine group ($p=0.113$). Mean BMI, menstrual cycle regularity, and infertility type and factors showed no significant differences between the groups. Baseline laboratory parameters, including FSH, LH, AMH, and others, were similar across groups. Only the right AFC was slightly higher in the hydroxychloroquine group (p-value = 0.037).

Post-Intervention laboratory parameters and outcomes

Three days after oocyte retrieval, laboratory findings and outcomes were broadly similar between groups (Table 2). Key laboratory parameters, such as hemoglobin, hematocrit, sodium, potassium, BUN, and creatinine, did not significantly differ between the cabergoline and Hydroxychloroquine groups ($p>0.05$ for all). Reported

Table 1 Baseline characteristics of the participants

Characteristic		Total ($N=40$)	Hydroxychloroquine ($N=19$)	Cabergoline ($N=21$)	*p*-value
Demographic and Clinical					
Age (SD)		30.90 (5.00)	29.58 (4.78)	32.10 (5.00)	0.113
BMI (SD)		27.08 (5.09)	25.88 (4.68)	28.17 (5.30)	0.158
Regular menstrual cycle (%)	**No**	15 (37.50%)	7 (36.84%)	8 (38.10%)	0.616
	Yes	24 (60.00%)	12 (63.16%)	12 (57.14%)	
	Oligomenorrhea	1 (2.50%)	0 (0.00%)	1 (4.76%)	
Primary infertility (%)	**No**	11 (27.50%)	6 (31.58%)	5 (23.81%)	0.583
	Yes	29 (72.50%)	13 (68.42%)	16 (76.19%)	
Secondary infertility (%)	**No**	30 (75.00%)	13 (68.42%)	17 (80.95%)	0.361
	Yes	10 (25.00%)	6 (31.58%)	4 (19.05%)	
Female factor infertility (%)	**No**	4 (10.00%)	2 (10.53%)	2 (9.52%)	0.916
	Yes	36 (90.00%)	17 (89.47%)	19 (90.48%)	
Laboratory					
FSH (SD)		5.21 (1.78)	5.33 (2.00)	5.11 (1.59)	0.695
LH (SD)		5.47 (2.43)	5.46 (2.68)	5.48 (2.24)	0.972
AMH (SD)		5.84 (3.69)	6.36 (4.35)	5.38 (3.00)	0.407
TSH (SD)		2.07 (0.92)	1.81 (0.89)	2.31 (0.91)	0.085
PRL (SD)		134.11 (143.00)	118.89 (117.41)	148.56 (165.49)	0.524
Progesterone (SD)		4.75 (6.12)	5.51 (7.28)	4.07 (4.91)	0.466
Estradiol (SD)		36.03 (36.22)	31.83 (34.84)	39.84 (37.87)	0.492
Vitamin D (SD)		27.50 (11.14)	29.89 (14.19)	25.34 (7.10)	0.201
Testosterone (SD)		17.86 (18.35)	14.95 (19.66)	20.48 (17.14)	0.348
Sonographic					
AFC right (SD)		12.83 (2.22)	13.69 (2.44)	12.15 (1.81)	**0.037**
AFC left (SD)		13.33 (2.14)	13.69 (2.70)	13.05 (1.57)	0.382
Trigger Day a-GNRH					
Progesterone (SD)		1.25 (0.62)	1.19 (0.49)	1.30 (0.72)	0.568
Estradiol (SD)		2100.60 (466.31)	2187.74 (441.45)	2021.76 (484.65)	0.266
Trigger Cycle					
rFSH cinal (%)	**75**	3 (7.50%)	2 (10.53%)	1 (4.76%)	0.299
	150	10 (25.00%)	7 (36.84%)	3 (14.29%)	
	225	24 (60.00%)	9 (47.37%)	15 (71.43%)	
	300	3 (7.50%)	1 (5.26%)	2 (9.52%)	

Abbreviations: Body mass index (BMI), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Anti-müllerian hormone (AMH), Prolactin (PRL), Antral follicle count (AFC)

Table 2 Laboratory parameters, outcomes, and the side effects three days after pick up

