Observational Study

Medicine

OPEN

Comparison of dual-trigger and human chorionic gonadotropin-only trigger among polycystic ovary syndrome couples who underwent controlled ovarian stimulation and intrauterine insemination

A retrospective cohort study

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Abstract

The dual-trigger regime, consisting of gonadotrophin releasing hormone agonist and human chorionic gonadotropin (HCG), has been shown to offer advantage over the HCG-only trigger regime. However, little is known about the influence of dual-trigger or HCG-only trigger regime on the reproductive outcome of polycystic ovary syndrome (PCOS) couples undergoing controlled ovarian stimulation (COS) and intrauterine insemination (IUI). A total of 404 cycles of COS and IUI treatments from couples with PCOS were enrolled, and divided, according to the regime of trigger, into dual-trigger group (n = 109, 0.1–0.2 mg gonadotrophin releasing hormone agonist plus 6000 IU HCG) and HCG-only group (n = 295, 10,000 IU HCG or 250 μg recombinant HCG). Baseline characteristics of the 2 groups were comparable (all $P > .05$). In dual-trigger group, live birth rate, clinical pregnancy rate and β-HCG positive rate were all higher as compared to the HCG-only group (20.18% vs 18.98%, 25.69% vs 23.39% and 28.44% vs 25.08% respectively), despite the differences failed to achieve statistical significances (all $P > .05$). Moreover, early miscarriage rate and multiple pregnancy rate of the dual-trigger group were lower than those of the HCG-only group (17.86% vs 18.84% and 3.57% vs 7.25% respectively), although no statistical significances were found (all $P > .05$). Additionally, logistic regression analysis revealed that age contributed significantly to the live birth of couples with PCOS ($P = .043$, OR = 0.900). Dual-trigger regime for oocyte maturation seems to associate with beneficial improvements in reproductive outcomes of PCOS couples undergoing COS and IUI. Instead of HCG-only trigger, dual-trigger regime might be an alternative option in COS and IUI cycles for couples with PCOS.

Abbreviations: COS = controlled ovarian stimulation, GnRH-a = gonadotrophin releasing hormone agonist, HCG = human chorionic gonadotropin, HMG = human menopausal gonadotropin, IUI = intrauterine insemination, OHSS = ovarian hyper-stimulation syndrome, PCOS = polycystic ovary syndrome.

Keywords: dual-trigger, GnRH-a, HCG, IUI, PCOS

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, accounting for 15% to 20% of the infertile women.[1,2] Patients with PCOS are clinically featured by oligo-anovulation, hyperandrogenism and polycystic ovaries.[3] Unfortunately, effective medication is currently unavailable for PCOS, and the strategy primarily concentrates on ameliorating symptoms and maintaining a healthy lifestyle to reduce the risk of complication.[4] Generally, women with PCOS face difficulties conceiving children as a result of oligo-anovulation. However, with controlled ovarian stimulation (COS), women with PCOS may overcome this obstacle and resume ovulation.[5,6]

In department of reproductive medicine, intrauterine insemination (IUI) is a commonly-used method to enhance the likelihood of pregnancy before moving forward to complex therapy of in vitro fertilization and embryo transfer, for the reason that it is easy to operate, patient-friendly and economical.[7] COS, together with IUI, is now regarded as the first choice of infertile treatment for couples with PCOS.[8]

During COS, proper application of various trigger drugs plays a vital role in enhancing oocyte quality, improving reproductive outcome and minimizing risk of ovarian hyper-stimulation

This study was supported by Guangdong Science and Technology Department (No. 2016A020218015). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Wang B, Li Z. Comparison of dual-trigger and human chorionic gonadotropin-only trigger among polycystic ovary syndrome couples who underwent controlled ovarian stimulation and intrauterine insemination: A retrospective cohort study. Medicine 2023;102:5(e32867).

