

# Combined Treatment with Prednisone and Bromocriptine does not Influence the Pregnancy Outcome in Fresh Embryo Transfer Cycles

Tao Wang

Reproductive Medicine Institute: Instituto de Medicina Reproductiva

Yan Xia (✉ [airxia@126.com](mailto:airxia@126.com))

reproductive medicine center

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## Research

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# Abstract

**Background:** Ovarian hyperstimulation syndrome (OHSS) is a potentially serious complication of ovarian stimulation in assisted reproduction technology (ART). The aim of this study was to evaluate if the combined treatment with prednisone and bromocriptine will reduce the risks of ovarian hyperstimulation syndrome (OHSS) and influence the pregnancy outcomes in fresh embryo transfer cycles.

**Method:** Retrospective study was performed and Infertile patients undergoing assisted reproduction techniques were recruited.

**Results:** The cancellation rate for OHSS in the combined group was 31.45%, while the control group was 40.88%. There was a significant reduction of the OHSS cancellation rate between the combined group and the control group ( $P < 0.001$ ). The single embryo transfer had been completed in 350 cycles in the combined group, and 495 cycles for double embryos transfer. Single embryo transfer were just only 227 cycles for the control group, while 517 cycles for double embryos transfer ( $P < 0.001$ ). As for the total successful embryo implantation, 509 cycles were in the combined-treated group (40.88%), while the 442 cycles in the control group which have the statistical differences between them (38.30%,  $P = 0.012$ ). There was no statistical difference in clinical pregnancy rate ( $P = 0.492$ ), miscarriage rate ( $P = 0.792$ ), ongoing pregnancy rate ( $P = 0.719$ ), live birth rate ( $P = 0.295$ ), the congenital abnormalities rate ( $P = 0.081$ ), and the ectopic pregnancy occurrence rate ( $P = 0.649$ ) between the combined group and the control group.

**Conclusion** Compared with the bromocriptine single using, combined-treated bromocriptine with prednisone can better reduce the OHSS occurrence rate dramatically and effectively and not affect the pregnancy outcomes in fresh embryo transfer cycles.

## Introduction

Ovarian hyperstimulation syndrome (OHSS)(1) occurred as a severe complication during the controlled ovarian stimulation (COS) for infertile patients with the assisted reproduction technology (ART), which characterized the multiple follicle developments, enlarged ovaries, high estrogen levels, and increased capillary permeability(2). It can also cause pleural ascites, blood concentration, liver, and kidney function abnormalities. Some complications may occur for the severe cases such as thrombosis, multiple organ failure, and even threaten patients' life and need hospitalization(3, 4). Sherwal(5) described OHSS diagnosis standard in the research that the symptoms of mild OHSS included abdominal distension, discomfort, mild nausea/vomiting and diarrhea. Moderate OHSS not only has the mild OHSS features but also occurred the ultrasonographic evidence of ascites (perpendicular fluid pocket of  $> 9 \text{ cm}^2$ ). Severe OHSS considered a series of features that required clinical evidence of ascites and/or hydrothorax and breathing difficulties or one of the following criteria: 1) increased blood viscosity i.e. hematocrit at least 45%, or leucocyte count at least 20,000 per cubic millimeter. 2) coagulation abnormality. 3) diminished renal perfusion and function (S.creatinine  $> 1.2 \text{ mg/dl}$ ). 4) liver dysfunction, defined when transaminases (AST or ALT) are more than 40u/ml. Although many studies have been conducted for OHSS prevention,

there still have no more effective measures for reducing the above related symptoms in clinical practices. Therefore, exploring an effective prevention measure for OHSS has become a clinical research hotspot in ART treatment.