Parameters		Total (*N* = 40)	Hydroxychloroquine (*N* = 19)	Cabergoline (*N* = 21)	*p*-value
Laboratory					
Hb (SD)		11.87 (1.10)	11.86 (1.27)	11.89 (0.96)	0.938
HCT (SD)		35.92 (2.90)	36.22 (3.35)	35.64 (2.47)	0.536
Na (SD)		140.43 (1.97)	140.74 (0.81)	140.14 (2.61)	0.348
K (SD)		4.08 (0.15)	4.07 (0.15)	4.09 (0.16)	0.726
BUN (SD)		10.33 (3.71)	9.36 (2.08)	11.20 (4.61)	0.118
Cr (SD)		0.85 (0.09)	0.85 (0.08)	0.85 (0.10)	0.993
ALT (SD)		21.05 (10.44)	18.63 (6.25)	23.24 (12.91)	0.166
AST (SD)		19.70 (7.92)	18.26 (6.32)	21.00 (9.08)	0.281
ALK (SD)		133.73 (28.15)	129.79 (29.08)	137.29 (27.50)	0.407
Outcomes and Side Effects					
Transvaginal sonography (%)	No	15 (37.50%)	8 (42.11%)	7 (33.33%)	0.534
	Mild	18 (45.00%)	9 (47.37%)	9 (42.86%)	
	Moderate	7 (17.50%)	2 (10.53%)	5 (23.81%)	
Nausea (%)	No	20 (50.00%)	10 (52.63%)	10 (47.62%)	0.524
	Mild	16 (40.00%)	6 (31.58%)	10 (47.62%)	
	Moderate	3 (7.50%)	2 (10.53%)	1 (4.76%)	
	Severe	1 (2.50%)	1 (5.26%)	0 (0.00%)	
Vomiting (%)	No	38 (95.00%)	18 (94.74%)	20 (95.24%)	0.366
	Mild	1 (2.50%)	0 (0.00%)	1 (4.76%)	
	Moderate	1 (2.50%)	1 (5.26%)	0 (0.00%)	
Abdominal distention (%)	No	20 (50.00%)	10 (52.63%)	10 (47.62%)	0.682
	Mild	17 (42.50%)	7 (36.84%)	10 (47.62%)	
	Moderate	3 (7.50%)	2 (10.53%)	1 (4.76%)	
Abdominal pain (%)	No	18 (45.00%)	8 (42.11%)	10 (47.62%)	0.826
	Mild	17 (42.50%)	8 (42.11%)	9 (42.86%)	
	Moderate	5 (12.50%)	3 (15.79%)	2 (9.52%)	
Oliguria (%)	No	33 (82.50%)	16 (84.21%)	17 (80.95%)	0.344
	Mild	5 (12.50%)	3 (15.79%)	2 (9.52%)	
	Moderate	2 (5.00%)	0 (0.00%)	2 (9.52%)	
Dyspnea (%)	No	38 (95.00%)	18 (94.74%)	20 (95.24%)	0.942
	Mild	2 (5.00%)	1 (5.26%)	1 (4.76%)	
OHSS (%)	No	20 (50.00%)	10 (52.63%)	10 (47.62%)	0.704
	Mild	15 (37.50%)	6 (31.58%)	9 (42.86%)	
	Moderate	5 (12.50%)	3 (15.79%)	2 (9.52%)	
Treatment for OHSS (%)	No	39 (97.50%)	18 (94.74%)	21 (100.00%)	0.287
	Yes	1 (2.50%)	1 (5.26%)	0 (0.00%)	
Hospitalization (%)	No	38 (95.00%)	17 (89.47%)	21 (100.00%)	0.127
	Yes	2 (5.00%)	2 (10.53%)	0 (0.00%)	
Treatment hospitalization (%)	No	37 (92.50%)	17 (89.47%)	20 (95.24%)	0.489
	Yes	3 (7.50%)	2 (10.53%)	1 (4.76%)	

Abbreviations: Hemoglobin (Hb), Hematocrit (HCT), Sodium (Na), Potassium (K), Blood urea nitrogen (BUN), Creatinine (Cr), Alanine transaminase (ALT), Aspartate Transferase (AST), Ovarian hyperstimulation syndrome (OHSS)

side effects, including nausea, vomiting, abdominal distension, pain, and oliguria, were comparable. OHSS incidence did not significantly differ between groups, with mild and moderate cases evenly distributed. None of the patients in the cabergoline group required treatment for OHSS, compared to one (5.26%) patient of hydroxychloroquine patients, although this difference was not statistically significant ($p = 0.299$).

