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Original Article

Dual versus Single Ovulation Triggers in In Vitro Fertilization and Intracytoplasmic Sperm Injection: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Infertility remains a significant global health concern. Optimizing hormonal triggers, such as human chorionic gonadotropin (HCG) with or without gonadotropin-releasing hormone (GnRH) agonists, is crucial to enhance reproductive outcomes. We aim to evaluate and compare the reproductive success rates of dual trigger protocols (HCG + GnRH agonist) versus HCG alone in women undergoing assisted reproductive technologies (IVF/ICSI).

Methods: A systematic search was conducted in PubMed, Scopus, and Web of Science for studies published up to January 2025. Studies comparing reproductive outcomes in women undergoing IVF/ICSI who received either dual trigger (HCG + GnRH agonist) or HCG alone were included. Data were analyzed using RevMan version 5.4 and R Studio version 4.4.1. The primary outcome was the clinical pregnancy rate. Secondary outcomes included live birth rate, fertilization rate, and embryo quality metrics.

Results: Seventeen studies with a total of 2,239 women were included: 1,118 in the dual trigger group and1,121in the HCG onlygroup.Thedualtriggergroupshowedsignificantlybetteroutcomesinterms of total oocytes retrieved, fertilized oocytes, follicles >15mm on trigger day, viable embryos, two pronuclei (2PN) formation, clinical pregnancy, biochemical pregnancy, live birth rate, good quality embryos, and fertilization rate.

Conclusions Dual triggering with HCG and GnRH agonist appears to significantly enhance reproductive outcomes compared to HCG alone in women undergoing IVF or ICSI. These findings support the broader adoption of dual trigger protocols in assisted reproductive practice.

1. Introduction

Infertility is defined as a failure to achieve conception after 1 year of regular unprotected sexual intercourse, according to the World Health Organization (WHO). Around 16-17.5% of couples suffer from infertility. [1]. To address these growing health issues, many drugs and interventions have emerged. The most commonly used intervention worldwide was assisted reproductive technology (ART), which is a tool that reshapes human reproduction to help millions of couples suffering from infertility to conceive. It involved In Vitro Fertilization (IVF) and Intracytoplasmic sperm injection (ICSI) [1, 2] In the 1990s, ICSI technology emerged as an intervention aid, especially in male infertility, to achieve a higher pregnancy rate [3, 4]. To improve the success rate and improve pregnancy outcomes in ART technology, many protocols have emerged, such as Controlled ovulation hyper stimulation (COH); these treatment protocols are used during IVF intervention to retrieve high-quality numbers of eggs and embryos and thus improve the success rate of pregnancy [5]. The basis of using COH depends on mimicking physiological luteinizing hormone (LH) surge through administration of a single dose of human chorionic gonadotropin (HCG) after 18 hours of LH surge to stimulate division of meiosis and final follicular maturation [6, 7].

However, hCG injections can trigger final oocyte maturation even without a concomitant FSH surge, leading to a prolonged luteotropic effect that is associated with an increased risk of ovarian hyperstimulation syndrome (OHSS).[8, 9] In response to reduce this risk, several studies searched for ovulation triggers other than HCG, for example, GnRH agonist (GnRH) was first introduced thirty years ago [10]. GnRH has a pharmacological action that mimics the physiological mid-cycle hormonal profile that occurs during the natural ovulation through inducing simultaneous surges of both LH and FSH to stimulate oocyte maturation [11]. By adding benefits for reducing the prevalence of OHSS[12]. This reduces risk through endogenous release of physiological LH, which is more physiological than HCG [13]. Although other studies found that using GnRH trigger leads to luteal phase defect resulting in decreased implantation, pregnancy rate, and abortion, notably in fresh embryo transfer cycles than HCG triggers IVF cycles [8].

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In recent years, many studies have used both GnRH and a low dose of HCG. They called "Dual Triggers," which has been very effective for final oocyte maturation [14], increasing pregnancy rate, and decreasing risk of OHSS compared with single HCG triggers [15]. We aimed from this systematic review and meta-analysis to investigate Dual triggers versus single HCG triggers in women undergoing IVF/ICSI cycles in different reproductive outcomes.

2. Methods

2.1. Study Registration

This study is a systematic review and meta-analysis design, outlined in the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [16]. Each procedural step was precisely executed according to the methodologies outlined in the Cochrane Handbook for Systematic Reviews of Interventions [17]. This review was registered in the PROSPERO database under registration number (CRD420251036833) on 13 March 2024.

2.2. Literature Search Strategy and Information Sources

We searched for a comprehensive search of many electronic databases, including MEDLINE via PubMed, Scopus, Web of Science, and previously published meta-analyses. The search strategy incorporated a combination of Medical Subject Headings (MeSH) and free-text terms, integrated with Boolean operators ("AND" and "OR") to ensure a balance between sensitivity and specificity. The key search terms included Articles were identified using the following strategy: ("reproductive outcome" OR "pregnancy outcome" OR "birth outcome") AND "in vitro fertilization" OR "IVF" OR "ICSI" AND "HCG))" OR "human chorionic gonadotropin" AND "GnRH" OR "gonadotropin-releasing hormone". The detailed search strategy is included in the Online Resource. No restrictions by language or publication period were employed.

