

A Comparative Study of the Effect of Novel Dual Trigger and Delayed HCG With Dual Trigger in Poor Responder Poseidon Group 4 Patients in Antagonist IVF Cycles

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Abstract

Background: Decreased Ovarian Reserve (DOR) is a significant challenge in infertility treatment. This study, which compared the effects of Novel Dual Trigger and Delayed Human Chorionic Gonadotropin (HCG), holds promise for improving IVF outcomes.

Materials and Methods: This was a randomized, double-blinded clinical trial on 90 infertile women. An antagonist regimen was used, which included approximately 300 units of gonadotropins, consisting of 150 units of Human menopausal gonadotropin (hMG) and 150 units of Synal-F. After administering a dose of Strotide injection followed by Decapeptyl and Ovitrelle injections, 12 hours later, a single HCG 5000-unit injection was administered, and 36 hours later, the puncture procedure was performed.

Results: Although the frequency of chemical pregnancy, Implantation rate, and ongoing pregnancy was higher in the Novel double trigger with delayed HCG group, and the frequency of zero oocytes and fetus was lower in this group, this difference was not statistically significant.

Conclusion: This study showed that using Novel Dual Trigger and Delayed HCG, compared to Dual Trigger, did not significantly differ in the number of oocytes, embryos, or secondary pregnancy outcomes. These findings suggest that the Novel Dual Trigger and Delayed HCG methods could be equally effective in improving IVF outcomes for poor responder patients, providing a potential alternative for ovarian stimulation in these cases and instilling optimism for the future of IVF treatments.

Keywords: Delayed hCG, dual trigger antagonist IVF cycles, dual trigger, novel dual trigger, poor responder

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BACKGROUND

Decreased Ovarian Reserve (DOR) is a common condition in reproductive age, with its occurrence in infertile women predicted to be about 10%.^[1] In sufferers with faded ovarian reserve, choosing the perfect protocol for ovarian stimulation to increase the range of mature oocytes and transferable embryos is one of the most critical challenges in IVF remedies.^[2,3]

Individuals with adverse ovarian reactions in ovulation induction cycles are classified into four categories in line with the Poseidon standards, with category four being patients over 35, antral follicle count (AFC) <5, and anti-Müllerian Hormone (AMH) <1.2.^[4-6] An inadequate reaction to controlled ovarian hyperstimulation (COH) is a substantial issue characterized by a deficiency in the number of oocytes recovered. This increases

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the risk of cancellations and decreased pregnancy rates.^[6] HCG is an alternative treatment to imitate the natural LH surge for oocyte maturation in IVF cycles.^[7] Using HCG as a cause for oocyte maturation in IVF cycles has been the choice over many years due to its molecular similarity to LH. However, it can raise the Ovarian Hyperstimulation Syndrome (OHSS) rate.^[8] Gonadotropin-freeing hormone (GnRH) agonists can act as a stimulatory factor and substitute for HCG.^[9] Because the method of follicular rupture and oocyte maturation is a time-bound technique and varies among ladies, using GnRH agonists can bring about beneficial effects, including elevated LH, greater mature oocytes, and decreased occurrence of OHSS.^[10,11] Dual trigger has been proven to enhance oocyte maturation and enhance embryo quality, pregnancy, and live birth rates in ovarian hypo-responsive cases.^[12] In regular responders, using GnRH-a and hCG together significantly improved oocyte maturation in patients with low maturation rates in hCG-triggered cycles.^[13]

Numerous modifications have been investigated across various fields to improve prognosis, including pretreatment with different medications, modified controlled ovarian stimulation (COS) strategies, and a variety of supplements. Nevertheless, these attempts have produced limited outcomes, highlighting the urgent need for further enhancement in IVF methodologies. According to the research findings, more investigation into the effectiveness of Dual Triggers seems necessary and promising. Our research advances this ongoing effort by examining the comparative effects of Novel Dual Triggers with delayed HCG and Dual Triggers in Responders undergoing antagonist IVF cycles.

MATERIALS AND METHODS

Study design

This study was conducted as a randomized, double-blind clinical trial at the Hazrat Maryam Infertility Center of Shahid Beheshti Hospital. The inclusion criteria for the study were women under 43 who belonged to Poseidon group 4 (over 35 years old, AMH less than 1.2, and AFC less than five). The exclusion criteria included BMI >30, diabetes, thyroid disorders, history of RIF (recurrent implantation failure) more than three times, history of recurrent miscarriages, azoospermia, severe endometriosis, and hydrosalpinx diagnosed via ultrasound. The required sample size for this study was calculated using the following formula.