Received: 3 December 2022 / Received in final form: 16 January 2023 / Accepted: 17 January 2023

http://dx.doi.org/10.1097/MD.0000000000032867

syndrome (OHSS).[9] Traditional way of triggering during COS involves use of human chorionic gonadotropin (HCG) to mimic the physiological surge of luteinizing hormone, which, in turn, and results in oocyte maturation and ovulation eventually.[9] However, the prolonged luteotropic effect of HCG can increase the risk of OHSS in women of high ovarian response, particularly those with PCOS.[10,11] In contrast, gonadotrophin releasing hormone agonist (GnRH-a), an alternative drug for HCG, can concurrently induce ovulation and minimize the risk of OHSS.[12] However, some studies have pointed out that GnRH-a alone could compromise oocyte maturation and pregnancy owing to inhibition of luteinizing hormone and short duration of efficacy.[13,14] The dual-trigger regime, consisting of GnRH-a and HCG, has been proved to minimize risk of OHSS, and enhance oocyte quality and improve reproductive outcome in the field of in vitro fertilization.[15–18]

Up to now, little is known about the potential effects of different regimes of trigger drugs on the reproductive outcomes of PCOS couples undergoing COS and IUI.[19] In this retrospective cohort study, we compared the clinical impact of dual-trigger regime with that of the HCG-only trigger regime in PCOS couples underwent COS and IUI.

2. Materials and methods

2.1. Study design and subject

The present study included data from PCOS couples underwent COS and IUI treatments at our center between January 1, 2016 and December 31, 2020. Clinical and demographic information were obtained from the medical archives. PCOS was diagnosed with the Rotterdam consensus.[3] The exclusion criteria were sperm anomality (the male factor), women with body mass index ≥ 30 kg/m^2, endometriosis, obstruction of fallopian tube, and uterine or pelvic anomaly demonstrated either by hysterosalpingography or hysteroscopy. As depicted in the flowchart of Figure 1, a total of 404 cycles of COS and IUI treatments were finally enrolled, and divided into 2 groups according to the regime of trigger, that is the dual-trigger group (GnRH-a plus HCG, n = 109) and the HCG-only group (n = 295). Upon the first visit, each couple underwent a standard infertility workup in our center. For men, sperm analyses were performed after 3 to 5 days of sexual abstinence. For women, basal serum hormone measurements were conducted on day 3 to 5 of the menstrual cycle. This study was approved by The institutional ethics committee of our hospital (Approval number: 2015). Written informed consents were obtained from all the couples. This study was conducted according to the principles of the declaration of Helsinki.

2.2. COS and IUI protocols

Initial dose of ovarian stimulation was customized by fertility doctor after fully assessing each patient age, body mass index, and current ovarian reserve and previous history of ovarian response. Generally, ovarian stimulation started 3 to 5 days after the menstruation.

For stimulation cycles using human menopausal gonadotropin (HMG), ovarian stimulation was performed in a step-up fashion, with an initial dose of 37.5 to 150 IU HMG (Renjian Pharmaceutical Group, China). Transvaginal ultrasonography was conducted to evaluate the ovarian response, and HMG