2.3. Eligibility Criteria

Studies were eligible if they included women of childbearing age undergo IVF/ICSI, treated with dual trigger treatment combination between (HCG + GnRH agonist) as a primary intervention compared to (HCG alone) and reported outcomes such as mature oocyte, total oocyte, clinical pregnancy, biochemical pregnancy, implantation, abortion, fertilization, ongoing pregnancy, live birth, good quality embryo, embryo transferred, duration of stimulation, follicle size, oocytes retrieval, and duration of stimulation. Eligible study designs included randomized controlled trials (RCTs). On the other side, excluded Study designs involving observational, retrospective, non-RCTs, case series, case reports, reviews, and expert opinions. Additionally, studies that were only available as conference abstracts or protocols, those lacking complete full texts, and non-English studies were excluded.

2.4. Study Selection

Four authors [M.W, A.E, E.M, and A.M] independently screened the studies according to the previously mentioned eligibility criteria. Where Eligibility screening was performed in two steps by Rayyan software [18], the first step was to screen the titles and abstracts for eligibility. In the second step, full-text articles of eligible abstracts were retrieved and screened for inclusion eligibility. With discrepancies resolved by consensus or consultation with another reviewer [E.E].

2.5. Primary and secondary outcomes

The primary outcomes of interest were pregnancy outcomes (oocyte, clinical pregnancy, biochemical pregnancy, implantation, and abortion). Whereas, the secondary outcomes were as 2PN, cleavage rate(oocyte &embryo), fertilization, ongoing pregnancy, live birth, good quality embryo, embryo transferred, Viable embryo, cancellation rate, multiple pregnancy, duration of stimulation, follicles >10 mm at trigger day, follicles >15 mm at trigger day, cryopreserved, oocyte /follicle aspirate, oocytes retrieval, duration of stimulation, endometrial thickness on trigger, total dose gonadotropin, estradiol level (E2) on trigger day, and progesterone level on trigger day.

2.6. Data Extraction

Three authors shared independently extracted data using a standardized electronic form, recording key information. The extracted data encompassed several comprehensive categories of information from the included studies. First, they recorded summary information including authors, year, study design, intervention, and measured outcomes from each study. Additionally, they documented baseline characteristics such as authors, year, age, BMI, infertility duration, primary and secondary infertility classifications, causes of infertility including tubal and male factors, and basal hormonal levels including FSH/IU, LH, IU/l, E2 pmol/l, and AMH ng/ml. The extraction process also involved assessing risk of bias domains for each study, along with capturing the study outcomes that were previously identified as primary and secondary endpoints. Discrepancies during data extraction were resolved by re-verification and discussions through the senior investigator. The extracted data were organized into tables to ensure consistency and facilitate subsequent analysis.

2.7. Quality Assessment

We assessed the risk of bias for randomized controlled trials (RCTs) using the Risk of Bias 2.0 (RoB 2) tool [17]. Bias was evaluated by an intention-to-treat perspective across seven key domains. These domains included random sequence generation, allocation concealment, deviations from intended interventions, measurement of the outcome, including blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain and the overall study were assigned a risk of bias rating of 'low', 'some concerns', or 'high'. An overall 'low' risk of bias was given only if all domains were rated 'low'; an overall 'some concerns' rating was assigned if one or more domains were rated 'some concerns'; and an overall 'high' risk of bias was assigned if one or more domains were rated 'high' **Figure S2**. Evaluating domains such as randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. One reviewer performed the assessments, and discrepancies were resolved through discussion with the senior author.

2.8. Statistical Analysis

All statistical analyses were conducted using Review Manager (RevMan) version 5.4. Continuous outcomes were evaluated using the mean difference (MD) with corresponding 95% confidence intervals (CI), while dichotomous outcomes were assessed using odds ratios (OR) and the Mantel-Haenszel method. Heterogeneity among the included studies was evaluated using both the Chi-square test and the I^2 statistic. And I^2 value exceeding 50% was interpreted as indicative of significant heterogeneity, warranting the use of a random-effects model. Heterogeneity was interpreted by the Cochrane Handbook (Chapter 9), with I^2 values categorized as follows: 0–40% (low), 30–60% (moderate), 50–90% (substantial), and 75–100% (considerable). A Chi-square p-value of less than 0.1

was considered statistically significant for heterogeneity, while a p-value < 0.05 was deemed statistically significant for all other analyses. To assess potential publication bias, funnel plots were visually inspected, and Egger's regression test was performed using the standard error of the observed outcomes as predictors to detect asymmetry.

Heterogeneity was assessed through visual inspection of the forest plots and measured using the I^2 and Chi-square tests. Heterogeneity was considered significant when the chi-square test p-value is less than 0.1 and the I^2 test is greater than 50%, following the recommendations of the Cochrane Handbook for Systematic Reviews and Meta-Analysis. Using a random effect model for the outcome reveals significant heterogeneity (chi-square p-value < 0.1 and I^2> 50%), and the meta-analysis excludes studies with missing outcomes.

We performed sensitivity analyses to ensure that none of the included studies affected the results and to examine whether the overall effect size is statistically significant among them. In each scenario, we excluded one study to ensure the overall effect size was not dependent on any single study. Additionally, we focused only on RCTS and cohort studies and excluded case-control studies and cross-sectional studies. In cases of significant heterogeneity (Chi-Square P<0.1& I^2 > 50%), sensitivity analyses were conducted to address the heterogeneity. **Figure S1** PRISMA flow diagram for new systematic reviews that included searches of databases and registers only.

3. Results

3.1. Search and Screening:

The initial search yielded 7897 records from three electronic databases, trial registries, and previous meta-analyses. After removing 1022 duplicates, 6875 records remained for title and abstract screening. Of these, 6784 records were excluded based on irrelevance to the research question, inappropriate study design, or population mismatch. The full texts of 91 articles were reviewed for eligibility, and 17 studies met the inclusion criteria. Ultimately, 17 studies were included in qualitative and quantitative synthesis (meta-analysis) (Supplementary file).

