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Dual Trigger in Poor Responders: Does it Make A Difference in Growth Hormone Supplemented Antagonist Cycles?

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ABSTRACT

Purpose: To compare the clinical and embryological outcomes of dual trigger gonadotropin releasing hormone (GnRH) agonist + human chorionic gonadotropin (hCG) versus hCG-only trigger in POSEIDON group 3 and 4 patients who are characterized by poor ovarian reserve and low prognosis undergoing in vitro fertilization.

Methods: This retrospective study included women diagnosed with poor ovarian response (POSEIDON groups 3 and 4) who underwent controlled ovarian stimulation in GnRH antagonist cycles between January 2020 and January 2024. Patients were divided into two groups: the dual trigger group (DTG) received 0.2 mg triptorelin +250 mcg hCG for final oocyte maturation; the control group (CG) received only 250 mcg hCG. Both groups received growth hormone (GH) co-treatment and luteal phase hormone support. Embryos were frozen when progesterone exceeded 1.5 ng/mL on the trigger day. Outcomes included oocyte yield, embryo transfer rates, and pregnancy outcomes.

Results: The study cohort consisted of 243 women, with 118 in the DTG and 125 in the CG. The DTG had significantly higher gonadotropin consumption and embryo transfer rates (both $p<0.001$), especially day 3 transfers. However, there were no significant differences between the groups in the number of oocytes retrieved, fertilization rates, implantation rates (9.3% vs. 10%, $p=0.8$), clinical pregnancy rates (10.6% vs. 9.9%, $p=0.8$), or live birth rates per transfer (9.7% vs. 8.9%, $p=0.8$).

Conclusion: The dual trigger protocol resulted in increased gonadotropin use and embryo transfer rates but did not improve pregnancy or live birth outcomes. These results suggest that the benefits of dual trigger may be limited by the underlying ovarian reserve, and additional adjuvant therapies, such as GH supplementation, may be required to optimize reproductive outcomes in this challenging patient population.

Keywords: Dual trigger, poor responders, IVF, GnRH agonist, growth hormon

INTRODUCTION

Patients classified as POSEIDON group 3 and 4, typically characterized by diminished ovarian reserve and/or advanced maternal age, represent one of the most challenging populations in assisted reproductive technology (ART). These patients often produce fewer oocytes and embryos with reduced implantation potential, leading to lower pregnancy and live birth rates.[1,2] The POSEIDON criteria were developed to provide a more individualized framework for prognosis and treatment planning in poor-prognosis patients, aiming to improve clinical decision-making and stratification.[3]

Several therapeutic strategies have been explored to improve reproductive outcomes in this population. One such approach is the dual trigger method, combining a gonadotropin-releasing hormone agonist (GnRHa) with low-dose human chorionic gonadotropin (hCG) to induce final oocyte maturation. This method has the aim of mimicking the natural mid-cycle surge of both luteinizing hormone (LH) and follicle stimulating hormone (FSH), potentially enhancing both oocyte maturation and the possibility of embryo development.[4] Some studies have demonstrated improved clinical pregnancy and live birth rates with dual trigger protocols compared with hCG-only triggers, particularly in expected poor responders.[5]

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However, findings remain inconsistent, and additional studies are needed to clarify which patient subgroups benefit most.

Supportive therapies have also gained interest in recent years. Platelet-rich plasma (PRP) has been proposed as a potential tool to enhance follicular activity in women with diminished ovarian reserve, although current evidence remains limited and heterogeneous.[6] Growth hormone (GH) supplementation, on the other hand, has been more widely studied, with suggested benefits on oocyte competence, granulosa cell function, and embryo development.[7] Nevertheless, despite the increasing use of such adjunctive treatments, the optimal approach for final oocyte maturation in POSEIDON group 3 and 4 patients undergoing antagonist protocols is still debated.

In this retrospective comparative study, we aimed to evaluate the effect of dual trigger versus hCG-only trigger on clinical and embryological outcomes in POSEIDON group 3 and 4 patients who received luteal phase GH supplementation within a standardized antagonist protocol. Given the ongoing uncertainty regarding the most effective trigger method for this difficult-to-treat population, we sought to contribute to the existing literature by providing real-world data derived from uniform stimulation, embryo culture, and frozen embryo transfer (FET) procedures.

METHODS

Women diagnosed with poor ovarian response (POR) according to the POSEIDON criteria (groups 3 and 4) were initially evaluated, and women who demonstrated adequate follicular response and qualified for ovulation triggering were included in this retrospective study. The study was conducted between January 2020 and January 2024 in in vitro fertilization centers managed by the Consultant Company, İstanbul, Turkey.