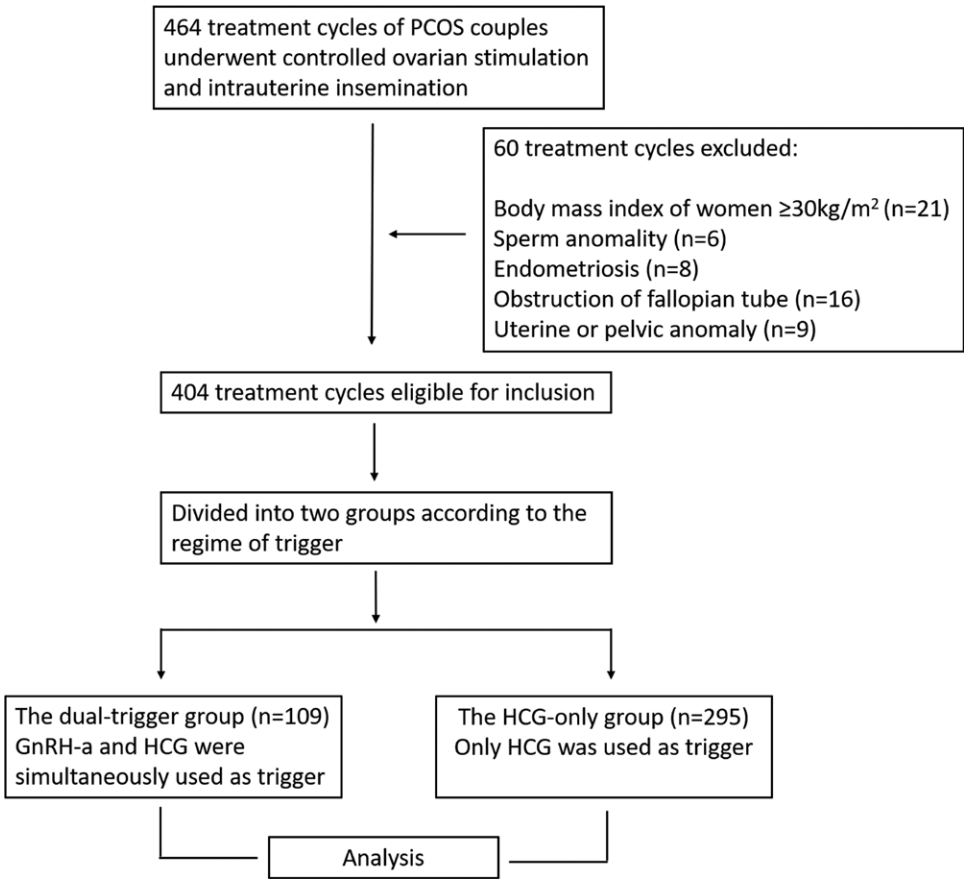

Figure 1. Flowchart describing subject selection. PCOS, polycystic ovary syndrome; GnRH-a, gonadotrophin releasing hormone agonist; HCG, human chorionic gonadotropin. GnRH-a = gonadotrophin releasing hormone agonist, HCG = human chorionic gonadotropin, PCOS = polycystic ovary syndrome.

dose was then adapted individually according to the follicular growth. When a dominant follicle emerged, HMG dose remained unchanged until the follicle had reached a diameter of ≥ 18mm.

For stimulation cycles using clomiphene or letrozole, women were individually administrated with 50 to 100 mg clomiphene (Codal Synto Ltd, Cyprus) once a day or 2.5 to 5 mg letrozole (Haizheng Pharmaceutical Group, China) once a day for 5 consecutive days. Ovarian response was then monitored by transvaginal ultrasonography accordingly. In case of stimulation cycle insensitive to clomiphene or letrozole, individualized dose of HMG was then given to further promote follicle development until a dominant follicle of appropriate size emerged, as stated above.

Cycles were triggered either with (I) 10000 IU HCG (Livzon, China) or 250 μg recombinant HCG (Merck Serono, Switzerland) or (II) 0.1 to 0.2 mg GnRH-a (IPSEN PHARMA, France) plus 6000 IU HCG when at least 1 dominant follicle had reached a diameter of ≥ 18mm. Cycles with more than 3 dominant follicles were canceled to prevent multiple pregnancy and ovarian hyper-stimulation syndrome. IUI operation was carried out 24 to 36 hours after administration of trigger drug, with the aid of a disposable IUI catheter. Women were then instructed to stay in supine position for 30 minutes after IUI. Serum β-human chorionic gonadotropin was detected 2 weeks after the day of IUI to check the presence of pregnancy.

Starting from the next day of IUI, luteal support was provided individually in the form of 10 mg tablet Dydrogesterone (Abbott Laboratories, USA) twice or 3 times a day for 15 to 16 days. If a viable intrauterine pregnancy was detected, the luteal support was extended for 10 to 12 extra weeks.

Clinical pregnancy was defined as an intrauterine sac or fetal heart activity detected on transvaginal scan 5 to 6 weeks after the day of IUI. Early miscarriage was defined as pregnancy loss before 12 weeks of pregnancy. Live birth was defined as delivery of a viable fetus of more than 23 weeks of gestation.

2.3. Measurement of hormones

The hormone levels were assessed with chemiluminescence (Abbott Biologicals B.V., Weesp, Netherlands) according to the instruction of manufacturer, in the department of clinical laboratory. Inter-assay and intra-assay coefficients of variation were < 10% for any of the assays.

2.4. Semen specimen analysis

Sperm analyses were carried out in accordance with the world health organization criteria in the andrology laboratory. Semen specimens were obtained by masturbation after 3 to 5 days of sexual abstinence. Collections of semen were conducted a few hours prior to the scheduled time of insemination. Sperm preparations were performed using the density gradient centrifugation method as previously described.[20] The total number of motile sperm were $> 10 \times 10^6$ after processing.

