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Original Research Article

Impact of trigger protocol and embryo transfer type on IVF pregnancy outcomes: a single-center, retrospective, observational study

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ABSTRACT

Background: Infertility, defined as the inability to conceive after 12 months of regular, unprotected intercourse, affects over 186 million people globally, with a significant burden in developing countries. Assisted reproductive technology (ART), particularly in vitro fertilization (IVF), has evolved as a key intervention for infertility, with advancements such as ovulation triggers playing a crucial role. This study investigates the effectiveness of single versus dual trigger methods between fresh and frozen embryo transfers and their impact on IVF outcomes.

Methods: This observational study was conducted at Srushti Fertility Centre and Women's Hospital from 2022 to 2023. A consecutive sampling of 140 participants undergoing ART was performed, categorizing them into Single Trigger (n=48) and Dual Trigger (n=92) groups. Key parameters such as age, hormonal levels (AMH, FSH, LH), endometrial thickness, and serum progesterone levels were measured and analyzed in relation to IVF outcomes.

Results: The study found that optimal endometrial thickness (8-9 mm, $p=0.031$) and low progesterone levels (<0.5 ng/mL, $p=0.003$) were significantly associated with positive IVF outcomes. Fresh transfers with low progesterone levels ($p=0.016$) and dual trigger methods produced better embryo development. However, IVF outcomes did not differ significantly between fresh and frozen embryo transfers ($p=0.276$).

Conclusions: The dual trigger method, especially with frozen transfers, enhances embryo quality and pregnancy rates. However, overall differences between frozen and fresh transfers were not statistically significant, emphasizing individualized hormonal management for better outcomes. This study highlights the importance of optimizing endometrial thickness and managing progesterone levels to improve pregnancy success in ART.

Keywords: Dual vs single trigger, Fresh & frozen embryo transfers, IVF outcomes

INTRODUCTION

Infertility is a condition affecting the male or female reproductive system, characterized by the inability to conceive after 12 months or more of regular, unprotected sexual activity.¹ Globally, over 186 million people are affected by infertility, with the majority living in developing countries.² In developing countries, the prevalence of infertility among women of reproductive age is estimated to affect one in every four couples.³ The three primary factors influencing the natural likelihood of conception are the duration of unintended non-conception,

the age of the female partner, and infertility due to medical conditions.¹⁻⁴ Additionally, a decline in semen quality, exposure to endocrine-disrupting chemicals, and consanguinity are other contributing factors.⁵ Infertility treatments often include ovulation induction, which involves the use of medications to stimulate ovulation, and ovarian stimulation, aimed at producing multiple mature ovarian follicles. Fertilization can be achieved either through follicular monitoring with or without intrauterine insemination (IUI) during ovulation. Alternatively, mature oocytes can be directly retrieved from the ovary using an ultrasound-guided needle for fertilization, a process

known as in vitro fertilization (IVF).⁶ Since its introduction, IVF technology has advanced and become more widely accessible around the globe.⁷ Since the pioneering days of in vitro fertilization (IVF), human chorionic gonadotropin (hCG) has been employed as a substitute for the natural mid-cycle luteinizing hormone (LH) surge.⁸ Administering hCG leads to a prolonged luteotrophic effect and elevated levels of estradiol and progesterone beyond normal physiological ranges. This sustained luteotrophic effect may contribute to the development of ovarian hyperstimulation syndrome (OHSS).⁹ More than 30 years ago, Nakano et al, described that a single injection of a gonadotropin-releasing hormone agonist (GnRH-a) could trigger an endogenous LH surge sufficient for ovulation induction.¹⁰ Unfortunately, this finding was soon underestimated, as GnRH-a rapidly became the first-line treatment to prevent premature luteinization, which precluded its use for inducing final follicular maturation.