Prednisone is a class of intermediate-acting glucocorticoids, which has a good effect on reducing the leakage of vasoactive substances and vascular permeability. As a common immunomodulatory agent, prednisone is often used for those infertile patients with repeated embryo implantation failures (6–8), and improve the reproductive outcomes(9, 10). Prednisone also has the effect of reducing exudation and eliminating edema in some inflammation situation or diseases. Tan(11)and Lainas(12)and other studies confirmed that prednisone had no side effect on IVF pregnancy rate. Moreover, compared with other preventive measures such as albumin, hydroxyethyl starch, and cycles cancellation, oral prednisone for the prevention and treatment for OHSS had no risk of blood-origin diseases and reduced the financial burden of patients. Some studies showed prednisone does not affect the IVF pregnancy rate, minimal side effects(13), and significant advantages in terms of economic burden, administration route.

Bromocriptine, one of the dopamine receptor agonists (DA)(5, 14, 15),which inhibits the vascular permeability by blocking VEGF-receptor binding pathways has been found to reduce the angiogenic factors releasing and the vascular permeability for OHSS prevention by inhibiting VEGF receptors' phosphorylation (16–20). Some studies showed that vaginal administration of bromocriptine could reduce the probability of adverse reactions in the digestive tract and nervous system, and has a preventive effect on OHSS(15). Bromocriptine as dopamine receptor agonists is currently often used for the OHSS prevention (21). Spitzer, D., *et al.* (22)found that bromocriptine and cabergoline have similar OHSS preventive effects. A systematic review (23)showed that prophylactic treatment with the dopamine agonist can reduce the incidence, but not the severity of OHSS, without compromising pregnancy outcomes. Both of the cabergoline and Bromocriptine can be administered all women at increased risk for OHSS by stimulated the dopamine D2 receptor(22, 24, 25). In the early stage of acute inflammation, it can increase the tension of blood vessels, reduce congestion, and reduce capillaries permeability. The release of the inflammatory mediator has the effect of reducing exudation and eliminating edema, so that it may have a preventive effect on OHSS. However, there is no clinical application study about bromocriptine and prednisone combination using in IVF, and their long-term influence study of the pregnancy outcome has not been confirmed. Therefore, this study aims to compare these prophylactic treatments in preventing OHSS for female patients with a high risk of OHSS who undergo in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) and to evaluate the effects of the combination medication on the human embryo qualities and patients' pregnancy outcomes.

## Study Design And Methods

### Institutional approval

This study was approved by the Ethics Review Board of the Northwest Women's and Children's Hospital, Xi'an, China.

## Patients and groups

The retrospective study recruited 4114 cycles of infertile patients who underwent IVF or ICSI treatments from January 2014 to May 2017. All the patients which the serum estradiol (E2) levels reached 4800 pg/ml on the trigger day have been divided into the combined-treatment group and the control group (single-treated). The inclusion criteria are as follows: (1) infertility couples. (2) IVF/ICSI treatments; (3) E2 level reached 4800pg/ml on trigger day. (4) prednisone and/or bromocriptine treatments. The exclusion criteria: (1) cycles canceled prior to oocyte retrieval. (2) cycles with oocyte donation or sperm donation. (3) abnormal liver function or kidney function. (4) incomplete follow-up or medical records (Supplement Figure 1).

## Ovarian stimulation and medications

Patients with agonist protocol were monitored to see whether pituitary down-regulation achieved, with  $E2 < 25 \text{ pg/ml}$ , luteinizing hormone (LH)  $< 5 \text{ U/L}$ , the diameter of the ovarian follicles, monitoring by B-ultrasound, measuring  $< 5 \text{ mm}$ , and the endometrial thickness  $< 5 \text{ mm}$ . Patients commenced ovarian stimulation with an initial dose of gonadotropin (Gn) for 150–225IU daily which was adjusted according to the body mass index (BMI), ovarian antral follicle count (AFC), ovarian reserve, and ovarian response this cycle or in the past IVF/ICSI cycles. Follicles developing and E2 levels were monitored by transvaginal sonography (TVS) and blood testing. Gn doses adjusted could be followed the hormonal level changes, ovarian volume, oocyte sizes, and numbers. When at least two dominant follicle reached 18 mm in diameter or three follicles reached diameters of 17 mm, recombinant hCG of 250 micrograms was administered as trigger. Patients in combined-treated group were administrated both tablet bromocriptine 2.5 mg for rectal insertion and tablet prednisone 5mg for oral administration. The patients of the control group just only administrated bromocriptine 2.5 mg for rectal insertion. These two groups were administrated for the consecutive days from the trigger day to the seven days after the oocyte retrieval.

