

The Effect of Dual Trigger With GnRH Agonist and hCG on Cumulative Live-Birth Rate For Normal Responders in GnRH-Antagonist Cycles

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Abstract

It has been widely acknowledged that the dual triggering for final oocyte maturation with a combination of gonadotropin-releasing hormone (GnRH) agonist and human chorionic gonadotropin (hCG) improve clinical outcomes in high responders during IVF-ICSI GnRH-antagonist cycles. However, it remains elusive whether this dual trigger is also beneficial to the normal responders. The aim of this study was to investigate this issue. In the present study, we retrospectively analysed the data generated from a total of 469 normal responders from 1st January to 31st December 2017 and final oocyte maturation was performed with dual trigger with GnRH agonist combined hCG (n=270) or hCG alone (n=199). All the patients were followed up for three years. Cumulative live birth rate was calculated as the first live birth achieved after all cycles having an embryo transfer (fresh cycles as well as thawing cycles) among both groups. Subjects in the dual trigger group achieved a slightly higher number of oocytes retrieved (11.24 vs. 10.24), higher number of two-pronuclear embryo (2PN) (8.37 vs. 7.67) and a higher number of embryos available (4.45 vs. 4.03). But the cumulative live birth rate, an all-inclusive success rate for assisted reproductive technology, was similar between the two groups (54.07% vs. 59.30%). This study showed that the dual trigger was not superior to only hCG trigger for normal responders in GnRH antagonist cycles in terms of cumulative live birth rate.

Introduction

In gonadotropin-releasing hormone (GnRH) antagonist cycles, human chorionic gonadotropin (hCG) is routinely used to induce final oocyte maturation ¹. However, the administration of hCG results in supraphysiologic steroid levels in the luteal phase due to its long half-life and is consequently associated with an increased risk of ovarian hyperstimulation syndrome (OHSS) ². To eliminate the risk of OHSS, gonadotropin-releasing hormone agonists were introduced to promote final oocyte maturation in GnRH antagonist cycles at the end of the last century ³. The single bolus of GnRH agonist (GnRHa) can stimulate the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland ⁴ to mimic the natural mid-cycle LH surge required for final oocyte maturation. Meanwhile, comparing to the administration of exogenous hCG, the GnRHa-induced LH surge has a shorter duration and smaller amplitude which may help to reduce the risk of OHSS ^{3,5}. However, significantly reduced implantation rate and higher abortion rate were observed for lone GnRHa triggered cycles due to defective luteal phase function and decreased endometrial receptivity ^{6,7}.

Therefore, the dual trigger method combines a single dosage of GnRHa with a reduced dosage of hCG has been proposed to minimize the risk of OHSS and improve clinical outcomes ⁸. Several studies focusing on high responders have demonstrated significant improvements in both ongoing pregnancy rates ⁹ and live-birth rates ¹⁰ when a dual trigger was used instead of a lone GnRHa trigger, all without conferring a significant increase in the OHSS rate. However, insufficient evidence is available regarding the impact of a dual trigger on reproductive outcome in normal responders. Some studies reported significantly improved ongoing pregnancy rate and live birth rate in fresh cycles for the dual trigger group

compared with the hCG trigger group in normal responders^{1,11}. By contrast, several studies demonstrated that dual trigger of oocyte maturation was not associated with any change in the live birth rate in fresh cycles for normal ovarian responders^{12,13}. However, these researches did not focus on the cumulative live birth rate which provided an all-inclusive success rate for assisted reproductive technology (ART).

The aim of the present study was therefore to investigate whether dual triggering of final oocyte maturation with a combination of a single dose of GnRH agonist and a low dosage of hCG can improve cumulative live-birth rate for normal responders in GnRH-antagonist IVF-ICSI cycles.

Materials And Methods

Study design

In the present retrospective cohort study, a review of medical records from 1st January to 31st December 2017, was performed for all IVF-ICSI cycles with a GnRH-antagonist protocol at the Reproductive Center of Peking University Peoples' Hospital in Beijing City, China. The study protocol was approved by the institutional review board of Peking University Peoples' Hospital. All of the included patients read and signed the informed consent form and all the treatments in the present study were performed strictly in accordance with the Declaration of Helsinki for Medical Research.

