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Comparing the Effectiveness of Standard, Dual, and Triple Triggering on Antagonist Cycles in IVF Outcomes for Patients with Poor Ovarian Response: A Randomized Controlled Trial

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ABSTRACT

Background: The trend of delaying parenthood and increasing age of women during their first pregnancy are significant factors contributing to the rise in infertility. Consequently, infertility clinics are witnessing an increase in the number of women exhibiting poor ovarian response (POR) and less than optimal reactions to conventional stimulation techniques. This study aimed to assess the impact of standard, dual, and triple triggering on antagonist cycles in relation to in vitro fertilization (IVF) outcomes among patients with POR.

Methods: In a clinical trial at Al-Zahra Educational Hospital, Tabriz, Iran, women with a POR were enrolled from March to September 2023. They were divided into three treatment groups, for triggering, Group I received human chorionic gonadotropin (hCG), Group II received hCG and Decapeptyl, and Group III received hCG, Decapeptyl, and menotropin (hMG). All treatments were administered via injection for stimulation, and oocyte retrieval was performed 36-40 hours post injection. The oocytes were retrieved and evaluated for maturation. Fertility rates were assessed at 24 h, and embryos were observed during the 48 h and 72 h intervals. All the embryos were freezing by vitrification technique. In the HRT cycles for endometrial preparation On the transfer day, endometrial thickness was measured, Two embryos in cleavage stage were transferred, and pregnancy was confirmed two weeks later using a clinical pregnancy test. All analyses were performed in SPSS software (version 22). A p-value of less than 0.05 was considered statistically significant.

Results: This study included 108 patients who were eligible for POR. Of these, 20 patients (18.51%) had positive pregnancy test. chemical pregnancy was confirmed in 11.11% of patients in both the I and III groups and in 33.33% of the patients in the II group. However, there were no significant differences in chemical pregnancy rates among the three groups ($P>0.05$). Age, BMI, AMH, duration of infertility, number of simulation cycles, dose of hMG administration, dose of FSH administration, and endometrial thickness on the day of transfer showed no significant differences among the three groups ($P>0.05$). The II group had significantly higher numbers of MII oocytes and total oocytes, as well as a higher number of embryos after both 24 h and 72 h than the other groups ($P<0.05$).

Conclusion: The study found no significant differences in positive pregnancy test results across the groups, possibly due to triptorelin's minimal impact on fertility rates. It suggests that embryo quality is influenced by the patient's condition and treatment process. The dual trigger method is recommended for POR patients as it led to higher embryo formation at 24 and 72 hours compared to the single and triple trigger groups. The study's small sample size calls for further research with larger samples, and future studies should focus on pregnancy results and fetal outcomes.

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INTRODUCTION

The task of effectively treating couples facing infertility is substantial because of the extensive variety of the underlying causes. It is important to note that in vitro fertilization (IVF) continues to yield lower success rates in women who do not respond optimally to controlled ovarian stimulation, a group often referred to as poor responders (1). The number of retrieved oocytes, which mirrors the ovarian reaction to ovarian stimulation, serves as a cornerstone of the IVF cycle. Furthermore, it independently influenced the treatment outcome (2). Patients exhibiting a poor ovarian response (POR) pose a significant hurdle in IVF.

KEYWORDS:
Decapeptyl, Human chorionic gonadotropin (hCG), Menotropin (hMG), In vitro fertilization (IVF), Poor ovarian response (POR).

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These individuals were less likely to produce an optimal number of oocytes after ovarian stimulation. Typically, the optimal response after ovarian stimulation is considered to be the production of 8-15 oocytes. This lower yield reduces the chance of conception. Furthermore, they face a high risk of cycle cancellation (3).

The global prevalence of POR after ovarian stimulation varies between 6% and 35% (4). The broad spectrum of incidence rates of POR can be attributed to the initial absence of a unified definition. This led to the formulation of the Bologna criteria by the European Society of Human Reproduction and Embryology (ESHRE). According to the Bologna criteria, POR is characterized by the presence of at least two of the following conditions: (A) a history of poor response, indicated by the retrieval of three or fewer oocytes following standard ovarian stimulation; (B) advanced maternal age, specifically over 40 years; or (C) an abnormal ovarian reserve test, marked by an antral follicle count (AFC) of fewer than 5-7 follicles and/or an anti-Mullerian hormone (AMH) level of less than 1.1 ng/mL (5). The Bologna criteria have been criticized for not considering the effect of age on oocyte quality and success rates, resulting in a diverse POR group (6). The criteria also lack guidelines for clinical decisions, counseling, and POR patient management. Accurate identification of at-risk patients is crucial for personalized counseling and intensive infertility treatments. Hence, assessing ovarian response potential before enrolling in an IVF program is vital (7).