3.2. Study Characteristics

A total of 17 studies were included, comprising randomized controlled trials. Intervention groups received human chorionic gonadotropin (HCG) hormones, combined with gonadotropin-releasing hormone (GnRH). At the same time, control groups received human chorionic gonadotropin hormones (HCG) only. Women were predominantly childbearing age, with mean ages ranging from 20 to 40 years **Figure S1**.

3.3. Risk of bias assessment

We assessed the risk of bias in the included studies using The Cochrane risk of bias 2 (RoB 2.") tool used for randomized controlled trial studies (RCTs), where most often of the included RCTs (14 studies) had low risk of bias for overall judgement other than three study was some concerns, where all studies had a low risk of bias judgment for 3 domains (randomization, missing outcome, and selection of reported results), a moderate risk of bias judgment for 2 domains (blinded outcome assessment, and other bias) With only one study high in risk due to not mentioned data about randomization. Careful revision of the data presented in the published articles (**Figure s2**).

3.4. Outcomes

Seventeen studies involving a total of 2239 women were included in this quantitative analysis that compares reproductive outcomes among patients who received human chorionic gonadotropin hormones (HCG) and who received (human chorionic gonadotropin hormones (HCG) combined with gonadotropin-releasing hormone (GnRH)).

3.4.1. Total Oocyte

Four studies [19, 20, 21, 22] involving a total of 380 women measured the total oocyte count. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger favored the dual trigger group (pooled MD: 2.05, 95% CI [0.44; 3.67], P= 0.0125). The Pooled studies were homogenous (Chi-square P= 0.19, I^2= 36.8%) with mild heterogeneity **Figure S3**.

3.4.2. Mature Oocyte (MII)

Twelve studies [23, 8, 24, 25, 2, 22, 26, 27, 28, 29, 30, 11] involving a total of 1714 women measured the MII. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger did not favor either of the two groups (pooled MD: 2.91, 95% CI [-1.03; 6.85], P= 0.148). Pooled studies were not homogenous (Chi-square P< 0.0001, I^2 = 88.3%) **Figure S4**. To resolve the heterogeneity, we conducted a sensitivity analysis in multiple scenarios, excluding one study in each scenario. Heterogeneity was best resolved by omitting Meng-Han Yan, 2023 MD: 0.74, 95% CI [0.50; 0.98], (P = 0.47, I^2 = 0%) **Figure S35**.

3.4.3. Oocyte Retrieval

Eleven studies [23, 8, 25, 2, 26, 27, 28, 29, 31, 30, 11] involving a total of 1528 women measured the oocyte retrieval. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger favored the dual trigger group (pooled MD: 0.71, 95% CI [0.38; 1.03], P< 0.0001). Pooled studies were homogenous (Chi-square P= 0.09, I^2= 37.9%) with mild heterogeneity **Figure S5**.

3.4.4. Fertilized Oocytes

Four studies [19, 2, 26, 31] involving a total of 393 women measured the fertilized oocytes, the overall Mean Difference (MD) between the Dual trigger and the HCG trigger favored the dual trigger group (pooled MD: 0.50, 95% CI [0.12; 0.87], P= 0.0098). Pooled studies were homogenous (Chi-square P= 0.55, I^2= 0.0%) **Figure S6**.

3.4.5. Cryopreserved Oocyte

Four studies [8, 24, 29, 31], involving a total of 393 women, measured the cryopreserved oocyte. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger did not favor either of the groups (pooled MD: 0.87, 95% CI [- 0.04; 1.79], P=0.06). Pooled studies were not homogenous (Chi-square P=0.02, I^2 = 68.9%). **Figure S7**. To resolve the heterogeneity, we conducted a sensitivity analysis in multiple scenarios, excluding one study in each scenario. Heterogeneity was best resolved by excluding the study of Svenstrup (2024 (I^2 = 24.3%) **Figure S28**.

3.4.6. Follicles > 10mm on trigger day

Four studies [8, 20, 27, 31], involving a total of 488 women, measured the Follicles > 10mm on the trigger day. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger did not favor either of the groups (pooled MD: 0.37, 95% CI [- 0.24; 0.97], P= 0.23). Pooled studies were homogenous (Chi-square P= 0.41, I^2= 0.0%) **Figure S8**.

Table 1: Baseline characteristics and hormonal parameters across included studies*