Study participants

We included in women aged less than 40 years, body mass index (BMI) ranges from 18 to 30 kg/m², who had a normal response to controlled ovarian stimulation (4–20 retrieved oocytes). Patients with either high or poor response to controlled ovarian hyperstimulation (COH) were excluded. Poor ovarian response was defined as the number of retrieved oocytes≤4. High ovarian response was defined as the number of retrieved oocytes≥20. Other exclusion criteria were occult ovarian failure (day-3 follicle stimulating hormone [FSH] concentration of ≥10 IU/L), patients with more than three IVF and/or ICSI attempts, presence of endocrine disorders (diabetes mellitus, hyperprolactinemia, thyroid dysfunction, congenital adrenal hyperplasia, Cushing syndrome, or polycystic ovary syndrome), or uterine anomaly confirmed by either hysterosalpingography or hysteroscopy. In order to evaluate the effect of dual trigger on the cumulative live birth rate until first live birth, only the patients achieved the first live birth or had used up all of the fresh and frozen embryos acquired from this GnRH antagonist stimulated cycle were included.

Ovarian stimulation protocols

All the patients received a flexible GnRH antagonist protocol in the COH and they did not receive oral contraceptive pill before the IVF cycle. Ovarian stimulation began on day 2 of the menstrual cycle with recombinant FSH (Gonal-F; Merck Serono, Coinsins, Switzerland) 150 to 225 IU daily for 3 consecutive days. The starting dosage was determined by patient age, ovarian reserve, body mass index, and previous response to COH. The recombinant FSH dosage was then adjusted according to serum estrogen (E2) and follicular growth, monitored by serial transvaginal ultrasound. The administration of GnRH-antagonist

(0.25 mg daily of Ganirelix or Cetrotide, 10:00 am) was initiated based on a flexible protocol, generally when the lead follicle was 13 to 14 mm in diameter, and was continued until the day of hCG administration. When at least two leading follicles had reached 18 mm in diameter, final oocyte maturation was triggered by either 250 mg of recombinant hCG (Ovidrel; Merck Serono S.p.A., USA) alone, which was equivalent to approximately 6,500 IU hCG according to the manufacturer's data, or by 0.2 mg of triptorelin (Ferring International Center SA, Switzerland) plus 2000 IU of hCG (Chorionic Gonadotropin, Livzon, Zhuhai, China). Oocyte retrieval was performed by transvaginal ultrasonography 35–37 hours later. Intracytoplasmic sperm injection (ICSI) was performed for patients experiencing severe male factor infertility.

Embryo culture

Fertilization was assessed 16–18 hours after insemination for the appearance of two distinct pronuclei and two polar bodies. The zygotes were cultured in a cleavage medium (Cook Medical). Embryonic development was assessed daily. Fresh embryo transfer was performed at day 3 after oocyte retrieval and supernumerary embryos of excellent quality were cryopreserved (slow freezing protocol). Embryos of excellent quality were defined if they met the following criteria: 7 or 8 cells stage at day three after fertilization, fragmentation is less than 10 % and homogenous blastomeres.

If it does not meet the criterion of excellent quality embryos, embryos were cultured to the blastocyst stage in blastocyst medium (Cook Medical). Blastocyst quality scoring was performed on day 5 according to Gardner's criteria ¹⁴. The score depended on blastocyst expansion, inner cell mass development, and trophectoderm appearance. Inner cell mass and trophectoderm scoring was performed, and according to their morphologic appearance blastocysts were graded as top quality (grade 1) (AA), good quality (grade 2) (AB and BA), average quality (grade 3) (AC, CA, BB), and poor quality (grade 4) (BC, CB, CC). Blastocysts with a score ≥ 3 BB were vitrified either on day 5 or day 6. All embryos would be frozen if a patient had issues related to a thin endometrial lining (<7 mm), intrauterine fluid, hydrosalpinx, elevated progesterone level (>1.5 ng/mL) on the day of hCG administration, or had a high risk of ovarian hyperstimulation.

Embryo transfer

Fresh embryo transfer was performed at day 3 after oocyte retrieval. In frozen-thawed embryo transfer cycles, embryos were transferred in natural cycles or in hormonal replacement cycles. Patients who failed ovulate were given estradiol valerate (Progynova, Bayer, German) from cycle day 2 to 3 of the menstrual cycle (3 mg twice daily orally). Progesterone (intramuscular progesterone at a daily dose of 60 mg) was administered when the thickness of the endometrium reached ≥ 8 mm. The number of transferred embryos varied from one to two, depending on embryo quality and patient age.