The various protocols have been explored to enhance IVF outcomes in POR patients. These include pretreatment with oral Estradiol, subcutaneous human chorionic gonadotropin (hCG) injections, skin application of androgel, adjunctive treatment with luteinizing hormone (LH), clomiphene citrate, aromatase inhibitors, high-dose follicle-stimulating hormone (FSH), and the use of gonadotropin-releasing hormone (GnRH) agonists and antagonists (8). Ovarian triggering with GnRH or hCG analogs has been the focus of most studies because of their superior response. GnRH agonists , initially stimulating LH and FSH secretion in mid cycle that can potentiate hCG effect (4, 9). However, their routine use has been linked to lower implantation rates, in fresh embryo transfer cycles. possibly due to an inadequate luteal phase and poor endometrial receptivity (10).

Studies have shown that the simultaneous use of GnRH and hCG agonists to ovulation triggering in women with poor ovarian reserve yields better and more consistent results. hCG is often used as a surrogate for LH, which is necessary for final oocyte maturation in an IVF cycle before oocyte retrieval (11). Dual trigger has been found to increase the number of retrieved eggs and metaphase II eggs, total number of embryos, and number of transferred embryos. Therefore, it has been suggested to improve egg quality and follicular maturation in patients with POR (12). However, in 2019, the ESHRE stated that dual trigger was not recommended for norm responders. There are no clear guidelines on the use of dual trigger in patients with POR, indicating the need for more controlled trials to evaluate its effectiveness in this group (13).

Given the importance of ovulation stimulation cycles and the need for mature eggs, coupled with the risks of ovarian hyperstimulation syndrome and limited experience with dual trigger, this study aimed to evaluate the effectiveness of standard, dual, and triple triggering on antagonist cycles in IVF outcomes in patients with POR.

MATERIAL AND METHODS

In this clinical trial, women with POR who were referred to the infertility department of Al-Zahra Educational Hospital, Tabriz, Iran, between March 2023 and September 2023, were enrolled as participants. The study included women who had been diagnosed with POR according to the Bologna criteria, had an indication for IVF, were aged between 24 and 38 years, had a body mass index (BMI) between 19 and 27, and had a spouse with a normal sperm sample according to the world health organization (WHO) criteria. Patients with uterine anomalies, severe male factor infertility, severe endometriosis (grade IV or III), drug sensitivity, medical conditions such as hypothyroidism, hyperprolactinemia, or those who did not consent to participate in the experiment were excluded from the study.

In this study, we utilized the block randomization method with SAS statistical analysis software. The total number of blocks was 36, with each block containing three individuals. The sequence within the blocks determines the order of entry into the study groups (I, II, and III). Based on the average number of high-quality embryos obtained from previous studies (14) using both the dual and single methods and considering a clinically significant difference of one for the average number of quality embryos when comparing methods and a 10% rate of oocyte maturation, the sample size was calculated. Considering a type I error of 5% and a power of 80%, the sample size was estimated to be at least 36 individuals for each group, totaling 108 individuals (Figure 1).