Five days post-retrieval, laboratory parameters remained comparable (Table 3). Incidence of OHSS was low and similar between groups, with mild cases reported in one of patients in both groups ($p = 0.942$). Side effects, including abdominal pain and distension, were reported at low rates and did not differ significantly. Other side effects were not observed in both of the groups.

In conclusion, the incidence of OHSS and side effect profiles were similar between cabergoline and

Table 3 Laboratory parameters, outcomes, and the side effects five days after pick up

Parameters		Total (*N* = 40)	Hydroxychloroquine (*N* = 19)	Cabergoline (*N* = 21)	*p*-value
Laboratory					
Hb (SD)		12.30 (1.08)	12.26 (1.46)	12.33 (0.62)	0.841
HCT (SD)		37.37 (2.91)	37.26 (3.80)	37.47 (1.86)	0.824
Na (SD)		140.00 (1.20)	140.11 (1.10)	139.90 (1.30)	0.604
K (SD)		4.02 (0.13)	4.04 (0.14)	4.00 (0.13)	0.389
BUN (SD)		11.15 (2.99)	10.42 (2.61)	11.81 (3.22)	0.145
Cr (SD)		0.89 (0.09)	0.88 (0.08)	0.90 (0.10)	0.579
ALT (SD)		31.38 (16.21)	30.37 (19.52)	32.29 (12.94)	0.714
AST (SD)		28.10 (16.03)	28.58 (21.19)	27.67 (9.83)	0.860
ALK (SD)		141.65 (31.52)	137.21 (27.94)	145.67 (34.62)	0.404
Outcomes and Side Effects					
Transvaginal sonography (%)	**No**	36 (90.00%)	17 (89.47%)	19 (90.48%)	0.916
	Mild	4 (10.00%)	2 (10.53%)	2 (9.52%)	
Nausea (%)	**No**	38 (95.00%)	18 (94.74%)	20 (95.24%)	0.942
	Mild	2 (5.00%)	1 (5.26%)	1 (4.76%)	
Abdominal distention (%)	**No**	38 (95.00%)	18 (94.74%)	20 (95.24%)	0.942
	Mild	2 (5.00%)	1 (5.26%)	1 (4.76%)	
Abdominal pain (%)	**No**	37 (92.50%)	18 (94.74%)	19 (90.48%)	0.609
	Mild	3 (7.50%)	1 (5.26%)	2 (9.52%)	
OHSS (%)	**No**	38 (95.00%)	18 (94.74%)	20 (95.24%)	0.942
	Mild	2 (5.00%)	1 (5.26%)	1 (4.76%)	

Abbreviations: Hemoglobin (Hb), Hematocrit (HCT), Sodium (Na), Potassium (K), Blood urea nitrogen (BUN), Creatinine (Cr), Alanine transaminase (ALT), Aspartate Transferase (AST), Ovarian hyperstimulation syndrome (OHSS)

Table 4 Comparison of OHSS and clinical symptoms between Cabergoline and hydroxychloroquine groups on days 3 and 5 after pick-up

Variables	Day 3		Day 5	
	OR	*P*-value	OR	*P*-value
Transvaginal Sonography	1.455 (0.402–5.260)	0.568	0.895 (0.113–7.064)	0.916
Nausea	1.222 (0.353–4.235)	0.752	0.900 (0.052–15.466)	0.942
Abdominal Distention	1.222 (0.353–4.235)	0.752	0.900 (0.052–15.466)	0.942
Abdominal Pain	0.800 (0.229–2.793)	0.726	1.895 (0.158–22.751)	0.614
OHSS	1.222 (0.353–4.235)	0.752	0.900 (0.052–15.466)	0.942

Abbreviations: Odds ratio (OR), Ovarian hyperstimulation syndrome (OHSS)

hydroxychloroquine, with no significant differences observed in laboratory parameters or clinical outcomes after oocyte retrieval.

On Day 3, the NNT for hydroxychloroquine versus cabergoline was 20, indicating that 20 patients would need to be treated with hydroxychloroquine (rather than cabergoline) to prevent one additional case of OHSS. No significant harm (NNH) was observed at this time point. By Day 5, the effect of hydroxychloroquine diminished, with no detectable preventive benefit (NNT not applicable). However, the NNH was 200, suggesting that 200 patients would need to receive hydroxychloroquine (instead of cabergoline) to result in one additional case of OHSS, reflecting a minimal and clinically insignificant risk.