2.5. Typing criteria of endometrium

With reference to the typing criteria previously defined by Gonen Y,[21] endometrial ultrasound type was determined by comparing the reflectivity or gray-scale appearance of the endometrium to that of the adjacent myometrium. The changes in reflectivity varied from brighter than the myometrium (hyperechogenic), to equal to the appearance of the myometrium (isoechogenic), to darker than the myometrium (hypoechogenic). Type A endometrium was a multilayered pattern consisting of a prominent midline and outer hyperechogenic lines with hypoechogenic regions between the lines (also known as the "triple-line" pattern). Type A- endometrium was a "triple-line" pattern with a prominent but slightly broken central line. Type B endometrium was an isoechogenic pattern showing the same reflectivity compared to the surrounding myometrium, but the central echogenic line was non-prominent. Type C endometrium was hyperechogenic compared to the myometrium, the central echogenic line was invisible.

2.6. Follow-up

Follow-up surveys began 2 weeks after the day of IUI, every other month. Information regarding the health status and pregnancy were collected through phone calls by senior nurses. Follow-ups were terminated when one of the following circumstances occurred: negativity of serum β-HCG 2 weeks after IUI; Early miscarriage as defined previously; delivery of a live fetus. Strict policies were implemented in our center to ensure that all couples were adequately followed. The follow-up rate was 100% in this study.

2.7. Statistical analysis

Statistical analysis was performed with the Statistic Package for Social Science 20.0 for Windows (IBM, NY). Kolmogorov-Smirnov normality test was first taken to clarify the distribution of continuous data. Continuous data were presented as mean ± standard deviation or median (25th–75th percentiles) depending on their distributions. Continuous data with normal distribution were compared with the *t* test, those with abnormal distribution were compared with the Mann–Whitney *U* test. Categorical data were expressed as number or percentage. Categorical data were compared using Pearson Chi-square test or Fisher exact test. In our study, we constructed a logistic regression model to explore possible predictive factors for live birth of PCOS couples. In this model, occurrence of live birth (categorical variable, yes = 1, no = 0) was designated as the dependent variable, type of endometrium (categorical variable, type C = 0, type B = 1, type A = 2, type A = 3), along with other factors, were included as the independent variables. The independent variables could be categorical or continuous. Binary logistic regression analysis was then performed in the SPSS statistical program with default settings. β was the regression coefficient of the model, a parameter indicating the degree of contribution of any specific factor to the occurrence of live birth. OR (odds ratio) was the exponential function of the β value (OR = exp[β]). Similarly, OR also indicated the degree of contribution of any specific factor to the occurrence of live birth. β or OR was statistically significant only when the corresponding *P* value ≤.05. Wald value could be calculated by the following formula: Wald= (β/standard error) 2. Wald value was used to calculate the corresponding *P* value. Missing data were addressed using the Listwise Deletion method as recommended by SPSS. A 2-tailed *P* value of < .05 was considered significant statistically.

3. Results

3.1. Baseline characteristics of HCG-only group and dual-trigger group

As shown in Table 1, we compared the baseline characteristics of HCG-only group and dual-trigger group. Age, duration of infertility and etiology of infertility were all comparable between the 2 groups. Distribution of IUI cycle number was not significantly different between the 2 groups. Likewise, basal serum hormones (luteinizing hormone, follicle-stimulating hormone, and estradiol and progesterone) of the 2 groups were similar. In addition, body mass index of HCG-only group did not significantly different from that of the dual-trigger group (22.04 ± 2.49 vs 21.48 ± 2.58, $P > .05$).

Antral follicle count, a reliable indicator of ovarian reserve,[22] was also comparable between the 2 groups,

Table 1

Baseline characteristics of HCG-only group and dual-trigger group.

