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Original Article

Safety and effectiveness of dual trigger (GnRH agonist + HCG) versus HCG alone in patients with high ovarian response

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Abstract: Objective: To compare the safety and effectiveness between long-term GnRH agonist plus HCG (dual trigger) and HCG trigger alone in high ovarian responders. Methods: A retrospective study was conducted on clinical data from 314 cases of high ovarian response who underwent in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment at Hunan Provincial Maternal and Child Healthcare Hospital from July 2018 to January 2023. Participants were divided into two groups based on their triggering regimen: the Combined treatment group (GnRH agonist + HCG) and the HCG group (HCG alone). Blood routine, ovary ultrasound parameters, baseline hormone levels, clinical outcomes of controlled ovarian stimulation, clinical outcomes of the first transplantation, and incidence of ovarian hyperstimulation syndrome (OHSS) were compared between the two groups. Results: There were no significant differences in patient characteristics, blood routines, ovary ultrasound parameters, clinical pregnancy rate, implantation rate and abortion rate between the two groups (all $P > 0.05$). However, the incidence of Ovarian Hyperstimulation Syndrome (OHSS) in combined treatment group was significantly lower than that in HCG group (mild OHSS: 31% vs. 46.26%, $P=0.015$; moderate/severe OHSS: 3.00% vs. 11.68%, $P=0.021$). Conclusion: Long-term GnRH agonist plus HCG (dual trigger) does not affect the number of metaphase II (MII) oocytes, high-quality embryos, or clinical pregnancy rate in patients with high ovarian response. Furthermore, the incidence of OHSS is significantly lower with the dual trigger compared to the HCG trigger alone.

Keywords: High ovarian response, dual trigger, OHSS, GnRH agonist protocol

Introduction

Infertility is diagnosed when a couple has failed to conceive after one year of regular, unprotected sexual intercourse [1]. The challenge of infertility, often referred to as the "infertility predicament", imposes significant physical, social, and economic pressures, profoundly affecting individuals' lives [2]. Globally, infertility is a widespread medical issue, impacting approximately 10-15% of couples of reproductive age, with the incidence in China estimated to be between 12.5% and 15% [3].

Assisted reproductive techniques, such as in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), are essential interventions for couples facing infertility [4]. The variability in response to ovulation-inducing drugs can significantly affect their success rates. Although ovarian stimulation can yield multiple eggs, it also poses risks, including reduced egg quality, decreased endometrial receptivity, and ovarian hyperstimulation syndrome (OHSS). As a result, there is growing interest in optimizing the type and dosage of medications used to prevent OHSS in patients undergoing ovarian stimulation [5].

Controlled ovarian stimulation (COS) is a fundamental component of assisted reproductive technology (ART) cycles and involves adminis-

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tering gonadotropins to stimulate the development of multiple follicles [6]. Two extensive retrospective analyses have demonstrated a direct correlation between the number of oocytes retrieved and pregnancy/live birth rates in cycles with immediate fresh embryo transfers. This relationship is nearly linear up to a point, beyond which live birth rates plateau or decline with excessively high oocyte counts [7, 8]. However, COS can lead to complications such as ovarian hyperstimulation syndrome (OHSS), occurring in approximately 20-30% of cycles and potentially resulting in severe consequences [9]. To reduce the risks of OHSS, various strategies have been investigated, including the use of gonadotropin-releasing hormone (GnRH) agonists and human chorionic gonadotropin (HCG) triggers [10].