Study ID	Group	Tubal	Male	FSH (IU/l)	LH (IU/l)	E2 (pmol/l)	AMH (ng/ml)
Abed, 2020 [19]	Intervention	14 (35%)	NA	6.81 (2.51)	5.13 (2.63)	36.25 (16.43)	NA
	Control	8 (20%)	NA	6.04 (2.38)	4.98 (2.63)	34.05 (13.33)	NA
Ali, 2020 [23]	Intervention	10 (12.5%)	29 (36%)	5.65 (2.23)	3.74 (2.03)	NA	2.38 (1.59)
	Control	16 (32%)	36 (45%)	5.95 (2.22)	3.75 (2.71)	NA	2.05 (1.34)
Decleer, 2014 [24]	Intervention	NA	NA	6.9 (3.4)	NA	2164.57 (262.13)	NA
	Control	NA	NA	7.5 (2.3)	NA	2207.78 (173.71)	NA
Eftekhar, 2017 [25]	Intervention	NA	NA	6.59 (2.76)	NA	2164.57 (262.13)	NA
	Control	NA	NA	6.14 (2.59)	NA	2207.78 (173.71)	NA
Farouk, 2024 [2]	Intervention	NA	NA	9.27 (0.97)	5.9 (1.3)	46.38 (6.93)	0.674 (0.15)
	Control	NA	NA	9.5 (0.89)	5.8 (0.75)	45.73 (6.46)	0.719 (0.12)
Haas, 2020 [20]	Intervention	NA	17 (22%)	NA	NA	8120 (4273.65)	22.41 (14.4)
	Control	NA	17 (21%)	NA	NA	6818 (3614.75)	20 (18.18)
Keskin, 2023 [22]	Intervention	NA	NA	NA	NA	NA	2.45 (0.71)
	Control	NA	NA	NA	NA	NA	2.98 (1.44)
Kim, 2014 [26]	Intervention	32 (53.3%)	28 (46.7%)	6.2 (1.9)	5.5 (1.8)	48.9 (18.5)	NA
	Control	35 (58.3%)	25 (41.7%)	6 (2)	5.7 (1.9)	46.7 (14.8)	NA
Maged, 2020 [27]	Intervention	24 (30%)	21 (26.3%)	12.3 (1.8)	6.1 (1.6)	NA	0.9 (0.1)
	Control	26 (32.5%)	20 (25%)	12.2 (1.6)	5.8 (1.2)	NA	0.9 (0.1)
Meng-Han Yan, 2023 [30]	Intervention	14 (35.9%)	24 (61.5%)	6.46 (2.16)	4.95 (3.65)	40 (23.3)	2.96 (1.46)
	Control	18 (52.9%)	16 (47.1%)	6.96 (1.83)	4.33 (1.98)	38.2 (16.1)	3.58 (1.41)
Schachter, 2008 [32]	Intervention	17 (16%)	52 (49.5%)	7.2 (4.1)	NA	NA	NA
	Control	14 (13%)	50 (47%)	6.9 (2.8)	NA	NA	NA
Singh, 2023 [29]	Intervention	NA	NA	5.82 (1.7)	4.38 (1.89)	2539.86 (252.8)	2.75 (0.87)
	Control	NA	NA	5.54 (1.77)	4.17 (1.93)	2765.86 (271.29)	2.79 (0.84)
Svenstrup, 2024 [31]	Intervention	2 (8%)	10 (40%)	6.2 (1.5)	7.8 (4.3)	NA	NA
	Control	1 (5%)	6 (27%)	5.7 (1.8)	5.9 (3.0)	NA	NA
Zhou, 2022 [15]	Intervention	93 (56.7%)	20 (12.2%)	9.83 (3.58)	4.86 (2.53)	164.13 (74.69)	1.77 (1.84)
	Control	89 (54.3%)	29 (17.7%)	9.63 (3.07)	4.9 (2.58)	163.69 (71.71)	1.84 (1.51)
Mahajan, 2016 [28]	Intervention	NA	NA	7.7 (3.0)	5.3 (3.1)	NA	2.3 (1.3)
	Control	NA	NA	7.2 (2.5)	4.8 (2.8)	NA	2.0 (1.0)
Alleyassin, 2018 [8]	Intervention	NA	NA	4.91 (2.30)	8.31 (4.32)	NA	4.29 (3.5)
	Control	NA	NA	5.54 (2.45)	10.22 (7.29)	NA	3.72 (2.39)
Humaidan, 2006 [21]	Intervention	NA	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA	NA

AMH, anti-Müllerian hormone; E2, estradiol; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HCG, human chorionic gonadotropin; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; LH, luteinizing hormone; NA, not available. *Note: Continuous variables are described as Mean (SD), and the categorical variables are described as N (%).

3.4.7. Follicles >15mm on trigger day

Five studies [25, 27, 29, 30, 11], involving a total of 816 women, measured the Follicles > 15mm on the trigger day. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger favored the dual trigger group (pooled MD: 0.51, 95% CI [0.16; 0.86], P= 0.004). Pooled studies were homogenous (Chi-square P= 0.40, I^2 = 0.0%) **Figure S9**.

3.4.8. Cleavage Rate Oocyte/ Embryo

Four studies [25, 27, 31, 11], involving a total of 741 women, measured the cleavage rate of oocyte/embryo. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger did not favor either of the two groups (pooled MD: 0.88, 95% CI [- 0.06; 1.82], P=0.06). Pooled studies were not homogenous (Chi-square P= 0.09, I^2= 53.2%). **Figure S10**, to resolve the heterogeneity, we

Table 2: Baseline demographic and infertility characteristics across included studies