When third-generation GnRH antagonists were introduced in the 1990s for ovarian stimulation protocols, it became possible to trigger final oocyte maturation and ovulation with a single bolus of GnRH-a as an alternative to hCG.¹¹ Although some studies have suggested an increase in the percentage of mature oocytes retrieved with GnRH-a compared to HCG, it has been found that triggering ovulation with GnRH agonist leads to a suboptimal luteal phase.^{12,13} The term "dual trigger" was first defined as the combination of a GnRH agonist and a low dose of hCG for triggering final oocyte maturation and preventing ovarian hyperstimulation syndrome (OHSS) in GnRH antagonist cycles.¹⁴

Lin et al, conducted a retrospective study involving normal responders undergoing IVF with a GnRH antagonist protocol. They demonstrated significant improvements in the total number of retrieved oocytes, the number of mature (MII) oocytes, and rates of embryo implantation, clinical pregnancy, ongoing pregnancy, and live birth when the dual trigger regimen was used.¹⁵ Similarly, Lu et al. presented a retrospective analysis of medical records where final oocyte maturation was triggered using either GnRH alone (Decapeptyl 0.1–0.2 mg) or in combination with hCG (1,000, 2,000, or 5,000 IU). They concluded that employing a dual trigger with a low dose of hCG (1,000 IU) as an adjunct to GnRH-a significantly improved the oocyte retrieval rate in suboptimal responders.¹⁶

Despite advancements in IVF technology and trigger methods, optimizing assisted reproductive technology (ART) outcomes remains a challenge. The effectiveness of different strategies, such as single versus dual trigger methods, varies and may influence key factors such as oocyte retrieval rates, embryo development, and pregnancy success. This study aims to determine the most effective strategies for enhancing ART success by comparing various trigger methods and evaluating their impact on oocyte and embryo development, hormonal profiles, and overall IVF outcomes.

Objectives

To assess the impact of trigger protocol (Single vs. Dual) and embryo transfer type (Fresh vs. Frozen) on IVF outcomes in ART patients. To assess the influence of endometrial thickness, and serum progesterone levels on IVF outcomes.

METHODS

This observational study was conducted at Srushti Fertility Centre and Women's Hospital in Chennai, Tamil Nadu, India, from January 2023 to February 2024. Consecutive sampling method was employed to select 140 participants undergoing assisted reproductive technology (ART), based on specific inclusion criteria aligned with the research objectives. The participants were categorized into two groups according to the trigger method used: single trigger (n=48) and dual trigger (n=92). Various parameters were assessed, including age, hormonal levels (AMH, FSH, LH), endometrial thickness, serum progesterone levels, and IVF outcomes. Hormonal assays were conducted to measure AMH, FSH, and LH, while endometrial thickness and serum progesterone levels were evaluated through ultrasound and blood tests, respectively.

The inclusion criteria comprised participants aged less than 35 years, with normal semen parameters, ovarian reserve greater than 1.50, and antral follicle count (AFC) greater than 8. Exclusion criteria included participants older than 35 years, severe male infertility, AMH less than 1.5, AFC less than 3, previous IVF failure (recurrent implantation failure), and recurrent pregnancy loss. The study also examined the efficacy of different drug regimens, such as HCG, Decapeptyl, and their combinations, in achieving positive IVF outcomes.

Ovarian stimulation protocol

All patients commenced controlled ovarian hyperstimulation (COH) on day 2 or 3 of their menstrual cycle. The initial treatment involved a daily administration of either highly purified human menopausal gonadotropin (hMG, Materna HMG 150 IU, Emcure Pharmaceuticals Ltd, India) or recombinant FSH (rFSH, Gonal-F 150 IU, Merck Serono, S.P.A, Italy) administered subcutaneously and intramuscularly for a duration of 10–12 days. The treatment continued until the final oocyte maturation injection was administered.

The starting dosage was tailored based on the patient's age, antral follicle count (AFC), body mass index (BMI), serum FSH and AMH levels on days 2–3, as well as the patient's previous response to COH. Dosage adjustments were made according to serum estradiol levels and follicular growth, monitored through serial transvaginal ultrasound. When at least one follicle reached 14 mm in diameter, or upon the development of ten follicles, patients also began a daily subcutaneous injection of GnRH antagonist cetrorelix (Cetrotide, Merck Serono, S.P.A., Italy) at a

dosage of 0.25 mg, administered alongside the hMG or FSH. The GnRH antagonist continued until the trigger day for final oocyte maturation with periodic follicular tracking and serum estradiol levels. Final oocyte maturation was triggered when at least two leading follicles reached 18 mm in diameter. The trigger was administered as follows.