## Statistical analysis

Data statistical analysis was performed by using SPSS software (version 23.0). Results were presented as the mean  $\pm$  standard deviation (SD) or as a percentage (%). For the quantitative data subjected to the normal distribution, it was performed by the independent sample *t* test, and for those quantitative data which not subjected to the normal distribution, it was performed by the Wilcoxon test. For categorical variables, data were described as frequency with rate and compared by Chi-square test or Fisher's exact test as appropriate. All P values were two-sided, and  $P < 0.05$  was considered statistically significant.

# Results

## 1. Basic characteristics

It showed the basic characteristics of patients in the combined-treated bromocriptine with prednisone group and control group (Table 1). It included age, BMI, AFC, AMH, FSH, LH, E2, progesterone levels, and

the duration of infertility were comparable between the two groups ( $P > 0.05$ ). As for the infertility factors in the combined group, the male factors were 465 cycles and the tubal factors with 848 cycles, 125 cycles with anovulation and 17 cycles with endometriosis, and 289 cycles with the bilateral factors. In the control group, 452 cycles of the male factors, 859 cycles of the tubal factors, 172 cycles of the anovulation, 14 cycles of endometriosis, and 315 cycles of the bilateral factors of the couples. All the infertile patients have performed the controlled ovarian hyperstimulation and we compared all the infertile causes such as anovulatory factor, the fallopian tube factor, endometriosis, male factor, and other factors and found that the fallopian tube factor was the most common infertility factor between the two groups (Supplement Fig. 2). There were statistical differences in the endometrium thickness on trigger day, total Gn dose, Gn duration, hormone levels on trigger day, and actual oocytes retrieval numbers, and some hormone levels have changed with statistical differences, others had no statistical differences (Supplement Table 1).

Table 1  
Basic characteristics of the study population.

Characteristics	Combined (2057)	Single (2057)	<i>P</i>
Age(years)	29.30 ± 3.79	29.06 ± 3.89	0.055
Cycles	1.12 ± 0.408	1.10 ± 0.395	0.119
Basal FSH (mIU/ml)	6.34 ± 1.74	6.25 ± 1.74	0.071
Basal LH (mIU/ml)	5.93 ± 4.45	6.10 ± 3.78	0.179
Basal E2(pg/ml)	40.64 ± 18.58	41.29 ± 17.66	0.263
Basal P(ng/ml)	0.65 ± 0.42	0.62 ± 0.60	0.054
AMH (ng/ml)	5.19 ± 4.32	6.38 ± 3.85	0.059
AFC (Antral Follicle counts)	7.72 ± 2.72	7.89 ± 2.79	0.060
Infertility type(P/S)	1237/807	1277/776	0.269
infertility Duration	3.45 ± 2.319	3.52 ± 2.416	0.287
BMI (kg/m <sup>2</sup> )	21.65 ± 3.08	22.02 ± 8.56	0.067

*Note: Values are presented as mean ± SD. P < 0.05 was considered significant. FSH: follicle-stimulating hormone. LH: luteinizing hormone. E2: Estrodial. P: progesterone. AMH: Anti-mullerian hormone. AFC: antral follicle counts. P/S: primary infertility/secondary infertility. BMI: body mass index.*

## 2. Fresh Transfer Cycles Cancellation For Ohss

Some cycles in this study cancelled as the symptoms of OHSS occurred, and some for other reasons such as hydrosalpinx, abnormal higher P levels, endometriosis, preimplantation genetic diagnosis/

preimplantation genetic screening (PGD/PGS), intrauterine effusion or abnormal endometrium or patients' personal reasons. In 1489 cycles of cancellation for OHSS, 648 cycles were in the combined group, and 841 cycles were in the control group. The OHSS cancellation rate of the combined group was 31.45%, while the control group was 40.88% with the statistical differences which was higher than that in the combined group (Table 2).