Study ID	Group	Age (Mean ± SD)	BMI	Infertility duration (years)	Primary infertility	Secondary infertility
Abed, 2020 [19]	Intervention	28.63 (4.71)	26.82 (3.21)	6.1 (3.46)	29 (72.5%)	11 (27.5%)
	Control	28.18 (5.88)	26.11 (3.40)	6.7 (4.4)	31 (77.5%)	9 (22.5%)
Ali, 2020 [23]	Intervention	29.88 (4.45)	27.25 (3.52)	7.3 (4.16)	NA	NA
	Control	30.45 (4.55)	27.96 (4.08)	7.39 (4.23)	NA	NA
Decleer, 2014 [24]	Intervention	30 (3.6)	23.8 (4.6)	NA	NA	NA
	Control	30.5 (4.1)	23.5 (5.1)	NA	NA	NA
Eftekhar, 2017 [25]	Intervention	30.06 (5.3)	24.13 (2.87)	6.34 (3.85)	71 (71.3%)	27 (28.7%)
	Control	30.49 (4.79)	24.07 (2.98)	6.23 (4.09)	78 (78.4%)	20 (21.6%)
Farouk, 2024 [2]	Intervention	41 (1.12)	29.6 (1.77)	NA	NA	NA
	Control	41 (0.99)	29.9 (1.86)	NA	NA	NA
Haas, 2020 [20]	Intervention	35.4 (3.52)	23.6 (3.52)	NA	NA	NA
	Control	36 (3.55)	24.1 (4.85)	NA	NA	NA
Keskin, 2023 [22]	Intervention	34.23 (4.62)	NA	NA	NA	NA
	Control	32.75 (4.65)	NA	NA	NA	NA
Kim, 2014 [26]	Intervention	36.2 (3.7)	21.7 (2.0)	46.6 (24.2)	NA	NA
	Control	35.8 (3.8)	21.4 (2.2)	49 (29.1)	NA	NA
Maged, 2020 [27]	Intervention	39.1 (2.5)	27.3 (1.8)	5.7 (3.1)	NA	NA
	Control	38.9 (2.2)	26.9 (1.4)	5.2 (2.9)	NA	NA
Meng-Han Yan, 2023 [30]	Intervention	31.26 (4.05)	22.5 (4.65)	3 (2.5)	19 (48.7%)	20 (51.3%)
	Control	30.97 (3.65)	22.1 (4.0)	3 (2.75)	24 (70.6%)	10 (29.4%)
Schachter, 2008 [32]	Intervention	33.7 (5.6)	NA	NA	NA	NA
	Control	34.7 (4.7)	NA	NA	NA	NA
Singh, 2023 [29]	Intervention	30.98 (4.34)	24.37 (3.59)	NA	NA	NA
	Control	30.88 (3.70)	24.6 (2.64)	NA	NA	NA
Svenstrup, 2024 [31]	Intervention	30.1 (3.9)	23.93 (3.88)	2 (1.58)	NA	NA
	Control	30.9 (3.6)	24.7 (5.66)	2.3 (0.79)	NA	NA
Zhou, 2022 [15]	Intervention	38.49 (3.19)	22.49 (2.62)	4.56 (3.54)	68 (41.5%)	96 (58.5%)
	Control	38.88 (2.95)	22.6 (2.53)	4.59 (3.6)	66 (40.2%)	98 (59.8%)
Mahajan, 2016 [28]	Intervention	32.4 (4.5)	25.8 (3.9)	NA	NA	NA
	Control	33.1 (4.1)	24.2 (3.2)	NA	NA	NA
Alleyassin, 2018 [8]	Intervention	32.09 (5.52)	NA	NA	NA	NA
	Control	31.57 (6.02)	NA	NA	NA	NA
Humaidan, 2006 [21]	Intervention	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA

BMI, body mass index; NA, not available; SD, standard deviation.

conducted a sensitivity analysis in multiple scenarios, excluding one study in each scenario that did not solve the heterogeneity

3.4.9. Viable embryo

Three studies [27, 29, 11] involving a total of 588 women, measured the viability of the embryo. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger favored the dual trigger group (pooled MD: 0.98, 95% CI [0.33; 1.62], P= 0.002). Pooled studies were not homogenous (Chi-square P= 0.06, I^2= 63.8%). **Figure S11** shows the results of a sensitivity analysis conducted in multiple scenarios, excluding one study in each scenario. Heterogeneity was best resolved by excluding the study of Singh (2023 (P = 0.22, I^2 = 0%), (MD: 0.73, 95% CI [0.46; 1.00]) **Figure S33**.

3.4.10. Duration of Stimulation

Sixteen studies, [23, 8, 24, 25, 2, 20, 21, 22, 26, 33, 27, 28, 32, 29, 31, 30, 11], A total of 2159 women were involved, and the duration of stimulation was measured. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger favored the HCG group (pooled MD: 0.16, 95% CI [0.05; 0.28], P= 0.004). Pooled studies were homogenous (Chi-square P= 0.135, I^2= 28.7%) **Figure S12**.

3.4.11. Endometrial thickness on trigger day

Seven studies [23, 8, 2, 26, 27, 32, 31], involving a total of 970 women, measured the endometrial thickness on trigger day. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger favored the HCG group (pooled MD: -0.15, 95% CI

[-0.28; -0.02], P= 0.026). Pooled studies were homogenous (Chi-square P= 0.26, I² = 21.3%). With mild heterogeneity, **Figure S13**.

3.4.12. Estradiol level (E2) on trigger day

Eleven studies [19, 23, 24, 25, 20, 27, 28, 32, 29, 30, 11], involving a total of 1655 women, measured the estradiol level (E2) on trigger day. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger did not favor either of the groups (pooled MD: 86.64, 95% CI [-38.78; 212.06], P=0.175). Pooled studies were not homogenous (Chi-square P< 0.0001, I²= 78.3%) **Figure S14**. We conducted a sensitivity analysis across multiple scenarios, excluding one study in each scenario, to avoid leading to a solution **Figure S29**.