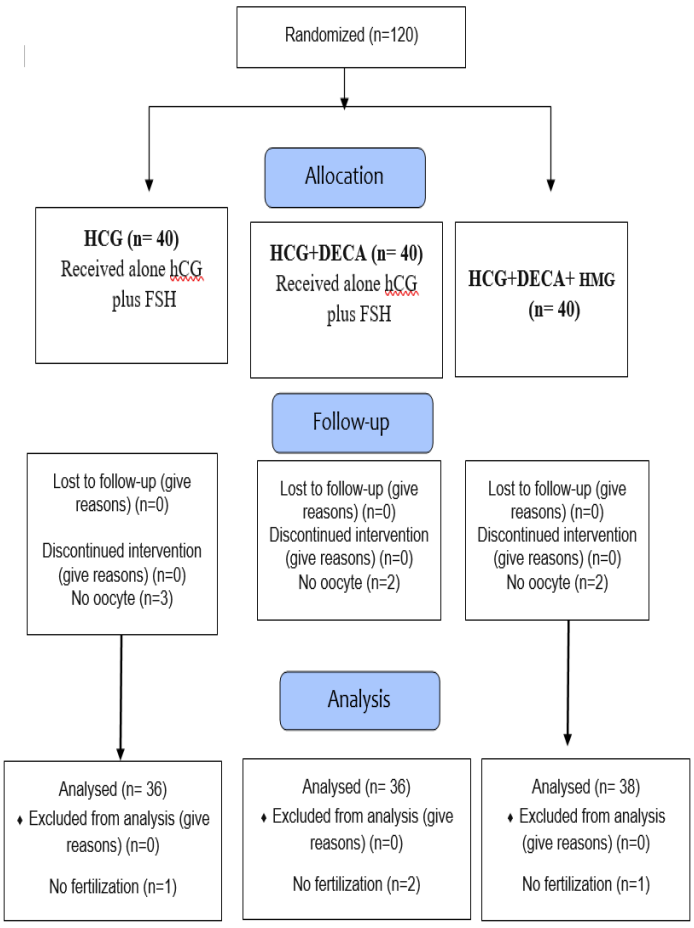

Figure1. CONSORT flow diagram of the trial

Stimulation protocol

Initially, all patients with POR were treated with an antagonist protocol. This involved controlled ovarian stimulation using letrozole 2.5 mg twice a day, starting from the 2nd or 3rd day of the cycle. Two days later, recombinant FSH (The Cinal F, CinnaGen company product) was administered at a daily dose of 225-300 units. From the 7th to the 8th day of the cycle, daily injections of human menopausal gonadotropin (hMG, PD homog a product of poyesh Daru company, 75U) ampoules were initiated. On the 7th or 8th day of the cycle, follicle size was assessed by using vaginal ultrasound. If the size of follicle reached 13-14 mm, treatment with an antagonist (cetrorelix, CinnaGen company product 0.25 mg) was started to prevent the premature LH surge. The serum progesterone levels of the subjects were measured to determine whether a premature LH surge had occurred. and it should be less than 1.5 ng/ml. When the diameter of the follicles reached 17-18 mm, triggering for oocyte maturation was performed. Therefore, Patients with POR were divided into three groups for triggering. Group I received hCG (PD homog product of Poyesh Daru company 5000U) (hCG group), Group II received hCG and decapeptyl simultaneously (Varian farmed company product 0.2 mg) (hCG + DECA group), and Group III received hCG, decapeptyl, and menotropin (hCG + DECA + hMG group) via injection simultaneously for triggering. All subjects underwent oocyte retrieval at 36-40 hours post-injection. Oocyte retrieval was performed under the guidance of vaginal ultrasound and light sedation with propofol using a Wallace Single Lumen Needle, 17g. An embryologist evaluated the number of retrieved eggs and their maturation levels in the three test groups. Depending on the stage of maturation the eggs were divided into three phases (metaphase of MI and MII or germinal vesicle). The M2 oocytes were fertilized under ICSI method(intracellular cytoplasmic sperm injection), and the number of the embryos were checked and recorded (15). Furthermore, the eggs, were examined to ascertain the fertility rate at three distinct intervals: 24, 48, and 72 h. The embryos were frozen by vitrification technique and utilized for the next transfer hormone replacement therapy (HRT) was used to prepare the endometrium in women. we use Estradiol valerat 6 mg daily to prepare the endometrium and the endometrium was followed by using trans vaginal sonography, and when the endometrial thickness was more than 8 mm, we added IM progesterone (progesterone in oil) with 100 mg daily dose was started and two cleavage stage embryos were transferred at four days of progesterone. Transferring is under abdominal sonography guidance is performed and the endometrial thickness was measured by transvaginal sonography and documented. All patients evaluated two weeks after embryo transfer by serum B-HCG test to confirm pregnancy.

Statistical analysis

After gathering data from all of patient's descriptive statistics were presented as means, standard deviations, and/or percentages. Initially, the Kolmogorov-Smirnov test was utilized to verify the normality of the data distribution. For the comparison of quantitative variables among the three groups, the one-way analysis of variance was employed if the data were normal. Conversely, the Kruskal-Wallis test was used in case of non-parametric data. Additionally, the Chi-square test was applied to compare qualitative and categorized variables. All statistical analyses were conducted using SPSS software (version 21, Chicago, IL, USA), and a p-value of less than 0.05 was deemed to indicate statistical significance.