GnRH agonists are commonly used in IVF cycles for pituitary suppression, facilitating the synchronization of follicular development and preventing spontaneous luteinizing hormone (LH) surges [11]. The long GnRH agonist protocol is a traditional strategy for controlled ovarian stimulation (COS) due to its efficiency in recruiting multiple follicles for synchronous development and suppressing spontaneous LH surges, which enhances egg quality [12]. However, prolonged use of GnRH agonists can elevate the risk of ovarian hyperstimulation syndrome (OHSS) because of excessive follicle development, imposing significant psychological and physical burdens on patients [13]. HCG is typically used to trigger final oocyte maturation in IVF cycles [14]. Despite its effectiveness, HCG triggers can heighten the risk of OHSS, particularly in patients with high ovarian response, as it mimics the physiological LH surge but may intensify OHSS symptoms. To mitigate the risk of OHSS while preserving the advantages of both GnRH agonists and HCG, a dual trigger approach has been proposed. This involves combining a GnRH agonist with a lower dose of HCG, aiming to replicate the natural hormonal milieu during oocyte maturation [15]. The GnRH agonist initiates a positive feedback mechanism on the hypothalamic-pituitary-ovarian (HPO) axis, releasing follicle-stimulating hormone (FSH), which is crucial for oocyte development, while the HCG component provides the LH-like effect necessary for final oocyte maturation. Research indicates that this dual trigger method can significantly reduce the incidence of moderate to severe OHSS (< 2%) and increase the number of mature oocytes [16]. Therefore, combining a GnRH agonist with a low-dose HCG trigger retains the benefits of the classic protocol while reducing OHSS occurrences.

Currently, there is no research examining the long-term safety and efficacy of GnRH agonists and HCG triggers in patients with high ovarian response. This study aims to explore the safety and effectiveness of HCG triggering compared to a combined GnRH agonist and HCG trigger in patients undergoing ovarian stimulation.

Materials and methods

Patients

A retrospective analysis was conducted on the clinical data from 314 cases of IVF/ICSI that performed at Hunan Provincial Maternal and Child Healthcare Hospital from July 2018 to January 2023. Patients were divided into a combined treatment group (GnRH-a + HCG) (n=100) and an HCG group (n=214) based on different trigger methods. The study was approved by the ethics committee of Hunan Provincial Maternal and Child Healthcare Hospital. Since this study solely utilized de-identified patient data, informed consent on this study was exempted.

Inclusion and exclusion criteria

Inclusion criteria: (1) age ≤ 35 years; (2) patients underwent long protocol of GnRH-a and IVF/ICSI treatment; (3) first treatment with IVF-ET or IntraCytoplasmic Sperm Injection with Embryo Transfer (ICSI-ET); (4) patients with ovarian stimulation showing serum estradiol (E2) ≥ 15000 nmol/ml, anti mullerian hormone (AMH) level ≥ 4.5 ng/ml, or number of oocytes retrieved ≥ 15 [17].

Exclusion criteria: (1) patients with intrauterine adhesions or endometriosis; (2) body mass index (BMI) ≥ 28 kg/m^2; (3) patients with poor ovarian reserve.

Treatment method

Ovarian stimulation: Ovarian stimulation was performed using GnRH-a for all patients. Patients were injected with 1.0-1.875 mg of

Leuprorelin (Takeda Pharmaceutical Company Ltd., Japan) at the mid-luteal stage of their last menstrual period. Serum concentrations of FSH, LH and progesterone (P) were tested, the number and size of ovarian effect follicles were evaluated by ultrasound after two weeks. A starting dose of 112.5-225 IU of recombinant FSH (Lizhu Pharmaceutical Trading Co., Zhuhai, China) was administered for all patients, with gonadotropins (Gn) dosage fine-tuned based on the patient's reaction.

Oocyte retrieval: Final maturation of oocytes was initiated immediately upon the presence of a dominant follicle reaching or exceeding 18 mm in diameter, which was achieved through the administration of 0.2 mg of the GnRH agonist triptorelin-acetate (GeneScience Pharmaceuticals Co., Ltd., Changchun, China) plus 2000 IU of HCG (Chorionic Gonadotrophin, Lizhu Pharmaceutical Trading Co., Zhuhai, China) in combined treatment group or 250 μg of rHCG (Merck Serono, Geneva, Switzerland) alone in HCG Group. Transvaginal ultrasound-guided oocyte retrieval was performed 36 hours later, and the collected oocytes were inseminated through IVF/ICSI.

Embryo freezing: Embryos of grades I and II, with 6-9 cells on day 3, were defined as "top-quality embryos". In the combined treatment group, all fresh embryos were cryopreserved (freeze-all approach). In the HCG Group, embryo transfer was canceled, and all embryos were cryopreserved if the E2 level was ≥ 20000 nmol/L, the number of oocytes retrieved was ≥ 20, the mean diameter of unilateral ovaries on the day of transfer was ≥ 7 cm, significant pelvic effusion was present, or if poor endometrial morphology or hydrosalpinx was observed.