3.4.13. Progesterone level on trigger day

Six studies [19, 28, 32, 29, 31, 30], involving a total of 587 women, measured the Progesterone level on trigger day. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger did not favor either of the two groups (pooled MD: - 1.87, 95% CI [- 5.31; 1.57], P= 0.28). Pooled studies were not homogenous (Chi-square P< 0.0001, I²= 82.8%). In **Figure S15**, we conducted a sensitivity analysis in multiple scenarios, excluding one study in each scenario. Heterogeneity was best resolved by excluding the study of Svenstrup 2024 MD: -0.01, 95% CI [-0.16; 0.14], (P = 0.19, I² = 35.2%) **Figure S32**.

3.4.14. X2 Pronucleate (2PN)

Five studies [24, 28, 29, 30, 11], Involving a total of 697 women, the X2 Pronucleate (2PN) was measured. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger favored the dual trigger group (pooled MD: 1.89, 95% CI [- 0.07; 3.85], P= 0.058). Pooled studies were not homogenous (Chi-square P < 0.0001, I²= 88.6%). In **Figure S16**, we conducted a sensitivity analysis in multiple scenarios, excluding one study in each scenario. Heterogeneity was best resolved by excluding the study of Meng Han, 2023, with (MD: 0.91, 95% CI [0.0, 1.82]) I²= 63.0%) **Figure S31** .

3.4.15. Biochemical Pregnancy Rate

Fifteen studies [19, 23, 8, 25, 2, 20, 21, 22, 33, 27, 32, 29, 31, 30, 11], involving a total of 1818 women, measured the Clinical Pregnancy. The overall Risk Ratio (RR) between the Dual trigger group and the HCG trigger group favored the dual trigger group (pooled RR: 1.30, 95% CI [1.15; 1.46], P< 0.0001). Pooled studies were homogenous (Chi-square P= 0.21, I²= 21%) **Figure S34**.

3.4.16. Clinical pregnancy

Six studies, [23, 8, 25, 2, 27, 11], involving a total of 925 women, measured the biochemical Pregnancy. The overall Risk Ratio (RR) between the Dual trigger group and the HCG trigger group favored the dual trigger group (pooled RR: 1.26, 95% CI [1.02; 1.55], P= 0.031). Pooled studies were homogenous (Chi-square P= 0.52, I²= 0.0%) **figure S36**.

3.4.17. Ongoing Pregnancy Rate

Five studies [8, 24, 25, 32, 15], involving a total of 790 women, measured the ongoing pregnancy rate. The overall Risk Ratio (RR) between the Dual trigger and the HCG trigger did not favor either of the groups (pooled RR: 1.14, 95% CI [0.92; 1.4], P= 0.23). Pooled studies were homogenous (Chi-square P = 0.21, I²= 30.4%) **Figure S26**.

3.4.18. Implantation Rate

Nine studies [23, 24, 25, 20, 21, 26, 27, 32, 11], Involving a total of 1900 women, the overall Risk Ratio (RR) between the Dual trigger and the HCG trigger did not favour either of the two groups (pooled RR: 1.24, 95% CI [1.04; 1.48], P= 0.0176). Pooled studies were not homogenous (Chi-square P = 0.0169, I-square 57.1%). **Figure S25** with best case scenario by omitting Decleer, 2014 with (RR: 1.37, 95%CL [1.11, 1.68], I² =35.5%)

3.4.19. Live Birth Rate

Six studies [23, 20, 22, 33, 30, 11], involving a total of 775 women, reported the live birth rate. The pooled analysis showed that the Dual trigger group had a significantly higher live birth rate compared to the hCG trigger group (pooled RR: 1.38, 95% CI [1.12; 1.68], P=0.0019). Pooled studies were homogenous (Chi-square P= 0.705, I²= 0%). The absolute live birth rates were 42.5% in the Dual trigger group and 30.8% in the hCG trigger group **Figure S24**.

3.4.20. Abortion Rate

Seven studies [23, 8, 25, 21, 22, 26, 11], involving a total of 552 women, measured the abortion rate. The overall Risk Ratio (RR) between the Dual trigger and the HCG trigger did not favor either of the groups (pooled RR: 0.95, 95% CI [0.58; 1.56], P= 0.83). Pooled studies were homogenous (Chi-square P = 0.455, I²= 0.0%) **Figure S22**.

3.4.21. Cancellation rate

Three studies [8, 2, 27], involving a total of 432 women, measured the cancellation rate. The overall odds Ratio (OR) between the Dual trigger and the HCG trigger did not favor either of the groups (pooled OR: 0.56, 95% CI [0.29; 1.07], P= 0.08). Pooled studies were homogenous (Chi-square P = 0.31, I²= 14.1%) with mild heterogeneity **Figure S23** .

3.4.22. Embryo transfer

Five studies [25, 2, 26, 27, 32], involving a total of 664 women, measured the embryo transfer. The overall Risk Ratio (RR) between the Dual trigger and the HCG trigger did not favor either of the groups (pooled RR: 1.28, 95% CI [1.03; 1.59], P= 0.02). Pooled studies were homogenous (Chi-square P = 0.62, I²= 0.0%) **Figure S17**.

3.4.23. Multiple pregnancy

Three studies [23, 22, 26], involving a total of 325 women, measured the multiple pregnancy. The overall odds Ratio (OR) between the Dual trigger and the HCG trigger did not favor either of the groups (pooled OR: 1.49, 95% CI [0.75; 2.95], P= 0.25). Pooled studies were homogenous (Chi-square P = 0.52, I²= 0.0%). **Figure S18** .

3.4.24. Good quality embryo odds ratio (OR)

Three studies [24, 22, 11], involving a total of 565 women, measured the good quality of embryos. The overall odds Ratio (OR) between the Dual trigger and the HCG trigger favored the dual trigger group (pooled OR: 2.20, 95% CI [1.29; 3.76], P= 0.0038). Pooled studies were homogenous (Chi-square P = 0.149, I²= 47.4%) **Figure S19**.

