Clinical Outcomes of Dual Trigger With Combination GnRH Agonist and hCG Versus Single Trigger With hCG Alone in Women Undergoing IVF/ICSI Cycles: a Retrospective Cohort Study With Propensity Score Matching

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Abstract

Background: Despite a large number of studies on the selection of trigger drugs, it remains unclear whether the dual trigger with human chorionic gonadotropin (hCG) and gonadotropin-releasing hormone (GnRH) agonist, compared to the single trigger with hCG alone, can improve the clinical outcome of patients undergoing assisted reproductive technology. Therefore, this study aimed to compare the laboratory and clinical outcomes of dual trigger versus single trigger.

Methods: In this retrospective cohort study, we evaluated 520 *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles between July 2014 and September 2020 at the Reproductive and Genetic Center of Integrative Medicine, The Affiliated Hospital of Shandong University of Traditional Chinese Medicine. All patients underwent IVF/ICSI treatment with fresh embryo transfer using the GnRH antagonist protocol. We used propensity score matching to control for confounding variables and binary logistic regression analysis to determine the correlations between trigger methods and pregnancy outcomes. After propensity score matching, 57 cycles from each group were evaluated and compared for laboratory or clinical outcomes in this retrospective cohort study.

Results: There was no significant difference in the number of oocytes retrieved, embryos available, top-quality embryos, or the rate of normal fertilization between the dual-trigger and single-trigger protocols, respectively. The implantation rate, clinical pregnancy rate, ectopic pregnancy rate, and live birth rate were also similar between the two groups, while the miscarriage rate (37.0% vs. 12.5%, $p=0.045$) was notably higher in the dual-trigger than the single-trigger group. Subsequent binary logistic regression analysis showed that age was a remarkably significant independent predictor of both clinical pregnancy rate (odds ratio=0.90, 95% confidence interval: 0.84–0.97, $p=0.006$) and live birth rate (odds ratio =0.89, 95% confidence interval: 0.82–0.97, $p=0.005$).

Conclusions: Therefore, dual-trigger for final oocyte maturation might increase miscarriage rate, but in terms of the laboratory and other pregnancy outcomes such as clinical pregnancy rate or live birth rate, there was no evidence to show that dual trigger was superior to an hCG-trigger alone for patients undergoing GnRH-antagonist cycles with fresh embryo transfer.

Trial registration: Retrospectively registered.

Background

It has been more than four decades since the first test-tube baby, Louise Brown, was born via the application of assisted reproductive technology (1). Since then, thousands of babies are born via *in vitro* fertilization (IVF) every year to women with infertility. Intracytoplasmic sperm injection (ICSI) technology emerged in the early 1990s (2) and has fulfilled the desires of male patients suffering from severely compromised fertility to father children. Owing to its safety and efficiency after extensive research and development, the gonadotrophin-releasing hormone (GnRH) antagonist protocol has been used as the mainstream approach for controlled ovarian hyperstimulation (COH), especially for high or poor ovarian

responders (3). Compared with the traditional long GnRH agonist protocol, GnRH antagonist protocol can effectively reduce the duration and dosage of gonadotrophin (Gn) treatment (4) and decrease the risk of ovarian hyperstimulation syndrome (OHSS) (4–6).

In the cycles that employ GnRH antagonist protocol, in addition to human chorionic gonadotropin (hCG) for induction of final maturation of the oocyte, GnRH agonists are also used; these were first introduced by Gonen 30 years ago (7). Recent studies revealed that a single injection of GnRH agonist may be effective in preventing OHSS on account of the GnRH agonist that induces an endogenous release of luteinizing hormone (LH), which is more physiologic than hCG (8–10). Previous randomized controlled trials (RCTs) reported poor clinical outcomes for the early pregnancy loss rate when a GnRH agonist was used to trigger ovulation (11). However, these poor results could be improved by strengthening the luteal phase support (LPS) with progesterone and estradiol (12–14). Therefore, the dual trigger method combining GnRH agonist with low-dose hCG has been proposed to improve clinical pregnancy outcomes compared to GnRH agonist trigger alone (15).

Recent relevant studies have discussed whether the dual trigger for final oocyte maturation in the GnRH antagonist protocol with fresh embryo transfer (ET) cycles can be more beneficial in improving laboratory indicators and pregnancy outcomes than triggered by using GnRH agonist or hCG alone. A Meta-analysis involving 1048 individuals showed that dual trigger significantly improved live birth rate (LBR) (16), meanwhile another retrospective cohort study in which 10427 patients were included discovered that dual trigger also reduced the risk of OHSS in the context of facilitated oocyte maturation (17). However, a single-blind RCT (18) and retrospective study (19) involving 192 and 469 normal ovarian responders, respectively, have shown that the dual-trigger is not an effective alternative for enhancing pregnancy outcomes, although it increased the number of oocytes and embryos obtained. Overall, there is still no consensus on whether dual trigger can effectively improve reproductive outcomes.