Ethical considerations

The study protocol underwent review and received approval from the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran, as part of its endorsement of the research project (No: IR.TBZMED.REC.1402.287). Furthermore, the study was officially registered with the Iranian Registry for Clinical Trials (code: IRCT20230702058644N1).

RESULTS

The study involved 108 patients who were eligible for POR. The demographic and baseline information of study population are presented in Table 1. Statistical analysis of the demographic information for the three groups revealed no significant differences in age, BMI, AMH, duration of infertility, and history of previous simulation cycles (P>0.05). This suggests that three groups were comparable.

Table 1. Demographic and baseline information of study population (Mean ± SD)

Variables	hCG (n=36)	hCG+DECA (n=36)	hCG+DECA+hMG (n=36)	p-value*
Age (year)	33.31±6.01	33.78±4.84	36.11±4.09	0.068
BMI (kg/m^2)	22.70±5.23	23.10±5.68	23.50±6.12	0.919
AMH (ng/mL)	1.05±0.50	1.03±0.18	0.97±0.13	0.492
Infertility duration (year)	5.42±3.32	5.81±3.97	4.38±3.26	0.069
Count of simulation cycle	1.18±0.78	1.72±0.77	1.76±0.78	0.919
AMH: anti-Mullerian hormone, BMI: body mass index * For comparison between the groups Kruskal–Wallis				

The mean ± SD of total hMG ampuls were used in three different groups: the group I had a 10.66 ± 2.74, the group II had used 10.86 ± 5.46 and the group III had used 10.07 ± 2.66 ampuls. Statistical analysis revealed no significant differences in total hMG should which used among the three groups (P=0.469). Each patient was administered total FSH in a range of 2500-3000 units, per cycle, and on average, hMG was used at a rate of 750 units per cycle for each patient. As we used FET cycles after endometrial preparation, On the day of transfer, the mean ± SD of endometrial thickness was 9.54 ± 0.54 mm for the group I, 9.46±0.85 mm for the group II, and 9.31±0.58 mm for the group III. Statistical analysis indicated no significant differences in endometrial thickness among the three groups (P=0.486). Consequently, all three groups were comparable in terms of

endometrial thickness on the day of the transfer. The total oocytes retrieved and embryos count are presented in Table 2. According to the data obtained, there were no significant differences among the three groups in the number of germinal vesicle-stage oocytes (GV− oocytes) and mature I (MI) (P>0.05). However, the number of MII oocytes (P=0.015) and total number of oocytes (P=0.001) were significantly higher in the group II than in the other two groups. Additionally, the number of embryos in the group II was significantly higher than that in the other two groups after both 24 h (P=0.011) and 72 h (P=0.005) respectively. However, after 48 h the number of embryos in the group II and I was nearly the same and significantly exceeded that of the group III (P=0.037).

Table 2: The numbers of oocytes and embryos by study groups

Variables		hCG (n=36)	hCG+DECA (n=36)	hCG+DECA+hMG (n=36)	p-value*
Numbers of oocytes (Mean ± SD)	GV	1.3±1.2	1.7±1.4	1.3±1.5	0.314
	MI	1.0±1.3	2.2±1.7	1.8±1.7	0.216
	MII	3.3±1.9	4.1±2.5	2.6±2.1	0.015
	Total	6.1±2.4	7.9±3.03	5.9±2.7	0.001
The numbers of embryos (Mean ± SD)	After 24 h	3.5±1.8	4.6±4.9	3.3±2.3	0.011
	After 48 h	3.8±1.6	3.8±2.07	2.8±2.1	0.037
	After 72 h	2.4±1.3	3.4±1.9	2.2±1.5	0.005
GV: Germinal vesicle-stage oocytes, M1oocyte without polar body, M2: oocyte in metaphase 2 stage * **Kruskal-Wallis**					

Overall, of the 108 patients across all three groups, 20 (18.51%) tested positive for pregnancy. Statistical analysis showed no significant differences in chemical pregnancy rates among the three groups (P=0.912). Due to time limitation, we could not follow the pregnancy period of patients (Table 3).