3.4.25. Good quality embryo Mean Difference (MD)

Five studies [23, 8, 29, 30, 11], involving a total of 787 women, measured the good quality embryo. The overall Mean Difference (MD) between the Dual trigger and the HCG trigger favored the dual trigger group (pooled MD: 1.23, 95% CI [0.54; 1.92], P=

0.0005). Pooled studies were not homogenous (Chi-square P= 0.0009, I^2= 78.5%). We conducted a sensitivity analysis in multiple scenarios, excluding one study in each scenario. Heterogeneity was best resolved by excluding the study of Singh, 2023 (P = 0.48, I^2 = 0.0%) **Figure S20**.

3.4.26. Total dose gonadotropin

There was no statistically significant difference in the total gonadotropin dose between the dual trigger and HCG trigger groups (MD: 16.02 IU/m, 95% CI [-47.60, 79.65], P = 0.6216). This confirms non-significance, with I^2 = 0.0%, indicating that the studies were highly consistent **Figure S21**.

4. Discussion

This study has been the most comprehensive systematic review and meta-analysis, including seventeen RCTs for reproductive outcomes and different types of ovulation triggers, which included women during IVF/ICSI. Ovulation trigger is the most essential step that dramatically contributes to the success of IVF. Therefore, the optimal timing of ovulation trigger and the pharmacokinetics and pharmacodynamics of the triggering agents were crucial in fertility treatment. This determination was essential for ending the follicular phase, selecting triggering agents, determining doses, timing oocyte retrieval, and mitigating potential consequences.

For decades, human chorionic gonadotropin (HCG) has been utilized as controlled ovarian stimulation (COS) during ovulation trigger to stimulate the development of multiple follicles and induce final oocyte maturation as a substitute for the natural endogenous LH surge in IVF, as HCG has similar structures and biological functions to luteinizing hormone (LH). There is only one receptor for them. It's inducing ovulation, resumption of meiosis in the oocyte, and formation of the corpus luteum. Moreover, HCG had a pivotal role in facilitating implementation through improving endometrial receptivity. [34, 35] However, HCG can lead to complications such as ovarian hyperstimulation syndrome (OHSS), which occurs in approximately 20-30% of cycles and potentially leads to severe consequences [36]. Consequently, scientists investigated various strategies to decrease the prevalence of OHSS, including a combination of gonadotropin-releasing hormone (GnRH) agonists and human chorionic gonadotropin (HCG) triggers (dual trigger). Where GnRH stimulates the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are the most critical hormones for the maturation of the follicles. Therefore, dual trigger has been an effective way to maintain the optimal luteal phase function and decrease the time of using HCG alone, thus significantly reducing the prevalence of OHSS [37, 36]. This discussion summarizes the results of available studies in our systematic review and meta-analysis regarding the use of two different triggering methods (HCG only compared with Dual trigger). Firstly, these comparisons between both groups represented a statistically significant favor of dual trigger groups for (total oocyte, oocytes retrieval, fertilized oocytes, follicles >15mm at trigger day, viable embryo, X2 Pronucleate (2PN), clinical pregnancy, biochemical pregnancy rate, live birth rate, good quality embryo, and fertilization rate) more than HCG group. Secondly, these results illustrated that there were no statistically significant favor between both groups for (mature oocyste (MII), cryopreserved oocyte, follicles > 10mm at trigger day, cleavage rate oocyte/embryo, estradiol level (E2) on trigger day, progesterone level on trigger day, ongoing pregnancy rate, implantation rate, abortion rate, cancellation rate, embryo transfer, and multiple pregnancy). Moreover, there was a statistically significant favor for the HCG group for the duration of stimulation and endometrial thickness on trigger day, more than the dual trigger group.

A comparison of the current results with previous studies of systematic review and meta-analysis, as Chen et al. conducted research titled Dual triggering with GnRH agonist plus hCG versus triggering with hCG alone for IVF/ICSI outcome in GnRH antagonist cycles and reported that dual trigger favored more than HCG regarding (total oocytes, retrieval oocytes, mature oocytes, and good quality embryos) in several studies that agreed with the current results [38]. Moreover, Bourdon et al., who performed a systematic review and meta-analysis of randomized trials for Dual trigger improves the pregnancy rate in fresh in vitro fertilization (IVF) cycles compared with the human chorionic gonadotropin (hCG) trigger and matched with these results where, revealed that dual trigger had significant higher number of retrieved oocytes, number of mature oocytes, pregnancy rate, and live birth rate than HCG only trigger [39].

In addition, Zhang et al. study was carried out to assess the outcomes comparison of IVF/ICSI among different trigger methods for final oocyte maturation: A systematic review and meta-analysis, which illustrated that dual trigger had a significantly higher number of MII oocytes retrieved and fertilized oocytes, supporting the results of this study [40]. At the same line, Bourdon et al. evaluated whether gonadotropin-releasing hormone agonist (GnRH) triggering improves oocyte maturation, pregnancy outcomes, and safety compared with human chorionic gonadotropin (hCG) triggering during controlled ovarian stimulation, and indicated that there was a statistically significantly higher number of oocytes retrieved and mature oocytes after utilizing dual triggering compared with HCG alone [39]. In addition to the results of other systematic reviews Hu et al. reported that dual trigger was associated with a significantly higher live birth rate (LBR) per started cycle, as well as higher rates of ongoing pregnancy, implantation, clinical pregnancy, oocytes, mature oocytes, fertilized oocytes, and a higher number of usable embryos compared to HCG trigger [41]. Furthermore, Sloth et al. demonstrated an increase in both clinical pregnancy and live birth rates in the dual trigger group compared to the HCG trigger [42]. It was reported that there was no significant difference between the two groups regarding implantation rate.

