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Posted Date: 11 December 2025

doi: 10.20944/preprints202512.1026.v1

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Article

GnRH-Agonist for Luteal Phase Support Following Dual Trigger: A Proof-of-Concept Study

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Abstract

This study evaluated whether a gonadotropin-releasing hormone (GnRH) agonist can be effectively used for luteal phase support following a dual trigger in IVF. A total of 284 patients undergoing fresh embryo transfer were included: 116 received a dual trigger and 168 an hCG trigger. All patients received luteal support with Nafarelin nasal spray twice daily for two weeks, starting on the day of oocyte retrieval. Women in the dual trigger group were older (36.2 vs. 32.3 years, $p < 0.01$), had lower antral follicle counts (7.0 vs. 17.5, $p = 0.03$), and received higher total gonadotropin doses (3000 vs. 2041 IU, $p < 0.01$). There were no significant differences between groups in retrieved and mature oocytes, fertilization rate, or blastulation rate. Positive pregnancy rate (β -hCG ≥ 25 mIU/mL) was 46.6% in the dual trigger group and 41.1% in the hCG group, without a significant difference, with similar live birth and miscarriage rates. Logistic regression identified maternal age as a predictor of positive pregnancy (OR = 0.95; 95% CI: 0.90–0.99; $p = 0.024$), while trigger type was not. Propensity score matching confirmed comparable IVF and pregnancy outcomes between groups. These findings indicate that a dual trigger followed by luteal-phase GnRH agonist support yields IVF and pregnancy outcomes similar to an hCG trigger.

Keywords: HCG; GnRH agonist; dual trigger; luteal phase support

1. Introduction

Luteal phase hormonal support is essential for addressing luteal phase deficiency and improving pregnancy rates in in-vitro fertilization (IVF) treatments [1]. Several protocols are available, including the use of progesterone, estrogen, human chorionic gonadotropin (hCG), or combinations of these hormones. Recently, there has been increasing interest in using gonadotropin-releasing hormone (GnRH) agonists for luteal phase support. These can be administered as a single dose or in combination with other agents, typically via subcutaneous injection or nasal spray. Common GnRH agonists include Nafarelin (Synarel), Triptorelin, and Buserelin, which may be used as one-time treatments or repeatedly. Studies have shown that GnRH agonist therapy during the luteal phase can significantly increase implantation and live birth rates compared to placebo [2] or progesterone alone [3]. As a result, this approach has gained wide acceptance and is now commonly used in IVF centers worldwide.

In IVF cycles, final oocyte maturation is typically triggered using hCG, a GnRH agonist, or a combination of both - referred to as the "Dual trigger." One advantage of using a GnRH agonist as a trigger is the physiological-like surge in luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resembling the natural cycle. The presence of an FSH surge has been linked to an increased yield of retrieved and mature oocytes through multiple mechanisms [4]. The dual trigger approach has been subject to ongoing debate, particularly regarding patient selection and its overall benefit [5,6]. Nevertheless, multiple prospective studies and meta-analyses have demonstrated that

compared with hCG trigger, the use of the dual trigger is associated with higher rates of oocyte retrieval, maturation, clinical pregnancy, and live births [4,7–9].

To date, studies investigating GnRH agonist support during the luteal phase have focused on cycles in which either hCG or GnRH agonist was used as sole trigger. For instance, luteal phase support has been provided using a single 0.1 mg dose of Decapeptyl six days after intracytoplasmic sperm injection (ICSI) or oocyte retrieval following a trigger with 250 µg Ovitrelle [10], 10,000 IU Chorigon [11], or 0.2 mg Decapeptyl [12]. In other studies, nasal Nafarelin at a dose of 200 µg twice daily for two weeks was administered after a trigger with 250 µg Ovitrelle [3] or 0.2 mg Decapeptyl [13]. Another study explored luteal support with 100 µg of Buserelin administered three times daily for 16 days, beginning the day after a 200 µg Buserelin trigger [14].

To the best of our knowledge, no studies have yet examined the use of GnRH agonist treatment for luteal phase support following a dual trigger.

2. Materials and Methods

Study Design

This retrospective case-control study was conducted at a single tertiary IVF center between June 2020 and April 2025. Data was collected from patients' medical records and anonymized for analysis. The study was approved by the Institutional Ethics Committee (0359-24-SZMC) and adhered to the ethical principles outlined in the Declaration of Helsinki.