Characteristics	HCG-only group (n = 295)	Dual-trigger group (n = 109)	*P* value
Age(yr)	28.71 ± 3.24	28.17 ± 3.23	.145
Duration of infertility(yr)	3.47 ± 1.77	3.17 ± 1.62	.111
Etiology of infertility			
Primary	225 (76.27%)	83 (76.15%)	.979
Secondary	70 (23.73%)	26 (23.85%)	
IUI cycle			
The 1st cycle	165 (55.93%)	53 (48.62%)	.509
The 2nd cycle	95 (32.20%)	39 (35.78%)	
The 3th cycle	27 (9.15%)	14 (12.84%)	
Cycles after 3 attempts	8 (2.71%)	3 (2.75%)	
Body mass index (kg/m2)	22.04 ± 2.49	21.48 ± 2.58	.052
Antral follicle count	26.48 ± 7.73	25.73 ± 7.29	.381
Basal LH (mIU/mL)	9.35 ± 5.73	9.61 ± 5.35	.665
Basal FSH (mIU/mL)	6.55 ± 3.06	6.71 ± 1.70	.501
Basal estradiol (pg/mL)	49.49 ± 22.40	54.38 ± 28.44	.109
Basal progesterone (ng/mL)	0.68 ± 2.02	0.56 ± 0.40	.385
Composition of COS protocols			
CC	7 (2.37%)	1 (0.92%)	.470
HMG	35 (11.86%)	10 (9.17%)	
LE	27 (9.15%)	7 (6.42%)	
CC + HMG	24 (8.14%)	5 (4.59%)	
LE + HMG	201 (68.14%)	86 (78.90%)	
Others	1 (0.34%)	0	
Total dosage of gonadotrophin used (IU)	542.91 ± 376.39	536.43 ± 345.57	.877
Number of follicles with diameter ≥ 18mm on the trigger d	0.91 ± 0.53	1.08 ± 0.58	.656
Number of follicles with diameter ranging from 14mm to 17.5mm on the trigger d	0.38 ± 0.59	0.50 ± 0.77	.914
Endometrium thickness on the trigger d (mm)	9.87 ± 1.88	9.93 ± 2.16	.799
Type of endometrium on the trigger d			
Type C	3 (1.03%)	0	.659
Type B	17 (5.84%)	4 (3.67%)	
Type A-	24 (8.25%)	11 (10.09%)	
Type A	247 (84.88%)	94 (86.24%)	

Values are presented as mean ± SD or number (percentage) unless stated otherwise.

CC = clomiphene, COS = controlled ovarian stimulation, FSH = follicle-stimulating hormone, HCG = human chorionic gonadotropin, HMG = human menopausal gonadotropin, IUI = intrauterine insemination, LE = letrozole, LH = luteinizing hormone.

suggesting the ovarian reserve of the 2 groups were equivalent. Additionally, no significant differences were found between the 2 groups in composition of COS protocols and the total dosage of gonadotropin used. On the trigger day, number of follicles with diameter ≥ 18mm and those with diameter ranging from 14mm to 17.5mm were also comparable between the 2 groups respectively. Moreover, type and thickness of endometrium on the trigger day were also similar between the 2 groups.

3.2. Reproductive outcomes of HCG-only group and dual-trigger group

In order to unveil the possible influence of HCG-only trigger or dual-trigger on the reproductive outcomes of PCOS couples underwent COS and IUI, we evaluated and compared the live birth rate, clinical pregnancy rate, β-human chorionic gonadotropin (β-HCG) positive rate, and early miscarriage rate and multiple pregnancy rate in HCG-only group and dual-trigger group. As described in Table 2, no significant differences were found between the 2 groups in terms of these 4 indicators (all P values > 0.05). However, dual-trigger group associated with improved reproductive outcomes, characterized by higher live birth rate (20.18% vs 18.98%, Table 2), higher clinical pregnancy rate (25.69% vs 23.39%, Table 2), higher β-HCG positive rate (28.44% vs 25.08%, Table 2), and lower early miscarriage rate (17.86% vs 18.84%, Table 2) and lower multiple pregnancy rate (3.57% vs 7.25%, Table 2). These data suggest a beneficial improvement associated with the dual-trigger regime. In addition, no case of ovarian hyper-stimulation syndrome was found in our study.

3.3. Predicted factors for live birth of PCOS couples underwent COS and IUI

We constructed a logistic regression model to explore possible predicted factors for live birth of PCOS couples underwent COS and IUI. Results of Table 3 reveal that age contributed significantly to live birth of PCOS couples underwent COS and IUI (*P* = .043, OR = 0.900, 95% confidential interval:0.812–0.997). Additionally, other factors, as stated in Table 3, were not eligible as contributing factors.

4. Discussion

In this study, we found that live birth rate, clinical pregnancy rate and *β*-HCG positive rate of the dual-trigger group were all higher when compared to the HCG-only group. Moreover, early miscarriage rate and multiple pregnancy rate of the dual-trigger group were lower than those of the HCG-only group.

