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CLINICAL ARTICLE

Obstetrics

Comparison of bromocriptine and hydroxyethyl starch in the prevention of ovarian hyperstimulation syndrome

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Abstract

Objective: To evaluate the effectiveness of bromocriptine for prevention of ovarian hyperstimulation syndrome (OHSS).

Methods: The retrospective study included women at risk of OHSS who were receiving gonadotropin-releasing hormone antagonist protocols, including 52 women given 2.5 mg bromocriptine by rectal insertion, 52 women given 500 ml intravenous hydroxyethyl starch (HES), and 40 women who received no intervention. Treatments were administered daily for 5 days beginning on the day of oocyte retrieval. Baseline information and data related to OHSS were compared.

Results: No significant differences were found among groups in estradiol concentration on the day of trigger or in number of retrieved oocytes. Incidence of mild OHSS was not significantly different among groups, respectively 13.5%, 15.4%, and 17.5% ($P > 0.05$). The incidence of moderate to severe OHSS was significantly lower in the bromocriptine and HES groups compared with the control group, respectively 7.7%, 5.8%, and 22.5% ($P < 0.05$). D-dimer levels were significantly lower in the bromocriptine and HES groups compared with the control group on Day 5 after oocyte retrieval ($P < 0.05$). No differences in liver or renal function were found in the three groups.

Conclusion: Bromocriptine was apparently as effective as intravenous HES in patients with high risk of OHSS.

KEYWORDS
bromocriptine, hydroxyethyl starch, in vitro fertilization, ovarian hyperstimulation syndrome, prevention

1 | INTRODUCTION

Assisted reproductive technology therapy may be accompanied by ovarian hyperstimulation syndrome (OHSS), a complication that is connected to controlled ovarian hyperstimulation, which can be potentially fatal. During OHSS, the ovaries become enlarged and an acute shift in fluids occurs from the intravascular to the third space, sometimes resulting in fluid accumulation in the peritoneal and thoracic cavities, with subsequent hemoconcentration, elevated hematocrit, and decreased organ perfusion.[1] Kidney failure, respiratory distress, and death are all complications associated with OHSS.[2]

As many as 20%–33% of in vitro fertilization (IVF) cycles may be affected by mild OHSS, whereas moderate to severe OHSS can reportedly occur in 3%–8% of patients, respectively.[3] Some studies have proposed that OHSS-related fluid accumulation may develop in high-risk women as the result of greater vascular permeability associated

with stimulation by ovarian steroids and treatment with human chorionic gonadotropin. Moreover, several hormones and factors have been identified as potential etiologic agents in OHSS, including prostaglandins, inhibin, the renin-angiotensin-aldosterone system, as well as several inflammatory factors,[4] with vascular endothelial growth factor (VEGF) serving as the primary mediator of this syndrome.[1]

A systematic literature review revealed that prophylactic administration of a dopamine agonist (DA) can significantly reduce the incidence of OHSS.[5] A growing number of studies have evaluated cabergoline for reducing OHSS incidence and severity. However, cabergoline is unavailable in many parts of the world, including mainland China. An alternative DA, bromocriptine, which is widely available, has also been previously reported to attenuate OHSS, but has received less research attention.[6] This study aimed to compare the effects of prophylactic rectal bromocriptine administration with that of hydroxyethyl starch (HES) infusion in women with high risk of OHSS.

2 | MATERIALS AND METHODS

2.1 | Study design and study women

This retrospective study was performed at the Department of Human Reproductive Medicine, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing. The data were analyzed from 144 infertile women at high risk of developing OHSS from among the patient population with IVF or intracytoplasmic sperm injection (ICSI) cycles between February 2019 and December 2020. High risk of OHSS was defined as serum estradiol levels greater than 3000 pg/ml at the time of trigger, and/or retrieval of 20 or more oocytes.[7] All embryos were frozen for all patients included in this study. The patients included both women with and women without polycystic ovary syndrome (PCOS). All patients had no history of cancer, did not have unilateral ovary, and did not use a coasting protocol. The Institutional Review Board and Ethical Committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing approved this study. Patients were allocated to the bromocriptine (n = 52), I.V. HES (n = 52), or control (n = 40) groups based on the treatment modalities they received after oocyte retrieval. All participants gave informed consent.