Embryo transfer: Daily intramuscular progesterone 60 mg (Zhejiang Xianju Pharmaceutical Co., Ltd., Taizhou, China) was started on the day of fresh embryo transfer. Serum β-HCG levels were tested 14 days post-transfer, and pregnancy was confirmed if serum β-HCG levels exceeded 10 U/L. Progesterone was continued until 8-10 weeks of gestation.

Patients with frozen embryo transplantation and without bilateral ovarian cysts were given oral administration of estradiol valerate (Bayer, Germany), at a dosage of 2 mg administered bi-daily, increasing to 3 mg twice per day after 3 days. Drug dosages were adjusted based on endometrial thickness as determined by ultrasonography. Intramuscular injection of progesterone, 40-60 mg per day, was administered for endometrial transformation when estradiol valerate administration exceeded 12 days, and the endometrial thickness was ≥ 8 mm. The timing of embryo thawing and transfer was determined based on the duration of estradiol valerate administration. Serum β-HCG levels were measured 14 days post-transfer, and pregnancy was confirmed if serum β-HCG level > 10 U/L. Progesterone was continued until 8-10 weeks of gestation.

A summary of the treatment methods for the patients are shown in **Figure 1**.

Baseline information

Demographic information and disease-related indicators of patients were extracted and documented from the medical records system, including age, BMI, smoking history, alcohol consumption, hypertension, diabetes, infertility duration, primary infertility and polycystic ovary syndrome (PCOS).

Blood test

A complete blood count and hormone level assessment was conducted on the day of medication administration. Fasting venous blood samples of 4 mL were collected from all patients in the morning, allowed to stand for 2 hours, and then centrifuged at 3000 rpm for 10 minutes. The upper serum was stored at -20°C for further analysis. Hemoglobin, red blood cell count, white blood cell count, neutrophil count, and platelet count were measured using an automated blood cell analyzer (Sysmex Corporation, XT-4000i). Serum levels of anti-Mullerian hormone (AMH) (Ashlab, USA) were assessed using commercially procured kits. E2 and P were analyzed utilizing the Immulite 1000 assay based on chemiluminescence (DPC, Poway, CA).

Ultrasound examinations

Before treatment, patient underwent an ultrasound examination of the ovaries. Ultrasounds were performed using an Aloka SSD-650 or SSD-620 (Aloka Co., Tokyo, Japan), equipped with a 5 MHz probe to evaluate endometrial