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 [P_1(1-P_1) + P_2(1-P_2)]}{(P_1 - P_2)^2}$$

Z1, the confidence coefficient for 95% confidence, is 1.96.

Z2, the test power coefficient, is 0.8. Z1

Study protocol

After obtaining approval from the university's ethics committee, we randomly (using a random number generator)

and blindly (patients and the person responsible for analysis were blinded) assigned patients with poor ovarian response, those with AFC <5 or AMH less than 1.2, and those aged over 35 years (Poseidon group 4) into two groups. Both groups followed an antagonist regimen, which included approximately 300 units of gonadotropins, consisting of 150 units of HMG and 150 units of Synal-F. In the study group, when a follicle larger than 14 mm was observed, one ampoule of Strotide was administered. When two follicles greater than 17 mm were observed in the first group, 0.2 mg of Decapeptyl and one ampoule of Ovitrelle 250 were injected as a trigger. In the second group, 0.2 mg of Deacetyl, one ampoule of Ovitrelle, and 12 hours later, one ampoule of HCG 5,000 units was injected. Thirty-six hours later, all patients underwent a puncture procedure, and three days later, the number of embryos was determined. If conditions were suitable, an abdominal ultrasound guided embryo transfer. After the transfer, luteal phase support was provided with an intramuscular injection of 100 mg of progesterone. A BHCG test was conducted 2 weeks after the transfer, and if positive, it was considered a clinical pregnancy. A vaginal ultrasound was performed one week later to assess clinical pregnancy and check for the pregnancy sac, and if the pregnancy continued, further assessment of fetal heart rate (FHR) was conducted. Finally, the collected data, including age, BMI, AMH, the number of oocytes, number of MII oocytes, number of embryos, clinical pregnancy rates, and secondary outcomes such as clinical pregnancy and fetal heart rate detection, were analyzed using SPSS software version 24 with independent t-tests and Chi-square tests. The gynecology resident in charge of data collection had no extra assistance.

Ethics approval and consent to participate

This research was conducted in accordance with the Helsinki Declaration and received approval from the ethics committee at Isfahan University of Medical Science (IR.ARI.MUI.REC.1403.039), as well as from the Iranian Registry of Clinical Trials (IRCT20240610062068N2).

Statistical analysis

We analyzed the data using the Statistical Package for Social Sciences, version 16.0 (SPSS, USA). The continuous variables were expressed as mean $\pm$ SD, and the categorical values were expressed as percentages and were analyzed using the Chi-square test. An independent sample *t*-test was used to measure continuous variables with a normal distribution. We used the odds ratio to evaluate the association of outcomes across the groups. *P* value < 0.05 was considered statistically significant [Figure 1].

RESULTS

A comparison of age and baseline characteristics of 90 patients (45/group) who were enrolled in this study is outlined in Table 1. The mean ages of patients were 37.7 ± 3.31 and 38.537 ± 3.11 in the Dual trigger and Novel double trigger with delayed HCG groups, respectively, which were not significantly different [Table 1]. The comparison of baseline characteristics in Dual trigger and Novel double trigger with