Table 3: The results of chemical pregnancy

Variables		hCG (n=36)	hCG+DECA (n=36)	hCG+DECA+hMG (n=36)	p-value*
Chemical pregnancy	Positive	7	6	7	0.912
	Negative	29	30	29	

*Chi-square(x2)

DISCUSSION

Dual triggering in IVF cycles is highlighted not only in normal responders but also in patients with POR, in those with a large number of immature oocytes in the previous cycle, and in those who have shown suboptimal responses to triggering with GnRH or hCG analogs alone (16). However, owing to the diverse and sometimes contradictory results concerning the effectiveness of this type of triggering, the current study examined the effect of hCG triggering, both with dual triggering of hCG + DECA and triple triggering of hCG + DECA + hMG. The results of this study indicate that 18.51% chemical pregnancy rate across all three groups tested. The three groups were similar based on age, BMI, AMH, duration of infertility, number of simulation cycles, hMG administration, rate of FSH administration, and endometrial thickness on the day of the transfer. The number of MII oocytes and total number of oocytes were significantly higher in the group II than in the other two groups. Additionally, the number of embryos in the group II significantly exceeded those in the other two groups after 24 and 72 h. However, after 48 h, the number of embryos in the group of II and I significantly surpassed that in the group III. Statistical analysis revealed no significant differences in chemical pregnancy rates among the three groups, it related to asynchronous embryo development.

This study indicates that the use of GnRH agonist for the final maturation and ovulation of oocytes is linked to a higher prevalence of MII oocytes, in contrast to the commonly used hCG trigger. The GnRH agonist trigger prompts surges in both LH and FSH, mirroring the natural mid-cycle gonadotropin surge, thereby making it a more physiological approach than the hCG trigger (17). It has been postulated in various studies that the elevated occurrence of MII oocytes in relation to the GnRH agonist trigger is due to this FSH surge (18). In a retrospective study conducted by Şükür et al., the number of high-quality embryos in cycles utilizing a dual trigger was relatively high. Interestingly, this number was found to be analogous to the number of retrieved oocytes or MII oocytes retrieved (19). In the research conducted by Dakhly et al., growth hormone was added to the microflare and antagonist protocols. The study found that while growth hormone supplementation did enhance several factors such as mean E2 levels on the day of hCG administration, endometrial thickness, the number of collected oocytes, MII oocytes, fertilized oocytes, transferred embryos, cryopreserved embryos, and cycles with cryopreserved embryos, it did not lead to an improvement in the clinical pregnancy rate and live birth rate (20). The outcomes of our research align with those of prior studies, which have reported comparable pregnancy rates when using a dual trigger as opposed to an hCG trigger alone, during aGnRH antagonist cycle. The current study showed that the number of MII oocytes and total number of oocytes were significantly higher in the group II than in the other two groups. The studies found an increase in the number of collected oocytes and MII oocytes, suggesting that hCG improves ovarian response to gonadotropin stimulation. hCG also seems to enhance the quality of oocytes and embryos, leading to more fertilization and embryos available for transfer and cryopreservation (21, 22). Sood et al., found that while hCG appears to improve early clinical parameters and shorten the days of stimulation, there is no evidence to suggest an increased chance of live birth for

women receiving hCG as a supplement for ovulation induction (23). This finding contradicts a Cochrane review that reported a significant improvement in the live birth rate with the use of hCG (24).). In another study, Chen et al. found no significant difference in the number of mature or fertilized oocytes retrieved between hCG alone triggering and dual triggering with hCG and GnRH agonists. However, the clinical pregnancy rate with dual triggering was significantly higher than that with hCG-alone administration alone. This suggests that the use of GnRH agonists in combination with hCG to trigger final oocyte maturation can lead to comparable or significantly improved outcomes compared to using hCG alone (25). Inferior pregnancy outcomes have been observed for IVF cycles triggered by GnRH agonists compared with those triggered by hCG in GnRH antagonist-based protocols. The stronger binding affinity of hCG, along with GnRH agonists, to GnRH receptors has led to the hypothesis that hCG can displace the antagonist from the receptor in the endometrium, potentially improving implantation (26). This could be due to a detrimental effect on endometrial receptivity secondary to defective corpus luteum function or early luteolysis resulting from the shorter LH surge induced by GnRH agonists. Co-administration of hCG is believed to restore corpus luteum function and improve conception rates with GnRH agonist triggering. This is supported by meta-analysis results showing higher pregnancy rates in completed cycles with dual triggering. However, retrospective studies, which are considered less reliable due to potential bias, have consistently demonstrated significantly higher rates of clinical pregnancy and live birth with adjuvant hCG to GnRHa triggering (27).