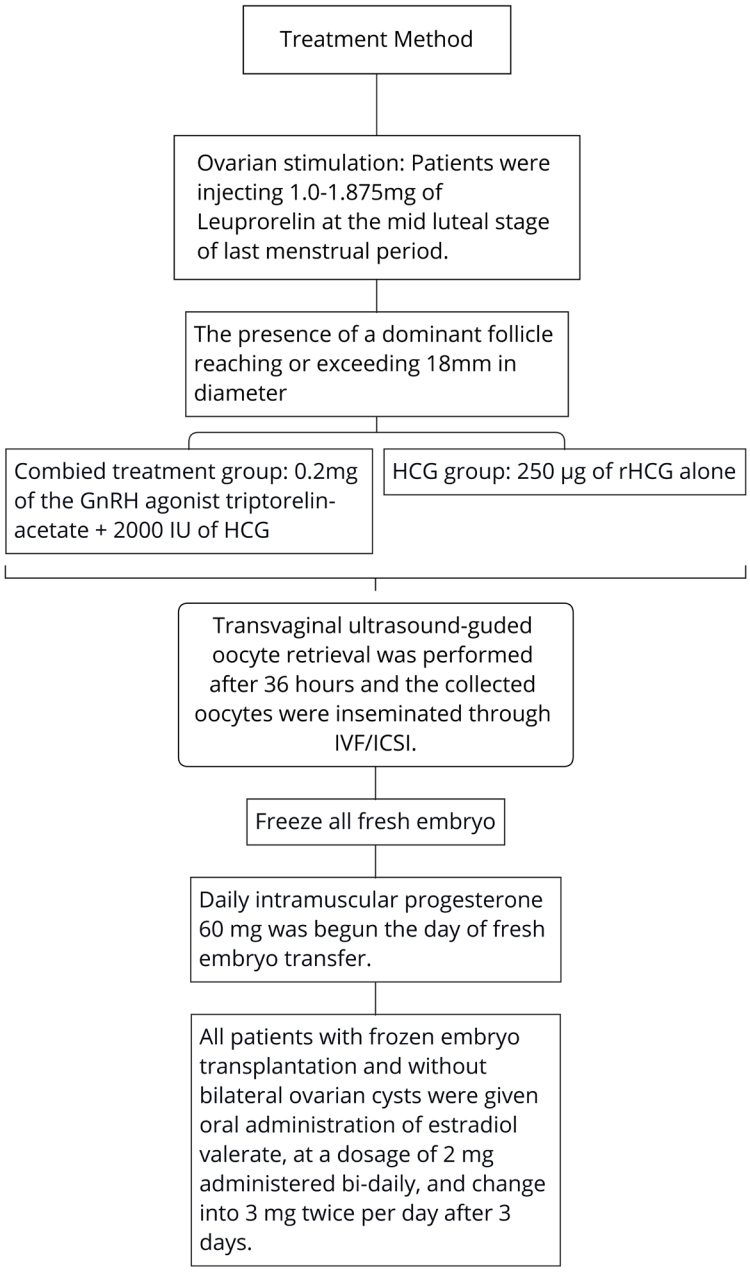

Figure 1. Flowchart of treatment procedures. Note: HCG: human chorionic gonadotropin; IVF/ICSI: in-vitro fertilization/intracytoplasmic sperm injection.

thickness. The assessment included measuring endometrial thickness and ovarian diameter, as well as checking for ascites, ovarian tissue damage, premature ovarian failure, and invasion of other organs.

OHSS occurrence rate

The incidence of OHSS was the primary outcome measure. The occurrence of OHSS was recorded throughout the treatment cycle. Mild OHSS: abdominal distension, mild abdominal pain, ovarian size < 8 cm^3; Moderate OHSS: increased abdominal distension, abdominal pain, nausea, and/or vomiting, ascites confirmed by ultrasound, ovarian size of 8-12 cm^3; Severe OHSS: ascites (or pleural effusion), oliguria (< 300 ml/day or < 30 ml/hour), hematocrit > 0.45, hyponatremia (serum sodium < 135 mmol/L), hyperkalemia (serum potassium > 5 mmol/L), hypoproteinemia (serum albumin < 35 g/L), and ovarian size > 12 cm^3.

Clinical outcomes

Post-treatment, various clinical outcomes were recorded, including duration of Gn administration, total Gn dosage, follicle diameter, total number of oocytes obtained, fertilization rate, metaphase II (MII) oocytes, 2 pronuclei (2PN) embryos, available embryos, and high-quality embryos. High-quality embryos were defined as those reaching the 6-8 cell stage, with cytoplasmic particles covering no more than 10% of the embryo's outer surface, and uniform size. The fertilization rate was calculated by dividing the count of 2PN embryos by the total number of fertilized oocytes. Clinical parameters recorded during the treatment cycle included clinical pregnancy rate, implantation rate, and abortion rate.

Statistical analysis

Statistical analysis was performed using SPSS 29.0 software (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was employed to ascertain the normality of continuous variables. For continuous variables that conformed to a nor-

Table 1. Comparison of baseline characteristics between the two groups

Parameters	Combined treatment group (n=100)	HCG Group (n=214)	t/χ^2	*P*-value
Age (years)	28.85 ± 3.29	29.12 ± 3.23	0.691	0.491
BMI (kg/m^2)	23.27 ± 3.67	22.95 ± 2.62	0.780	0.436
Smoking history	12 (12.00%)	21 (9.81%)	0.153	0.696
Alcohol consumption	23 (23.00%)	37 (17.29%)	1.092	0.296
Hypertension	7 (7.00%)	12 (5.61%)	0.052	0.820
Diabetes	5 (5.00%)	9 (4.21%)	0.001	0.981
Infertility duration (years)	3.45 ± 0.83	3.62 ± 0.95	1.623	0.106
Primary infertility	44 (44.00%)	83 (38.79%)	0.568	0.451
PCOS	56 (56.00%)	118 (55.14%)	0.000	0.983

HCG: human chorionic gonadotropin; BMI: body mass index; PCOS: polycystic ovary syndrome.

mal distribution, results were expressed as mean ± standard deviation and analyzed using Student's t-test with corrected variance. Categorical variables, displayed as frequencies, were compared using the chi-square test. Statistical significance was established at $P < 0.05$.