Previous researches concerning the impact of trigger drugs were mainly conducted in the settings of in vitro fertilization and embryo transfer.[16,18,23–26] Studies about the possible influences of different regimes of trigger drugs on the reproductive outcomes of PCOS couples undergoing controlled ovarian stimulation and intrauterine insemination are limited.[19] Our study

Table 2

Reproductive outcomes of HCG-only group and dual-trigger group.

Characteristics	HCG-only group (n = 295)	Dual-trigger group (n = 109)	*P* value
Live birth			
Yes	56 (18.98%)	22 (20.18%)	.786
No	239 (81.02%)	87 (79.82%)	
Clinical pregnancy			
Yes	69 (23.39%)	28 (25.69%)	.631
No	226 (76.61%)	81 (74.31%)	
β-HCG positivity			
Yes	74 (25.08%)	31 (28.44%)	.495
No	221 (74.92%)	78 (71.56%)	
Early miscarriage			
Yes	13 (18.84%)	5 (17.86%)	.910
No	56 (81.16%)	23 (%)	
Multiple pregnancy			
Yes	5 (7.25%)	1 (3.57%)	.669
No	64 (92.75%)	27 (96.43%)	
OHSS	0	0	NA

Values are presented as number (percentage).

HCG = human chorionic gonadotropin, NA = not applicable, OHSS = ovarian hyper-stimulation syndrome, β-HCG = beta human chorionic gonadotropin.

Table 3

Exploration of predicted factors for live birth of PCOS women underwent controlled ovarian stimulation and intrauterine insemination.

	Live birth (n = 404)			
Factors investigated	**β**	**Wald**	**OR (95%CI)**	***P* value**
Age	−0.106	4.091	0.900(0.812–0.997)	**.043**
Duration of infertility	−0.151	1.903	0.860(0.694–1.066)	.168
Etiology of infertility	0.299	0.581	1.348(0.625–2.907)	.446
Number of IUI cycle	0.016	0.006	1.016(0.673–1.532)	.941
Body mass index	0.008	0.014	1.008(0.884–1.149)	.907
Antral follicle count	0.004	0.034	1.004(0.960–1.051)	.854
Basal luteinizing Hormone	0.037	1.647	1.038(0.980–1.099)	.199
Basal follicle-stimulating hormone	0.092	1.802	1.096(0.959–1.253)	180
Basal estradiol	−0.004	0.350	0.996(0.983–1.009)	.554
Basal progesterone	0.147	0.653	1.158(0.811–1.652)	.419
COS protocol	0.091	0.234	1.095(0.758–1.583)	.629
Total dosage of gonadotrophin used	0.000	0.832	1.000(0.998–1.001)	.362
Number of follicles with diameter ≥ 18mm on the trigger d	0.255	0.819	1.291(0.743–2.243)	.366
Number of follicles with diameter ranging from 14mm to 17.5mm on the trigger d	0.379	2.637	1.460(0.925–2.307)	.104
Endometrium thickness	0.094	1.306	1.099(0.935–1.292)	.253
Type of Endometrium on the trigger d	0.218	0.522	1.244(0.688–2.248)	.470
HCG-only trigger or dual-trigger	0.102	0.094	1.108(0.577–2.125)	.759

CI = confidence interval, COS = controlled ovarian stimulation, HCG = human chorionic gonadotropin, IUI = intrauterine insemination, OR = odds ratio, PCOS = polycystic ovary syndrome.

is the first report to have investigated and compared the potential effects of dual-trigger with that of HCG-only trigger among PCOS couples underwent controlled ovarian stimulation and intrauterine insemination.

In our study, we found that the dual-trigger regime associated with better reproductive outcomes as compared to the HCG-only trigger regime. The beneficial improvements associated with dual-trigger regime were characterized by higher live birth, higher clinical pregnancy, higher *β*-HCG positivity, and lower early miscarriage and lower multiple pregnancy (Table 2). This finding concurs with previous studies that explored the clinical impacts of different regimes of trigger drugs on the reproductive outcomes of both intrauterine insemination and in vitro fertilization cycles.[15,19,23,24,27]