Study Participants and Protocol

The study included women who underwent treatment with the GnRH antagonist protocol. Ovarian stimulation was initiated with gonadotropins (GT) on days 2–3 of the menstrual cycle. Upon identification of a leading follicle ≥ 14 mm, a GnRH antagonist (Orgalutran or Cetrotide) was administered daily alongside GTs until trigger for final oocyte maturation. Ovulation was triggered when three or more follicles ≥ 17 mm were observed. Patients were assigned to one of two groups based on the trigger protocol; the study group included women who received a dual trigger with 250 µg Ovitrelle and 0.2 mg Decapeptyl, while the control group included women who received an hCG trigger with 250 µg Ovitrelle.

On the evening of ovum pick-up (OPU), all patients began luteal support with Nafarelin (Synarel nasal spray 200 µg twice daily), continued for two weeks until the day of serum β -hCG testing. Luteal support was discontinued at that point, regardless of pregnancy outcome.

Retrieved oocytes were fertilized using either ICSI or conventional IVF. Embryos were cultured and assessed for quality by the IVF laboratory team until the day of embryo transfer (ET). Embryo quality was scored using standard morphological criteria. For the statistical analysis, in cases where more than one embryo was transferred, the morphology score of the more advanced and higher-grade embryo in each cycle was used.

Inclusion criteria included women aged 18–45 years, BMI 19–35 kg/m², who underwent IVF using an antagonist protocol with a fresh ET. Exclusion criteria were triggering with GnRH agonist alone, use of additional luteal support besides Nafarelin, recurrent implantation failure (defined as three consecutive IVF cycles with high-quality ET and no pregnancy), uterine malformations, hydrosalpinx, moderate to severe endometriosis, and use of surgically retrieved sperm.

Outcomes

The primary outcome was positive pregnancy rate (defined as serum β -hCG ≥ 25 IU/L, measured two weeks after ET). The secondary outcomes included IVF cycle outcomes (the numbers of retrieved oocytes, metaphase II [M2] oocytes, 2 pronuclei [2PN] zygotes, fertilization and blastulation rates), and pregnancy outcomes, including clinical pregnancy (defined as the presence of fetal heartbeat on ultrasound), miscarriage rate, and live birth rate.

Statistical Analysis

Continuous descriptive data are presented as means ± standard deviation, medians (interquartile range), while categorical data are presented as frequencies and percentages. Groups were compared by Student’s t-test, Wilcoxon rank sum test, χ^2 , Fisher’s exact test, as appropriate, by the distribution of the variable.

Logistic regression was used to assess predictors of pregnancy. Variables included in the regression were: women’s age, men’s age, BMI, infertility diagnosis, maximal endometrial thickness, peak E2, sperm parameters (volume, count, motility), total GT dose, and final oocyte maturation trigger group.

Propensity score matching was performed to create treatment groups with well-balanced baseline characteristics. The propensity score was estimated using logistic regression, with the final oocyte maturation trigger as the exposure variable. Matching was conducted using nearest-neighbor matching with a caliper of 0.1 on the propensity score. Not all relevant variables could be included in the matching because of missing data; for these variables, balance was evaluated after matching to ensure that no residual confounding remained. Covariate balance was assessed using standardized mean differences (SMD), where an SMD<0.1 indicated good balance.

P-value <0.05 was considered significant, and all analyses were computed in R Studio version 4.3.2.

3. Results

A total of 284 women were included in the study; of these, 168 received an hCG trigger, while the other 116 received a dual trigger.

Baseline characteristics are shown in Table 1. Women in the dual trigger group were older than those in the hCG group (median 36.24 [30.6, 41] vs. 32.3 [28,37], $p < 0.01$). They also exhibited lower ovarian reserve parameters, with a significantly reduced antral follicular count (AFC) compared to the hCG group (7.00 [3.5, 18] vs. 17.50 [13.8, 24], $p = 0.05$). The most common indications for IVF in the dual trigger group were age-related and low ovarian reserve (28%), whereas in the hCG group, male factor infertility was more prevalent (36.8%).