Addressing the insufficiency of the luteal phase, which is a consequence of the sole use of GnRHa trigger, has been a pivotal aspect in achieving final oocyte maturation. This has led to the introduction of the dual trigger approach (28). In a retrospective cohort study conducted by Dong et al., the laboratory and clinical outcomes of IVF/ICSI were assessed by comparing dual-trigger (using GnRH agonist and hCG) versus hCG trigger alone in GnRH antagonist cycles. Their findings suggested a marginal superiority of the dual trigger over the hCG trigger alone in terms of the quantity of retrieved oocytes and the quality of embryos. However, these differences were not statistically significant. Furthermore, the rate of normal fertilization was slightly elevated in the dual-trigger group compared to the hCG trigger-alone group, but these differences were also not statistically significant (29). Similarly, a previous study indicated that in patients with a history of retrieving more than 25% of immature oocytes in prior IVF cycles, the application of a dual trigger for oocyte maturation resulted in a notably higher quantity of mature oocyte retrieval compared to the use of hCG alone (30). The current study revealed more M2 oocytes number retrieved within group II in comparison with other groups. Another research study illustrated that for patients who had previously experienced a high incidence of immature oocytes in past IVF cycles, the implementation of a dual trigger resulted in a significantly increased count of mature oocytes and transferred embryos. Furthermore, there was an enhancement in the number of top-quality embryos (31).

In a particular research investigation, an evaluation was conducted on 156 antagonist cycles. The study revealed that ovidrel (recombinant hCG) was used in 51 patients, whereas decapeptyl was employed in 105 patients. Despite these findings, the study did not offer detailed results concerning the application of hCG and decapeptyl in patients who responded poorly (32). Similar to our study, a study was conducted on patients with a poor response and a history of fertilization failure. The study included three groups: one triggered with hCG, another with hCG and GnRHa, and a third with hCG, GnRHa, and hMG. The triple combination group showed a significant increase in the number of MII oocytes, fertilization, and D5 embryo transfer (33). In another study, Duarte-Filho et al. observed that the combination of follitropin delta and menotropin resulted in elevated estradiol levels on trigger day, along with an increase in both the quantity and quality of blastocysts. However, they found no significant differences in the rates of pregnancy, implantation, miscarriage, and live births following initial embryo transfer (34). However, the results of the current study show that the number of MII oocytes and embryos significantly increased in the hCG and DECA groups compared to the other two groups. The potential for discrepancies in the findings might be attributed to the study design, which utilized a retrospective historical control group. Additionally, the intervention group exhibited a lower number of antral follicles than the control group. This factor is particularly significant in studies focusing on ovarian stimulation and responses. The perceived advantage of integrating menotropin for ovarian response is thought to be not solely due to its FSH activity but also its inherent LH activity. It has been demonstrated that supplementing FSH with LH can enhance ovarian response in women with diminished ovarian reserve, seemingly through a mechanism involving an LH-triggered enhancement in FSH responsiveness (35). Further research is required to substantiate this hypothesis. The findings of this study revealed no significant differences in the parameters of positive pregnancy tests across the groups studied. This could be attributed to the negligible impact of triptorelin on fertility rates. The quality of embryos is influenced by the patient's inherent condition and the treatment process during stimulation and ovulation. Another factor to consider is the small sample size examined, which warrants further investigation with a larger sample size in future studies. For developing study by using a time-lapse microscope, the effects of different drug protocols can be observed. However, due to time constraints, it was not possible to track the pregnancy outcomes of individuals. Future studies are recommended to investigate pregnancy results and fetal outcomes. Given that the formation of embryos at 24 and 72 hours was higher in the double trigger group compared to the single and triple trigger groups, it is suggested that the double trigger should be considered the preferred method for POR patients. Conclusion The study found no significant differences in positive pregnancy test parameters across the groups, possibly because of the minimal impact of triptorelin on fertility rates. Embryo quality is influenced by the patient's condition and the treatment process. While the effects of different drug protocols on embryos can be observed, tracking individual pregnancy outcomes was not possible due to time constraints. The study suggests using the double trigger method for POR patients, as it resulted in higher embryo formation at 24 and 72 h compared to the single and triple trigger groups. The small sample size calls for further research with larger samples, which also suggests that future studies should investigate pregnancy results and fetal outcomes.

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