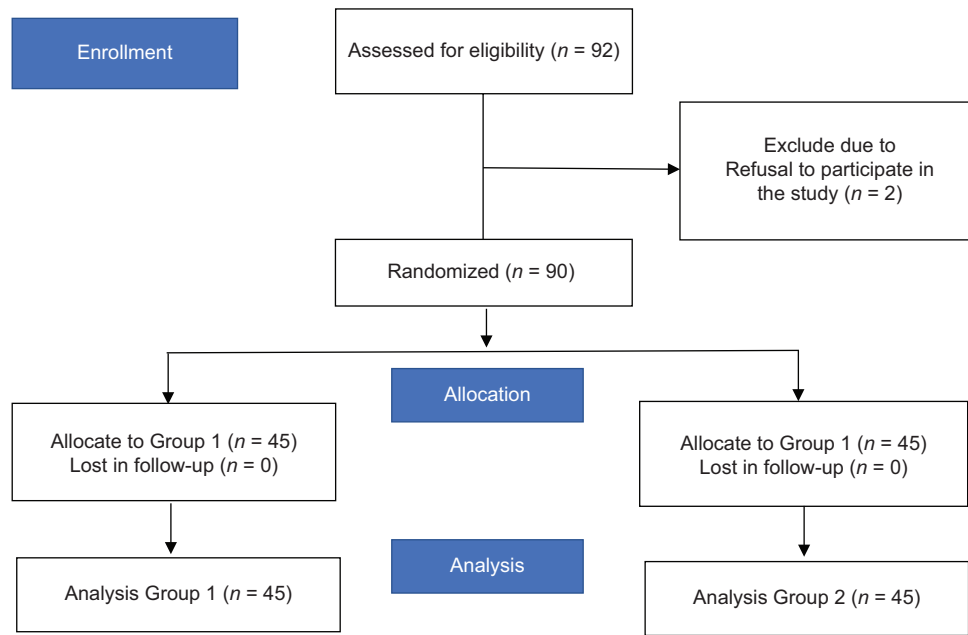


Figure 1: The study process is shown in the CONSORT flow diagram

Table 1: Comparison of baseline characteristics between two groups

	Dual trigger <i>n</i> =45		Novel double trigger with delayed HCG <i>n</i> =45		<i>P</i> *
	Mean	SD	Mean	SD	
Age	37.77	3.31	38.53	3.11	0.268
AMH	0.68	0.28	0.57	0.29	0.073
AFC	3.02	1.17	3.40	1.03	0.109
Days of stimulation	8.66	1.44	8.46	1.09	0.462
Estradiol peak	1024.00	706.64	1021.33	710.54	0.987
Gonadotropin dosage	2600.00	433.79	2540.00	329.87	0.462
Number of oocytes	2.20	1.57	2.46	1.47	0.409
Number of fetuses	1.06	0.83	1.28	0.92	0.234

*Statistical significance is based on an independent T-test

delayed HCG groups showed that the two groups were not significantly different in the mean of AMH, AFC, days of stimulation, estradiol peak, and gonadotropin dosage [Table 1]. Also, the mean number of oocytes and fetuses was not significantly different in the two groups [Table 1] [Figure 2].

The comparison of pregnancy outcomes in Dual trigger and Novel double trigger with delayed HCG groups is summarized in Table 2 and Figure 3. Although the frequency of chemical pregnancy, Implantation rate, and ongoing pregnancy was higher in the Novel double trigger with delayed HCG group, and the frequency of zero oocytes and fetus was lower in this group, this difference was not statistically significant. ($P > 0.05$, Chi-square test) [Table 2]. Also, the two groups had no significant difference in clinical pregnancy [Table 2] [Figure 3].

No cases were withdrawn from the study.

DISCUSSION

This study compared the effects of Novel Dual Trigger with Delayed HCG and Dual Trigger in Poor Responders. Our findings showed no significant differences between the two groups in AMH levels, antral follicle count (AFC), stimulation duration, peak estradiol levels, or gonadotropin doses. Although the number of oocytes, embryos, chemical pregnancy, implantation rate, and ongoing pregnancy rate were higher in the Novel Dual Trigger group, these differences were not statistically significant.

hCG does not exhibit FSH activity. Unlike hCG alone, the use of GnRH-a triggers increases endogenous LH and FSH levels, mimicking the gonadotropin surge seen during the mid-phase of a natural cycle.^[14] The LH pathway in the patient could be hindered for unknown reasons, while GnRH agonists might activate an alternate route.^[15] Another option is to prolong the interval between the ovulation trigger and oocyte retrieval. The LH surge begins 34–36 hours before follicular rupture in a regular cycle. To achieve optimal oocyte maturation, the LH levels must be maintained above a certain threshold for 14–27 hours.^[16] The oocyte maturation and follicular rupture processes depend on timing and can vary in duration for different individuals. Some patients are thought to require a more extended period for cumulus expansion to aid in releasing the egg from the follicular wall.^[17]

Previous retrospective analyses have indicated that the double trigger method (which involves the simultaneous administration of GnRH agonist and hCG for final oocyte maturation, occurring 40 and 34 hours before oocyte retrieval, respectively) markedly enhanced the quantity of cleaving embryos and resulted in a higher quality of embryos.^[18] Additional research has demonstrated that in patients with

a limited number of mature oocytes or suboptimal ovarian response, the dual trigger approach boosted the total number of retrieved oocytes, the proportion of mature oocytes (MII), and the number of transferable embryos.^[19,20] In the dual trigger technique, GnRH agonist and hCG are administered at the same time, 36 to 38 hours before oocyte retrieval. Several studies have indicated that this approach raises the number of high-quality embryos in patients with either diminished or normal ovarian response.^[21-23] Nonetheless, other research has yielded conflicting findings, with some indicating that this approach did not lead to a meaningful increase in pregnancy rates.^[24-26] A comparable review indicated that administering a dual injection (hCG combined with a GnRH agonist) in contrast to hCG alone did not significantly alter implantation rates, clinical pregnancy outcomes, or the count of high-quality

embryos. Consequently, this investigation implies that this strategy cannot be endorsed as a more efficient method for patients with DOR.^[27] It has been reported that dual therapy is a safe and effective approach for individuals with normal or high ovarian responses, as it not only decreases the risk of OHSS, but also supports maintaining pregnancy outcomes.^[28] One study found that doses of 250 and 500 micrograms of r-hCG did not differ in the number of mature oocytes collected, fertilization rates, or the number of embryos generated. Nonetheless, the higher dosage resulted in more oocytes retrieved per follicle. Although raising the dosage did not lead to a significant enhancement in pregnancy rates, the outcomes imply that higher doses of r-hCG might be advantageous for certain groups of women with poor ovarian