2.2 | Protocols for ovarian stimulation

All patients (25–39 years old) underwent ovarian stimulation using a protocol that combined recombinant follicle-stimulating hormone (Gonal F®; Merck), highly purified urinary menopausal gonadotropins (Menopur®; Ferring), Menotrophin (Ferti® M; Livzon), and gonadotropin-releasing hormone (GnRH) antagonist (Cetrotide® 0.25 mg; Merck). The initial dose was individualized based on patient age, ovarian reserve tests, body mass index (calculated as weight in kilograms divided by the square of height in meters), and subsequent doses were tailored according to her response after the first 5 days of stimulation. Follicular development was monitored by transvaginal ultrasound and serum estradiol, progesterone, and luteinizing hormone levels (measured by chemiluminescence). When an echography revealed at least three follicles larger than 18 mm in diameter, 0.2 mg GnRH Agonist (Decapeptyl®, 0.1 mg; Ferring) was administered subcutaneously. Transvaginal ultrasound-guided oocyte retrieval was then scheduled for 36 h after the trigger.

2.3 | OHSS preventive treatment administration

The study investigated 144 patients at high risk of OHSS: the bromocriptine group (n = 52) received 2.5 mg bromocriptine through daily rectal administration for 5 days, starting on the day of oocyte retrieval (i.e., Day 0), the HES group (n = 52) received a slow intravenous infusion of 500 ml HES daily for 5 days, beginning on the day of oocyte retrieval, and the control group (n = 40) received no pharmacologic intervention.

2.4 | Assessment of ovarian hyperstimulation syndrome

OHSS was diagnosed and classified as previously described by Humaidan et al.[8] Patients were assessed for clinical symptoms, signs, and laboratory data of OHSS at 5 days after oocyte retrieval. "Early OHSS" was defined as occurring 9 days or less after oocyte retrieval, whereas presentation of OHSS later than 9 days was classified as "late OHSS."[9]

In the three groups, hematologic tests were performed before ovarian stimulation (i.e., baseline) and on the 5th day after oocyte retrieval (i.e., Day 5) to determine the hematocrit content, white blood cell (WBC) count, platelet count, liver and renal function, and coagulation and fibrinolytic parameters.

2.5 | Statistical analysis

Statistical analysis was performed using SPSS (Version 16, SPSS Inc.,). Results of the study were expressed as means ± standard deviation or number (percentage). One-way analysis of variance followed by the least squares difference t test or χ^2 test were performed to evaluate the statistical differences between the variables. A P value less than 0.05 was considered significant.

3 | RESULTS

3.1 | Baseline characteristics

There were no significant differences between the three groups with regard to age, body mass index, duration of infertility, basal serum follicle-stimulating hormone levels, basal luteinizing hormone levels, basal estradiol levels, or type of infertility (all $P > 0.05$). In addition, their characteristics related to OHSS risk factors, including

anti-Müllerian hormone levels and ovarian antral follicle count were also similar among the three groups (all $P > 0.05$) (Table 1).

3.2 | Ovarian stimulation outcomes

No significant differences were found among the three groups in terms of their duration of ovarian stimulation in days ($P > 0.05$), total amount of gonadotropin dose ($P > 0.05$), and endometrial thickness on the day of trigger ($P > 0.05$). The participants' characteristics related to OHSS-associated risk factors, including estradiol levels on the day of trigger and the number of retrieved oocytes, were also similar among groups (all $P > 0.05$) (Table 2).

3.3 | OHSS outcomes

No significant differences were observed in the incidence of mild OHSS between the three groups ($P > 0.05$). Moderate OHSS was observed in four patients (7.7%) in the bromocriptine group, three cases (5.8%) occurred in the HES group, and five patients (12.5%) in the control group. There were no cases of severe OHSS in the bromocriptine or HES groups, but four patients (10.0%) in the control group developed severe OHSS. These cases were all categorized as early OHSS, whereas no cases of late OHSS were observed in any of the three groups. Both bromocriptine and HES treatments led to a significantly reduced incidence of moderate to severe OHSS and overall incidence of OHSS compared with that in the control group (all $P < 0.05$) (Table 3).

There were no significant differences found between the three groups in their baseline hematocrit, WBC count, and platelet count, i.e. before ovarian stimulation, (all $P > 0.05$). However, on the 5th day after oocyte retrieval, WBC counts were significantly higher in the three groups compared with their baseline WBC count ($P < 0.05$). WBC counts and hematocrit were both significantly higher in the bromocriptine group compared with the HES group (all $P < 0.05$) on the 5th day after oocyte retrieval. WBC counts and hematocrit were both significantly lower in the HES group compared with the control group ($P < 0.05$) on the 5th day after oocyte retrieval (Table 4).