Table 4 presents the comparison of OHSS and clinical symptoms between the cabergoline and hydroxychloroquine groups on days 3 and 5 post-oocyte retrieval. The ORs and corresponding p-values indicate no statistically significant differences between the two groups for any of the assessed variables, including transvaginal sonography findings, nausea, abdominal distention, abdominal pain, and OHSS (all p-values > 0.05). These results suggest that neither cabergoline nor hydroxychloroquine demonstrated a superior effect in reducing the risk of OHSS or associated symptoms during the early post-retrieval period.

Discussion

This randomized clinical trial evaluated the comparative effectiveness of cabergoline and hydroxychloroquine in preventing OHSS in patients with PCOS. In this study, patients were administered 0.5 mg of oral cabergoline daily, while another group was prescribed 400 mg of hydroxychloroquine for 8 days, starting on the trigger day. The findings presented in this study showed no statistically significant difference between the two groups in reducing the risk of OHSS in patients with PCOS at risk for developing OHSS.

Cabergoline, a dopamine agonist, has been extensively studied for its ability to counteract the effects of vascular endothelial growth factor (VEGF), a key mediator in the increased vascular permeability seen in OHSS [37–39]. Several systematic reviews and meta-analyses have revealed that by reducing VEGF receptor-2 phosphorylation, dopaminergic agonists minimize excessive fluid buildup and successfully prevent moderate-severe OHSS [16, 40, 41]. In two studies, cabergoline effectively reduced OHSS risk in high-risk women undergoing IVF/ICSI [42]. Also, data suggest the use of cabergoline in the management of patients with PCOS to provide better clinical control of ovarian response and consequently a reduction of the risk of OHSS, with no decrease in pregnancy rate [43]. Several clinical trials have suggested the effectiveness of cabergoline as a preventive therapy for OHSS compared to alternative interventions such as albumin [44], cetrorelix [45], and calcium gluconate [46]. In line with our results, these studies suggest that

cabergoline is an optimal strategy for reducing OHSS incidences in high-risk patients.

Our analysis shows that hydroxychloroquine is comparable to cabergoline in reducing the incidence of OHSS. Therefore, hydroxychloroquine is as effective as cabergoline in lowering the risk of OHSS in patients with PCOS who are at risk for developing OHSS. Numerous qualities of hydroxychloroquine, including its well-established safety profile and positive outcomes in long-term use, make it a promising candidate for clinical trials [47]. A better understanding of the mechanisms of hydroxychloroquine's action has thus promoted recent advances in its therapeutic landscape. It has immunomodulatory and anti-inflammatory actions, which include enhancing Treg proliferation, suppressing pro-inflammatory cytokines, lysosomal membrane stabilization, and inhibition of phospholipase [47–49]. It is reasonable to hypothesize that hydroxychloroquine could mitigate the inflammatory aspects of OHSS. This study represents a novel exploration of hydroxychloroquine's potential role in this context. To our knowledge, this is the first study to investigate the potentiality of hydroxychloroquine treatment in managing OHSS in patients with PCOS. Research on the safety of hydroxychloroquine for treating malaria and rheumatic conditions, including SLE, indicates that it does not significantly increase the risk of common adverse pregnancy outcomes, such as miscarriage, preterm birth, or restricted fetal growth [50–53]. Additionally, a clinical study confirmed that hydroxychloroquine is safe for use during pregnancy in women with autoimmune disorders [54]. Some studies suggest that hydroxychloroquine has a potential role in improving reproductive outcomes in patients with autoimmune or inflammatory conditions [55, 56]. Two clinical trials investigated the ability of hydroxychloroquine to modulate the immune system by the balance of pro-inflammatory and anti-inflammatory immune responses in women with repeated implantation failure (RIF) [47, 57]. Another trial study highlighted the protective effect of hydroxychloroquine in recurrent pregnancy loss (RPL) [58]. A systematic review and meta-analysis have demonstrated that hydroxychloroquine administration may positively influence embryo transfer outcomes, including improved live birth and fertilization rates [59]. A study has shown hydroxychloroquine's efficacy in improving adverse pregnancy outcomes related to placental dysfunction, such as preeclampsia [60]. Recent reports indicate that hydroxychloroquine is efficacious in improving adverse pregnancy outcomes [60, 61]. In line with previous studies, our findings suggest that hydroxychloroquine may be a suitable candidate for preventing OHSS in patients with PCOS.