Luteal phase support

For fresh embryo transfer cycles, the luteal phase support included daily intramuscular injection of 40 mg of progesterone in oil (Progesterone, Xianju, Taizhou, China), along with oral supplementation of 30 mg of dydrogesterone (Duphaston, Abbot Biologicals, Olst, The Netherlands), starting on the day of oocyte retrieval. For frozen-thawed embryo transfer cycles, intramuscular injection of 60 mg of progesterone in oil (Progesterone, Xianju, Taizhou, China) from day of endometrial transformation. Serum β -hCG was measured 14 days after embryo transfer, and a value above 5 IU/mL was considered to be a positive pregnancy. Luteal support was continued until 10 weeks of pregnancy.

Outcome variables

The primary outcome measure in this study was cumulative live birth rate. The cumulative live birth rate was calculated as the number of women who achieved the first live birth (>28 weeks of gestation) in the fresh or in the subsequent frozen-thawed cycles divided by the two group patients.

Other analyzed variables included the number of oocyte retrieved, the number of MII oocytes, fertilization rate, the implantation rate, the clinical pregnancy rate, miscarriage rate. The fertilization rate was defined as the number of the fertilized oocytes divided by the total number of the retrieved oocytes. The implantation rate was calculated by dividing the total number of fetal cardiac activity detected by the total number of transferred embryos. Clinical pregnancy was defined as a pregnancy confirmed by ultrasound visualization of the gestational sac between the 5th to 6th weeks of gestation. The miscarriage rate was defined as the number of the cases with pregnancy loss within 28 weeks of gestation starting from the day of oocyte fertilization divided by the number of clinical pregnancies. Live birth rate was defined as total number of the cases with at least one baby born after 28 weeks of gestation divided by the total number of the cycles in the fresh embryos transfer cycles. Cumulative live birth rate was calculated as the first live birth achieved after all cycles having an embryo transfer (fresh cycles as well as thawing cycles) among both groups.

Statistical analysis

Data analyses were performed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA). Samples were tested with the Shapiro-Wilk test to determine the normality of the distribution. Based on the results, parametric tests were preferred. Continuous variables were presented in terms of mean \pm SD then compared using a t-test or

Mann-Whitney U test. For categorical variables, the values were presented as frequency and percentage. Chi-square test was used for comparison between groups. For analysis, $p < 0.05$ was considered to be significant.

Results

During the study period, a total of 469 women met the inclusion criteria and were included in the analysis (270 in the dual trigger group and 199 in the hCG alone

group). The baseline characteristics and demographics did not statistically significantly differ between the study and control groups in terms of age, BMI, duration and cause of infertility (Table 1). Additionally, there was no difference regarding AFC, Day-3 FSH level between both groups. The ovarian stimulation characteristics for each group were presented in Tables 2. There was a statistically significant difference in the starting dose of gonadotropins used in stimulation for both dual trigger and hCG groups (189.95 ± 54.92 vs. 217.71 ± 54.43 , $p = 0.00$). Otherwise, no differences regarding the total dose of gonadotrophins stimulation, total days of gonadotrophins stimulation, P (progesteron) levels and endometrial thickness at the day of trigger were found. In comparison to the hCG group, women who received dual trigger had a slightly higher number of retrieved oocytes (11.24 ± 4.76 vs. 10.24 ± 4.27 , $p = 0.02$), higher number of 2PN (7.37 ± 3.69 vs. 6.62 ± 3.26 , $p = 0.02$) and more embryos obtained (4.45 ± 2.41 vs. 4.03 ± 2.20 , $p=0.04$). There was no difference in fertilization rates, number of MII oocytes retrieved and number of top quality embryos between the two groups.

There were 93 cases received fresh embryo transfer cycles in the dual trigger group versus 71 cases in the hCG trigger group. Out of them a slightly higher abortion rate was showed in the dual trigger group, but this did not reach a statistical significance (17.95% vs. 10.34% , $p = 0.38$) (Table 3). The implantation rate, clinical pregnancy rate and live-birth rate were similar between the two groups in the fresh embryo transfer cycles (Table 3).

Furthermore, we analyze the cumulative pregnancy outcome of the two groups. Finally, Table 4 showed that no significant difference among both groups regarding the implantation rate, abortion rate and cumulative live birth rates. Tough the abortion rate was also slightly higher in the dual trigger group (8.73% vs. 6.81% , $p=0.37$) compared to the hCG trigger group.

Discussion

The aim of this retrospective cohort study was to investigate the effect of the dual trigger with GnRHa and hCG for final oocyte maturation on clinical reproductive outcomes in normal responder women. In the present study, we demonstrated that dual trigger by GnRH agonist and hCG slightly increased the numbers of oocytes retrieved, 2PN embryos and embryos available for normal responders in GnRH antagonist IVF/ICSI cycles. The abortion rate was higher in the dual trigger group than in the hCG only group, this difference was not statistically significant. Therefore, the cumulative live birth rates were comparable among the dual trigger and hCG trigger groups.

