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Comparison of Reproductive and Embryological Outcomes of Dual Trigger (hCG + GnRH Agonist) versus hCG-Only Trigger in GnRH Antagonist IVF/ICSI Cycles: A Randomized Controlled Study.

Neelam Kumari[1]*, Sapna Basandani[2], Alka Gahlot[3]

[1]M.Ch. Resident, Department of Reproductive Medicine & Surgery, National Institute of Medical Sciences & Research, Jaipur.

[2]Professor, Department of Reproductive Medicine & Surgery, National Institute of Medical Sciences & Research, Jaipur.

[3]Professor & HOD Department of Reproductive Medicine & Surgery, National Institute of Medical Sciences & Research, Jaipur.

Correspondence:
Neelam Kumari.
M.Ch. Resident, Department of Reproductive Medicine & Surgery, National Institute of Medical Sciences & Research, Jaipur.

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Abstract

Background: Assisted reproductive technology (ART) has become helpful in improving mature oocytes numbers, embryo quality and maximizing pregnancy and live births. Induction of full maturation of oocyte is performed with the help of a luteinizing hormone surge, which has been substituted by human chorionic gonadotropin (hCG). A new concept of ''dual trigger'' combines hCG with a GnRH agonist for maturation of oocytes. ***Aim:*** To evaluate reproductive outcomes of 'dual trigger (hCG and GnRH Agonist)' versus 'hCG-only trigger' in an antagonist cycle. ***Methods:*** A randomized controlled study of 92 normal-responder infertile women undergoing IVF/ICSI under a GnRH antagonist protocol, allocated to a dual trigger (leuprolide 1 mg + hCG 10,000 IU; n = 46) or hCG-only trigger (10,000 IU; n = 46). ***Results:*** Baseline and stimulation characteristics were comparable. The dual trigger group had significantly more mature (MII) oocytes (8.0 ± 3.3 vs. 6.0 ± 2.8, p = 0.003), 2PN embryos (7.4 ± 3.1 vs. 5.3 ± 2.6, p = 0.001), Grade I embryos (4.4 ± 2.1 vs. 2.0 ± 1.7, p < 0.001) and frozen embryos (2.9 ± 2.3 vs. 1.0 ± 1.5, p < 0.001). Clinical pregnancy rate did not differ significantly (22.8% vs. 20.3%, p = 0.77). ***Conclusion:*** The 'dual trigger' (hCG + GnRH agonist) protocol demonstrated superior embryological performance while maintaining equivalent stimulation profiles and safety outcomes.

Keywords: Assisted Reproductive Technology (ART), In Vitro Fertilization (IVF), Oocyte maturation, Ovulation trigger, GnRH agonist, Human chorionic gonadotropin (hCG).

INTRODUCTION

Assisted reproductive technology (ART) has become helpful in improving mature oocytes numbers, embryo quality and maximizing pregnancy and live births and helpful in reducing various reproductive risks. IVF involves various steps but maturation of oocyte is critical which is path of further steps like ovulation and competence of oocyte [1,2]. Gonadotropin surge includes FSH and LH surge, which favours ovulation and full maturation of oocyte along with restart of meiosis [6,7]. The ovulation trigger is used prior 35–37 hours before retrieval of oocyte in controlled manner stimulation of ovary in IVF.

Induction of full maturation of oocyte and restarting of reductional division is performed with the help of luteinizing hormone surge, which has been substituted by human chorionic gonadotropin (hCG) in past few years. hCG is helpful in long lasting luteotropic stimulation; but in patients who show exaggerated response for stimulation enhance chances of OHSS. Among various methods for maturation of oocyte in antagonist regimens of GnRH, its agonist is closer biologically and physiologically and acts by increasing the level of FSH and LH like normal middle cycle as compared to hCG. It also reduces the time period of luteotropic stimulation [13].