Results

Baseline characteristics

Table 1 summarizes the fundamental patient characteristics. Comparisons of mean age, BMI, smoking history, alcohol consumption history, hypertension, and diabetes status revealed no significant differences between the two groups (all $P > 0.05$). Additionally, comparison of disease-related indicators, including infertility duration, primary infertility, and PCOS also revealed no significant differences between the two groups (all $P > 0.05$).

Routine blood tests

Examination of routine blood indices showed no notable disparities between the two cohorts concerning hemoglobin levels, red blood cell counts, white blood cell counts, neutrophil counts, and platelet counts (all $P > 0.05$, **Figure 2A-E**).

Ultrasound examination

Comparison of clinical outcomes between the two groups showed no significant differences in endometrial thickness (14.27 ± 1.96 mm vs. 14.52 ± 2.08 mm), ovarian diameter (6.35 ± 1.51 cm vs. 6.41 ± 1.48 cm), ascites (9.00% vs. 11.21%), ovarian tissue damage (2.00% vs. 3.27%), premature ovarian failure (1.00% vs. 1.87%), and organ invasion (0% vs. 0.47%) (all $P > 0.05$, **Table 2**).

Baseline hormone level

Before treatment initiation, serum hormone levels in both groups were tested and compared. There were no significant differences observed in the baseline levels of AMH, E2, and P between the two groups (all $P > 0.05$) (**Table 3**).

Clinical outcomes of the controlled ovarian stimulation

As shown in **Table 4**, no significant differences were noted between the two groups regarding the duration of Gn administration, total Gn dosage, number of oocytes retrieved, MII stage count, and the number of available and high-quality embryos (all $P > 0.05$). However, the follicle diameter (18.78 ± 5.32 vs. 17.47 ± 4.42, $t=2.145$, $P=0.033$) and the number of 2PN embryos (11.09 ± 3.37 vs. 8.64 ± 4.60, $t=5.316$, $P < 0.001$) were significantly higher in the combined treatment group compared to the HCG group.

Clinical outcomes of the first transplantation in the two groups

The clinical outcomes of the first transplantation in the two groups are shown in **Table 5**. The clinical pregnancy rate in combined treatment group was 58%, compared to 49.53% in the HCG group ($P=0.078$). Additionally, there were no significant differences in the embryo implantation rate ($P=0.265$) and abortion rate ($P=1.000$) between the two groups.