Our data seem to indicate that dual-trigger regime can improve oocyte quality and achieve a steady pregnancy. Previous studies have proved that administration of GnRH-a elicited an increase of endogenous luteinizing hormone and follicle-stimulating hormone that mimicked the natural mid-cycle surge of gonadotropin as compared to HCG alone. The surge of follicle-stimulating hormone can activate resumption of the oocyte meiotic process and cumulus expansion at the final stage of oocyte maturation.[28] In fact, prior studies focusing on high, and normal and poor ovarian responders all indicated that GnRH-a trigger contributed to higher percentage of metaphase II oocytes in contrast to HCG trigger alone.[13,26,27,29] More importantly, in a prospective randomized control trial of PCOS women underwent in vitro fertilization cycles, Krishna D et al[30] showed that the use of GnRH-a trigger yielded more mature oocytes and good quality embryos when compared to the HCG trigger. Study by Griffin D et al[16] also demonstrated that dual-trigger regime led to a significantly higher maturation rate of oocytes as compared to the HCG-only trigger. Moreover, Griffin D et al[31] indicated in another retrospective cohort study that dual-trigger of oocyte maturation with GnRH-a and low-dose HCG in high ovarian responders improved the probability of conception and live birth without increasing the risk of ovarian hyper-stimulation syndrome. However, controversy remains as to the impact of dual-trigger regime. Decleer W et al[25] reported a lower pregnancy rate of dual-trigger regime as

compared to HCG trigger regime, despite the difference failed to achieve significance statistically.

Another possible explanation for the improved reproductive outcomes of dual-trigger regime may be the enhancement of endometrial receptivity that promotes embryo implantation.[26] Schachter et al[32] found a significantly higher rate of embryo implantation among women who adopted the dual-trigger regime, as compared to those with the HCG-only trigger. Schachter et al[32] believed that GnRH-a manifested a higher affinity for the GnRH receptor of the endometrium and therefore enhanced the proper post-receptor actions of implantation. Additionally, using in vitro cultivation of human extra-villous cytotrophoblasts and decidual stroma cells, Chou CS et al[33] confirmed that GnRH was able to activate urokinase type plasminogen activator, a critical component in mediating decidualization and trophoblast invasion. Hence, inclusion of GnRH-a as part of dual-trigger regime seems to play an important role in improving the implantation rate.

Moreover, recent evidences have proved that dual-trigger regime could facilitate luteal phase recruitment and consequently improve reproductive outcomes.[23] Humaidan P et al[13] demonstrated in a prospective randomized study that GnRH-a-only trigger regime associated with luteal phase deficiency, reduced clinical pregnancy rate and increased rate of early spontaneous abortion. Study from Shapiro et al[15] reported that, in comparison to GnRH-a-only trigger regime, pregnancy rate was remarkably improved when dual-trigger regime or enhanced luteal support was employed.

Most importantly, some studies have showed that the application of dual-trigger tended to reduce the incidence of ovarian hyper-stimulation syndrome and secure the ongoing pregnancy rate.[31,34] Unfortunately, evaluation of the impact of dual-trigger regime or HCG-only trigger regime on ovarian hyper-stimulation syndrome was infeasible because no case of ovarian hyper-stimulation syndrome was observed in our study. This phenomenon may be possibly attributed to the strict cycle-canceling policies and discreet controlled ovarian stimulation protocols during our clinical practices.

Our study has some strengths: Strict inclusion and exclusion criteria were applied and the baseline characteristics of the 2 groups were comparable, biases resulted from potential confounding factors were reduced as much as possible; In addition to β-HCG positivity and clinical pregnancy, we also included live birth, and early miscarriage and multiple pregnancy as important indicators for assessment of reproductive outcomes. Evaluation of the impact of different regimes of trigger drugs may therefore be more reliable.

5. Conclusion

Albeit the absence of significant difference, dual-trigger regime for oocyte maturation seems to associate with beneficial improvements on reproductive outcomes of PCOS couples undergoing controlled ovarian stimulation and intrauterine insemination. Our findings suggest that, instead of HCG-only trigger, dual-trigger regime might be an alternative option in treatment cycles of PCOS couples undergoing controlled ovarian stimulation and intrauterine insemination. Our study also argues for more applications of dual-trigger regime during ovulation induction in the field of assisted reproduction. However, interpretation of the result requires consideration of its retrospective design and relatively small sample size. Further prospective randomized studies with sufficient cycles are warranted to confirm such beneficial improvements.

Author contributions

Conceptualization: Bin Wang, Zhiling Li.
Funding acquisition: Zhiling Li.
Methodology: Bin Wang, Zhiling Li.
Supervision: Zhiling Li.
Validation: Bin Wang.
Writing – original draft: Bin Wang.
Writing – review & editing: Zhiling Li.

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