Various past studies showed that GnRH agonist or hCG treatment, if used separately, has various complications for respondents regarding outcomes or results of pregnancy, so there is a new concept of ''dual trigger'' started in which both are used as combined treatment for maturation of oocytes. Studies have shown that ''dual trigger'' is far better than single human chorionic gonadotropin administered in terms of successful pregnancy rate, fertility rate improvement and enhance live births of babies [26,24,27,28]. Building on these prior findings, the present study had proposed as randomized controlled research in normal responder women, comparing 'dual trigger (GnRH agonist + hCG)' and 'hCG only' protocols

that is given 35–37 hours prior to retrieval of oocytes, to examine their respective effects on reproductive and embryological outcomes.

AIM AND OBJECTIVES

The aim of this study was to evaluate and compare the reproductive and embryological outcomes of a 'dual trigger (hCG + GnRH agonist)' versus an 'hCG-only trigger' in GnRH antagonist IVF cycles — assessing oocyte yield, metaphase II (MII) oocytes, 2PN embryos, cleavage and high-quality embryo counts (primary outcomes), along with cycle cancellation rate, frozen embryo count, and clinical pregnancy rate (secondary outcomes).

MATERIALS AND METHODS

This randomized controlled study was conducted in the Department of Reproductive Medicine & Surgery, NIMS & R, and Evaa IVF Centre, Jaipur, over 18 months (July 2024 to December 2025), after ethics committee approval and informed consent. The sample size of 92 (46 per group) was based on a previous study [31]. Randomization used a computer-generated sequence with allocation concealment via sealed opaque envelopes. Infertile women aged 21–38 years with tubal factor or unexplained infertility and normal ovarian reserve were included; those with a thin endometrium, prior uterine surgery, PCOS, poor ovarian reserve (POSEIDON 3 & 4), or medical comorbidities were excluded.

All patients underwent a GnRH antagonist protocol: gonadotropin from day 2, with a GnRH antagonist (0.25 mg) added from day 6 until the trigger day. When at least three follicles >18 mm were seen on transvaginal sonography, patients were randomized to the trigger. Group A received the 'dual trigger' (leuprolide 1 mg + 10,000 IU hCG) and Group B received hCG 10,000 IU alone. Oocyte retrieval with ICSI was performed 36 h later, followed by luteal phase support. Oocytes were denuded and only mature oocytes with a visible first polar body were microinjected; embryos were cultured at 37°C in 5% CO2 and transferred between days 3 and 5 under ultrasound guidance. Pregnancy was confirmed by serum hCG >30 IU/ml at 14 days, and clinical pregnancy was defined as a viable intrauterine gestation on the 6-week scan.

RESULTS

General Basic Characteristics of Patients

The average age of patients in the 'dual trigger' group was 31.6 ± 4.4 years, while in the hCG Only group it was 30.2 ± 3.7 years. The difference between the two groups was not statistically significant (p = 0.23). Age distribution showed that the majority of patients in both groups were between 27–32 years (43.5% in 'dual trigger' vs. 47.8% in hCG Only).

Table 1: Age of patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Age (years)	21–26	10 (21.7%)	12 (26.1%)	0.23
	27–32	20 (43.5%)	22 (47.8%)	
	33–38	16 (34.8%)	12 (26.1%)	
	Mean ± SD	31.6 ± 4.4	30.2 ± 3.7	

The baseline demographic and hormonal characteristics were comparable between the 'dual trigger' and hCG Only groups, with no statistically significant differences observed across the age parameter of the patients. The mean age indicates that most participants were within the reproductive age range.

The mean BMI was 24.0 ± 3.5 kg/m² in the 'dual trigger' group and 25.1 ± 3.1 kg/m² in the hCG Only group, indicating that both groups had participants predominantly in the overweight category, with no significant difference between groups (p = 0.19).