TABLE 1 Baseline characteristics and clinical features of patients in the three groups[a]

Variables	Bromocriptine ($n = 52$)	Intravenous HES ($n = 52$)	Control ($n = 40$)	*P* value
Age, years	31.31 ± 3.85	29.68 ± 3.06	30.58 ± 3.21	0.303
BMI	22.36 ± 2.33	24.07 ± 4.15	24.83 ± 4.24	0.449
Duration of infertility, years	2.33 ± 1.15	3.14 ± 2.03	3.36 ± 1.25	0.253
Basal FSH, mIU/ml	6.20 ± 1.72	6.00 ± 1.18	6.01 ± 1.45	0.760
Basal LH, mIU/ml	5.01 ± 4.05	5.79 ± 2.35	5.95 ± 2.42	0.175
Basal E_2, pg/ml	48.49 ± 14.71	44.97 ± 14.11	41.50 ± 14.32	0.521
Basal AMH, ng/ml	8.38 ± 5.37	9.52 ± 4.62	8.31 ± 4.09	0.092
Antral follicle count	18.09 ± 4.25	19.10 ±3.30	18.25 ± 4.19	0.534
Type of infertility				
Primary infertility	27 (51.9)	29 (55.8)	21 (52.5)	0.916
Secondary infertility	25 (48.1)	23 (44.2)	19 (47.5)	

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); E_2, estradiol; FSH, follicle-stimulating hormone; HES, hydroxyethyl starch; LH, luteinizing hormone.

[a]Data are presented as means ± standard deviation or as number (percentage).

TABLE 2 Ovarian stimulation outcomes in the three groups[a]

Variables	Bromocriptine ($n = 52$)	Intravenous HES ($n = 52$)	Control ($n = 40$)	*P* value
Stimulation length, d	10.27 ± 1.74	9.61 ± 1.99	10.35 ± 1.53	0.559
Gonadotropin dose, IU	2059.09 ± 304.40	2057.14 ± 552.45	2391.67 ± 599.89	0.080
E_2 on the day of trigger, pg/mL	5811.88 ± 1940.20	6083.99 ± 2159.79	5931.31 ± 2144.59	0.381
LH on the day of trigger, mIU/mL	1.35 ± 1.11	1.83 ± 2.21	1.79 ± 0.97	0.466
P on the day of trigger, ng/mL	1.11 ± 0.42	1.25 ± 0.63	1.35 ± 0.66	0.180
Endometrial thickness on the day of trigger, mm	10.80 ± 2.22	10.67 ± 2.21	9.65 ± 2.09	0.873
Number of retrieved oocytes,	23.89 ± 4.01	24.75 ± 3.06	22.48 ± 7.57	0.091

Abbreviations: E_2, estradiol; HES, hydroxyethyl starch; LH, luteinizing hormone; P, progesteron.

[a]Data are presented as means ± standard deviation.

TABLE 3 Incidence of OHSS in the three groups[a]

OHSS incidence	Bromocriptine ($n = 52$)	Intravenous HES ($n = 52$)	Control ($n = 40$)
Mild OHSS	7 (13.5)	8 (15.4)	7 (17.5)
Moderate to severe OHSS	4 (7.7)[b]	3 (5.8)[b]	9 (22.5)
Overall OHSS	11 (21.2)[b]	11 (21.2)[b]	16 (40.0)
Early OHSS	11 (21.2)[b]	11 (21.2)[b]	16 (40.0)

Abbreviations: HES, hydroxyethyl starch; OHSS, ovarian hyperstimulation syndrome.

[a]Data are expressed as number (percentage).

[b]Compared with the control group, $P < 0.05$.

TABLE 4 Blood-related parameters before ovarian stimulation and on Day 5 after oocyte retrieval[a]

Variables	Bromocriptine ($n = 52$)	Intravenous HES ($n = 52$)	Control ($n = 40$)	*P* value
HCT, %				
Baseline	40.23 ± 2.42	40.00 ± 2.35	38.23 ± 2.93	0.063
On Day 5	41.43 ± 1.93[b]	39.52 ± 3.29[c]	42.40 ± 3.81	0.012
WBC count, $\times 10^9$/L				
Baseline	7.28 ± 2.82	6.41 ± 1.25	6.32 ± 1.63	0.211
On Day 5	13.95 ± 4.51[b,d]	10.83 ± 2.88[c,d]	12.76 ± 4.94[d]	0.042
Platelet count, $\times 10^9$/L				
Baseline	260.75 ± 61.97	282.26 ± 54.01	289.81 ± 78.73	0.556
On Day 5	302.70 ± 74.42	297.76 ± 51.11	326.08 ± 84.97	0.337

Abbreviations: HCT, hematocrit; HES, hydroxyethyl starch; WBC, white blood cells.