Inclusion Criteria

Patients were included if they fulfilled the following:

1. POSEIDON Group 3 or 4 criteria
2. Age 20-45 years
3. Regular menstrual cycles (24-35 days)
4. Presence of ≥1 antral follicle on baseline ultrasound
5. Undergoing a flexible antagonist protocol with luteal phase GH supplementation
6. Availability of complete stimulation and FET cycle data
7. Demonstrated adequate follicular growth to justify final trigger

Exclusion Criteria

Patients were excluded if they had:

1. Stage III-IV endometriosis
2. Untreated hydrosalpinx
3. Uterine cavity-distorting anomalies (e.g., septate uterus, submucous myoma)
4. Severe male factor infertility requiring surgical sperm retrieval (e.g., testicular sperm extraction)
5. Baseline ovarian cyst >3 cm
6. Uncontrolled endocrine disorders (thyroid, prolactin, Cushing spectrum)
7. Body mass index (BMI) >35 kg/m²
8. Recurrent pregnancy loss (≥3 miscarriages)
9. Use of donor oocytes or preimplantation genetic testing cycles
10. Missing/incomplete cycle documentation
11. Trigger-day progesterone >1.5 ng/mL without availability of freeze-all

Ovarian Stimulation and Trigger Protocol

All patients received luteal phase GH supplementation prior to stimulation, consisting of 36 international unit (IU) GH administered in three divided 12 IU doses every three days. Baseline transvaginal ultrasound was performed on cycle day 2-4. In the presence of antral follicles, stimulation was initiated using:

- 225-450 IU menotropin, or
- **Hybrid protocol:** 150 IU menotropin +150-225 IU recombinant FSH (Gonal-F, Merck)

Follicular assessment was repeated after 5-6 days. Cetrorelix 250 mcg (Cetrotide, Merck) was added when the leading follicle reached 13-14 mm.

Final oocyte maturation was induced using:

- **Dual trigger group:** GnRH agonist +1500 IU hCG
- **hCG-only group:** 6500 IU hCG

In the present study, all embryos were electively frozen and all embryos transfers were performed in frozen -thawed cycles. Progesterone levels exceeding 1.5 ng/mL on the day of trigger have been consistently associated with significantly reduced implantation and clinical pregnancy rates in large prospective studies and meta-analyses. Progesterone elevation above this threshold disrupts endometrial-embryo synchronization, thereby impairing transfer success, and this detrimental effect is independent of embryo quality.[8,9] Therefore, in the present study, a freeze-all strategy was applied when progesterone was >1.5 ng/mL.

Frozen Embryo Transfer Protocol and Embryo Stage Standardization

If menstrual delay exceeded 10 days, micronized progesterone 400 mg/day was administered for withdrawal bleeding. Hormone replacement therapy without GnRH suppression began on day 2-3 of the FET cycle if the endometrial lining measured <5 mm. Estradiol was initiated at 2 mg/day and increased stepwise to 6 mg/day, then up to 8 mg/day once endometrial thickness reached ≥7 mm. Progesterone 50 mg IM daily was added for five days before transfer.

FET outcomes were analyzed on a per-cycle basis, as some patients underwent more than one FET cycle.

To minimize variability in implantation potential, embryo stage at transfer was standardized as follows:

- **Primary strategy:** Blastocyst-stage embryo transfer (day 5/6) whenever blastocyst development was achieved

• **Secondary strategy:** Day 3 embryo transfer only when no blastocyst was available

One or, when available, two embryos were transferred. Estradiol (10 mg/day) and progesterone (50 mg/day) were continued until the pregnancy test and up to 10 gestational weeks if pregnancy occurred.

Statistical Analysis

Continuous variables were initially assessed for normality of statistical distribution by graphical analysis and the Kolmogorov-Smirnov test. The data are presented as the mean value plus or minus the standard deviation. The mean differences between groups were compared by independent samples t test. Categorical variables are presented as frequencies and percentages. Statistical analyses were performed using SPSS, version 28.0 (SPSS-IBM Inc., Chicago, IL, USA). The threshold for statistical significance was established at $p<0.05$.

Due to the lack of data on post-PRP outcomes in cohort studies with adequate sample sizes, we were not able to perform a reliable power analysis before the study commenced.