Table 2: Body Mass Index (BMI) of patients

Parameter	Category	'Dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
BMI (kg/m²)	< 23 (Normal)	17 (37.0%)	13 (28.3%)	0.19
	23–27 (Overweight)	21 (45.7%)	23 (50.0%)	
	≥ 27 (Obese)	8 (17.4%)	10 (21.7%)	
	Mean ± SD	24.0 ± 3.5	25.1 ± 3.1	

The baseline demographic and hormonal characteristics were comparable between the 'dual trigger' and hCG Only groups, with no statistically significant differences observed across the Body Mass Index parameter of the patients.

The mean duration of infertility was 4.8 ± 2.4 years in the 'dual trigger' group and 5.5 ± 2.6 years in the hCG Only group (p = 0.21). Most patients had infertility for 4–6 years (43.5% and 39.1%, respectively).

Table 3: Duration of Infertility of patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Duration of Infertility (years)	≤ 3	11 (23.9%)	9 (19.6%)	0.21
	4–6	20 (43.5%)	18 (39.1%)	
	≥ 7	15 (32.6%)	19 (41.3%)	
	Mean ± SD	4.8 ± 2.4	5.5 ± 2.6	

This comparability indicates that both groups had a similar reproductive history, minimizing any bias related to the chronicity of infertility that could affect ovarian responsiveness or treatment outcomes.

The mean baseline FSH was 5.9 ± 1.8 IU/L in the 'dual trigger' group and 5.4 ± 2.0 IU/L in the hCG Only group (p = 0.28). Similarly, the mean baseline LH was 4.5 ± 2.0 IU/L and 4.0 ± 1.7 IU/L in the 'dual trigger' and hCG Only groups, respectively (p = 0.33).

Table 4: Baseline FSH Level among patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Baseline FSH (IU/L)	< 5	18 (39.1%)	17 (37.0%)	0.28
	5–8	23 (50.0%)	25 (54.3%)	
	> 8	5 (10.9%)	4 (8.7%)	
	Mean ± SD	5.9 ± 1.8	5.4 ± 2.0	

Equivalent baseline FSH levels suggest similar intrinsic ovarian reserve and pituitary function across groups. This parity ensures that observed differences in ovarian stimulation or oocyte yield, if any, are not due to pre-existing variations in gonadotropin secretion or ovarian sensitivity.

Table 5: Baseline LH Level among patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Baseline LH (IU/L)	< 3	9 (19.6%)	10 (21.7%)	0.33
	3–6	29 (63.0%)	27 (58.7%)	
	> 6	8 (17.4%)	9 (19.6%)	
	Mean ± SD	4.5 ± 2.0	4.0 ± 1.7	

No significant difference in baseline LH levels was observed between the groups (p > 0.05). Comparable LH profiles indicate similar hypothalamic–pituitary–gonadal axis activity before stimulation, ensuring that subsequent differences in ovulatory response can be attributed to the trigger method rather than endogenous hormonal discrepancies.

The mean AMH levels were 3.0 ± 0.9 ng/mL in the 'dual trigger' group and 2.6 ± 0.8 ng/mL in the 'hCG-only' group (p = 0.24), showing comparable ovarian reserve between the groups.

Table 6: Baseline AMH Level among patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
AMH (ng/mL)	< 2.0 (Low reserve)	8 (17.4%)	10 (21.7%)	0.24
	2.0–3.5 (Normal)	28 (60.9%)	26 (56.5%)	
	> 3.5 (High)	10 (21.7%)	10 (21.7%)	
	Mean ± SD	3.0 ± 0.9	2.6 ± 0.8	