In our study the number of MII oocytes retrieved and top quality embryos were similar in both study groups; however, the number of oocytes retrieved, 2PN, embryos available were higher in the dual trigger group. These data suggested that the dual trigger could improve the quantity of oocytes and embryos. Compared with hCG alone, administration of GnRH agonist induces an increase of endogenous LH and FSH that resembles the natural mid-cycle surge of gonadotropins. The surge in FSH could activate resumption of the oocyte meiotic process and cumulus expansion at the final stage of oocyte maturation¹⁵. In addition, a GnRHa trigger can also activate the GnRH receptors on granulosa cells, which may

regulate ovulation¹⁶. Our results are consistent with many studies of the use of dual trigger for oocyte maturation in normal responders^{1,11,12,17}. Though several studies showed that there was no significant difference in the number of MII oocytes and the number of 2PN oocytes with the use of dual trigger in comparison to hCG alone. This may be due to the small sample size included in their studies and the heterogeneity of infertility population^{18,19}.

In the present study, we included the pregnancy outcomes not only in the fresh embryo transfer cycles but also in the frozen-thawed embryo transfer cycles. In the fresh embryo transfer cycles, there was not significant difference between the dual trigger (93 patients) and hCG alone trigger (71 patients) groups in terms of the implantation rate, clinical pregnancy rate and live birth rate. The results indicated that in the fresh embryo transfer cycles, the dual trigger for oocyte maturation could not be superior to hCG trigger. Despite the slightly higher number of oocytes retrieved (11.24 vs. 10.24) and higher number of embryos available (4.45 vs. 4.03) in the dual trigger group, these advantages did not result in a higher implantation rate and live birth rate. Furthermore, much higher abortion rate was demonstrated in the dual trigger group (17.95% vs. 10.34%), although this difference was not statistically significant. Our results agreed with Zhou who reported no difference between the two study groups regarding the implantation rate, clinical pregnancy rate and live birth rate in a retrospective cohort study including a big sample size (220 patients in dual trigger group and 110 control patients)¹². In addition, two randomized controlled trial (RCT) studies by Shymaa and Alleyassin explored the effect of dual trigger for oocyte maturation on the pregnant outcome in fresh embryo transfer cycles in normal responders^{17,20}. The similar implantation rate and clinical pregnancy rate were shown between the two groups in the both RCT and similar live birth rate in the fresh embryo transfer cycles was demonstrated in the RCT by Shymaa including 120 patients. On the contrary, Lin and Kim et al. reported that the dual-trigger group showed statistically significant improved rates of implantation, clinical pregnancy, and live birth^{11,21}. Thus in the fresh embryo transfer cycles, the benefits of the dual trigger for oocyte maturation in normal responders was still controversial.

Given that the cumulative birth rate can provide an all-inclusive success rate for ART, we focus on the cumulative live birth as the primary outcome. In the present study, all the patients were followed up for three years. 177 patients in dual trigger group and 128 patients in hCG group received frozen embryos transfer. The cumulative live birth rate was calculated by including the first live birth generated during the complete this IVF cycle (including fresh and frozen embryos transfer cycles) as the numerator and the denominator was defined as all women enrolled in the two groups. We observed that the cumulative live birth rate was comparable between the two groups (54.07% in dual trigger group vs 59.30% in hCG alone group, p=0.26). There was another study explored the cumulative live birth rate after frozen-thaw embryos transfer cycle. It was also showed that no significant difference among both groups regarding the cumulative pregnancy and cumulative live birth rates in the RCT by Shymaa in which only 19 patients (11 for dual trigger group vs. 8 for hCG group) received frozen thawed embryo transfer. These results demonstrated that dual trigger with GnRH agonist and hCG for oocyte maturation was not superior to only hCG trigger for normal responders in GnRH antagonist cycles with respect to cumulative pregnancy outcome.

The strengths of our study include that a large sample size and a long follow up period. In the study, 469 patients (270 patients in dual trigger group and 199 patients in hCG group) were included. Furthermore, 305 subjects received frozen-thaw embryos transfer and we calculated the cumulative live birth rate in the two groups which provided an all-inclusive success rate for ART. A limitation of our study was its retrospective design.

