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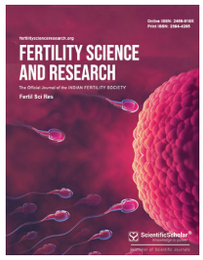

Review Article *Infertility*

Dual Trigger in IVF—A SWOT Analysis

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ABSTRACT

The typical agent used for final oocyte maturation and resumption of meiosis in in-vitro fertilisation (IVF) has been human chorionic gonadotropin (hCG). This acts as a surrogate for the physiological spontaneous luteinising hormone (LH) surge. Gonadotropin-releasing hormone agonist (GnRH-a) has been used as an alternative trigger in cycles where endogenous LH control is achieved using GnRH-antagonist and has been shown to be an effective method of reducing the risk of OHSS. However, GnRHa trigger is associated with poor corpus luteum function, leading to impaired endometrial receptivity.

A combination of a GnRHa and hCG (dual trigger) was proposed to improve IVF cycle outcomes, especially in poor and normo-responder patients. Dual trigger aims to provide a more physiological alternative to HCG-only trigger while obviating some of the problems associated with GnRHa alone. Clinical evidence now supports the value of dual trigger where there has been a previous low proportion of mature eggs or where there is a suboptimal LH response to GnRHa alone. In poor responders, dual triggers could be considered as an effective first line. Dual trigger allows for comparable outcomes in normal and high responders, allowing the possibility of fresh embryo transfer with good clinical pregnancy and live birth rates while minimising OHSS risk.

Keywords: Dual trigger, GnRH agonist, hCG

INTRODUCTION

The gold standard agent for inducing final oocyte maturation and resumption of meiosis in in vitro fertilisation (IVF) has historically been human chorionic gonadotropin (hCG), which acts as a surrogate for the physiological spontaneous luteinising hormone (LH) surge. Gonadotrophic releasing hormone (GnRH) agonists (GnRHa) were introduced as an alternative trigger in GnRH antagonist cycles, specifically with the advantage of a reduced risk of ovarian hyperstimulation syndrome (OHSS). However, the use of GnRH agonist trigger alone is associated with poor corpus luteum development, causing impaired endometrial receptivity and a reduced chance of successful implantation. Subsequently, a combination of a bolus of GnRHa and hCG (dual trigger) was proposed to improve IVF cycle outcomes, especially in poor and normo-responder patients. Different studies with significant heterogeneity have reported conflicting data about the effect of this trigger combination on various outcome parameters.

The aim of this strength-weaknesses-opportunities-threats (SWOT) analysis was to summarise the currently available evidence regarding the use of dual trigger for final oocyte maturation and trigger in normal and poor responder patients in comparison to the standard hCG trigger.

Evolution of Dual Trigger

A study in 1973 demonstrated that GnRH agonists given intravenously can induce the LH surge.[1] In the early 1990s, two small case series demonstrated that a bolus of GnRHa was shown to effectively trigger final oocyte maturation.[2,3] However, the initial randomised trials comparing GnRHa and hCG triggers in normal responder patients using standard luteal support showed very low live birth rates of 4–6% in the GnRHa group.[4,5]

Schachter et al. demonstrated significantly improved ongoing pregnancy rates in completed antagonist IVF cycles with dual triggering, using a combination of hCG (5000 IU) and GnRH agonist (triptorelin 0.2 mg).[6] They suggested that the GnRH agonist helps in displacing the antagonist binding to endometrial receptors, thereby unblocking 'pro-implantation post-receptor events' which had been potentially interfered with by the GnRH antagonist treatment in the pre-ovulatory phase.

Physiology of Dual Trigger

In a normal menstrual cycle, GnRH neurones in the mediobasal hypothalamus release GnRH in hourly pulses into the hypothalamo-hypophyseal portal system. Anterior pituitary gonadotrophs respond to this by releasing FSH and LH in hourly pulses. These gonadotropins act synergistically on the ovary to induce follicular growth and rising oestradiol levels (the two-cell, two-gonadotropin model).[7] The rising oestradiol level (and a small rise in progesterone) at mid-cycle induces the release of GnRH from the hypothalamus, mediated by Kisspeptin[8] released by neurones in the periventricular and arcuate nuclei of the hypothalamus. The positive feedback created, leads to a huge increase in the magnitude of LH and FSH pulses, commonly referred to as the 'LH surge.' The LH surge typically lasts for 48 hours, followed by a plateau maintained for 14 hours; the FSH surge is known to accompany the LH wave but with a smaller amplitude. Both are vital for ovulation, which occurs some 36–40 hours after the onset of the surge.