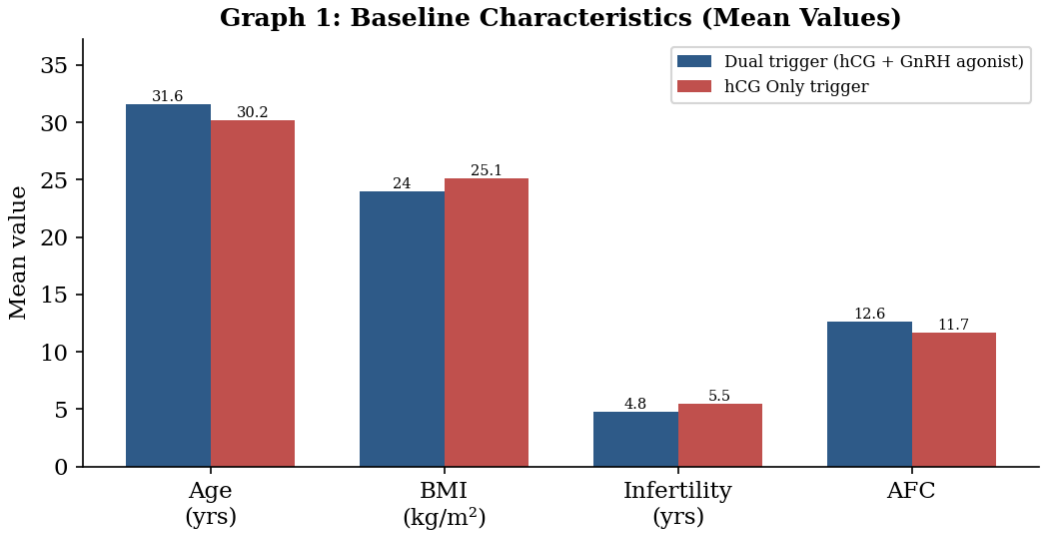
Baseline AMH levels were statistically similar between the 'dual trigger' and 'hCG-only' groups ($p > 0.05$). Since AMH is a robust indicator of ovarian reserve, this equivalence confirms that both cohorts had comparable follicular pools before treatment initiation.

The mean AFC was 12.6 ± 2.4 in the 'dual trigger' group and 11.7 ± 2.6 in the hCG Only group ($p = 0.17$), indicating similar ovarian follicular reserves between the groups.

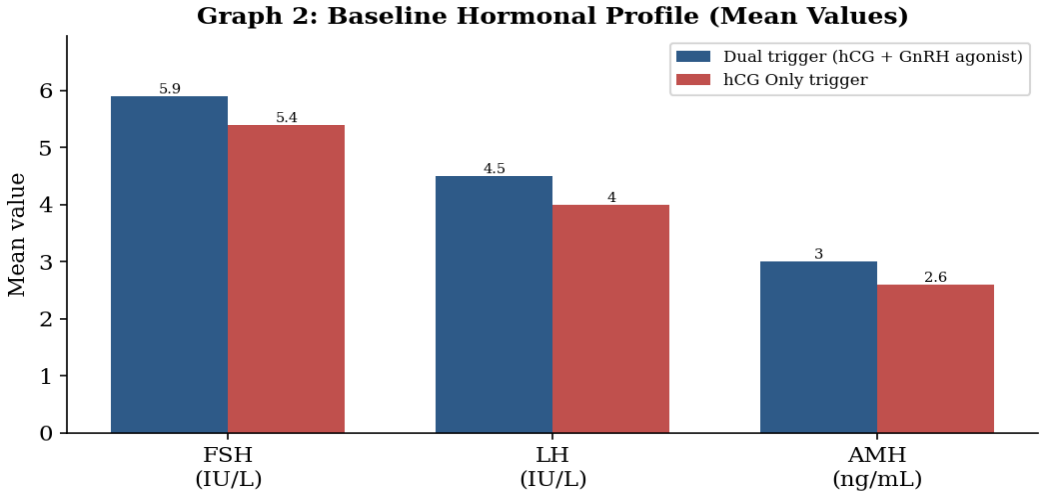
Table 7: Baseline Antral Follicle Count among patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Antral Follicle Count (AFC)	< 10	6 (13.0%)	9 (19.6%)	0.17
	10–15	27 (58.7%)	26 (56.5%)	
	> 15	13 (28.3%)	11 (23.9%)	
	Mean ± SD	12.6 ± 2.4	11.7 ± 2.6	

The mean AFC was comparable between the two groups ($p > 0.05$), reflecting equivalent ovarian reserve and recruitment potential at baseline. Balanced AFC distributions further support the consistency of baseline reproductive potential across groups, ensuring fair comparison of outcomes following stimulation and triggering.