[a]Data are presented as means ± standard deviation. Baseline represents before ovarian stimulation; On Day 5 represents on the 5th day after oocyte retrieval.

[b]Compared with the intravenous HES group at the same period, $P < 0.05$.

[c]Compared with the control group at the same period, $P < 0.05$.

[d]Compared with the same group at baseline before ovarian stimulation, $P < 0.05$.

There were no statistically significant differences in coagulation and fibrinolytic parameters before ovarian stimulation between the three groups (all $P > 0.05$). Fibrinogen and D-dimer were significantly higher in the three groups compared with their baseline levels (all $P < 0.05$). In comparison with the control group, D-dimer was significantly lower in the bromocriptine and HES groups (all $P < 0.05$) (Table 5).

In assays for liver and kidney function, we found no significant differences between the three groups at baseline before ovarian stimulation or on the 5th day after oocyte retrieval (all $P > 0.05$). The three groups showed significantly higher transaminase activities, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), on the 5th day after oocyte retrieval compared with baseline (all $P < 0.05$) (Table 6).

In addition, the medication was well-tolerated by all patients in the bromocriptine group, with no obvious adverse effects recorded in either the bromocriptine or HES groups.

4 | DISCUSSION

This study evaluated the effectiveness and safety of rectal bromocriptine administration in prophylactic OHSS treatment. The bromocriptine group had significantly lower incidence of moderate to severe OHSS compared with that in the control group. A similar proportion of patients given bromocriptine experienced moderate OHSS compared with that in the intravenous HES group, and in all cases the treatment was well-tolerated with no recorded adverse events. Overall, rectal administration of bromocriptine may represent an effective, safe, convenient, and relatively economical prophylactic approach to OHSS, with comparable effects to intravenous HES.

Estradiol levels and number of retrieved oocytes are the two most commonly-used risk markers for OHSS. The rate of OHSS incidence increases along with elevated serum estradiol,[9] although there is currently a lack of consensus on an appropriate threshold cut-off for estradiol-associated risk. By contrast, the number of oocytes retrieved can serve as a more precise marker for risk of OHSS development.[10] According to Papanikolaou et al.,[11] a threshold of 18 or more follicles at least 11 mm in diameter and/or serum estradiol at 5000 pg/ml or more yielded an 83% sensitivity rate with a specificity of 84% for predicting severe OHSS cases. In some studies, the patients were included if 20 or more oocytes could be retrieved and/or estradiol levels were more than 3000 pg/ml on the day of trigger.[7,10]

TABLE 5 Coagulation and fibrinolytic parameters at baseline and on Day 5 after oocyte retrieval[a]

Variables	Bromocriptine ($n = 52$)	Intravenous HES ($n = 52$)	Control ($n = 52$)	*P* value
FIB, g/L				
Baseline	2.82 ± 0.55	2.83 ± 0.58	3.05 ± 0.62	0.336
On Day 5	3.79 ± 0.69[b]	4.02 ± 1.09[b]	4.46 ± 1.37[b]	0.132
PT, s				
Baseline	11.17 ± 0.70	11.06 ± 0.46	11.04 ± 0.43	0.414
On Day 5	10.95 ± 0.56	10.95 ± 0.45	10.98 ± 0.55	0.177
PA, %				
Baseline	112.48 ± 17.46	116.39 ± 11.36	116.82 ± 9.48	0.570
On Day 5	119.74 ± 12.70	119.09 ± 9.53	118.79 ± 14.61	0.750
D-D, mg/L				
Baseline	0.27 ± 0.22	0.25 ± 0.11	0.30 ± 0.20	0.193
On Day 5	1.91 ± 1.46[b,c]	1.83 ± 1.29[b,c]	2.28 ± 1.65[b]	0.042

Abbreviations: D-D, D-dimer; FIB, fibrinogen; HES, hydroxyethyl starch; PA, plasminogen activator; PT, prothrombin time.