Table 1. Baseline characteristics.

	hCG trigger n=168	Dual trigger N=116	p
Age of woman (years)	32.3 [28,37]	36.24 [30.6, 41]	<0.01
Age of man (years)	35 [31,39]	36 [33,41]	0.06
BMI	24.6 [21.8, 29.4]	25.0 [21.3, 30.9]	0.99
Smoking, n (%)	20 (11.9)	7 (6.0)	NA
Obstetric history			
G	1.1 (1.3)	1.4 (1.5)	0.08
P	0.8 (1.0)	0.9 (1.2)	0.44
SA	0.3 (0.9)	0.5 (0.8)	0.22
TOP	0.01 (0.1)	0.03 (0.2)	0.43
EUP	0.02 (0.2)	0.04 (0.2)	0.54
CS	0.2 (0.5)	0.2 (0.6)	0.92
Infertility diagnosis, n (%)			0.01
Mechanical factor	8/160 (5)	3/100 (3)	
Male factor	59/160 (36.8)	25/100 (25)	
Anovulation	5/160 (3.1)	4/100 (4)	
Unexplained	43/160 (26.9)	23/100 (23)	
Age related	14/160 (8.8)	19/100 (19)	
Low reserve	5/160 (3.1)	9/100 (9)	
Mild endometriosis	0	2/100 (2)	

	hCG trigger n=168	Dual trigger N=116	p
Combined infertility	26/160 (16.3)	15/100 (15)	0.59
IVF for PGT, n (%)	12 (7.1)	11/116 (9.6)	
Infertility classification, n (%)			0.09
Primary	80/161 (49.7)	64/104 (61.5)	
Secondary	81/161 (50.3)	40/104 (38.4)	
Ovarian reserve parameters			
FSH (IU/L)	7 [5.7, 8.7]	7.5 [5.7, 9.5]	0.44
E2 (pmol/L)	158 [126.5, 207.5]	156 [127,219]	0.74
AFC	17.50 [13.8, 24]	7.00 [3.5, 18]	0.05
AMH (ng/ml)	1.74 [0.6, 2.9]	1.42 [0.7, 2.7]	0.80
Sperm parameters			
volume (ml)	3.12 (1.69)	3.53 (1.80)	0.21
count (million/ml)	40.77 (38.27)	30.05 (24.55)	0.11
motility (%)	49.41 (21.11)	41.90 (18.59)	0.07

Mean (SD) or median [IQR] is shown for continuous variables, and percentages are shown for dichotomous variables.

AFC= Antral follicle count, AMH=Anti-Müllerian hormone, BMI=Body Mass Index, CS=Caesarean section, E2=estradiol, EUP=extrauteinr pregnancy, FSH=Follicle Stimulating Hormone, G=gravity, P=parity, PGT=preimplantation genetic testing, SA=spontaneous abortion, TOP=termination of pregnancy.

IVF cycle characteristics are presented in Table 2. In the hCG group, most GT regimens included recombinant FSH (61.3% vs. 32.8% in the dual trigger group). Conversely, in the dual trigger group, a higher proportion of patients received highly purified human menopausal gonadotropin (HP-hMG) (22.4% vs. 4.8% in the hCG group, p < 0.01).

Table 2. Cycle characteristics.

	hCG trigger n=168	Dual trigger n=116	p
Cycle №	1.8 (1.4)	2.0 (1.5)	0.19
GT ingredients, n (%)			<0.01
FSH	103/168 (61.3)	38/116 (32.8)	
FSH+LH	57/168 (33.9)	52/116 (44.8)	
HP hMG	8/168 (4.8)	26/116 (22.4)	
Total GT (IU)	2041 [1484,3000]	3000 [2128.5, 4050]	<0.01
Stimulus Duration (days)	10 [9,11]	10 [9,11]	0.267
Peak E2 (pmol/L)	5035 [3489.5, 7122.5]	6348 [4262, 8254.8]	<0.01
Max. endometrial thickness (mm)	10.5 [8.8, 11.6]	10 [8.7, 12]	0.80
№ follicles >14 mm	7 [5,8]	6 [4,8]	0.09
№ oocytes retrieved	10 [5,13]	10 [6,15]	0.20
№ M2 oocytes	7 [4,10]	8 [5,11]	0.22
% M2 oocytes	82.1 [66.7, 91.1]	80 [66.7, 87.9]	0.36
№ 2PN zygotes	5 [3,7]	5 [3,8]	0.31
Fertilization method, n (%)			0.29
ICSI	160/166 (96.4)	94/101 (94.9)	
IVF	2/166 (1.2)	0	
IVF+ICSI	4/166 (2.4)	5/101 (5.1)	
Fertilization rate (%)	71.2 (22.3)	70.9 (21.6)	0.91
Blastulation rate (%)	27.06 (31.76)	20.22 (26.47)	0.10