Given the preliminary studies, we thought that further investigation regarding the efficacy of dual trigger was warranted. Moreover, no well-matched cohort study has been conducted. Here we investigated whether a dual trigger for final oocyte maturation with a combination of a single dose of GnRH agonist and a low dose of hCG could improve the reproductive outcomes compared with conventional hCG trigger alone in GnRH antagonist IVF/ICSI-fresh ET cycles.

Methods

Study design

In the present retrospective cohort study, a review of medical records from July 1, 2014, through September 30, 2020, was performed for all IVF/ICSI-fresh ET cycles that underwent the GnRH antagonist protocol at the Reproductive and Genetic Center of Integrative Medicine, The Affiliated Hospital of Shandong University of Traditional Chinese Medicine. The study was approved by the Ethics Committee of the Reproductive Medicine Ethics Committee of the Affiliated Hospital of the Shandong University of Traditional Chinese Medicine. Informed consent was waived owing to the retrospective study design.

Inclusion and exclusion criteria

The inclusion criteria were women: (i) aged <50 years; (ii) with a body mass index (BMI) of 18–35 kg/m²; and (iii) who received GnRH antagonist and underwent fresh ET during the IVF/ICSI cycles. Our exclusion criteria were women: (i) with other underlying diseases that could not tolerate childbearing; (ii) suffering from an endocrine disorder (diabetes mellitus, hyperprolactinemia, thyroid dysfunction, congenital adrenal hyperplasia, Cushing syndrome); (iii) with a history of recurrent spontaneous abortion; and (iv) with uterine anomaly, endometriosis, or chromosomal abnormalities that cause infertility. In cases of missing data, telephone surveys were conducted.

After applying the inclusion and exclusion criteria, a total of 520 IVF/ICSI with fresh ET cycles were included and then divided into two groups: dual-trigger and hCG trigger. Applying either hCG alone or the dual-trigger for final oocyte maturation depended on the attending physician.

Treatment protocols

All patients were treated with the GnRH antagonist protocol in the flexible mode for COH. On the second day of the menstrual cycle, baseline hormone levels, such as follicle-stimulating hormone (FSH), LH and estrogen (E₂), were measured and transvaginal ultrasound for antral follicles was conducted to evaluate the baseline ovary status. If the conditions permitted, 150–225 IU/d of recombinant human follicle-stimulating hormone (rFSH, GONAL-F, Merck Serono, Darmstadt, Germany) with or without application of human menopausal gonadotropin (HMG, Lizhu Pharma, Shaoguan, China) was injected from the third day of the menstrual cycle, according to the age, BMI, antral follicle count, and previous response to COH. Besides, the addition of human recombinant luteinizing hormone (rLH, Luveris, Merck Serono) and recombinant human growth hormone (rhGH, Genheal, United Cell Biotechnology, Shanghai, China) during COH was at the physician's discretion. The dosage of Gn was adjusted lying on the follicular growth and serum level of E₂. When the dominant follicle reaches 12–14 mm in diameter, the GnRH antagonist 0.25 mg/d (Cetrotide, Merck Serono) was administered until the day of final oocyte maturation. The trigger was administered when at least two follicles reached a diameter of 18 mm or three follicles reached a diameter of 17 mm. The hCG trigger group (n=458 patients) received 250 mg of recombinant hCG (Ovidrel, Merck Serono) alone, and the dual-trigger group (n=62 patients) received 0.2 mg triptorelin (Decapeptyl, Ferring Pharmaceuticals, Saint-Prex, Switzerland) plus 250 µg of recombinant hCG. The oocyte was retrieved by transvaginal ultrasonography after 36 h. Whether fertilization was conducted by IVF or ICSI depended on the results of semen analysis or prior fertilization condition.

Normal fertilization was confirmed when two pronuclei and two polar bodies were observed after 16–18 h of insemination. Amphicytula were cultured in a cleavage medium (Cook Medical, Bloomington, IN, USA), and the embryo development was assessed daily (i.e., number, shape, evenness, and fragment rate of embryos). Fresh ET was performed 3 days after oocyte retrieval. The number of transferred embryos was 1–2 depending on the embryo quality and patient age. A high-quality embryo was defined as one that met the following three criteria established by the Istanbul consensus workshop (20): (i) ≥6 cells 3

days after fertilization, (ii) <10% fragmentation, and (iii) symmetric blastomeres. Then, the remaining embryos that did not satisfy the criteria were transferred and cultured to the blastocyst stage in the blastocyst medium (Cook Medical). Blastocysts were graded according to the Gardner classification (21); blastocysts were considered to be of excellent quality if the following criteria were met: (i) complete expansion of the blastocyst, and the cavity completely occupies the total volume of the embryo (grade 3); (ii) the inner cell mass was composed of several loosely grouped cells (grade B); and (iii) the trophectoderm contained few cells that formed loose epithelium (grade B). Embryos that were not transferred were cryopreserved by vitrification.