Group A (dual trigger)

A single dose of recombinant HCG (Ovitrelle 250 mcg, Merck Serono, S.P.A., Italy) combined with 0.2 mg of triptorelin acetate (Decapeptyl, Ferring Pharmaceuticals, Germany).

Group B (single trigger)

A single dose of recombinant HCG (Ovitrelle 250 mcg, Merck Serono, S.P.A., Italy) alone.

These trigger protocols aimed to induce an endogenous LH surge coinciding with the LH-like effect of standard hCG administration, which occurred 34–36 hours before oocyte retrieval. Serum progesterone levels were measured on the day of the trigger. Oocyte retrieval was performed under conscious sedation, and both oocyte retrieval and embryo transfer procedures were conducted exclusively by the senior supervisor.

ICSI & embryo culture

The oocytes were screened and incubated for 3 hours. Semen preparation done by density gradient method. ICSI was done by senior embryologist. The injected oocytes were incubated and cultured to day 5 post fertilization. The viable embryos were cultured to the blastocyst stage and transferred on P5 in a fresh transfer and for those women whose serum progesterone was > 1.5 ng/dl the viable embryos were cryopreserved as 2-3 blastocysts in one cryolock.

Endometrial preparation

Fresh Embryo Transfer: Following oocyte pickup (OPU), endometrial preparation began with oral estradiol (Progynova 2 mg twice daily) and vaginal progesterone (Gestofit 400 mg twice daily). Embryo transfer was performed either on day 3 or day 5 post-OPU, with luteal phase support continuing in the same regimen.

Frozen Embryo Transfer: Baseline ultrasound scanning on day 2 initiated hormone replacement therapy with oral estradiol (Progynova 2 mg twice daily) up to day 8. From day 9, serial ultrasound monitoring was performed to assess endometrial thickness (targeting ≥ 8 mm), along with vaginal progesterone (400 mg twice daily) for five days. Cleavage-stage embryos (day 3) were transferred after 72 hours of progesterone, and blastocyst-stage embryos were transferred after 120 hours of progesterone.

The luteal support was continued until the 10th week of gestation after the establishment of luteo placental shift for all positive pregnancies.

Luteal phase support and confirmation of pregnancy

The luteal phase support included daily vaginal supplementation of progesterone 400 mg (C.Gestofit 400 mg OD, A; embic pharmaceutical) and 8% Crinone gel, Merck Serono, UK) starting on the day of oocyte retrieval (P0) along with Progynova (Estradiol valerate 2 mg twice daily) Serum β -hCG was measured 14 days after embryo transfer, with initial value of above 50 IU/ml with doubling of Beta HCG was considered being a positive pregnancy. The luteal support was continued until the 10th week of gestation after the establishment of luteal placental shift for all positive pregnancies.

Statistical analysis

The statistical analysis used descriptive statistics to summarize baseline characteristics. Chi-square tests evaluated associations between categorical variables, such as endometrial thickness and IVF outcomes, and differences between frozen and fresh embryo transfers. Receiver Operating Characteristic (ROC) curves assessed the predictive value of progesterone levels for IVF outcomes. Statistical significance was determined with p-values, with values less than 0.05 considered significant.

RESULTS

In Table 1, the baseline characteristics of the study population are summarized. The participants have a mean age of 31 years, with a standard deviation of 4.6 years. The mean basal endometrial thickness is 9.14 mm, with a standard deviation of 1.5 mm. The average baseline serum progesterone level is 0.56 ng/ml, with a standard deviation of 0.53 ng/ml. The mean basal Anti-Müllerian Hormone (AMH) level is 2.7 ng/ml, with a standard deviation of 2.3 ng/ml. Basal Follicle-stimulating hormone (FSH) levels have a mean of 6.4 mIU/ml, with a standard deviation of 2.45 mIU/ml, while luteinizing hormone (LH) basal levels average 3.7 mIU/ml, with a standard deviation of 1.8 mIU/ml.