	hCG trigger n=168	Dual trigger n=116	p
Embryo characteristics			
No ET	1.4 (0.5)	1.5 (0.6)	0.05
Day of ET, n (%)			
2	31/168 (18.4)	24/116 (20.7)	0.55
3	77/168 (45.8)	50/116 (43.1)	
4	7/168 (4.2)	8/116 (6.9)	
5	50/168 (29.8)	34/116 (29.3)	0.42
6	3/168 (1.8)	0	
Embryo morphology score, n (%)			
No of cells	6.6 (2.3)	6.5 (2.3)	0.77
Score 1.0	14/115 (12.2)	10/82 (12.2)	0.76
Score 1.5	36/115 (31.3)	35/82 (42.7)	
Score 2.0	35/115 (30.4)	25/82 (30.5)	
Score 2.5	16/115 (14.0)	11/82 (13.4)	
Score 3.0	1/115 (0.9)	0/82	
Blastocyst morphology score, n (%)			
Good	19/53 (35.8)	11/34 (32.3)	0.87
Fair	25/53 (47.1)	18/34 (52.9)	
Low	1/53 (1.8)	1/34 (2.9)	
OHSS rates, n (%)			
Early, mild	9/168 (5.4)	2/116 (1.7)	0.29
Early, moderate	3/168 (1.8)	2/116 (1.7)	0.84
Late, mild	4/168 (2.4)	0	Na

Mean (SD) or median [IQR] is shown for continuous variables, and percentages are shown for dichotomous variables.

E2=estradiol, ET=embryo transfer, FSH=FSH=Follicle Stimulating Hormone, GT=gonadotropin, HP hMG=highly purified human menopausal gonadotropin, ICSI=Intracytoplasmic sperm injection, IVF= in vitro fertilization, LH= Luteinizing hormone, M2=metaphase II oocyte, OHSS= Ovarian hyperstimulation syndrome, 2PN=pronuclei,

Women in the dual group required a significantly higher total dose of GT (3000 [2128.5, 4050] vs. 2041 [1484,3000], $p < 0.01$) and achieved higher peak estradiol levels (6348 [4262, 8254.8] vs. 5035 [3489.5, 7122.5], $p < 0.01$). There were no significant differences between the groups in the number of retrieved oocytes, M2 oocytes, 2PN zygotes, fertilization rate, or blastulation rate. There were 20 cases of ovarian hyperstimulation syndrome (OHSS); in the dual trigger group, there were four cases of early OHSS (3.4%), and in the hCG group, there were 12 cases of early OHSS (7.1%) and four cases of late OHSS (2.4%, not significant).

The day and morphology score of the ETs were comparable between the groups.

Pregnancy outcomes are exhibited in Table 3. The positive pregnancy rate was 46.6% in the dual trigger and 41.1% in the hCG groups ($p = 0.38$). There were no significant differences in pregnancy outcomes between the groups in terms of live birth (37% vs. 31%) and miscarriage rates (8.6% vs. 6%), respectively.

Table 3. Pregnancy Outcomes.

	hCG trigger n=168	Dual trigger n=116	p
<i>Serum test results</i>			
Measurement day from ET	13.0 (1.5)	13.6 (1.6)	0.02
Progesterone (nmol/L)	59.2 (64.1)	61.3 (61.3)	0.81
E2 (pmol/L)	3111.9 (4505.7)	2733.5 (3493.5)	0.50
βhCG (IU/L)	239.2 (736.6)	221.0 (358.8)	0.81
Positive pregnancy rate (β-hCG ≥25), n (%)	69/168 (41.1)	54/116 (46.6)	0.38
Clinical pregnancy, n (%)	63/168 (37.5)	53/116 (45.7)	0.31
Implantation Rate	34.1 (44.2)	36.3 (42.4)	0.69
Pregnancy outcome, n (%)			0.45
No pregnancy	99/168 (59.0)	62/116 (53.4%)	
Missed abortion	10/168 (6.0)	10/116 (8.6)	0.50
Live birth	52/168 (31.0)	43/116 (37.0)	0.31
Chemical pregnancy	5/168 (3.0)	1/116 (0.9)	
EUP	1/168 (0.6)	0	
TOP	1/168 (0.6)	0	
Time of pregnancy loss (weeks)	8 (3.2)	7 (3.7)	0.50
Pregnancy complications, n (%)			0.32
Antepartum bleeding	5/52 (9.6)	1/43 (2.3)	
IUGR	3/52 (5.8)	3/43 (7.0)	
GDM	2/52 (3.8)	4/43 (9.3)	
PIH\ PET	1/52 (1.9)	1/43 (2.3)	
Other	7/52 (13.4)	2/43 (4.7)	
Newborn sex, n (%)			0.45
Female	19/41 (46.3)	11/34 (32.4)	
Male	22/41 (53.7)	23/34 (67.6)	
Gestational age at delivery (Weeks)	37.83 (2.30)	38.55 (1.77)	0.14
Type of delivery, n (%)			0.63
Vaginal birth	24/41 (58.5)	23/34 (67.6)	
Caesarean section	17/41 (41.5)	11/34 (32.4)	
Birth weight (grams)	2764.1 (524.1)	3119.1 (562.3)	0.01
<i>Mean (SD) is shown for continuous variables, and percentages are shown for dichotomous variables.</i>			
<i>E2=estradiol, EUP=extrauterine pregnancy, GD Gestational diabetes mellitus, IUGR= Intrauterine growth restriction, PET= Pre-eclampsia, PIH= Pregnancy-Induced Hypertension, TOP=termination of pregnancy</i>			