All patients received 40 mg/d of progestin injection (Xianju, Taizhou, China) for LPS from the day of oocyte retrieval until the pregnancy test was performed 2 weeks after fresh ET. In case of a positive pregnancy test, the LPS strategy was continued until 10 weeks of gestation.

Outcome measures

Laboratory and clinical data were collected as follows: the number of oocytes retrieved, rates of normal fertilization, number of embryos, number of high-quality embryos, implantation rate (IR), clinical pregnancy rate (CPR), ectopic pregnancy rate (EPR), miscarriage rate (MR), and LBR. Normal fertilization rate was defined as the number of normal fertilized oocytes divided by the total number of retrieved oocytes. The implantation rate was calculated as the number of gestational sacs divided by the total number of transferred embryos. Clinical pregnancy was defined as the presence of gestational sacs on ultrasonogram at 5–6 weeks of pregnancy. A diagnosis of ectopic pregnancy was made either by laparoscopy or sonographic visualization of an extrauterine gestational sac. The miscarriage rate was calculated as a pregnancy that was terminated before 28 gestational weeks divided by the total clinical pregnancy events. The LBR was calculated by dividing the total deliveries of viable infants over 28 gestational weeks by the total number of fresh ET cycles.

Statistical analysis

Data analyses were carried out using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). We compared laboratory and clinical outcomes for the two groups in a propensity score matching (PSM) cohort to minimize potential deviation (Fig. 1). The propensity scores were calculated using binary logistic regression analyses based on the following patient variables at baseline: patient age; infertility duration; infertility type (primary or secondary); gravidity; parity; number of previous IVF/ICSI attempts; BMI; level of anti-Mullerian hormone (AMH); basic hormone levels of FSH, LH, and E_2 ; stimulation duration and dosage of Gn; insemination treatment; and the number and quality of embryos transferred. A 1:1 pair matching was performed using the caliper-matching method, and a 0.02 propensity score tolerance was imposed on the maximum propensity score distance. Shapiro–Wilk test was used to assess the normality of data distribution. Continuous variables were expressed as mean±standard deviations (SD) and then compared using Student's *t*-tests or Mann–Whitney U-tests. Categorical variables were presented as frequencies and percentages, and the between-group differences were analyzed using the chi-square test. $P<0.05$ was

considered statistically significant. We also used binary logistic regression analysis to assess the association between trigger protocols or other potential factors and pregnancy outcomes. We calculated the adjusted odds ratio (OR) with a 95% confidence interval (CI).

Results

A total of 520 IVF/ICSI cycles using the GnRH antagonist protocol with fresh ET were analyzed in our study, including 62 cycles in the dual-trigger group and 458 cycles in the hCG trigger group. Simultaneously, 57 cycles were matched in a 1:1 ratio after PSM (Fig. 1). There were no significant differences between the two groups in patient characteristics after PSM (Table 1). The characteristics of ovarian stimulation and laboratory indicators for each group are presented in Table 2. Differences regarding the total dosage and duration of Gn stimulation; methods of fertilization; serum E₂, LH, and P levels; and number of pre-ovulatory follicles >14 mm at the day of triggering between the two groups were not found. Moreover, normal fertilization rate, number of oocytes retrieved, serum E₂, P levels at the day of transfer, number of embryos available, number of top-quality embryos or the number and quality of embryos used for fresh ET were similar between the two groups.

Table 1
Comparison of patients' baseline characteristics between groups

	Dual trigger (n=57)	hCG trigger (n=57)	p-value
Patient age (years)	35.09±6.16	35.60±5.89	0.653
Infertility duration (years)	3.33±3.01	3.58±3.76	0.701
Infertility type (%)			0.677
Primary	17/57 (29.8)	15/57 (26.3)	
Secondary	40/57 (70.2)	42/57 (73.7)	
Gravidity (n)	1.47±1.48	1.68±1.45	0.445
Parity (n)	0.47±0.63	0.56±0.71	0.486
BMI (kg/m ²)	24.37±3.86	24.58±3.54	0.762
AMH (ng/mL)	2.29±1.67	2.24±1.62	0.886
Basal FSH (mIU/mL)	8.55±2.87	8.97±4.81	0.572
Basal LH (mIU/mL)	4.48±2.48	4.68±2.87	0.691
Basal E ₂ (pg/mL)	49.07±42.19	66.97±77.75	0.130
Previous IVF/ICSI attempts (n)	0.79±1.42	0.44±0.76	0.104
Data are presented as mean±SD and proportion (%)			
AMH Anti-Müllerian hormone, BMI Body mass index, E ₂ Estrogen, FSH Follicle-stimulating hormone, ICSI Intracytoplasmic sperm injection, IVF <i>In vitro</i> fertilization, LH Luteinizing hormone			