Our findings showed that on Day 3 post-oocyte retrieval, hydroxychloroquine had a modest preventive effect compared to cabergoline, with an NNT of 20. This suggests that 20 patients would need to be treated with hydroxychloroquine instead of cabergoline to prevent one additional case of OHSS. Importantly, no harm was observed at this time point, as reflected by the absence of a calculable NNH. By Day 5, however, the preventive effect of hydroxychloroquine appeared to wane, with the NNT becoming non-applicable and the NNH rising to 200, indicating a very low risk of harm. These findings suggest that while hydroxychloroquine may offer some early benefit, its impact is not sustained, and any potential risk remains minimal. Additionally, Table 4 shows no statistically significant differences between the two groups in terms of OHSS incidence or associated symptoms, including transvaginal sonography findings, nausea, abdominal distention, and pain. The calculated odds ratios and p-values support the conclusion that neither treatment demonstrated clear superiority in preventing OHSS or improving related clinical symptoms in the early post-retrieval period.

This trial has some limitations. One major limitation of this study is the small sample size, as it was designed as a pilot trial with only 42 participants. This limited statistical power restricts the ability to detect small but potentially meaningful differences in the efficacy of cabergoline and hydroxychloroquine. Additionally, the small number of OHSS cases observed on Day 5 limits the ability to detect meaningful differences between treatment groups at this time point. This low event rate reduces the statistical power of the analysis and may mask potential variations in efficacy. As such, the findings should be considered preliminary, and larger, adequately powered studies are necessary to validate and expand upon these results. Besides, pregnancy rates and live birth rates were not evaluated. Although the exact mechanisms remain primarily theoretical, our findings suggest that hydroxychloroquine warrants further investigation as a potential preventive therapy for OHSS.

Conclusion

This pilot randomized clinical trial suggests that both cabergoline and hydroxychloroquine may help prevent OHSS in PCOS patients, with no significant differences in efficacy observed in this small sample. However, given the limited sample size and the low incidence of OHSS, these findings should be interpreted with caution. The study lacks the statistical power to make definitive conclusions or generalize to a larger population. Further research with a larger sample size is warranted to better understand the relative efficacy of cabergoline and hydroxychloroquine in preventing OHSS.

Abbreviations

OHSS	Ovarian hyperstimulation syndrome
IVF	In vitro fertilisation

ICSI	Intracytoplasmic sperm injection
hCG	human chorionic gonadotropin
BMI	Body Mass Index
PCOS	Polycystic ovary syndrome
AFC	Antral follicle count
AMH	Anti-Müllerian hormone
OS	Ovarian stimulation
COS	Controlled ovarian stimulation
FSH	Follicle-stimulating hormone
ART	Assisted reproductive technology
SLE	Systemic lupus erythematosus
AFC	Antral follicle count
BUN	Blood urea nitrogen
LH	Luteinizing hormone
PRL	Prolactin
Hb	Hemoglobin
HCT	Hematocrit
Na	Sodium
K	Potassium
Cr	Creatinine
ALT	Alanine transaminase
AST	Aspartate Transferase
NNT	Number Needed to Treat
NNH	Number Needed to Harm
CI	Confidence intervals
ARR	Absolute risk reduction
ARI	Absolute risk increase
OR	Odds ratio

Supplementary Information

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Supplementary Material 1

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Author contributions
Conceptualization: ES, LK, AMData curation: KJFormal analysis: KJInvestigation: ESMethodology: ES, KJProject administration: ESSoftware: N/ASupervision: AMValidation: N/AVisualization: NAAWriting– original draft: NAA, ES, KJ Writing– review & editing: NAA, ES, KJ, LK, AMAll authors read and approved the final version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics and consent to participate
This study followed the principles outlined in the Declaration of Helsinki. The Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran, approved the study (Ethics Code: IR.TUMS.MEDICINE.REC.1402.699; 2024 March 04). After receiving the necessary information, all participants read and signed the informed consent.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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