An univariable logistic regression was conducted to examine the association between individual variables and positive pregnancy rate. Variables assessed included age, BMI, obstetric history, infertility diagnosis, total GT dose, endometrial thickness, peak E2 level, sperm parameters, number of ETs, day of ET, and embryo grade. Four statistically significant variables (maternal age, endometrial thickness, peak E2, and day of ET) were entered into a multivariable logistic regression model, together with trigger for final oocyte maturation as a clinically relevant factor (Table 4). The multivariable model demonstrated that the only variable independently associated with a positive pregnancy outcome was maternal age (OR = 0.95; 95% CI: 0.90-0.99; p = 0.02). Notably, the trigger for final oocyte maturation was not associated with a positive pregnancy outcome (Odds Ratio [OR] = 1.24; 95% Confidence Interval [CI]: 0.70-2.19; p = 0.5).

Table 4. Logistic regression analysis: significant association with pregnancy.

	OR	95% CI	p
Age of woman (years)	0.95	0.90, 0.99	0.02
Max. endometrial thickness (mm)	1.11	0.99, 1.25	0.07
Peak E2 (pmol/L)	1.00	1.00, 1.00	0.07
Day of ET	1.18	0.93, 1.50	0.2
Trigger for final oocyte maturation	1.24	0.70, 2.19	0.5

CI=confidence interval, E2=estradiol, ET=embryo transfer, OR=odds ratio

Propensity score matching was used to identify a group of patients with similar baseline characteristics between the two groups. The multiple logistic regression model was used to calculate the propensity score, with trigger for final oocyte maturation as the dependent variable (see Appendix Table 1). A total of 53 women were included in both the dual trigger and hCG groups. No significant differences were observed between the groups in either IVF cycle outcomes or pregnancy outcomes.

4. Discussion

This study aimed to investigate the use of GnRH agonist as sole luteal phase support following dual trigger compared with hCG trigger for final oocyte maturation. Our findings show no significant difference in positive pregnancy rate between the dual trigger and hCG groups (46.6% vs. 41.1%, respectively). This supports the rationale for GnRH agonist treatment at the luteal phase following a dual trigger that includes GnRH agonist. Additionally, the study reinforces the association between luteal support with GnRH agonist and a high pregnancy rate, with a positive hCG rate of 44.6% among all women included in the study.

We observed comparable IVF outcomes between the dual trigger and hCG groups, in terms of the number of retrieved oocytes, M2 oocytes, 2PN zygotes, fertilization rate, blastulation rate, morphology score of embryos and blastocysts, and OHSS rate. Prior studies comparing these groups have reported inconsistent findings, as some found similar numbers of oocytes, M2 oocytes, and embryos between the groups [15–17], while others demonstrated improved outcomes in the dual trigger group [4–8].

We also observed comparable pregnancy outcomes between the study groups, including clinical pregnancy, implantation, missed abortion, live birth, pregnancy complications, and delivery parameters. Similar to the IVF cycle outcomes discussed above, some previous studies have reported improved pregnancy outcomes with a dual trigger [5–8,15], whereas others found no benefit compared with hCG alone [4,17].