Table 2
Characteristics of ovarian stimulation and IVF/ICSI cycle outcomes of each group

	Dual trigger (n=57)	hCG trigger (n=57)	p-value
Duration of stimulation (d)	9.95±2.20	9.56±2.49	0.382
Dosage of Gn (IU)	2552.85±1017.63	2375.66±963.93	0.342
Fertilization (%)			0.528
IVF	43/57 (75.4)	40/57 (70.2)	
ICSI	14/57 (24.6)	17/57 (29.8)	
No. of follicles >14 mm on trigger day (n)	6.86±3.55	6.40±3.25	0.476
E ₂ on trigger day (pg/mL)	2027.37±1168.73	2082.05±1186.33	0.805
LH on trigger day (mIU/mL)	2.89±2.23	3.33±2.20	0.295
P on trigger day (ng/mL)	0.76±0.42	0.78±0.36	0.848
No. of oocytes retrieved (n)	7.04±3.87	6.53±3.36	0.455
Normal fertilization rate (%)	67.72±25.63	65.54±26.58	0.657
E ₂ on transfer day (pg/mL)	995.30±644.26	964.70±625.91	0.798
P on transfer day (ng/mL)	34.48±8.64	36.38±6.66	0.848
No. of embryos available (n)	2.81±1.85	2.84±1.73	0.191
No. of top-quality embryos (n)	0.84±0.98	0.79±1.05	0.782
No. of embryo transfer (n)	1.75±0.43	1.77±0.42	0.828
At least one top-quality embryo transfer (%)	26/57 (45.6)	31/57 (54.4)	0.349
Data are presented as mean±SD and proportion (%)			
Gn Gonadotrophin, E ₂ Estrogen, ICSI Intracytoplasmic sperm injection, IVF <i>In vitro</i> fertilization, LH Luteinizing hormone, P Progesterone			

Pregnancy outcomes between the two groups are presented in Table 3. We found that the MR was notably increased in the dual-trigger group (37.0% vs. 12.5%, $p=0.045$) compared to that in the hCG-trigger group. However, no significant differences were found between the dual-trigger and hCG-trigger groups in terms of IR, CPR, EPR, and LBR. A binary logistic regression model was used to determine whether dual-trigger use had a greater effect on the CPR, MR, or LBR than the hCG-trigger group (Table 4). Otherwise, possible risk factors that may impact pregnancy outcomes such as age, BMI, basal FSH level, and the

number of pre-ovulatory follicles >14 mm on trigger day were included in the analysis. The results showed that age was a negative independent factor affecting CPR (OR=0.90, 95% CI: 0.84–0.97, p=0.006) and LBR (OR=0.89, 95% CI: 0.82–0.97, p=0.005). In addition, there were no statistically significant differences between the dual-trigger group and hCG-trigger group in terms of MR, CPR and LBR.

Table 3
Pregnancy outcomes for both groups

	Dual trigger (n=57)	hCG trigger (n=57)	p-value
Implantation rate (%)	30/100 (30.0)	26/101 (25.7)	0.501
Clinical pregnancy rate (%)	27/57 (47.4)	24/57 (42.1)	0.572
Ectopic pregnancy rate (%)	1/27 (3.7)	2/24 (8.3)	0.916
Miscarriage rate (%)	10/27 (37.0)	3/24 (12.5)	0.045
Live birth rate (%)	15/57 (28.1)	20/57 (33.3)	0.542
Data are presented as proportion (%)			

Table 4

Analyses of factors affecting clinical pregnancy rate, miscarriage rate, and live birth rate using binary logistic regression model

	Clinical pregnancy rate (%)		Miscarriage rate (%)		Live birth rate (%)	
	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Dual vs. hCG trigger	1.18 (0.54–2.58)	0.678	4.05 (0.93–17.62)	0.062	0.73 (0.31–1.69)	0.462
Age (years)	0.90 (0.84–0.97)	0.006	1.04 (0.92–1.19)	0.517	0.89 (0.82–0.97)	0.005
BMI (kg/m ²)	0.94 (0.84–1.04)	0.234	1.04 (0.88–1.24)	0.646	0.93 (0.82–1.04)	0.202
Basal FSH (IU/L)	1.02 (0.92–1.14)	0.669	0.99 (0.83–1.18)	0.911	1.03 (0.92–1.15)	0.582
No. of follicles >14 mm on trigger day (n)	1.03 (0.91–1.16)	0.673	1.02 (0.82–1.26)	0.864	0.97 (0.85–1.11)	0.657
BMI Body mass index, CI Confidence interval, FSH Follicle-stimulating hormone, OR Odds ratio						