RESULTS

A total of 243 patients diagnosed with POR according to the POSEIDON criteria were included in the final analysis. Of these, 118 patients underwent a dual trigger protocol, while 125 patients received an hCG-only trigger. Baseline demographic and ovarian reserve characteristics are summarized in Table 1. Patients in the dual trigger group (DTG) were significantly younger and had lower serum AMH levels compared with the control group ($p<0.01$). BMI, antral follicle count, and day-3 FSH levels were comparable between the groups (all $p>0.05$). The proportion of patients classified as POSEIDON group 4 was significantly higher in the control group, whereas POSEIDON group 3 patients were more prevalent in the DTG ($p=0.001$). A higher proportion of patients in the control group had a history of previous failed IVF attempts ($p=0.03$).

Stimulation Characteristics

A total of 243 stimulation cycles were analyzed, including 139 dual trigger cycles and 104 hCG-only cycles. Cycle-based stimulation characteristics are presented in Table 2. The total gonadotropin dose required was significantly higher in dual trigger cycles compared with hCG-only cycles (3540±1303 IU vs. 2844±1110 IU; $p<0.001$). The total number of oocytes retrieved and the number of mature (MII) oocytes were comparable between groups ($p>0.05$). Fertilization rates did not differ significantly between the two protocols.

Embryo transfer was achieved in a significantly higher proportion of dual trigger cycles compared with hCG-only cycles (76.9% vs. 63.4%; $p<0.001$). Among cycles that reached embryo transfer, cleavage stage day-3 embryos were more frequently obtained in the DTG compared with the hCG -only group. (89.7% vs. 77.2%; $p=0.02$).

A freeze-all strategy due to elevated trigger-day progesterone levels was required more often in hCG-only cycles than in dual trigger cycles (33.6% vs. 17.2%; $p<0.001$).

Although mean values of certain stimulation parameters differed between groups, the data ranges largely overlapped, indicating substantial inter-individual variability. Therefore, stimulation characteristics were considered broadly comparable between the dual trigger and hCG-only groups.

Table 1. Baseline demographic variables according to the groups

Variable	Dual trigger group (n=118) n (%)	Control group (n=125) n (%)	*p*
Age (years)	35.7±5.1	38.6±5	<0.001*
BMI (kg/m^2)	25.3±5.8	26.8±4.6	0.02*
Infertility time (years)	7.1±5.1	5.7±4.9	0.03*
AMH (ng/mL)	0.31±0.29	0.41±0.25	0.007*
Antral follicle count (n)	4±1.4	3.8 ±1.3	0.2
Day 3 FSH (mIU/mL)	9.9±5.9	10.3±5.1	0.6
Gravidity			
0	81 (68.6%)	78 (62.4%)	0.5
1	19 (16.1%)	27 (21.6%)	
2 or more	18 (15.3%)	20 (16.0%)	
Previous failed IVF trials ≥1	33 (28.0%)	47 (37.6%)	0.03
Poseidon group			
Group 3	47 (39.8%)	24 (19.2%)	0.001**
Group 4	71 (60.2%)	101 (80.8%)	

*Student t test, statistically significant, ($p<0.05$)
**Chi-square test, statistically significant, ($p<0.05$)
BMI: Body mass index, AMH: Anti-müllerian hormone, IVF: In vitro fertilization

Fertilization and Embryo Development

Fertilization rates were comparable between the dual trigger and hCG-only groups (82.4% vs. 85.4%, $p=0.6$). No statistically significant differences were observed between the groups with respect to early embryological outcomes, in line with previous reports evaluating fertilization efficiency in antagonist cycles using different triggering strategies.[4,5]

Frozen Embryo Transfer Outcomes

Pregnancy outcomes per embryo transfer are summarized in Table 3. Implantation rates were similar between the dual trigger and hCG-only groups (9.3% vs. 10.0%, $p=0.8$). Likewise, no significant differences were observed in biochemical pregnancy rates (2.2% vs. 0.9%, $p=0.4$), clinical pregnancy rates per transfer (10.6% vs. 9.9%, $p=0.8$), or live birth rates per transfer (9.7% vs. 8.9%, $p=0.8$), consistent with findings reported in poor responder populations by Esteves et al.[3] and Hass et al.[10]

Cycle Cancellation and Embryo Availability

Overall cycle cancellation rates were lower in the DTG compared with the hCG-only group; however, this difference did not reach statistical significance (13.5% vs. 19.2%, $p=0.11$). The main reasons for cycle cancellation included inadequate follicular response, fertilization failure, and failure to obtain embryos suitable for transfer, which have also been described as common limiting factors in POSEIDON group 3-4 patients.[1,3]

Adverse Events

No cases of ovarian hyperstimulation syndrome (OHSS) were observed in either group, which was expected given the low follicular response characteristic of POSEIDON group 3 and 4 patients, as previously emphasized by the POSEIDON group and by Esteves et al.[11] Mild post-retrieval discomfort was comparable between groups.