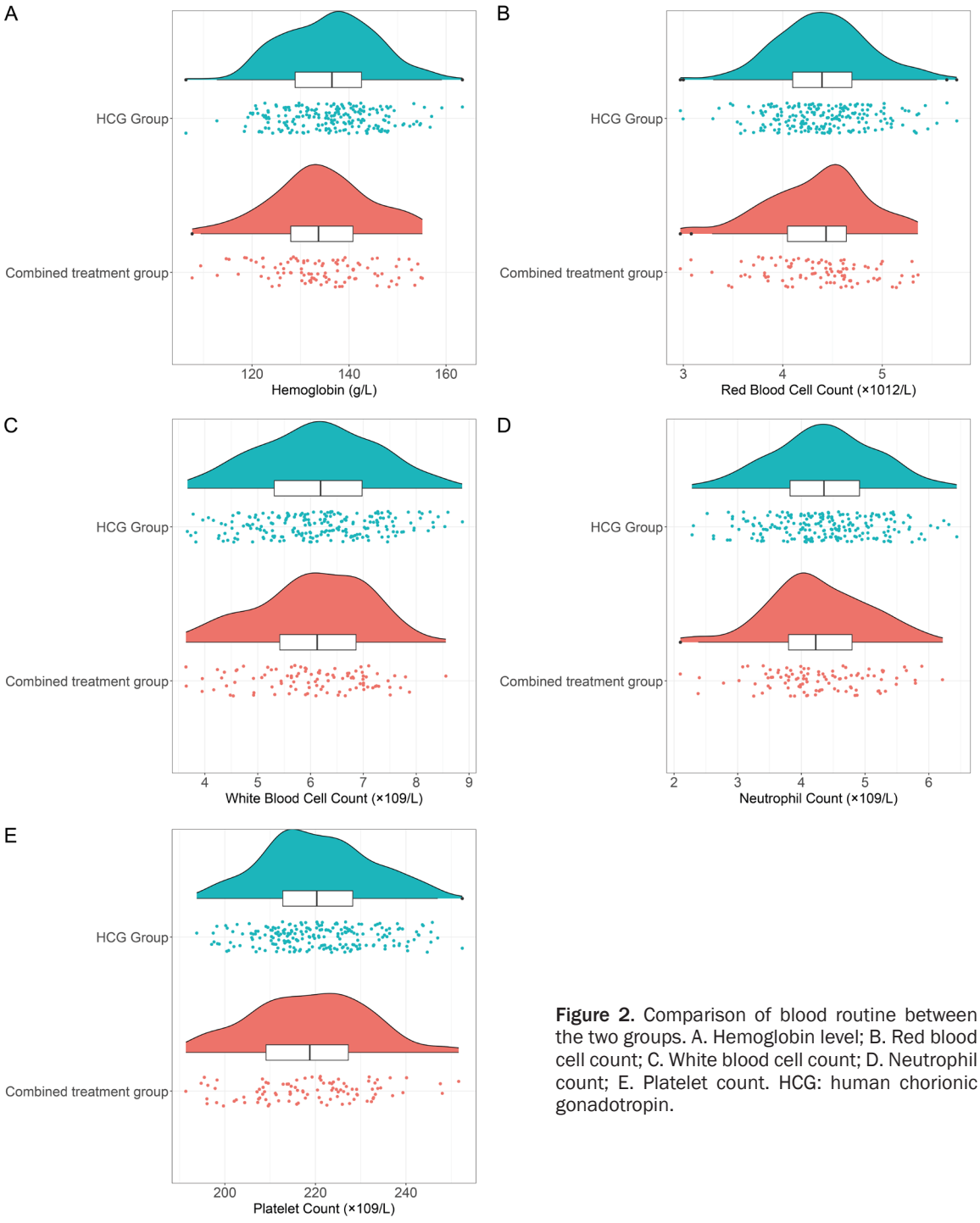

Figure 2. Comparison of blood routine between the two groups. A. Hemoglobin level; B. Red blood cell count; C. White blood cell count; D. Neutrophil count; E. Platelet count. HCG: human chorionic gonadotropin.

Incidence of ovarian hyperstimulation syndrome (OHSS)

In the combined treatment group, 31 cases developed mild OHSS and 3 cases developed moderate OHSS. There were 99 cases of mild OHSS and 25 cases of moderate or severe OHSS in HCG group (**Table 6**). The proportions of mild (χ^2=5.929, *P*=0.015) and moderate/severe OHSS (χ^2=5.302, *P*=0.021) were significantly higher in the HCG group compared to the combined treatment group.

Discussion

Infertility has emerged as a significant health issue affecting reproductive capabilities, with

Table 2. Comparison of ultrasonographic parameters of the ovary between the two groups

Characteristic	Combined treatment group (n=100)	HCG Group (n=214)	t/χ^2	*P*-value
Average endometrial thickness (mm)	14.27 ± 1.96	14.52 ± 2.08	1.007	0.315
Ovarian diameter	6.35 ± 1.51	6.41 ± 1.48	0.315	0.753
Ascites	9 (9.00%)	24 (11.21%)	0.356	0.551
Ovarian tissue damage	2 (2.00%)	7 (3.27%)	0.071	0.790
Premature ovarian failure	1 (1.00%)	4 (1.87%)	0.008	0.929
Invasion of other organs	0 (0.00%)	1 (0.47%)	None	1.000

HCG: human chorionic gonadotropin.