The table 2, details the association between endometrial thickness and IVF outcomes. For endometrial thickness of 8-9mm, there are 23(39%) positive outcomes and 16(19.7%) negative outcomes. In contrast, thicknesses <7mm and >10mm show fewer positive outcomes, with 6 (10.1%) in each respectively, and higher negative outcomes, with 9 (11.1%) and 17 (21%) respectively. For thicknesses 7-8 mm and 9-10 mm, positive outcomes are 4 (6.7%) and 20 (33.8%), while negative outcomes are 15 (18.5%) and 24 (29.6%). The p-value of 0.031 signifies that these differences in IVF outcomes across varying endometrial thicknesses are statistically significant, highlighting the influence of endometrial thickness on IVF outcomes.

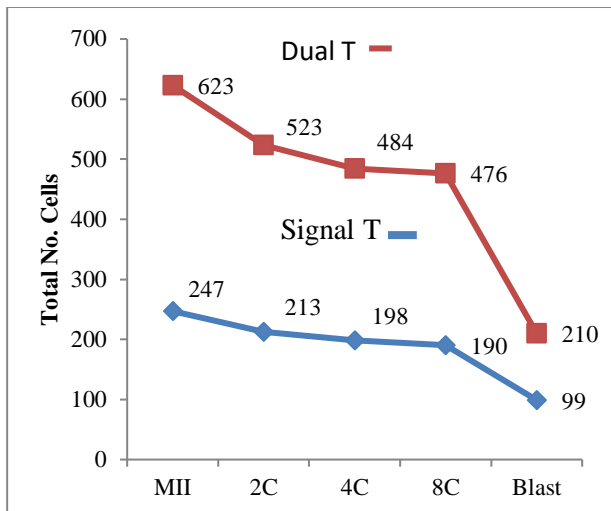


Figure 1: Progression of embryo development stages.

The table 3, shows the relationship between progesterone levels and IVF outcomes. Progesterone levels <0.5 mg/dl are associated with 45 (76.2%) positive outcomes and 38 (47%) negative outcomes, indicating a significant positive association with pregnancy success. In contrast, progesterone levels between 0.5-1.00 ng/dl are linked to fewer positive outcomes 6(10.1%) and more negative outcomes 29 (36%). For levels of 1.00-1.5 ng/dl and >1.5 ng/dl, positive outcomes are 4 (6.8%) in both ranges, with corresponding negative outcomes of 7 (8.6%) each. The p-value of 0.003 demonstrates that the differences in IVF outcomes across different progesterone levels are statistically significant, emphasizing the critical role of higher progesterone levels in achieving positive pregnancy results.

Table 4 illustrates the association between progesterone levels and IVF outcomes for fresh and frozen embryo transfers. Among fresh embryo transfers, progesterone levels below 0.5 ng/dl were associated with a higher percentage of positive IVF outcomes (28.8%) compared to those with levels above 0.5 ng/dl (18.6%). This difference was statistically significant ($P=0.016$), indicating that lower progesterone levels are more favourably associated with positive outcomes in fresh transfers.

In contrast, frozen embryo transfers with progesterone levels below 0.5 ng/dl also showed a higher percentage of positive outcomes (47.4%) compared to levels above 0.5 ng/dl (5%). However, this association did not reach statistical significance ($P=0.096$). The lack of significance in the frozen transfer group suggests that while there is a trend towards better outcomes with lower progesterone levels, the evidence is not strong enough to confirm a reliable association. Therefore, the significant finding in fresh transfers underscores the importance of maintaining lower progesterone levels to achieve more positive IVF outcomes. In Figure 1, the progression of embryo development stages from MII (Metaphase II) to blastocyst is analysed for single trigger and double trigger methods.

The double trigger method yielded a significantly higher number of MII oocytes (623) compared to the single trigger method (247). This trend continued across subsequent stages, with the double trigger group also producing more 2-cell embryos (523 vs. 213), 4-cell embryos (484 vs. 198), and 8-cell embryos (476 vs. 190). Additionally, the number of blastocysts was greater in the double trigger group (210) compared to the single trigger group (99). These findings indicate that the double trigger method is associated with a higher progression of embryos through development stages, culminating in a greater number of blastocysts.