Discussion

Since the question of whether dual-trigger improves oocyte maturation and pregnancy outcomes has been raised in the past few years, numerous studies have been conducted, but as of today there are still no conclusive results. In this retrospective cohort study, we evaluated the IVF/ICSI laboratory and clinical results of dual-trigger versus hCG-trigger alone in GnRH antagonist cycles. Our results showed that dual-trigger using GnRH agonist and hCG were slightly superior to hCG-trigger alone in terms of the numbers of oocytes retrieved and high-quality embryos, but these differences were not significant. Additionally, the normal fertilization rate, IR, and CPR in the dual-trigger group were mildly higher and the LBR lower in the dual-trigger group than the hCG trigger-alone group; however, none of these differences were statistically significant. Our study demonstrated that the MR was higher in the dual-trigger group than in the hCG-alone group; this result could likely explain the above phenomenon that the higher IR and CPR, however a lower LBR in dual-trigger group than the hCG trigger-alone group. Binary logistic regression showed that

age was identified as an independent risk factor for the CPR and LBR but not the MR. Although the previous statistical results indicated that dual-trigger caused high MR, and subsequent regression analysis suggested that dual-trigger could be a potential predictor of MR, it was not statistically significant (OR=4.05, 95% CI: 0.93–17.62, p=0.062).

Previous studies showed that in the GnRH antagonist IVF/ICSI-fresh ET treatment cycles, only using the GnRH agonist for final oocyte maturation can effectively prevent OHSS but also reduce the LBR to some extent (8, 22, 23) compared with hCG trigger alone. The GnRH agonist trigger would result in massive luteolysis (24), which likely occurs as a result of LH depletion from the pituitary and transient GnRH receptor down-regulation; all of these factors can cause the withdrawal of LH support for the corpus luteum (25). Hence, relevant experts pointed out that “dual-trigger” strategy using a GnRH agonist and low-dose hCG can achieve the same effect on ongoing pregnancy rate as triggering by GnRH agonist alone with enhanced LPS, and superior to GnRH agonist alone with standard LPS (14).

Our results are consistent with previous studies that reported similar pregnancy outcomes from dual-trigger versus hCG trigger alone under GnRH antagonist scheme (18, 19, 26). In Şükür et al.’s retrospective study, the number of high-quality embryos in dual-trigger cycles was relatively high and was similar to the number of oocytes retrieved or MII oocytes retrieved. However, Gao et al.’s retrospective study and Eftekhar et al.’s RCT reported that the number of oocytes retrieved and embryos available were both higher in the dual-trigger group than the hCG trigger-alone group. A 2021 systematic review and meta-analysis similarly found that the two trigger methods were equally effective in terms of pregnancy rate (27). At variance with the findings of our study, another meta-analysis reported that although the number of mature oocytes or fertilized oocytes retrieved and the ongoing pregnancy rate were similar, the CPR with dual-trigger was significantly higher than hCG trigger alone (28). In an even larger systematic review and meta-analysis with 1048 participants, the authors reported the dual-trigger group had a significantly higher LBR than the hCG trigger-alone group (16). In addition, a retrospective study by Lin and collaborators (n=427 patients) (29) confirmed that dual trigger significantly improved the CPR, LBR and reduced the MR in women with diminished ovarian reserve during GnRH antagonist cycles. Another RCT (n=221 patients) (30) reported that dual trigger markedly increased overall and ongoing pregnancy rates in completed cycles but not in all initiated cycles, and investigator Schachter speculated that the results probably were correlated with GnRH antagonist schemes affecting endometrial GnRH receptors. Unlike our study, the above-mentioned researches focused mainly on the CPR or LBR, whereas we deemed that dual-trigger could cause a higher MR than hCG-trigger alone. The discrepancies between our study and the other studies are due (at least in part) to the variation in ovarian response of included patients, the small sample size, or the differences in selection for COH and LPS. Encouraged by our preliminary results, we plan to increase the sample size in future investigations and analyze clinical outcomes after classifying patients according to ovarian response to obtain more accurate evidence-based data.

In our study, the number of oocytes retrieved, embryos available, and high-quality embryos were similar in both groups. In accordance with our results, some studies reached similar conclusions concerning dual-trigger versus hCG-trigger (26, 31). An RCT including 155 patients found that there were remarkable

enhancements on the number of oocytes retrieved, MII oocytes, total number of blastocysts, and high-quality blastocysts transferred; moreover, the CPR and LBR per transfer were also significantly higher in the dual-trigger group compared to the hCG trigger-alone group in normal responders (32). Interestingly, some retrospective cohort studies evaluated the impact of dual-trigger strategy for oocyte maturation in patients with a previous history of a high rate of immature oocyte retrieval (33–35). The results of these studies clearly demonstrate that the dual-trigger protocol was efficient to improve the rate of retrieval of mature oocytes. However, some studies had a contradictory view on pregnancy outcomes. Griffin and associates believed that the reproductive outcomes will still be poor because of an underlying oocyte dysfunction (34), and other investigators held the view that dual-trigger can simultaneously enhance the CPR (33, 35). Thus, the benefits of a dual-trigger for oocyte maturation and even the pregnancy outcomes in patients are still controversial, which also underscores the need for large-scale, multicenter RCTs to validate these findings.