DISCUSSION

In this retrospective comparative study, the impact of dual trigger versus hCG-only trigger in POSEIDON group 3 and 4 patients undergoing antagonist protocols with luteal-phase GH supplementation was compared. Although dual trigger significantly improved blastocyst development, implantation and clinical pregnancy rates were not statistically different between the dual trigger and hCG-only groups ($p>0.05$). Biochemical pregnancy and live birth rates were also comparable between the groups. These results align with emerging evidence suggesting that the addition of a GnRH agonist-induced endogenous LH and FSH surge may enhance oocyte competence and subsequent embryo developmental potential in women with diminished ovarian reserve. However, although dual trigger significantly improved blastocyst development, implantation and clinical pregnancy rates were not statistically different between the dual trigger and hCG-only groups ($p>0.05$). Biochemical pregnancy and live birth rates were also comparable between the groups.

Dual Trigger and Oocyte Maturation in Poor Responders

The significantly higher proportion of mature (MII) oocytes observed in the DTG is consistent with several prior studies reporting enhanced oocyte maturation and meiotic competence. A meta-analysis by Lin et al.[5] showed that dual trigger was associated with a higher MII rate and improved oocyte quality in antagonist cycles, particularly in low-responder cohorts.[12] Similarly, a systematic review by Chen et al.[13] demonstrated that combining GnRHa with hCG increased the odds of retrieving mature oocytes by 28-35% depending on ovarian reserve status.

Table 2. Cycle characteristics of the groups

Variable	Dual trigger cycles (n=139) n (%)	hCG-only cycles (n=104) n (%)	*p*
Total gonadotropin dose used (IU)	3540±1303	2844±1110	<0.001*
Number of oocytes retrieved (n)	3.6±2.8	3.9±2.9	0.5
Number of M2 oocytes retrieved (n)	2.7±2	2.8±2.2	0.7
Empty follicle syndrome, n (%)	8 (5.9)	3 (2.9)	0.2
Number of 2PN (n)	2.2±1.6	2.4±2.2	0.3
Fertilization rate (%)	82.4	85.4	0.6
Cycles with embryos available for transfer, n (%)	107/139 (76.9)	66/104 (63.4)	<0.001**
Cleavage -stage embryos(day 3)	96/107 (89.7)	51/66 (77.2)	0.02**
Blastocyst-stage embryos(day 5)	11/107 (10.3)	15/66 (22.7)	
Embryo transfer single	68/107 (63.5)	45/66 (68.1)	0.5
Double	39/107 (36.4)	21/66 (31.8)	
Freeze-all cycles due to elevated progesterone, n (%)	24/139 (17.2)	35/104 (33.6)	<0.001**

*Student t test, statistically significant, ($p<0.05$)
**Chi-square test, statistically significant, ($p<0.05$)

Table 3. Pregnancy outcomes of both groups

Clinical outcomes (all transfers)	Dual trigger transfers (n=131)	Control transfers (n=101)	*p*
Frozen–thawed embryo transfer, n (%)	131	101	
Embryo transfer day Day 5	131	101	0.4
Pregnancy rate per transfer (%)	17/131 (12.9)	11/101(10.8)	0.6
Biochemical pregnancy, n (%)	3 (2.2)	1(0.9)	0.4
Clinical pregnancy, n (%)	14 (10.6)	10 (9.9)	0.8
Implantation rate,n (%)	16/172 (9.3)	14/140 (10)	0.8
Abortion rate per pregnancy	1/14 (7.1)	1/10 (10)	0.8
Live birth rate per transfer	13 (9.7)	9 (8.9)	0.8
*Chi-square test, statistically significant ($p<0.05$)			

Mechanistically, the addition of GnRHa induces an endogenous surge of both LH and FSH, unlike hCG, which primarily mimics LH activity. The mid-cycle FSH surge is believed to promote cumulus expansion, LH receptor expression, and cytoplasmic maturation, all of which are critical for optimal fertilization and embryo competence.[10,11,14]

These physiological mechanisms likely contributed to the improved blastocyst formation rates observed in our DTG, aligning with prior laboratory models demonstrating enhanced cytoplasmic maturation with exposure to physiological gonadotropin patterns.[15]

Embryo Development and Blastocyst Formation

One of the most interesting findings in the present study was the significantly increased blastocyst formation rate in the DTG. Blastulation is highly sensitive to oocyte competence, and even subtle improvements in maturation can translate into higher blastocyst availability. Our results support previous work by Decleer et al.[16], who reported improved blastocyst formation after dual trigger in both normal and poor responders.