Table 3. Comparison of basal hormone levels between the two groups

Parameters	Combined treatment group (n=100)	HCG Group (n=214)	t	*P*-value
Basal AMH level (ng/ml)	7.11 ± 3.92	6.46 ± 2.82	1.482	0.141
Basal serum E2 level (pg/mL)	2645.00 ± 1101.00	2658.00 ± 1122.00	0.097	0.923
Basal serum progesterone level (ng/mL)	109.95 ± 14.75	111.57 ± 21.07	0.784	0.433

HCG: human chorionic gonadotropin; AMH: anti-Müllerian hormone; E2: estradial.

Table 4. Comparison of clinical outcomes of the controlled ovarian stimulation between the two groups

Parameters	Combined treatment group (n=100)	HCG Group (n=214)	t/χ^2	*P*-value
Duration of Gn administration	15.27 ± 3.68	15.18 ± 3.05	0.223	0.824
Total Gn dosage	1896.25 ± 411.83	1963.41 ± 510.42	1.244	0.215
Follicle diameter	18.78 ± 5.32	17.47 ± 4.42	2.145	0.033
Oocytes retrieved	13.11 ± 4.40	14.1 ± 5.60	1.702	0.090
IVF rate	82 (82.00%)	181 (84.58%)	0.171	0.680
MII oocytes	12.85 ± 3.99	12.71 ± 3.2	0.310	0.757
2PN embryos	11.09 ± 3.37	8.64 ± 4.60	5.316	< 0.001
Available embryo	5.24 ± 1.57	4.93 ± 1.36	1.704	0.090
High-quality embryo	11.2 ± 1.68	11.18 ± 1.46	0.107	0.915

HCG: human chorionic gonadotropin; Gn: gonadotropins; IVF: in vitro fertilization; MII: metaphase II; 2PN: 2 pronuclei.

Table 5. Comparison of clinical outcomes of the first transplantation between the two groups

Parameters	Combined treatment group (n=100)	HCG Group (n=214)	χ^2	*P*-value
Clinical pregnancy rate	58 (58.00%)	106 (49.53%)	1.634	0.201
Implantation rate	76 (76.00%)	148 (69.16%)	1.243	0.265
Abortion rate	2 (2.00%)	5 (2.34%)	0.000	1.000

HCG: human chorionic gonadotropin.

intracytoplasmic sperm injection (ICSI) and in vitro fertilization (IVF) serving as important treatment options [18, 19]. Ovarian hyperstimulation syndrome (OHSS) is a common complication in assisted reproduction and ovarian hyperstimulation, occurring in approximately 20% to 30% of cases [20, 21]. Severe OHSS can adversely impact liver and kidney function, lead to thrombosis, and even become life-threatening, imposing substantial economic and psychological burdens on patients [22, 23]. Currently, various strategies are employed to prevent OHSS in the context of IVF and embryo transfer (IVF-ET), including pretreatment with controlled ovarian hyperstimu-

Table 6. Comparison of OHSS rate between the two groups

Parameter	Combined treatment group (n=100)	HCG Group (n=214)	χ^2	*P*-value
Mild OHSS	31 (31.00%)	99 (46.26%)	5.929	0.015
Moderate/Severe OHSS	3 (3.00%)	25 (11.68%)	5.302	0.021

HCG: human chorionic gonadotropin; OHSS: Ovarian Hyperstimulation Syndrome.

lation (COH), individualized COH protocols, and Gn dosage reduction. Research focuses on drug selection and dosage adjustment on the trigger day as key measures to mitigate OHSS risk.

Since the introduction of GnRH-a in IVF controlled ovarian hyperstimulation in 1984, the GnRH-a long protocol has remained a classical strategy for controlled ovarian hyperstimulation (COH) for over 30 years. After pituitary down-regulation by GnRH-a, multiple follicles are effectively recruited for synchronized development while spontaneous LH surges are suppressed, enhancing egg quality [24, 25]. This results in the retrieval of more high-quality oocytes and reduces treatment cycle cancellation rates. Research indicates that GnRH-a not only improves oocyte quality and endometrial receptivity but also enhances the pelvic microenvironment, thereby increasing the success rate of assisted reproduction. However, prolonged GnRH-a therapy often heightens the risk of OHSS due to excessive follicle development, imposing significant psychological and physical burdens on patients [26, 27].