The Table 5 presents IVF outcomes for two types of embryo transfer: frozen and fresh cycles. For frozen embryo transfers, 26 (42%) resulted in a positive pregnancy, 30 (48.4%) were negative, 1 (1.6%) was ectopic, and 5 (8%) ended in miscarriage. In contrast, for fresh embryo transfers, there was 1 (1.3%) biochemical pregnancy, 25 (32%) positive results, 49 (63%) negative results, 1 (1.3%) ectopic pregnancy, and 2 (2.5%) miscarriages. The p-value of 0.276 indicates that there is no statistically significant difference in IVF outcomes between the two types of embryo transfer.

Table 1: Baseline characteristics of study participants.

Variables	Mean±SD
Age	31±4.6
Endometrium thickness	9.14±1.5
Baseline serum progesterone	0.56±0.53
Baseline AMH	2.7±2.3
Baseline FSH	6.4±2.45
Baseline LH	3.7±1.8

Table 2: Association between endometrial thickness and IVF outcomes.

Endometrium thickness	Pregnancy outcome		P value
	Positive (n=59)	Negative (n=81)	
<7 mm	6 (10.1%)	9 (11.1%)	0.031
7-8 mm	4 (6.7%)	15 (18.5%)	
8-9 mm	23 (39%)	16 (19.7%)	
9-10 mm	20 (33.8%)	24 (29.6%)	
>10 mm	6 (10.1%)	17 (21%)	

Table 3: Association between progesterone levels and IVF outcomes.

Progesterone level (ng/dl)	Pregnancy outcome		P value
	Positive (n=59)	Negative (n=81)	
<0.5	45(76.2%)	38 (47%)	0.003
0.5-1.00	6 (10.1%)	29 (36%)	
1.00-1.5	4 (6.8%)	7 (8.6%)	
>1.5	4 (6.8%)	7 (8.6%)	

Table 4: Association between progesterone levels and IVF outcomes between fresh and frozen embryo transfer.

Type of transfer	Progesterone level (ng/dl)	Pregnancy outcome		P value
		Positive (n=59)	Negative (n=81)	
Fresh	<0.5	17(28.8%)	15 (18.5%)	0.016
	>0.5	11 (18.6%)	35 (43.2%)	
Frozen	<0.5	28(47.4%)	23(28.4%)	0.096
	>0.5	3(5%)	8(9.87%)	

Table 5: Comparison of IVF outcomes between types of embryo transfers.

Type of embryo transfer	IVF outcomes					P value
	Biochemical pregnancy	Positive	Negative	Ectopic	Miscarriage	
Frozen(n=62)	-	26 (42%)	30 (48.4%)	1 (1.6%)	5 (8%)	0.276
Fresh cycle (n=78)	1 (1.3%)	25 (32%)	49 (63%)	1 (1.3%)	2 (2.5%)	

Table 6: Type of trigger and embryo transfer on positive IVF outcomes.

IVF outcomes	Trigger type	Types of embryo transfer		P value
		Frozen (n=31)	Fresh (n=28)	
Positive (n=59)	Single	7	12	0.162
	Dual	24	16	

In the Table 6, dual trigger with frozen embryos resulted in the highest number of positive IVF outcomes, with 24 positives compared to 16 positives with fresh embryos. In single trigger, fresh embryos led to more positive outcomes than frozen embryos.^{7,12} The p-value of 0.162 indicates that the differences in IVF outcomes between frozen and fresh embryos are not statistically significant. Thus, dual trigger with frozen embryos showed the highest success rate, though the overall effect of type of trigger and embryo transfer on IVF outcomes does not differ significantly.

DISCUSSION

The baseline characteristics of our study population indicate that participants had a mean age of 31 years. The baseline (day 2 of menstrual cycle) serum progesterone level was relatively low, averaging 0.56 ng/ml, while the Anti-Müllerian Hormone (AMH) and Follicle-stimulating hormone (FSH) levels were 2.7 ng/mL and 6.4 mIU/ml, respectively. Luteinizing hormone (LH) levels were also recorded, with a mean of 3.7 mIU/ml. These baseline characteristics provide a comprehensive understanding of the study cohort, serving as a foundation for analysing the impact of hormonal variations on IVF outcomes.