A higher pregnancy rate reported in previous studies among women receiving a dual trigger may also be attributed to the direct effect of the GnRH agonist on the endometrium during the luteal phase. Isoforms of GnRH are expressed in several extra-pituitary tissues, including the testis, prostate, mammary glands, endometrium, oviducts, ovary, and placenta [18]. In the endometrium, GnRH receptors are localized in epithelial glands and stromal cells, with peak expression during the luteal phase [19]. GnRH plays a regulatory role in the endometrial environment, supporting the interaction between the embryo and endometrium through several mechanisms. It promotes cell motility of decidual stromal cells, a process essential for implantation [20], and modulates folliculogenesis, implantation, and embryo development by regulating the synthesis and activity of insulin-like growth factor (IGF) and epidermal growth factor (EGF) [21]. These findings highlight GnRH agonists as potential therapeutic targets for improving implantation rates in infertility treatments. Supporting this concept, Schachter et al. suggested that administration of GnRH agonist as part of the dual trigger in GnRH antagonist protocols may displace the antagonist from the endometrial receptors owing to the agonist’s higher receptor affinity. This displacement reactivates

the GnRH receptors, leading to post-receptor effects that enhance implantation and pregnancy rates [22]. An observation of higher clinical pregnancy rates following a dual trigger with a fresh ET compared with a frozen-thawed ET provides additional evidence that the benefit of the dual trigger may be mediated through increased endometrial receptivity for embryos [7].

In our study, women who received hCG as the sole trigger were subsequently provided luteal support with a GnRH agonist. This approach likely provided a similar endometrial exposure to GnRH agonist as in dual trigger, which may explain the comparable pregnancy outcomes observed in both groups. Our interpretation is consistent with that of Tesarik et al., who conducted a prospective study in which patients who underwent either a long GnRH agonist protocol or GnRH antagonist protocol were randomized to receive a mid-luteal GnRH agonist (administered six days after ICSI) or placebo [10]. The addition of GnRH in the mid-luteal phase was associated with improved implantation and live birth rates. The authors concluded that GnRH agonist improves implantation through a direct effect on the endometrium, on the embryo (supported by higher serum β -hCG levels), and on the corpus luteum (reflected by increased estradiol and progesterone levels).

It should be noted that in our study, the dual trigger group included women of advanced reproductive age (36.24 [30.6, 41] in the dual trigger group and 32.3 [28,37] in the hCG group, $p < 0.01$). Two previous studies that explored the effect of dual trigger in advanced maternal age reported contrasting outcomes: while Maged et al. [5] observed improved IVF results in poor responders with a mean age of 39 receiving a dual trigger, Zhou et al. [17] found no significant differences in oocyte yield or pregnancy outcomes among women with an average age of 38 triggered with hCG alone, GnRH agonist alone, or a dual trigger. An important difference between the studies is the hCG dosage used in the dual trigger group; Maged et al. employed a dose of 10,000 IU, whereas Zhou et al. used a lower dose of 2,000 IU.

Logistic regression analysis identified maternal age as a significant predictor of positive pregnancy rate (OR = 0.95; 95% CI: 0.90–0.99; $p = 0.024$), while the trigger type was not. After propensity score matching to equalize baseline characteristics, including age, the trigger type remained unrelated to pregnancy outcomes. Notably, Hass et al. [8] reported higher live birth rates with dual trigger compared with hCG alone (36.2% vs. 22%, $p = 0.03$), though regression analysis suggested that the dual trigger was not independently associated with live birth, but mediated through improved embryo yield and quality.

Women in the dual trigger group were older, had lower AFC (7.00 [3.5, 18] vs. 17.50 [13.8, 24], $p = 0.03$), and were more frequently diagnosed with low ovarian reserve as the indication for IVF (9% vs. 3.1%) compared with those in the hCG trigger group. The effectiveness of the dual trigger in women with poor ovarian response or diminished ovarian reserve (DOR) remains controversial. Previous studies have reported that the dual trigger is superior to hCG alone in women classified as poor responders according to the Bologna criteria, showing improvements in IVF outcomes such as the number of retrieved oocytes, grade 1 embryos, and clinical pregnancy rates [5]. Its use has therefore been recommended in this subgroup to enhance both oocyte yield and the proportion of M2 oocytes [23]. Conversely, a retrospective study of women with DOR, defined by the POSEIDON criteria, found no significant differences in immediate IVF outcomes, including the number of retrieved oocytes and M2 oocytes [24].

The main limitation of our study is the retrospective design, as well as the limited sample size and inability to control all potential confounding factors.