Graph 1: Baseline characteristics of patients (mean values)



Graph 2: Baseline hormonal profile of patients (mean values)

Ovarian Stimulation Characteristics of Patients

In the 'dual trigger' group, the mean FSH dose was 2435 ± 625 IU, while in the hCG Only group, it was 2310 ± 585 IU, showing no statistically significant difference (p = 0.86).

Table 8: Total FSH Dose (IU) administered to patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Total FSH Dose (IU)	< 2000 IU	10 (21.7%)	9 (19.6%)	0.86
	2000–3000 IU	27 (58.7%)	28 (60.9%)	
	> 3000 IU	9 (19.6%)	9 (19.6%)	
	Mean ± SD	2435 ± 625	2310 ± 585	

These results suggest that the ovarian response to FSH stimulation was equivalent between the two triggering protocols. The 'dual trigger' group required a mean of 815 ± 690 IU of HMG, whereas the hCG Only group required 965 ± 760 IU (p = 0.91).

Table 9: Total HMG Dose (IU) administered to patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Total HMG Dose (IU)	< 500 IU	16 (34.8%)	14 (30.4%)	0.91
	500–1000 IU	18 (39.1%)	17 (37.0%)	
	> 1000 IU	12 (26.1%)	15 (32.6%)	
	Mean ± SD	815 ± 690	965 ± 760	

These findings confirm that the additional use of a GnRH agonist in the trigger protocol did not influence overall HMG usage during stimulation.

The average duration of ovarian stimulation was 9.5 ± 1.4 days in the 'dual trigger' group and 10.0 ± 1.3 days in the hCG Only group (p = 0.52).

Table 10: Duration of ovarian stimulation for patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Days of Stimulation	≤ 9 days	25 (54.3%)	21 (45.7%)	0.52
	10–11 days	18 (39.1%)	20 (43.5%)	
	≥ 12 days	3 (6.5%)	5 (10.9%)	
	Mean ± SD	9.5 ± 1.4	10.0 ± 1.3	

This similarity suggests that both groups achieved follicular growth and readiness for trigger within a similar time frame.

The mean Estradiol levels on the day of trigger were 2620 ± 275 pg/mL for the 'dual trigger' group and 2785 ± 290 pg/mL for the hCG Only group, showing no significant difference (p = 0.24).

Table 11: Estradiol levels on the day of trigger for patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Estradiol on Day of Trigger (pg/mL)	< 2500	17 (37.0%)	15 (32.6%)	0.24
	2500–3000	21 (45.7%)	22 (47.8%)	
	> 3000	8 (17.4%)	9 (19.6%)	
	Mean ± SD	2620 ± 275	2785 ± 290	

This indicates that the follicular response to stimulation was adequate and comparable in both treatment groups.

The mean progesterone level on the day of trigger was 1.35 ± 0.45 ng/mL in the 'dual trigger' group and 1.15 ± 0.50 ng/mL in the hCG Only group (p = 0.74).

Table 12: Progesterone levels on the day of trigger for patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Progesterone on Day of Trigger (ng/mL)	< 1.0	11 (23.9%)	14 (30.4%)	0.74
	1.0–1.5	23 (50.0%)	22 (47.8%)	
	> 1.5	12 (26.1%)	10 (21.7%)	
	Mean ± SD	1.35 ± 0.45	1.15 ± 0.50	

Since no significant difference was noted, it can be inferred that premature luteinization was minimal and equally controlled in both groups.

Oocyte Retrieval and Embryology Outcomes of Patients

Overall, the 'dual trigger' (hCG + GnRH agonist) group demonstrated a numerically higher oocyte yield and superior embryological outcomes compared to the 'hCG-only' group, with statistically significant differences observed in key parameters related to oocyte maturity and embryo quality.