The average basal endometrial thickness was 9.14 mm on the day of starting progesterone. The stimulation protocol with dual trigger and subsequent frozen embryo transfer has better IVF outcome than dual trigger with fresh embryo transfer or single trigger with respect to pregnancy rates however not statistically significant (24Vs16 p value 0.16). In a study by Xu et al, it was observed that among fresh embryo transfers, the clinical pregnancy rate significantly increased by approximately 10% with each

millimeter increment of endometrial thickness (ET) when ET was less than 12 mm.¹⁷ This finding underscores the critical role that endometrial thickness plays in successful IVF outcomes. Consistent with these results, the present study also highlights the importance of ET in predicting positive IVF outcomes. Specifically, our data revealed that an ET of 8-9 mm was associated with a significantly higher rate of positive outcomes, further emphasizing the influence of optimal endometrial thickness on achieving successful pregnancies. Contrastingly, in a study by Eleftheriadou et al, it was found that neither protocol type nor endometrial thickness were predictive of frozen embryo transfer (FET) outcomes.¹⁸

In a controlled trial by Yan et al, it was demonstrated that a dual trigger approach significantly improves both the quantity and quality of mature oocytes, as well as IVF outcomes.¹⁹ Aligning with these findings, the present study observed that the use of a dual trigger approach in combination with frozen embryos yielded the highest number of positive IVF outcomes, with 24 positives recorded, compared to 16 positives when using fresh embryos. This further supports the efficacy of the dual trigger method, particularly when applied in conjunction with frozen embryo transfers, in enhancing pregnancy success rates.

The study by Pitner et al, highlighted that elevated progesterone levels in assisted reproductive technologies (ART) could negatively impact pregnancy rates, yet the routine measurement of progesterone remains debatable due to the lack of randomized controlled trials.²⁰ In our study, we found a statistically significant difference (P=0.016), indicating that lower progesterone levels are more favourably associated with positive outcomes in

fresh embryo transfers. This suggests a potential benefit in monitoring progesterone levels to optimize ART outcomes, though the clinical value of such practice warrants further validation through randomized trials.

Further analysis of embryo development stages demonstrated that the double trigger method was more effective in producing higher-quality embryos compared to the single trigger method. The dual trigger group yielded significantly more MII oocytes and continued to show superior outcomes at subsequent stages, including the 2-cell, 4-cell, 8-cell, and blastocyst stages. The increased number of blastocysts in the dual trigger group underscores the potential benefits of this approach in enhancing embryo development and increasing the likelihood of successful implantation and pregnancy.

Finally, the comparison of IVF outcomes between frozen and fresh embryo transfers revealed no statistically significant differences, despite variations in success rates. Frozen embryo transfers showed a slightly higher positive pregnancy rate compared to fresh transfers, particularly when using a dual trigger approach. However, the lack of statistical significance suggests that while dual trigger with frozen embryos may offer an advantage, the overall impact of the type of trigger and embryo transfer on IVF outcomes is limited. This finding emphasizes the need for further research to clarify these trends and optimize clinical protocols for ART.

CONCLUSION

The outcome of this study demonstrates that optimizing endometrial thickness and managing progesterone levels are crucial for improving pregnancy success in assisted reproductive technologies (ART). The dual trigger method, particularly with frozen embryo transfers, shows promise in enhancing embryo quality and increasing pregnancy rates. However, while the dual trigger method offers some advantages, the overall differences between frozen and fresh transfers were not statistically significant. These findings suggest that careful monitoring and individualized approaches to hormonal management and trigger methods are essential for maximizing ART outcomes.

Recommendations

Routine monitoring of endometrial thickness

Given its significant impact on pregnancy success, monitoring and optimizing endometrial thickness should be an integral part of ART protocols, especially during fresh embryo transfers.

Progesterone level management

Clinicians should consider monitoring progesterone levels, particularly ensuring they remain within an optimal range,

to enhance the likelihood of successful implantation and pregnancy.

Consideration of dual trigger method

The dual trigger approach should be favoured, especially in combination with frozen embryo transfers, to maximize the quantity and quality of mature oocytes and improve overall IVF outcomes.

Further research

While this study provides valuable insights, additional randomized controlled trials are necessary to validate the clinical utility of routine progesterone measurement and to further explore the benefits of dual trigger methods across different ART settings.

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