5. Conclusions

Our study supports the concept that administering a GnRH agonist for luteal phase support after a dual trigger for oocyte maturation can achieve comparable IVF and pregnancy outcomes to an hCG trigger. Patients' reports on the convenient use of intranasal GnRH agonists make it an attractive luteal support following a dual trigger. Patients' reports on the convenient use of intranasal GnRH agonists make it an attractive luteal support following a dual trigger.

Further studies are warranted to clearly define the poor responder population and directly compare trigger strategies for oocyte maturation within this subgroup.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Propensity score matching will be published online alongside the manuscript.

Author Contributions: Study concept and design: AH, BA-I, data collection: AH, BE, NR, statistical analysis: AH, data analysis and interpretation: AH, DN, BA-I, writing of the manuscript: AH, BA-I, study supervision: BA-I.

Funding: This research received no external funding. The APC was covered by the 2025 Editorial Board waiver.

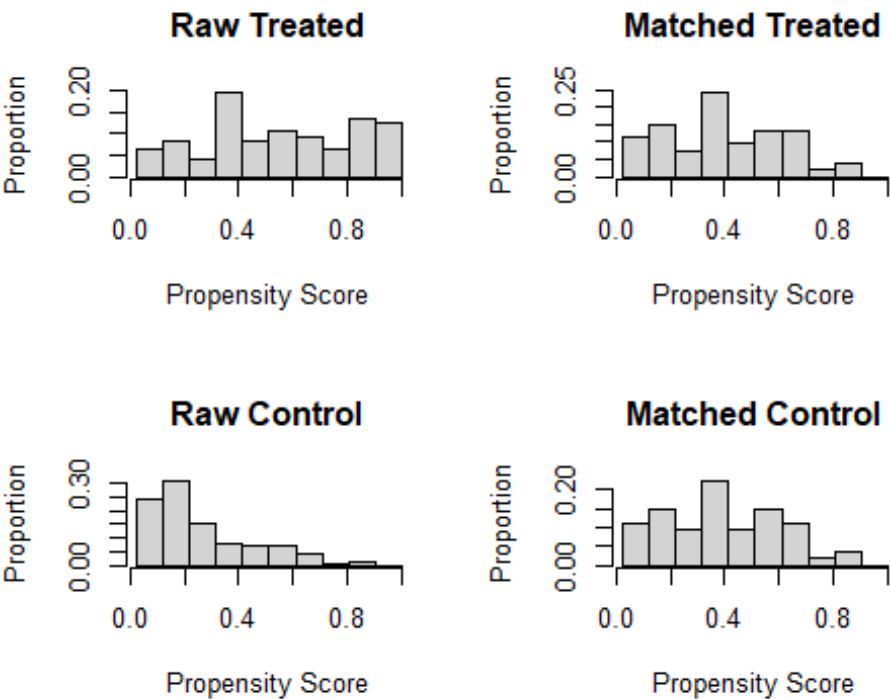
Institutional Review Board Statement: This research was approved by the Institutional Ethics Committee (0359-24-SZMC) and has been conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: The requirement for informed patient consent was waived because of the retrospective nature of the study, and all patient data were fully anonymized before analysis.

Data Availability Statement: Data can be available upon request.

Conflicts of Interest: Ido Ben-Ami serves on the Editorial Board of the Reproductive and Developmental Biology section of *Life*. The authors declare no other conflicts of interest.

Appendix A



Propensity score matching.
Matching covariates post matching.

	hCG trigger (n=53)	Dual trigger (n=53)	p	SMD
Age of woman (years)	33.89 (5.6)	34.15 (6.1)	0.82	0.045
Age of man (years)	35.04 (5.3)	35.55 (6.8)	0.76	0.083
Height (cm)	161.68 (5.3)	161.83 (4.5)	0.91	0.030
weight (kg)	66.96 (15.4)	65.65 (15.8)	0.73	0.084
BMI	25.62 (5.9)	25.18 (6.6)	0.77	0.071