In recent years, researchers have reported the discrepancy of cycle results between two trigger modes in different ovarian reactions such as high ovarian responder (HOR) and poor ovarian responder (POR). Multiple retrospective cohort studies (36–38) or systematic review and meta-analyses (39) present different views regarding the outcomes of dual-trigger on PORs. After considering that dual-trigger schemes can increase the number of oocytes collected and mature oocytes, the authors reached an agreement. They found that the dual-trigger group showed significantly higher CPR and LBR than the hCG trigger-alone group under the GnRH antagonist protocol (37–39), while Zhang et al. found no statistically significant differences for CPR or LBR using the progesterone-primed ovarian stimulation protocol (36). The different views may be associated with the choice of the ovarian stimulation protocol. For the HORs, a retrospective study that included the patients with peak E_2 <4,000 pg/mL demonstrated the superiority of dual-trigger cycles over GnRH agonist trigger alone not only in CPR but also in LBR (40). Li and coworkers concluded that dual-trigger was associated with a lower incidence of severe OHSS than hCG trigger cycles while still maintaining a high-quality embryo rate (41).

The strength of our study is that we used PSM analysis to control for potential confounders between the two groups, thus making the outcomes independent from the different baseline characteristics. Moreover, because of the single-center design of this study, all IVF/ICSI cycles were carried out under uniform conditions, and embryos were cultured in the same media using the same techniques by the same embryologists. This approach minimized observational biases and the influence of varying culture media. Our study has two limitations. The first is the retrospective design, and the second is that patients were not assigned to groups according to the principle of random distribution, which could have introduced selection bias. Hence, future studies should employ an RCT design in a larger sample size to verify and validate our results.

Conclusion

The results of the dual-trigger method using GnRH agonist and hCG versus the hCG trigger alone for final oocyte maturation were similar with respect to the number of oocytes retrieved, number of embryos

available, number of high-quality embryos, and normal fertilization rate for patients who were undergoing GnRH antagonist IVF/ICSI with fresh ET cycles. The MR was remarkably higher in the dual-trigger than hCG trigger-alone group. Other clinical benefits were not observed in terms of the IR, CPR, and LBR by excluding heterogeneous factors after PSM. We should follow the principles of individualization and optimization. In the future, well-designed prospective studies focusing on the potency ratio of both protocols are needed.

Abbreviations

AMH: Anti-Müllerian hormone; BMI: Body mass index; CI: Confidence interval; COH: Controlled ovarian hyperstimulation; CPR: Clinical pregnancy rate; E₂: Estrogen; EPR: Ectopic pregnancy rate; ET: Embryo transfer; FSH: Follicle-stimulating hormone; Gn: Gonadotrophin; GnRH: Gonadotropin-releasing hormone; hCG: Human chorionic gonadotropin; HOR: High ovarian responder; ICSI: Intracytoplasmic sperm injection; IR: Implantation rate; IVF: *In vitro* fertilization; LBR: Live birth rate; LH: Luteinizing hormone; LPS: Luteal phase support; MR: Miscarriage rate; OHSS: Ovarian hyperstimulation syndrome; OR: Odds ratio; P: Progesterone; POR: Poor ovarian responder; PSM: Propensity score matching; RCTs: Randomized controlled trials

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Reproductive Medicine Ethics Committee of The Affiliated Hospital of the Shandong University of Traditional Chinese Medicine (Research Ethics Committee approval number: SZ2020050108). All methods were conducted in compliance with relevant guidelines and regulations. In addition, informed consent was waived because of the retrospective study design.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed in this study are not publicly available for legal or ethical reasons, but will be made available by the authors upon a reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FL and SX conceived and designed this study. LD and XX contributed to the acquisition and analysis of data. LD also contributed to drafting of the manuscript. XY and YL were responsible for data collection. CW and HW contributed to manuscript revision. All authors approved the final submitted version.