The LH surge is imperative for ovulation as it causes the resumption of oocyte meiosis and luteinisation of granulosa cells. But basic science studies in animals have also established a role for the FSH surge—e.g. in rats, a midcycle FSH surge determines which follicles will develop adequately in the following three cycles.[9] FSH promotes the formation of LH receptors on granulosa cells, expansion of the cumulus, and resumption of oocyte meiosis, leading to nuclear maturation.[10] Hyaluronic acid synthesis leading to cumulus expansion allows the COC to become free-floating in the follicular fluid. LH/FSH and progesterone activate proteolytic enzymes in the follicular fluid to digest the collagen layer of the follicle wall and cause ovulation.

In conventional IVF treatment, hCG has been most commonly used as a surrogate for the natural endogenous LH surge following controlled ovarian hyperstimulation.[11] However, the half-life of hCG is longer than that of endogenous LH, and as a result, the biological effect is maintained for several days, thereby increasing the risks of OHSS. Further, the hCG trigger does not mimic the FSH surge seen in physiology.

The alternative ovulation trigger, GnRHa, binds to the GnRH receptor, inducing a surge of both LH and FSH, which mirrors physiology in some respects. Following GnRHa, there is a rapid rise in LH, peaking at 4 hours and then a (slower) decline, returning to near baseline at 24 hours, thereby limiting the duration of the LH surge to about 24–36 hours, with no accompanying plateau due to early luteolysis and corpus luteum dysfunction. This contrasts with the physiological surge, which has 3 distinct phases, viz. the ascending phase (14 hours), plateau (14 hours), and descending phase (20 hours), lasting a total of 48–54 hours, as described by Shoham et al.[12]

Although there is a distinct advantage of reducing the risk of OHSS with GnRH agonist trigger, the poor corpus luteum function because of inadequate LH impairs endometrial receptivity and leads to decreased implantation and higher pregnancy losses.[5]

A dual trigger strategy, with a single dose of hCG and GnRHa as an ovulation trigger, has been proposed as a means of combining the benefits of both GnRH agonist and HCG. [13,14]

MATERIAL AND METHODS

We systematically searched MEDLINE (from 1948 to May 2023), EMBASE (from 1969 to May 2023), and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library to identify all reports of dual triggers. There were no language, publication date, or publication status restrictions applied. In addition, we performed a cross-reference search of all included studies and relevant reviews that were identified during the search process.

Studies were included if they: (1) were randomised controlled trials (RCTs), prospective or retrospective studies, (2) compared hCG trigger and dual trigger, and (3) reported at least one of the outcomes of interest: oocyte number, number of mature eggs, fertilisation rates, clinical pregnancy rates, live birth rate, implantation rate, and miscarriage rate. Studies failing to meet these were excluded.

RESULTS

We identified 271 citations through the electronic literature search and excluded 214 after screening titles and abstracts. After a detailed evaluation of the citations, 57 primary articles

SWOT Analysis

Table 1: SWOT Analysis.

Strengths	Weakness
1. Physiological mid-cycle surge 2. Improved oocyte maturation rate 3. Improved fertilisation rate	1. No consistent increase in live birth rate 2. Dose and type of GnRH agonist inconsistent between different studies 3. Similar euploidy rate 4. Similar embryological parameters 5. Increased cost of treatment
Opportunities	**Threats**
1. Possibility of individualised trigger strategy 2. Empty follicle syndrome 3. Poor responders 4. Advanced age	1. Ovarian hyperstimulation syndrome

GnRH: Gonadotrophin releasing hormone.

met the inclusion criteria, and their population was included in the evidence synthesis (either as a whole trial population or as a subgroup reported separately) for the SWOT analysis [Table 1].

Strengths

Physiological Mid-Cycle Gonadotrophin Surge

A single-dose administration of GnRHa results in the endogenous release of both FSH and LH, inducing a surge similar to that of the mid-cycle gonadotropins in a natural cycle,[15] unlike the hCG-only trigger, which, due to its structural similarity to the β-subunit, only mimics the LH peak. This close disposition to physiology has been evidenced in the form of significantly higher post-trigger serum levels of FSH and LH, resulting in higher ongoing pregnancy in women receiving a dual trigger.[6] The authors postulated that the additional FSH surge promoted oocyte meiosis resumption and exerted indirect advantages on the developing embryos through GnRH receptors. FSH also promotes the expression of LH receptors on granulosa cells and the development of the corpus luteum, thereby fostering the production of higher levels of ovarian oestrogen and progesterone.[8,16] In addition, the enhanced LH levels, by the actions of the dual trigger, may have some benefits for granulosa cells.