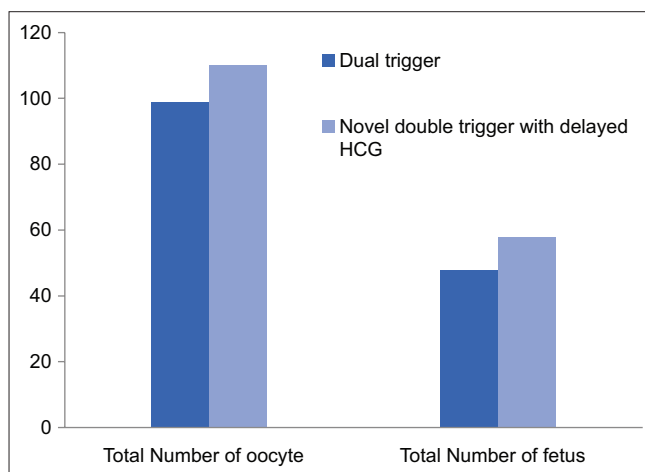


Figure 2: Comparison of the total number of oocytes and fetuses between two groups

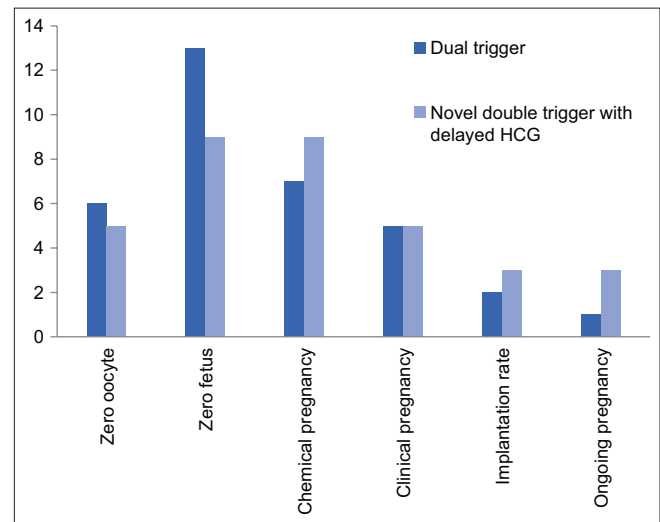


Figure 3: Comparison of pregnancy outcome between two groups

Table 2: Comparison of pregnancy outcomes between two groups

	Dual trigger <i>n</i> = 45		Novel double trigger with delayed HCG <i>n</i> = 45		<i>P</i> *
	Number	%	Number	%	
Zero oocyte	6	13.3	5	11.1	0.999
Zero fetus	13	28.9	9	20.0	0.462
Number of oocytes					
0	6	13.3	5	11.1	0.406
1	14	31.1	7	15.6	
2	5	11.1	11	24.4	
3	9	20.0	10	22.2	
4	7	15.6	8	17.8	
5	4	8.9	4	8.9	
Number of fetuses					
0	13	28.9	9	20.0	0.265
1	17	37.8	18	40.0	
2	14	31.1	15	33.3	
≥3	1	2.2	3	6.7	
Chemical pregnancy (Positive beta HCG test)	7	15.6	9	20.0	0.784
Clinical pregnancy (Gestational Sac in sonography)	5	11.1	5	11.1	1
Implantation rate (FHR+)	2	4.4	3	6.7	0.999
Ongoing pregnancy	1	2.2	3	6.7	0.616

*Statistical significance based on the Chi-square test

response.^[29] A limitation of this research is its small sample size, and further investigations involving larger sample sizes should be undertaken.

CONCLUSION

In patients classified as Poor Responder Poseidon group 4, Novel Dual Trigger may enhance the number of embryos, the chemical pregnancy rate, implantation success, and clinical pregnancy compared to Dual Trigger; however, these variations lacked statistical significance. Furthermore, there were no notable differences between the two groups regarding AMH levels, AFC, duration of stimulation, peak estradiol levels, or dosages of gonadotropins. This approach could improve IVF outcomes. More extensive studies are necessary to achieve more conclusive findings and evaluate this approach's effects on pregnancy and live birth rates.

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Conflicts of interest

There are no conflicts of interest.

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