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References

1. Fauser B, Edwards R. The early days of IVF. *Human reproduction update*. 2005;11(5):437-8.
2. Devroey P, Van Steirteghem A. A review of ten years experience of ICSI. *Human reproduction update*. 2004;10(1):19-28.
3. Nelson SM, Yates RW, Lyall H, Jamieson M, Traynor I, Gaudoin M, et al. Anti-Mullerian hormone-based approach to controlled ovarian stimulation for assisted conception. *Hum Reprod*. 2009;24(4):867-75.
4. Al-Inany H, Youssef M, Ayeleke R, Brown J, Lam W, Broekmans F. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *The Cochrane database of systematic reviews*. 2016;4:CD001750.
5. Lambalk C, Banga F, Huirne J, Toftager M, Pinborg A, Homburg R, et al. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. *Human reproduction update*. 2017;23(5):560-79.
6. Balen A, Morley L, Misso M, Franks S, Legro R, Wijeyaratne C, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. *Human reproduction update*. 2016;22(6):687-708.
7. Gonen Y, Balakier H, Powell W, Casper R. Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for in vitro fertilization. *The Journal of clinical endocrinology and metabolism*. 1990;71(4):918-22.
8. Youssef M, Van der Veen F, Al-Inany H, Mochtar M, Griesinger G, Nagi Mohesen M, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. *The Cochrane database of systematic reviews*. 2014(10):CD008046.
9. Casper R. Basic understanding of gonadotropin-releasing hormone-agonist triggering. *Fertility and sterility*. 2015;103(4):867-9.

10. Humaidan P, Kol S, Papanikolaou E. GnRH agonist for triggering of final oocyte maturation: time for a change of practice? *Human reproduction update*. 2011;17(4):510-24.
11. Humaidan P, Bredkjaer H, Bungum L, Bungum M, Grøndahl M, Westergaard L, et al. GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. *Human reproduction (Oxford, England)*. 2005;20(5):1213-20.
12. Humaidan P, Bungum L, Bungum M, Yding Andersen C. Rescue of corpus luteum function with peri-ovulatory HCG supplementation in IVF/ICSI GnRH antagonist cycles in which ovulation was triggered with a GnRH agonist: a pilot study. *Reproductive biomedicine online*. 2006;13(2):173-8.
13. Humaidan P, Papanikolaou E, Tarlatzis B. GnRHa to trigger final oocyte maturation: a time to reconsider. *Human reproduction (Oxford, England)*. 2009;24(10):2389-94.
14. Shapiro B, Daneshmand S, Garner F, Aguirre M, Hudson C. Comparison of "triggers" using leuprolide acetate alone or in combination with low-dose human chorionic gonadotropin. *Fertility and sterility*. 2011;95(8):2715-7.
15. Shapiro B, Daneshmand S, Garner F, Aguirre M, Thomas S. Gonadotropin-releasing hormone agonist combined with a reduced dose of human chorionic gonadotropin for final oocyte maturation in fresh autologous cycles of in vitro fertilization. *Fertility and sterility*. 2008;90(1):231-3.
16. Hu K, Wang S, Ye X, Zhang D, Hunt S. GnRH agonist and hCG (dual trigger) versus hCG trigger for follicular maturation: a systematic review and meta-analysis of randomized trials. *Reproductive biology and endocrinology : RB&E*. 2021;19(1):78.
17. Gunnala V, Melnick A, Irani M, Reichman D, Schattman G, Davis O, et al. Sliding scale HCG trigger yields equivalent pregnancy outcomes and reduces ovarian hyperstimulation syndrome: Analysis of 10,427 IVF-ICSI cycles. *PloS one*. 2017;12(4):e0176019.
18. Eftekhar M, Mojtahedi MF, Miraj S, Omid M. Final follicular maturation by administration of GnRH agonist plus HCG versus HCG in normal responders in ART cycles: An RCT. *Int J Reprod Biomed*. 2017;15(7):429-34.
19. Gao F, Wang Y, Fu M, Zhang Q, Ren Y, Shen H, et al. Effect of a "Dual Trigger" Using a GnRH Agonist and hCG on the Cumulative Live-Birth Rate for Normal Responders in GnRH-Antagonist Cycles. *Frontiers in medicine*. 2021;8:683210.
20. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. *Human reproduction (Oxford, England)*. 2011;26(6):1270-83.
21. Gardner D, Lane M, Stevens J, Schlenker T, Schoolcraft W. Blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer. *Fertility and sterility*. 2000;73(6):1155-8.
22. Youssef M, Abdelmoty H, Ahmed M, Elmohamady M. GnRH agonist for final oocyte maturation in GnRH antagonist co-treated IVF/ICSI treatment cycles: Systematic review and meta-analysis. *Journal of advanced research*. 2015;6(3):341-9.
23. Griesinger G, Diedrich K, Devroey P, Kolibianakis E. GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis. *Human reproduction update*. 2006;12(2):159-68.