	hCG trigger (n=53)	Dual trigger (n=53)	p	SMD
Smoking	1.00 (0)	1.00 (0)	NaN	<0.001
G	1.06 (1.2)	1.13 (1.1)	0.74	0.066
P	0.74 (0.9)	0.77 (0.8)	0.81	0.046
SA	0.30 (0.7)	0.36 (0.7)	0.68	0.081
TOP	0.02 (0.1)	0.02 (0.1)	1.00	<0.001
EUP	0.02 (0.1)	0.02 (0.1)	1.00	<0.001
CS	0.25 (0.6)	0.25 (0.6)	1.00	<0.001
PGT	0.06 (0.2)	0.08 (0.3)	0.70	0.075
Infertility Dx (%)			1.00	0.194
Tubal	2 (3.8)	2 (3.8)		
Male factor	16 (30.2)	15 (28.3)		
Anovulation	2 (3.8)	1 (1.9)		
Unexplained	11 (20.8)	10 (18.9)		
Age related	6 (11.3)	7 (13.2)		
Combined	11 (20.8)	11 (20.8)		
Low reserve	3 (5.7)	5 (9.4)		
FSH	7.88 (3.6)	8.18 (3.5)	0.74	0.084
E2	164.00 (71.9)	189.95 (116.7)	0.34	0.268
AFC	15.00 (8.6)	17.00 (8.9)	0.72	0.229
AMH	2.68 (3.1)	1.68 (1.0)	0.33	0.440
Cycle №	2.06 (1.7)	1.77 (1.0)	0.30	0.205
Total GT (IU)	2758.87 (1460.5)	2808.0 (1210.2)	0.85	0.037
Stimulus Duration (days)	9.87 (2.2)	9.98 (1.8)	0.77	0.056
Peak E2 (pmol/L)	5777.23 (2685.0)	5681.87 (2799.1)	0.86	0.035
Max. endometrial thickness (mm)	10.61 (2.7)	10.70 (2.9)	0.87	0.031

Mean (SD) is shown for continuous variables, and percentages are shown for dichotomous variables.

Outcomes by trigger group POST MATCHING.

	hCG trigger (n=53)	Dual trigger (n=53)	p
№ oocytes retrieved	9.1 (5.4)	10.3 (6.2)	0.26
№ Mature Oocytes	7.1 (4.1)	7.91(5.2)	0.36
Mature oocytes (%)	79.8 (17.9)	76.6 (18.0)	0.37
№ 2PN	4.9 (3.2)	5.6 (3.9)	0.33
Fertilization rate (%)	72.8 (21.4)	73.3 (20.5)	0.91
№ Blastocysts	1.3 (1.5)	1.5 (2.4)	0.67
Blastulation rate	25.8 (29.2)	18.6 (26.0)	0.27
Early OHSS mild	2/4 (50)	0	0.67
Early OHSS moderate	2/4 (50)	2/2 (100.0)	0.76
Late OHSS mild	2 (100)	0	NA
Progesterone (nmol/L)	55.6 (63.6)	56.8 (62.12)	0.93
βhCG (IU/L)	182.1 (321.8)	182.9 (300.1)	0.99
Estradiol (pmol/L)	2842.6 (4585.9)	2719.3 (3442.3)	0.89
Positive B-hCG pregnancy	18 (34.0)	22 (42.3)	0.50
Clinical pregnancy	17 (33.3)	20 (38.5)	0.74
№ gestational sacs	0.4 (0.6)	0.4 (0.6)	0.65

	hCG trigger (n=53)	Dual trigger (n=53)	p
No fetal hearts	0.3 (0.6)	0.4 (0.6)	0.64
Implantation Rate (%)	27.5 (41.6)	32.7 (44.2)	0.54
Pregnancy outcome (%)			0.52
Missed abortion	5 (27.8)	3 (13.6)	
Live birth	12 (66.7)	18 (81.8)	
Chemical pregnancy	1 (5.6)	1 (4.5)	
Time of pregnancy loss (weeks)]	6 [6,11]	5 [5, 6.5]	0.28
Pregnancy complications (%)			0.26
Antenatal bleeding	2 (3.3)	1 (20)	
IUGR	0	2 (40)	
GDM	1 (16.7)	0	
PIH\PET	0	1 (20)	
Other	3 (50)	1 (20)	
Sex of newborn			0.53
Female	5/10 (50)	3/13 (23)	0.53
Male	5/10 (50)	10/13 (77)	
Gestational age at delivery (Weeks)	37.5 [36.3, 38.8]	39 [38,40]	0.13
Type of delivery			0.72
Vaginal	3/10 (30)	6/13 (46)	
Caesarean section	7/10 (70)	7/13 (54)	
Birth weight (grams)	2953.5 [2692.5, 3141]	3280 [2696.3, 3675]	0.21
<i>Mean (SD) or median [IQR] is shown for continuous variables, and percentages are shown for dichotomous variables</i>			

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