The mean total number of oocytes retrieved was 9.8 ± 4.1 in the 'dual trigger' group and 8.0 ± 3.3 in the hCG Only group (p = 0.08), indicating a trend toward higher oocyte recovery with 'dual triggering'. However, the number of mature (Metaphase II) oocytes was significantly greater in the 'dual trigger' group (8.0 ± 3.3) compared with the hCG Only group (6.0 ± 2.8, p = 0.003). This finding suggests that the addition of GnRH agonist to hCG enhances maturation of oocyte, likely due to the more physiologic induction of both LH and FSH surges.

Table 13: Oocyte retrieval and maturation outcomes of patients

Parameter	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Total Oocytes Retrieved	< 6	9 (19.6%)	13 (28.3%)	0.08
	6–10	24 (52.2%)	22 (47.8%)	
	> 10	13 (28.3%)	11 (23.9%)	
	Mean ± SD	9.8 ± 4.1	8.0 ± 3.3	
Metaphase II (MII) Oocytes	< 5	8 (17.4%)	14 (30.4%)	0.003
	5–8	23 (50.0%)	25 (54.3%)	
	> 8	15 (32.6%)	7 (15.2%)	
	Mean ± SD	8.0 ± 3.3	6.0 ± 2.8	

The mean number of 2PN (normally fertilized) embryos was significantly higher in the 'dual trigger' group (7.4 ± 3.1) compared with the hCG Only group (5.3 ± 2.6, p = 0.001). The cleavage rate was slightly higher in the 'dual trigger' group (92.5 ± 6.0%) compared to the hCG Only group (88.2 ± 7.2%), though the difference was not statistically significant (p = 0.18). However, the mean number of Grade I embryos was significantly higher in the 'dual trigger' group (4.4 ± 2.1) versus the hCG Only group (2.0 ± 1.7, p < 0.001). Similarly, the number of embryos frozen was markedly greater following 'dual trigger' (2.9 ± 2.3 vs. 1.0 ± 1.5, p < 0.001), suggesting improved embryo quality and surplus for cryopreservation.

Table 14: Fertilization and embryo development of patients

Outcomes	Category	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
2PN Embryos (Normal Fertilization)	< 5	10 (21.7%)	18 (39.1%)	0.001
	5–8	27 (58.7%)	24 (52.2%)	
	> 8	9 (19.6%)	4 (8.7%)	
	Mean ± SD	7.4 ± 3.1	5.3 ± 2.6	
Cleavage Rate (%)	< 85	8 (17.4%)	11 (23.9%)	0.18
	85–95	30 (65.2%)	27 (58.7%)	