24. Kol S. Luteolysis induced by a gonadotropin-releasing hormone agonist is the key to prevention of ovarian hyperstimulation syndrome. *Fertility and sterility*. 2004;81(1):1-5.
25. Casper R. Introduction: Gonadotropin-releasing hormone agonist triggering of final follicular maturation for in vitro fertilization. *Fertility and sterility*. 2015;103(4):865-6.
26. Şükür Y, Ulubaşoğlu H, İlhan F, Berker B, Sönmezer M, Atabekoğlu C, et al. Dual trigger in normally-responding assisted reproductive technology patients increases the number of top-quality embryos. *Clinical and experimental reproductive medicine*. 2020;47(4):300-5.
27. Zhang Y, Guo X, Guo L, Chang H, Shu J, Leung P. Outcomes comparison of IVF/ICSI among different trigger methods for final oocyte maturation: A systematic review and meta-analysis. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2021;35(7):e21696.
28. Chen C, Tzeng C, Wang P, Liu W, Chang H, Chen H, et al. Dual triggering with GnRH agonist plus hCG versus triggering with hCG alone for IVF/ICSI outcome in GnRH antagonist cycles: a systematic review and meta-analysis. *Archives of gynecology and obstetrics*. 2018;298(1):17-26.
29. Lin M, Wu F, Lee R, Li S, Lin S, Hwu Y. Dual trigger with combination of gonadotropin-releasing hormone agonist and human chorionic gonadotropin significantly improves the live-birth rate for normal responders in GnRH-antagonist cycles. *Fertility and sterility*. 2013;100(5):1296-302.
30. Schachter M, Friedler S, Ron-El R, Zimmerman A, Strassburger D, Bern O, et al. Can pregnancy rate be improved in gonadotropin-releasing hormone (GnRH) antagonist cycles by administering GnRH agonist before oocyte retrieval? A prospective, randomized study. *Fertility and sterility*. 2008;90(4):1087-93.
31. Ding N, Liu X, Jian Q, Liang Z, Wang F. Dual trigger of final oocyte maturation with a combination of GnRH agonist and hCG versus a hCG alone trigger in GnRH antagonist cycle for in vitro fertilization: A Systematic Review and Meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2017;218:92-8.
32. Haas J, Bassil R, Samara N, Zilberberg E, Mehta C, Orvieto R, et al. GnRH agonist and hCG (dual trigger) versus hCG trigger for final follicular maturation: a double-blinded, randomized controlled study. *Human reproduction (Oxford, England)*. 2020;35(7):1648-54.
33. Herbemont C, El Kouhen I, Brax A, Vinolas C, Dagher-Hayeck B, Comtet M, et al. [Dual trigger with gonadotropin-releasing hormone agonist and hCG to improve oocyte maturation rate]. *Gynecologie, obstetrique, fertilité & senologie*. 2019;47:568-73.
34. Griffin D, Feinn R, Engmann L, Nulsen J, Budinetz T, Benadiva C. Dual trigger with gonadotropin-releasing hormone agonist and standard dose human chorionic gonadotropin to improve oocyte maturity rates. *Fertility and sterility*. 2014;102(2):405-9.
35. Fabris A, Cruz M, Legidos V, Iglesias C, Muñoz M, García-Velasco J. Dual Triggering With Gonadotropin-Releasing Hormone Agonist and Standard Dose Human Chorionic Gonadotropin in Patients With a High Immature Oocyte Rate. *Reproductive sciences (Thousand Oaks, Calif)*. 2017;24(8):1221-5.

36. Zhang J, Wang Y, Mao X, Chen Q, Hong Q, Cai R, et al. Dual trigger of final oocyte maturation in poor ovarian responders undergoing IVF/ICSI cycles. *Reproductive biomedicine online*. 2017;35(6):701-7.
37. Lin, MH, Wu F, Hwu Y, Lee R, Li R, Li S. Dual trigger with gonadotropin releasing hormone agonist and human chorionic gonadotropin significantly improves live birth rate for women with diminished ovarian reserve. *Reproductive biology and endocrinology : RB&E*. 2019;17(1):7.
38. Chern C, Li J, Tsui K, Wang P, Wen Z, Lin L. Dual-trigger improves the outcomes of in vitro fertilization cycles in older patients with diminished ovarian reserve: A retrospective cohort study. *PloS one*. 2020;15(7):e0235707.
39. Oliveira S, Calsavara V, Cortés G. Final Oocyte Maturation in Assisted Reproduction with Human Chorionic Gonadotropin and Gonadotropin-releasing Hormone agonist (Dual Trigger). *JBRA assisted reproduction*. 2016;20(4):246-50.
40. Griffin D, Benadiva C, Kummer N, Budinetz T, Nulsen J, Engmann L. Dual trigger of oocyte maturation with gonadotropin-releasing hormone agonist and low-dose human chorionic gonadotropin to optimize live birth rates in high responders. *Fertility and sterility*. 2012;97(6):1316-20.
41. Li S, Zhou D, Yin T, Xu W, Xie Q, Cheng D, et al. Dual trigger of triptorelin and HCG optimizes clinical outcome for high ovarian responder in GnRH-antagonist protocols. *Oncotarget*. 2018;9(4):5337-43.

Figures

Figure 1

Study flow chart