Table 2  
Cancellation rate for the fresh transfer cycle in two groups

Cancellation reasons	Group		$\chi^2$	<i>p</i>
	Combined	Single		
OHSS	648(31.45%*)	841(40.88%*)	36.625	0.001
Other	563	463		

\* OHSS cancellation rate. A chi-squared ( $\chi^2$ ) test was used and  $P < 0.05$  was considered significant.

### 3. Embryos Culture And Transfer

1601 cycles for fresh transfer were included in this study and other 2513 cycles transfer canceled. Of all the fresh cycles, 846 cycles were in the combined group, which included 826 cycles of the agonist protocol and 20 cycles of the antagonist protocol. In the meantime, 753 cycles were in the control group including 727 cycles with the agonist protocol and 26 cycles with the antagonist protocol. There was no statistical difference in the proportion of the different protocols for the fresh transfer cycles between the two groups (Supplement Table 2).

We compared the embryo culture and transfer between the two groups of the fresh transfer cycles. The high-quality embryos were defined by the embryologists according to the embryo evaluation standard, which was to calculate the optimal embryo numbers. For the 846 cycles in the combined group, 3670 embryos were the high-quality embryos, while as the control group, 3105 embryos were the high-quality ( $p = 0.144$ ). The average embryo transfer number was 1.59 in the combined group, while the control group was 1.70 (Table 3). The total number of transfer cycles in the combined group were 846 cycles, while the control group were 753 cycles. In the combined group, the single embryo transfer had been completed in 350 cycles in the combined group, and 495 cycles for double embryos transfer. Furthermore, 227 cycles were single embryo transfer in the control group, while 517 cycles for double embryos transfer ( $P < 0.001$ ). As for the total successful embryo implantation, 509 cycles were in the combined group (40.88%), while the 442 cycles in the control group which have the statistical differences (38.30%,  $P = 0.012$ ).

Table 3  
Embryo culture and transfer in fresh cycle

	Combined	Single	P
High-quality embryos numbers	3670	3105	$t = 1.463, p = 0.144$
Average embryo transfer number	1.59	1.70	
<b>Transfer types</b>			
Single	350	227	$\chi^2 = 20.361, p = 0.001^*$
Double	495	517	
Total transfer cycles	846	753	
Implantation numbers	509	442	$t = -2.527, p = 0.012^*$
Implantation rate	40.88%	38.30%	
Blastocysts numbers	2535	2248	$t = 0.082, p = 0.935$
Blastocysts formation rate	51.95%	51.76%	
<i>Note: descriptive data subjected to the normal distribution all assessed with the independent sample T test. A chi-squared (<math>\chi^2</math>) test was used for the transfer analysis. *<math>P &lt; 0.05</math> was considered significant.</i>			

## 4.clinical Pregnancy Outcomes

We compared the pregnancy outcomes of embryos transfer in the two groups and found that there was no statistical difference in clinical pregnancy rate, ongoing pregnancy rate, and live birth rate. Early abortion occurred in 50 cycles of the combined group, but 47 cycles in the control group with no statistical differences ( $P = 0.792$ ). Five fetal malformation cases occurred in the combined group and 3 cases in the control group ( $P = 0.081$ ). Six cases of ectopic pregnancy occurred in the combined group while 4 cases in the control group with no statistical difference ( $P = 0.649$ ). Besides these results, there was no statistically significant difference in the biochemical pregnancy rate and congenital abnormalities (Table 4). Although there was a dramatical difference in OHSS cancellation rate compared with these two groups, it showed with the above results, there have no statistical differences as for the pregnancy outcomes after the different medications.