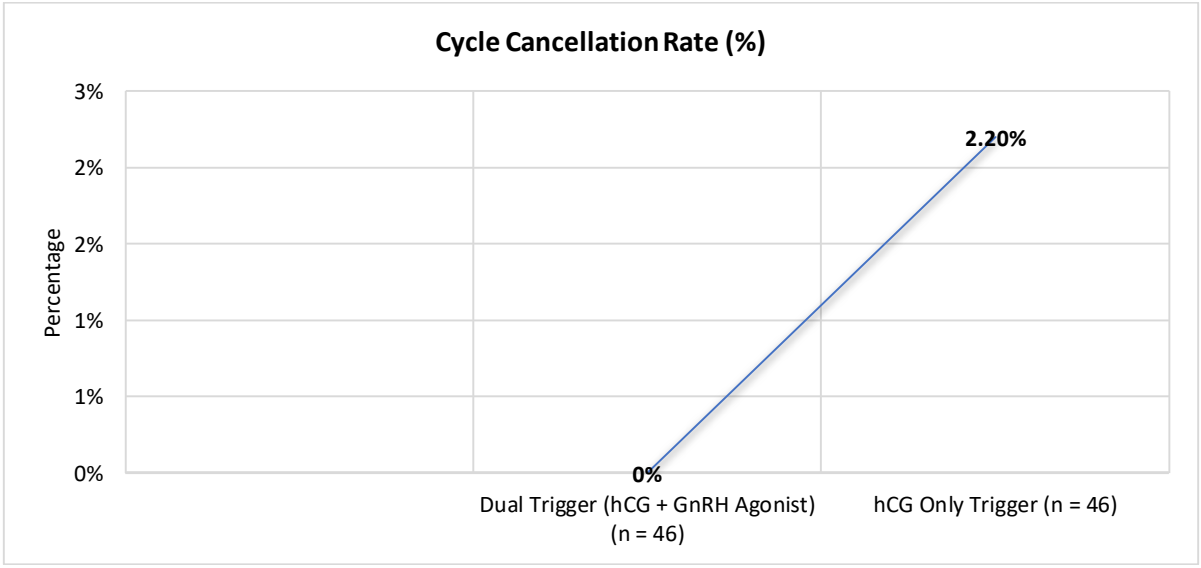
	> 95	8 (17.4%)	8 (17.4%)	
	Mean ± SD	92.5 ± 6.0	88.2 ± 7.2	
Grade I Embryos	< 3	14 (30.4%)	27 (58.7%)	<0.001
	3–5	23 (50.0%)	15 (32.6%)	
	> 5	9 (19.6%)	4 (8.7%)	
	Mean ± SD	4.4 ± 2.1	2.0 ± 1.7	
Embryos Frozen	0	8 (17.4%)	19 (41.3%)	<0.001
	1–3	27 (58.7%)	22 (47.8%)	
	> 3	11 (23.9%)	5 (10.9%)	
	Mean ± SD	2.9 ± 2.3	1.0 ± 1.5	

Cycle cancellation occurred only in the 'hCG-only' group (2.2%) and not in the 'dual trigger' group, though the difference was not significant (p = 0.56). The clinical pregnancy rate was slightly higher with 'dual triggering' (22.8%) than with hCG only (20.3%), but this difference was not statistically significant (p = 0.77), possibly due to the limited sample size.

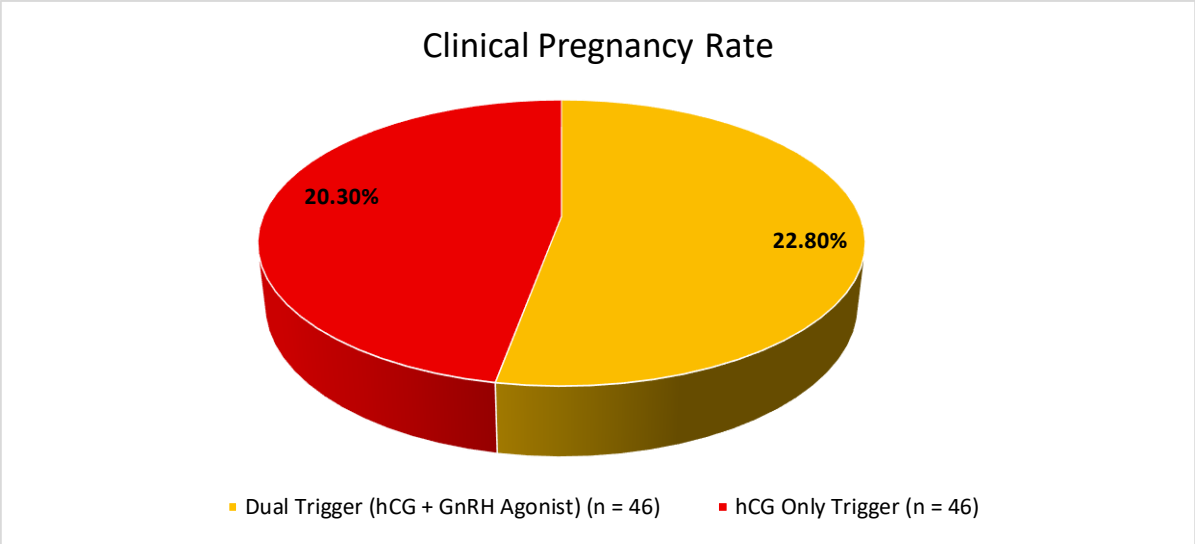
Table 15: Cycle cancellation and clinical pregnancy outcomes of patients