In several studies focusing on using different ovulation triggers Yuan et al. [36] reported that it was slightly lower than the MII oocyte rate in the dual-trigger group. However, there was a significantly higher ICSI oocyte fertilization rate. Both groups were approximately equal in the number of 2PN embryos and the high-quality embryo rate. Zhou et al. showed that there was a high statistical oocyte retrieval rate in the dual trigger group, which may indicate that dual trigger had a positive effect on oocyte maturation, in addition to a higher number of good-quality embryos, viable embryos [11]. Moreover Lin et al. revealed that There was no statistically significant difference between both groups regarding total r-FSH dose, duration of stimulation, endometrial thickness, hCG day serum hormone profiles, total retrieved oocytes and mature metaphase II (MII) oocytes but illustrated that dual trigger were a significantly higher for fertilization rate, clinical pregnancy rate and live birth rate more than HCG trigger group [43]. In addition, dual trigger had positive effects on the cycle cancellation rate and abortion rate, but there was no incidence of OHSS in either group. On the other hand, Guner et al. reported that there were no differences between the two groups regarding implantation rate, clinical pregnancy, miscarriage, and live births [44].

A study comparing dual triggers for final follicular maturation with HCG trigger in ovarian stimulation for freeze-all in vitro fertilization/intracytoplasmic sperm injection cycles found that dual trigger significantly improved cumulative live-birth rates. Specifically, it revealed a statistically significantly higher biochemical pregnancy rate, clinical pregnancy rate, and live birth rate compared to HCG trigger [15].

Furthermore, Dong et al, who carried out a retrospective cohort study with propensity score matching for Reproductive outcomes of dual trigger with combination GnRH agonist and hCG versus trigger with hCG alone in women undergoing IVF/ICSI cycles and reported that there was no significant difference between both groups for the number of oocytes retrieved, embryos available, top-quality embryos, or the rate of normal fertilization, the incidence of ovarian hyperstimulation syndrome, implantation rate, biochemical pregnancy rate, clinical pregnancy rate, ectopic pregnancy rate, early miscarriage rate, and live birth rate, while the miscarriage rate higher in dual trigger [45].

Two studies [26, 33] revealed that there was a higher statistically significant difference for the number of mature oocytes retrieved and the oocyte maturation rate for the dual trigger compared with HCG trigger, while there was no difference between both groups regarding the duration of stimulation, total dose of follicle-stimulating hormone, and total number of oocytes retrieved. [46] who reported that the number of oocytes, the number of M2 oocytes, and the number of 2PN embryos were higher in group HCG than in the dual trigger group. At the same time, there were no significant differences between the two groups in terms of fertilization rate, the number of embryos, chemical pregnancy, clinical pregnancy, ongoing pregnancy, and implantation rate. Addition. Tu et al. [47] showed that dual trigger cycles yielded a significantly higher number of 2PN cleavage embryos, top quality embryos (TQEs), number of cleavage stage embryos, 2PN cleavage stage embryos, and number of oocytes retrieved, clinical pregnancy rate, persistent pregnancy rate, and live birth rate compared to HCG trigger?

This discrepancy may be attributed to many factors such as embryo quality, endometrial receptivity, sample size, and baseline patient characteristics (age and BMI, highlighting the complexity of reproductive outcomes beyond fertilization success.

5. Limitations:

While the superiority of dual trigger in specific patient subgroups is evident, we need studies to clarify its impact on OHSS risk and long-term reproductive success. Despite these constraints, the current evidence supports dual trigger as a promising strategy for improving key IVF/ICSI outcomes.

6. Conclusion

Dual trigger group can improve the quantity and quality of embryos in normal responders where it associated with higher of statistically significant for (total oocyte, oocytes retrieval, fertilized oocytes, follicles >15mm at trigger day, viable embryo, X2 Pronucleate (2PN), clinical pregnancy, biochemical pregnancy rate, live birth rate, good quality embryo, and fertilization rate) more than HCG group. Moreover, there were no statistically significant favor between both groups for (mature oocyste (MII), cryopreserved oocyte, follicles > 10mm at trigger day, cleavage rate oocyte/embryo, estradiol level (E2) on trigger day, progesterone level on trigger day, ongoing pregnancy rate, implantation rate, abortion rate, cancellation rate, embryo transfer, and multiple pregnancy). On the other side, there was a statistically significant favor for the HCG group for the duration of stimulation and endometrial thickness on trigger day, more than the dual trigger group.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Large Language Model

None

Authors Contribution

EE supervised the project, provided a valid idea, contributed to the screening and data extraction, conducted quality assessments, wrote the discussion section and abstract, and was the first reviewer for the final manuscript. MW contributed to screening and data extraction, performed the meta-analysis, and was the second reviewer for the final manuscript. AE contributed to data extraction and wrote the introduction and methods. ENM contributed to screening, data extraction, and results. ASM contributed to screening and data extraction. All authors participated in the review and editing of the manuscript. Each author has read and approved the final manuscript.

Data Availability

All data supporting the findings are derived from previously published studies included in the systematic review and meta-analysis, which are fully cited in the References section.

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