In this study, patients with high ovarian response were treated with GnRH-a combined with 2000 IU HCG trigger. Our study showed that this regimen achieved optimal egg retrieval levels. In addition, the quantity of MII oocytes, 2PN embryos, and the rate of implantation and clinical pregnancy were slightly higher in the combined treatment group than those in the HCG group, while the incidence of OHSS was significantly lower. Several studies have compared the outcomes of dual trigger with HCG alone in patients undergoing IVF/ICSI. For instance, a study by Yan et al. found that the dual trigger approach led to a similar number of MII oocytes and high-quality embryos as the HCG trigger alone, with a significantly lower incidence of OHSS [28]. Similarly, another study found that the dual trigger group had a lower incidence of moderate/severe OHSS compared to the HCG group, with no significant difference in the clinical pregnancy rate [29]. These findings are consistent with our results, supporting the use of the dual trigger approach as a safe and effective option for high ovarian responders.

Studies have found that in a normal menstrual cycle, the final maturation of the egg is completed under the trigger of the FSH and the LH [30]. In the COH process of IVF-ET, HCG is used to mimic the physiological effect of LH peak in the human menstrual cycle. HCG combined with GnRH-a not only simulates the LH peak, but also provides positive feedback to the HPO axis, promoting the release of FSH, thereby more closely resembling natural hormonal changes during egg maturation. FSH plays an indispensable role in the development and maturation of oocytes. Research has confirmed that, compared with the HCG trigger alone, the additional application of the GnRH-a can greatly reduce the incidence of moderate to severe OHSS (< 2%), and can increase the number of mature eggs [31]. However, the luteinizing effect of GnRH-a can induce the inadequate luteal function and reduced endometrial receptivity, potentially lowering pregnancy rate and increasing miscarriage rate, which limits its clinical application [32, 33]. In this study, the fresh embryo transfer was canceled for the patients receiving the double-trigger treatment, replaced by frozen embryo transfer after cryopreservation, which mitigates the impact high estrogen environment on the endometrial receptivity and reduces the occurrence of moderate to severe OHSS after pregnancy. Long-term GnRH-a treatment effectively inhibits the premature ovulation and synchronizes follicular development during ovulation induction [34, 35]. The combination of long-term GnRH-a with a low-dose HCG trigger not only retains the advantages of the classic long-term treatment, but also reduces the occurrence of OHSS. Therefore, for patients with high ovarian response, GnRH-a combined with a low-dose HCG trigger can significantly reduce the incidence of OHSS, which is worthy of promotion and in-depth study.

The mechanism behind the reduced incidence of OHSS with the dual trigger approach is likely related to the combined effects of GnRH agonists and HCG. The GnRH agonist triggers a positive feedback loop that releases FSH, which is crucial for oocyte development. The HCG provides the necessary LH-like effect for final oocyte maturation, while the lower dose helps minimize the risk of OHSS. This synergistic effect ensures optimal oocyte maturity without significantly affecting the rates of MII oocytes, high-quality embryos, or clinical pregnancy in single embryo transfers. This approach offers a promising strategy for mitigating OHSS risks while maintaining high-quality embryo production.

Our study has several limitations. First, it is a retrospective analysis, which introduces potential biases and confounding factors. Second, the inclusion criteria have certain limitations, and the sample size is relatively small. Consequently, larger, multi-center randomized controlled studies are required to validate our findings. Future research should focus on optimizing the dual trigger regimen, particularly the timing and dosing of GnRH agonists and HCG, to further enhance its safety and effectiveness.

Conclusion

In patients with high ovarian response, the long-term use of GnRH-a combined with a low-dose HCG trigger does not significantly affect the rates of MII oocytes, high-quality embryos, or clinical pregnancy in single embryo transfers. Importantly, this approach significantly reduces the incidence of OHSS. With the serum E2 level ≥ 15000 pmol/L on the trigger day, a dual trigger treatment appears to effectively lower the incidence of OHSS.

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Disclosure of conflict of interest

None.

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