Table 4  
the embryo transfer outcomes in fresh transfer cycle of the two groups

	Combined	Single	$\chi^2$	<i>p</i>
Clinical pregnancy rate	60.52%(512)	58.83%(443)	0.472	0.492
Biochemical pregnancy rate	7.23%(37)	7.90%(35)	0.070	0.792
Ongoing pregnancy rate	54.02%(457)	53.12%(400)	0.129	0.719
Ectopic pregnancy occurrence rate	1.17%(6)	0.90%(4)	0.207	0.649
Miscarriage rate	9.77%(50)	10.61%(47)	0.070	0.792
Fetus malformation rate	0.98%(5)	0.68%(3)	3.050	0.081
Live birth rate	53.31%(451)	51.13%(385)	1.097	0.295
Birth defects rate	0.67%(4)	1.04%(4)	0.349	0.554
<i>Note: numbers in brackets is indicated the cycle numbers. A chi-squared (<math>\chi^2</math>) test was used and <math>P &lt; 0.05</math> was considered significant.</i>				

## Discussion

OHSS is a series of symptoms that the ovarian excessive responses to the exogenous gonadotropins, in which the specific pathogenesis is unclear it included an increased capillary permeability, a decreased perfusion of essential organs, electrolyte disturbance, and blood concentration(26). The clinical manifestations are bilateral ovarian enlargement, pleural and ascites, abdominal distension, liver, and kidney dysfunction, and other serious complications. VEGF is currently considered a critical factor in the occurrence of OHSS(27). Risk factors for OHSS included (1) patients' age < 35 years; (2) polycystic ovary syndrome or polycystic ovarian changes; (3) BMI < 18.5 or BMI > 24; (4) AMH > 3.36 ng/ml; (5) sinus follicles numbers: more AFC was also a sensitive indicator for OHSS prediction. (6) The follicular development and oocytes retrieval numbers; (7) With OHSS history in the former cycles. Some studies showed that (28)the OHSS risks for those young infertile patients aged < 35 years were higher than those patients aged > 35 years. Danninger et al. (29) followed 101 patients who received IVF assisted pregnancy and found that patients with OHSS had a significantly lower BMI than those without OHSS. AMH can identify the ovarian reactivity to exogenous gonadotropins during the ovulation cycle. Lee *Et al.* (30)have found that AMH was a predictor of OHSS when it was higher than 3.36 ng/ml. Jayaprakasan(31)and other researchers have showed the more numbers of AFC for the infertile patients, the more incidence and risks of the moderate to severe OHSS. It is a question that need to be answer in this retrospective study which one was better for the combined treatment or single medication for OHSS prevention and the pregnancy.

4114 cycles were included in this study according to the E2 levels and retrospective analyzed the embryos culture, the transfer cycles cancel and the pregnancy outcomes for the patients using

prednisone combined with bromocriptine or single using bromocriptine. It intended to clarify whether the combined treatments may decrease the cycle cancellation rate during the ovulation process and whether it will influence pregnancy outcomes. We found some differences between the two groups in Gn duration and the endometrial thickness on trigger day (Table 2). Although the Gn duration was different, in which lead to the progesterone and LH level differed on the trigger day, there was no statistical difference in the Gn doses and E2 levels between these two groups. As mentioned in the above that the OHSS diagnostic standard, some cycles in this study have the symptoms of a mild OHSS or even some other patients have no any symptoms of the abdominal distension, discomfort, mild nausea/vomiting and diarrhea and just only with a higher E2 level.

As for the fresh transfer cycle cancellation, it was determined to the ovarian size and hormone levels and whether it occurred pelvic effusion or ascites and its degrees. According to the diagnosis of OHSS, physicians determined whether to cancel the cycle based on the patient's B-ultrasound results, follicular developments, ovarian sizes, and hormone testing results. We compared the OHSS cancellation cycle between the combined and control groups and found a significant difference between these two groups. Among 1489 canceled cycles, 648 cycles were in the combined group, and 841 cycles were in the control group, the OHSS cancellation rate in the combined group was 31.45%, while in the control group it was 40.88%. These results showed a statistically significant difference between them and it also indicated that it was better that prednisone combined treatment with bromocriptine than bromocriptine single using for relieving OHSS and dramatically decrease the cancellation rate for the fresh embryo transfer cycle. Besides this, there was no statistical difference in the COS protocol proportion between these two groups, which mainly existed of the agonist protocols, but the antagonist protocols were in the minority.