In conclusion, the dual trigger with GnRH agonist and hCG can slightly improve the number of oocytes retrieved and embryos for normal responders in GnRH antagonist IVF cycles. But, no clinical benefit seems to exist in terms of cumulative live birth rates. Further prospective randomized controlled studies with large samples are needed to confirm the exact impact of the trigger of final oocyte maturation in normal responders undergoing ART cycles.

Declarations

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Author contributions

H.S. and H.J.H. conceived and designed this study. F.M.G. and Y.B.W. contributed to data acquisition, analysis. F.M.G also contributed to interpret and draft the manuscript. M.F., Q.X.Z. and Y.M.R. were responsible for the collection of data. H.J.H. contributed to revising the manuscript. All authors reviewed the manuscript.

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Competing interests

The authors declare no competing interests.

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Tables

Table 1. Comparison of the dual-trigger and hCG trigger group: baseline characteristics of patients.

	Dual trigger group (n = 270)	hCG group (n = 199)	p
Age (years)	32.66±3.53	33.24±3.64	0.08
BMI(kg/m ²)	22.66±2.69	22.72±2.69	0.81
Duration of infertility (years)	3.79±2.94	3.64±2.97	0.61
Antral follicle count (AFC)	10.60±5.41	10.55±4.50	0.91
Day-3 FSH level (IU/L)	7.17±1.63	7.12±1.38	0.83
Cause of infertility			0.06
Male factor	60±22.20%	39±19.6%	
Tubal factor	89±33.00%	55±27.60%	
Ovulation dysfunction	23±8.50%	33±16.50%	
Endometriosis	17±6.30%	16±8.00%	
Combined	59±21.90%	42±21.10%	
Unexplained	22±8.10%	14±7.00%	
Fertilization			0.27
IVF	138±51.10%	112±56.30%	
ICSI	132±48.9%	87±43.70%	

Note: Values are expressed as mean ± standard deviation or percentage.

HCG: human chorionic gonadotrophin, BMI: body mass index, FSH: follicle stimulating hormone, IVF: in vitro fertilization, ICSI: intracytoplasmic sperm injection

Table 2. Comparison of the dual-trigger and hCG trigger group: characteristics of ovarian stimulation.

	Dual trigger group (n = 270)	hCG group (n = 199)	p
Initial dose of gonadotropin (IU)	189.95±54.92	217.71±54.43	0.00
Total dose of gonadotropins (IU)	2100.41±721.56	2170.53±622.28	0.27
Duration of stimulation (d)	9.57±1.88	9.76±1.82	0.27
P on trigger day (ng/mL)	1.23±0.69	1.12±0.92	0.18
Endometrial thickness on trigger day (mm)	9.02±2.20	9.47±2.71	0.06
No. of oocytes retrieved	11.24±4.76	10.24±4.27	0.02
No. of MII oocytes retrieved	8.37±4.44	7.67±3.69	0.07
Fertilization rate (%)	84.40±17.71	83.44±22.20	0.60
No. of 2PN	7.37±3.69	6.62±3.26	0.02
No. of embryos available	4.45±2.41	4.03±2.20	0.04
No. of top quality embryos	1.53±1.53	1.31±1.40	0.10

Note: Values are expressed as mean±standard deviation.

HCG: human chorionic gonadotropin; MII: metaphase II; 2PN: two-pronuclear

Table 3. Reproductive outcome of fresh embryo transfer cycles in the study groups

	Dual trigger group (n = 93)	hCG group (n = 71)	p
Implantation rate (%)	28.83% (47/163)	28.00% (35/125)	0.88
Clinical pregnancy rate per ET (%)	41.94% (39/93)	40.85% (29/71)	0.89
Abortion rate (%)	17.95% (7/39)	10.34% (3/29)	0.38
Live-birth rate per ET (%)	34.41% (32/93)	36.62% (26/71)	0.77

Note: Values are expressed as percentage. ET: embryo transfer; hCG: human chorionic gonadotropin

Table 4. Cumulative reproductive outcomes in the study groups.

	Dual trigger group (n = 270)	hCG group (n = 199)	p
No. of embryos transferred per patient	2.60±1.22	2.61±1.15	0.97
No. of embryo transfer cycles per patient	1.44±0.64	1.42±0.63	0.75
Implantation rate (%)	36.66% (250/682)	35.81% (183/511)	0.76
Abortion rate (%)	8.73% (33/378)	6.81% (19/279)	0.37
Cumulative live birth rate	54.07% (146/270)	59.30% (118/199)	0.26
Fresh cycle Live birth	32	26	
Frozen cycle live birth	114	92	

Note: Values are expressed as percentage. hCG: human chorionic gonadotropin.