Parameter	'dual trigger' (hCG + GnRH Agonist) (n = 46)	hCG Only Trigger (n = 46)	p-value
Cycle Cancellation Rate (%)	0.0%	2.2%	0.56
Clinical Pregnancy Rate (%)	22.8%	20.3%	0.77

These results indicate that the 'dual trigger' protocol resulted in superior oocyte maturation and fertilization outcomes compared to the 'hCG-only' protocol, while maintaining similar stimulation and hormonal conditions.



Graph 3: Cycle cancellation rate



Graph 4: Clinical pregnancy rates

DISCUSSION

Baseline Demographic and Hormonal Characteristics

The two classes in the study (one given both hCG and GnRH, and the other given only hCG) were very similar at the start. They did not differ in age, how long they had been infertile, or their hormone levels (FSH, LH, AMH) and follicle quantity (AFC). This homogeneity confirms that both groups were well matched at baseline, minimizing potential confounding factors and strengthening the validity of subsequent comparisons related to ovarian response, oocyte maturity, and clinical outcomes. The comparable ovarian reserve parameters (AMH, FSH, LH, and AFC) suggest that both groups had similar baseline reproductive potential. Hence, any differences observed in oocyte maturation or fertilization outcomes can be confidently attributed to the triggering method rather than intrinsic biological variability. These results are very similar to many other studies, all of which have also found that the two classes ('dual-trigger' and 'hCG-only') were the same at the beginning.

Ovarian Stimulation Characteristics

Both groups responded the same during treatment. They needed similar amounts of medicine, had similar treatment duration, and similar hormone levels before the trigger. The estrogen level was high (more than 2500 pg/mL) in both groups, which means the ovaries responded well and made good follicles. The progesterone level was low (below 1.5 ng/mL) in most patients, which means there was no early problem. Our results are similar to Singh's study [31]. Dong et al. [33] similarly reported equivalent total gonadotropin doses and trigger-day estradiol concentrations when using propensity-score matching. Many other studies also demonstrated comparable stimulation and hormonal parameters between trigger strategies, reinforcing the reproducibility of these observations.

Oocyte and Embryological Outcomes

Even though both groups were similar in treatment and hormone levels, 'dual-trigger' class had better results. They produced more mature eggs, more fertilized embryos, better-quality embryos, and more embryos that could be frozen for later use. Many recent studies show that the dual-trigger method works better. Adding GnRH (with hCG) may help eggs develop better. This happens because it creates a more natural hormone peak (LH and FSH), like what happens in the body. The FSH hormone helps egg grow properly, restart its development through meiosis, and become stronger. Because of this, the eggs and embryos are of better quality.

CONCLUSION

Both groups were demographically and hormonally comparable at baseline, with equivalent gonadotropin dose, stimulation duration, and hormonal environment at trigger. Despite these similar stimulation profiles, the 'dual trigger' (hCG + GnRH agonist) protocol yielded remarkably more mature oocytes, 2PN embryos, and Grade I embryos, reflecting superior oocyte competence and embryological development, while pregnancy and cancellation rates did not differ significantly between groups. The inclusion of a GnRH agonist induces a physiologic LH and FSH surge that more closely replicates the natural mid-cycle endocrine profile, thereby enhancing oocyte maturation and fertilization potential. Overall, the 'dual trigger' protocol demonstrated superior embryological performance while maintaining equivalent stimulation profiles and safety

outcomes, representing a clinically valuable modification to conventional triggering in ART, particularly for patients with low oocyte maturity or frequent immature oocyte retrievals.

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