We compared the embryo qualities and embryo transfer outcomes and we want to know if prednisone combined with bromocriptine better than the single using of bromocriptine. The definition of the high-quality embryo was those embryos of the grade one and grade two. Our transfer standard for embryo transfer was performed according to the embryos quality evaluation by the embryologists and the patients' ages and heights, the cesarean delivery histories or other operation histories. According to the statistical analysis results, there had no statistical difference for the total number of the high-quality embryos and the blastocyst formation rate between the two groups. The average number of embryos transferred in the combined group was 1.59, while the average number of embryos transferred in the control group was 1.70, which was higher than it in the combined group with a significant statistical difference (Table 5). In terms of the total number of transfer cycles, 846 cycles were in the combined group, while 753 cycles were in the control group. The single embryo transfer in the combined group were 350 transfer cycles, and 495 cycles for double embryos transfer. In the control group, single embryo transfers were 227 cycles and 517 cycles were the double transfer ( $P < 0.001$ ). In terms of the embryo implantation, the numbers of implanted embryos in the combined group were 509 cycles, while that in the control group were 442 cycles. The implantation rate of the two groups had a statistically difference between them ( $P = 0.012$ ). The above results all indicated that combined bromocriptine with prednisone would not only relieve the symptom of OHSS but also wouldn't influence the transferred embryo qualities.

As for the pregnancy outcomes, we found no statistical differences in terms of clinical pregnancy rate, ongoing pregnancy rate, live birth rate, and early miscarriage rate between the two groups. Although the cycles of control group which we transferred just only one embryo were less than that of the combined group, in terms of implantation rate, the results in the combined group was significantly better than it in the control group. It demonstrated that the advantages of selective embryo transfer and the pregnancy outcome may be closely related to the embryo quality itself and little to do with the embryo transfer numbers. Although the fetal malformation occurred in five cycles in the combined group and three cycles in the control group, including congenital heart disease, six-finger deformity, and abdominal fissure malformation, there was no significant difference in the incidence of fetal malformation and ectopic pregnancy between the two groups. Furthermore, there were no significant statistical differences of the rates of biochemical pregnancy and congenital disabilities between the combined and control group.

## Conclusion

As a retrospective study, this study was mainly concerned if prednisone combined with bromocriptine was better than bromocriptine single using for both decreasing the OHSS occurrence probability and not influence embryo transfer outcomes. And we demonstrated in this study that this medication really does work for the patients who didn't not diagnose OHSS yet but perhaps developing to OHSS during controlled stimulation. Concerned the limitation of the retrospective study and all the relevant data were not randomized. We need to design and complete a further randomized experimental research to obtain a more reliable result to confirm this retrospective study results and to show if the combined medication really better than the single using for OHSS prevention in fresh transfer cycles.

## Abbreviations

OHSS  
ovarian hyperstimulation syndrome

ART  
assisted reproduction technology

IVF  
in vitro fertilization

ICSI  
intracytoplasmic sperm injection

AFC  
antral follicle counts

BMI  
body mass index

Gn  
gonadotropin

TVS

transvaginal sonography  
PGD/PGS  
preimplantation genetic diagnosis/ preimplantation genetic screening  
FSH  
follicle-stimulating hormone  
LH  
luteinizing hormone  
E2  
Estrodial  
P  
progesterone  
AMH  
Anti-mullerian hormone  
P/S  
primary infertility/secondary infertility

## Declarations

- **Ethical Approval and Consent to participate**

This study was approved by the Ethics Review Board of the Northwest Women's and Children's Hospital, China.

- **Consent for publication**

This work was original research that has not been published previously, and not under consideration for publication elsewhere in whole or in part. All authors approved the publication.

- **Availability of supporting data**

The datasets used during the current study are available from the corresponding author on reasonable request.

- **Competing interests**

The authors declare that they have no competing interests.

- **Funding**

Not applicable

- **Authors' contributions**

Tao has collected, sorted and analyzed the data. Yan has performed a major contributor for the data statistical analysis and the manuscript writing and revision. All authors read and approved the final manuscript.

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