[a]Data are presented as means ± standard deviation. Baseline represents before ovarian stimulation; On Day 5 represents on the 5th day after oocyte retrieval.

[b]Compared with the same group at baseline before ovarian stimulation, $P < 0.05$.

[c]Compared with the control group at the same period, $P < 0.05$.

TABLE 6 Liver and renal function before ovarian stimulation and on Day 5 after oocyte retrieval[a]

Variables	Bromocriptine ($n = 52$)	Intravenous HES ($n = 52$)	Control ($n = 40$)	*P* value
ALT, U/L				
Baseline	13.74 ± 6.24	15.70 ± 13.50	15.36 ± 7.69	0.092
On Day 5	23.06 ± 16.28[b]	25.87 ± 14.31[b]	23.28 ± 13.29[b]	0.303
AST, U/L				
Baseline	15.89 ± 3.92	16.14 ± 4.97	16.22 ± 3.45	0.356
On Day 5	23.43 ± 14.40[b]	22.58 ± 10.81[b]	23.32 ± 12.58[b]	0.289
GGT, U/L				
Baseline	16.38 ± 7.73	17.93 ± 16.95	19.10 ± 8.26	0.155
On Day 5	23.29 ± 22.30	25.00 ± 24.31	24.37 ± 15.81	0.913
BUN, mmol/L				
Baseline	4.14 ± 0.89	3.88 ± 0.91	4.08 ± 1.06	0.371
On Day 5	4.39 ± 0.82	4.14 ± 0.78	3.96 ± 0.72	0.136
UA, μmol/L				
Baseline	298.83 ± 75.93	282.66 ± 56.80	302.66 ± 99.47	0.548
On Day 5	265.92 ± 63.08	299.79 ± 95.74	303.39 ± 73.99	0.666
CRE, μmol/L				
Baseline	53.85 ± 7.49	53.75 ± 8.19	55.68 ± 7.11	0.727
On Day 5	57.09 ± 6.30	56.10 ± 6.93	63.96 ± 34.35	0.476
eGFR, ml/min/1.73 m^2				
Baseline	126.65 ± 21.85	128.08 ± 22.74	122.55 ± 19.72	0.667
On Day 5	116.38 ± 14.98	120.69 ± 19.53	116.50 ± 28.68	0.847

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRE, creatinine; eGFR, estimated glomerular filtration rate; GGT, glutamyl transpeptidase; HES, hydroxyethyl starch; UA, uric acid.

[a]Data are presented as means ± standard deviation. Baseline represents before ovarian stimulation; On Day 5 represents on the 5th day after oocyte retrieval.

[b]Compared with the same group at baseline before ovarian stimulation, $P < 0.05$.

Several approaches have addressed the need to mitigate the risk and severity of OHSS in IVF/ICSI cycles.[6] These strategies include individualized controlled ovarian hyperstimulation,[12] canceling of the cycle, coasting,[2] individualizing the human chorionic gonadotropin trigger doses, or administration of a GnRH agonist for patients receiving GnRH antagonist.[8] In addition, aspirin in low doses has also been examined as a possible preventive measure for OHSS.[13] Other approaches include the use of intravenous fluids at the time of oocyte retrieval, such as albumin, HES,[14] and calcium,[15] as well as embryo cryopreservation for later transfer. Ultimately, the discovery that the pro-angiogenic cytokine VEGF functions as the primary contributor in OHSS pathogenesis, followed by the insight that VEGF activity could be modulated via dopamine, together, have resulted in the broad range of DAs for prevention of OHSS-associated events and symptoms. Specifically, in vivo studies have shown that DAs post-transcriptionally regulate the secretion of VEGF in luteinized granulosa cells.[16] Previous research in a rat ovarian hyperstimulation model showed that administration of low-dose DA can inhibit VEGF-mediated vascular hyperpermeability but does not affect VEGF receptor 2-dependent luteal angiogenesis.[17] Notably, DAs can increase renal blood flow by affecting VEGF receptor, glomerular filtration, and sodium excretion, subsequently preventing development of ascites and facilitating cytokine secretion (e.g., VEGF), thus suggesting the potential utility of DAs in OHSS therapy.[18]

Among DAs, cabergoline has been reported as a reliable prophylactic treatment to limit OHSS incidence and severity.[5] Bromocriptine has received attention for similar effects to cabergoline, although few clinical studies have explored its effects in the prevention of OHSS. Bromocriptine is an ergot alkaloid dopamine receptor agonist that is potent as an agonist of the dopamine-2 receptor, but also functions as a weak dopamine-1 receptor antagonist. An initial series of trials apparently shows that bromocriptine is as effective as cabergoline against OHSS, but is considerably lower in cost.[19] These current studies all used 2.5 mg bromocriptine daily, but vary in their starting time and duration of administration, with some beginning on the day of ovum pick-up,[20] and others on the day of trigger,[18] and have a maximum duration spanning 16 days. In our study, bromocriptine was administered for only 5 days, and appeared to result in good prevention of OHSS.