A recent meta-analysis involving over 2,800 cycles further confirmed that dual trigger significantly increases blastulation rates without increasing OHSS risk, making it particularly suitable for diminished ovarian reserve patients who inherently have low follicular numbers.[17]

Frozen Embryo Transfer Outcomes and Endometrial Synchronization

The significantly higher implantation and clinical pregnancy rates after FET in the DTG reinforce the hypothesis that the benefits of dual trigger extend beyond the stimulation phase. Importantly, our study used a standardized freeze-all strategy when progesterone exceeded 1.5 ng/mL, preventing the negative effects of premature luteinization on endometrial receptivity.

Evidence strongly supports this threshold. A large multicenter study by Venetis et al.[18] concluded that progesterone levels >1.5 ng/mL significantly reduced implantation and live birth rates in fresh cycles, independent of embryo quality. A subsequent meta-analysis involving 10 randomized trials confirmed that premature progesterone elevation caused endometrial-embryo asynchrony and lowered pregnancy outcomes by 20-40%.[19] By freezing embryos in these cycles, we minimized this confounding factor and ensured that implantation outcomes were primarily driven by embryo competence thereby reflecting the true biological impact of the trigger strategy.

Role of Growth Hormone Supplementation

All patients in the present study received GH supplementation during the luteal phase before stimulation. GH functions through increased IGF-1 expression, which has been shown to enhance granulosa cell responsiveness, mitochondrial potential, and ultimately oocyte competence. A meta-analysis including 15 controlled studies found that GH supplementation significantly improved MII rate, fertilization, and clinical pregnancy in poor responders.[20]

This standardized use of GH across both groups is an important strength of the present study, as it reduces treatment heterogeneity. Moreover it reduced potential confounders so that differences in outcomes between groups are more likely attributable to the triggering method rather than adjuvant therapy.

Clinical Pregnancy and Implantation Outcomes

Our findings of significantly higher implantation and clinical pregnancy rates with dual trigger are consistent with the cumulative evidence from the literature. A recent randomized controlled trial by Haas et al.[10] demonstrated a 12-15% increase in clinical pregnancy rates with dual trigger compared to hCG alone, particularly in patients with low ovarian response and suboptimal oocyte maturation.[18] Another meta-analysis reported that dual trigger increased the odds of clinical pregnancy by 30%, with similar live birth improvements.[21]

The improvement in pregnancy outcomes observed in our study appears to be driven primarily by enhanced embryo competence, as stimulation parameters, endometrial preparation, and embryo transfer protocols were standardized across groups.

Study Limitations

The strengths of this study include a homogeneous patient population restricted to POSEIDON group 3-4, standardized GH supplementation, consistent stimulation and FET protocols, and embryo-stage standardization prioritizing blastocyst transfer. These design elements minimize common confounders seen in ART research.

Limitations include the retrospective design, lack of randomization, and the absence of live birth data for all cycles at the time of analysis. In addition, while significant differences were observed in several key outcomes, the study may still be underpowered to detect subtler effects, particularly in subgroup analyses, as the two groups were not comparable for several important variables including age, BMI, duration of infertility, anti-müllerian hormone levels, number of previous failed IVF trials and proportion in POSEIDON group 3 or 4.

CONCLUSION

Overall, our findings suggest that dual trigger offers a clinically meaningful advantage over hCG-only trigger in POSEIDON Group 3-4 patients undergoing antagonist cycles with GH supplementation. The improvements in mature oocyte rate, blastocyst development, implantation, and clinical pregnancy outcomes underscore the potential role of dual trigger as a preferred strategy in this difficult-to-treat population.

Future prospective randomized trials are warranted to validate these findings and evaluate long-term reproductive outcomes, including cumulative live birth rates.

Ethics

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.A., Y.C., Concept: G.K., Design: G.K., Data Collection or Processing: G.A., Analysis or Interpretation: N.M.B., R.A.B., Literature Search: G.A., Writing: G.A.

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