Although controversial among some clinicians, intravenous HES is generally regarded as an effective approach in the reduction or attenuation of OHSS incidence, and is widely used.[8] A prospective randomized placebo-controlled trial showed that the administration of HES prevented the development of moderate–severe OHSS.[7] In a review, Youssef and Mourad[14] reported that, despite some limitations in the original studies, administration of HES could reduce the incidence of severe OHSS to an average of 5% (range 2%–10%) compared with a prevalence of 16% in the untreated population. As HES administration can lead to significantly increased vascular system volume,[21] its administration therefore may also be accompanied by elevated osmotic pressure and decreased blood viscosity. Furthermore, the inhibition of platelet aggregation induced by HES can also reduce blood coagulation, so circumventing hypovolemia and hemoconcentration.[22] It also warrants mention that DAs inhibit the phosphorylation of VEGF receptor-2.[17] The activity of bromocriptine in decreasing vascular permeability and concurrent reduction in VEGF production can at least partially explain its mechanism of inhibiting OHSS. In this study, we observed that the incidence of overall OHSS, especially moderate to severe OHSS, was significantly lower in the bromocriptine and HES groups compared with that in the control group. There were no significant differences in the incidence of mild (13.5% vs. 15.4%) and moderate (7.7% vs. 5.8%) OHSS between the bromocriptine and HES groups ($P > 0.05$). Our results indicated that rectal administration of bromocriptine showed apparently equal effects to intravenous HES in women with high risk of OHSS. However, the WBC counts and hematocrit values were higher in the bromocriptine group on Day 5 after oocyte retrieval than in the HES group.

Levels of ALT and AST were also higher on Day 5 after oocyte retrieval than at the baseline before ovarian stimulation in the three groups; however, the values were within the normal range. This increase in ALT and AST may be related to the rise in estradiol levels in the patients during controlled ovarian hyperstimulation, which aggravates the burden on the liver. In addition, we found no significant difference in renal function between baseline and Day 5 after oocyte retrieval for either group. These results show that bromocriptine is sufficiently safe and does not appear to affect liver and renal function at these doses, which are appropriate for OHSS prevention.[18]

Disadvantages of bromocriptine include the known adverse effects of nausea, headaches, and orthostatic dysregulation.[23] In one study, 24% of the patients displayed transient gastrointestinal intolerance to DA treatment.[24] Notably, patients with OHSS may experience gastrointestinal symptoms including nausea and vomiting. Oral administration may have resulted in substantial aggravation of gastrointestinal reactions for patients with high-risk of OHSS. We therefore opted for bromocriptine administration via rectal insertion to avoid these adverse effects. Moreover, the relatively low dosage used in this study was apparently well-tolerated, and more convenient for patients than intravenous delivery. The lower price of bromocriptine compared with HES also provides a cost-saving benefit that is also appreciated by patients.

In conclusion, the present study showed that rectal administration of 2.5 mg bromocriptine daily for 5 days beginning on the day of oocyte retrieval appeared to have equivalent effects to intravenous HES in patients at high risk of developing OHSS. The absence of reported adverse effects among trial participants contributes to our conclusion that bromocriptine is safe at the doses tested here, and is more cost-effective and more conveniently administered than HES. Bromocriptine represents a new and promising alternative prophylactic treatment approach for OHSS. However, this study was accompanied by limitations. First, the intervention effects of bromocriptine on OHSS require further investigation in a multicenter, large sample, and randomized controlled trial. This study does not include any investigation of pregnancy outcomes because all embryos were frozen.

AUTHOR CONTRIBUTIONS

SW conceived and designed the experiments. QZ analyzed the data and wrote the manuscript. YM and CJ acquired the OHSS data according to patients' physical conditions and recorded all the basic information. XB and YL helped to collect and analyze the data. All authors participated in revising the manuscript and all approved the final version.

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CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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