Dual trigger also overcomes the problems associated with GnRHa alone—poor LH response, few mature eggs in patients with lower basal LH, and luteal phase defects with progesterone deficiency—by the effect of hCG on the corpus luteum and endometrium.[5]

Improved Oocyte Maturation Rate

FSH surge following a dual trigger has been found to influence oocyte maturation by expansion and stimulation of oocyte-cumulus complexes to secrete a meiosis-activating substance that assists the resumption of the meiotic division.[17] Yan et al. designed a prospective study in a normo-responder population with more than 50% immature eggs in previous fresh cycles where hCG had been used as an ovulation trigger and recently showed a significantly greater proportion of Meiosis II (MII) oocytes with the use of a dual trigger, translating into a higher number and better-quality embryos, and consequently, better cumulative clinical pregnancy rates.[18]

In an older retrospective study in a similar population by Fabris et al., patients with more than 50% immature oocytes in a previous IVF cycle triggered with human chorionic gonadotropin (hCG) had a significantly higher yield of mature oocytes in subsequent cycles triggered with both gonadotropin-releasing hormone agonist (GnRH-a) and hCG in comparison to that for hCG alone.[19]

Improved Fertilisation Rate

A retrospective cohort study by Elias et al., involving 427 patients with a history of a poor fertilisation rate of <20% in at least two prior intracytoplasmic sperm injection (ICSI) cycles, found that the combination of GnRH-a and hCG trigger in subsequent ICSI cycles resulted in increased oocyte maturity, fertilisation, clinical pregnancy, and live birth rates compared with previous hCG trigger alone.[20]

A prospective observational study by Pereira et al. in 318 patients with poor fertilisation in ICSI cycles, a second ICSI cycle with a similar stimulation protocol and combined GnRH-a and hCG trigger compared their outcomes. Dual trigger had higher odds of mature oocytes and fertilisation and higher odds of ICSI cycles resulting in day-3 embryo transfers. The odds of clinical pregnancy and live birth were 5.42 and 5.25 times higher, respectively, in the combined trigger group compared to the hCG group.[21]

Overcomes Risks of GnRHa-Only Trigger

Although the use of GnRH-a-only triggers has significantly decreased the risk of OHSS in modern IVF practice, clinicians are often worried about the risk of suboptimal response to a GnRH-a-only trigger, leading to the lack of an adequate LH surge, mandatory for the full maturation of the oocyte. Myers et al., in their study of 424 fresh IVF cycles, noted the incidence of this to be 5.2% and identified those at risk to have a history of long-term contraceptive therapy, low baseline FSH and LH levels, needing a longer period of ovarian stimulation, and having a low LH level following trigger (LH < 15IU/L).[22] The addition of hCG, even at a low

Table 2: Analysis of studies showing dual triggers in poor responders.

Author	Type of study	Study criteria (No. of subjects, type of PR)	Study parameters	Study conclusion	Comments
Keskin, 2023[41]	Prospective randomised study	225, Patient-oriented strategy encompassing individualized oocyte number (POSEIDON) Groups 3 and 4 (and normo-responders)	Retrieved oocytes, MII oocytes, good quality embryos live birth rates (LBR)	• Retrieved oocytes, MII oocytes, good quality embryos—comparable between groups • Live birth rates (LBR) per embryo transfer (ET) were significantly higher in the HCG group versus the dual trigger group	• Not systematically advantageous in dual trigger group in poor responders • Lack of homogeneity in the age or embryo and stage of embryos
Beebeejaun et al., 2023[24]	Abstract of systematic review and network meta-analysis	54 randomised controlled trials, 5838 women	Live birth rate	• Difference in live birth rate in the poor responder subgroup where dual trigger was used	• Abstract only • Limitations on the certainty of the evidence and a high risk of bias due to disconnected networks while stratifying results according to predicted ovarian response
Mutlu, 2022[42]	Retrospective study	1010 Bologna criteria	Retrieved oocytes, mature oocytes, top-quality embryos Fertilisation rates, implantation rates, clinical pregnancy rate and live birth rate	• Retrieved oocytes, mature oocytes, and the top-quality embryos—significantly higher in the dual trigger group • Fertilisation rates, implantation rates, clinical pregnancy rate per embryo transfer and live birth rate per embryo transfer—significantly higher in the dual trigger group as compared to the hCG trigger	• Poor responders as defined by Bologna criteria • Retrospective study • Higher Pregnancy rate in fresh ET group—possibly due to beneficial effects on the endometrium from the dual trigger
Tulek, 2022[43]	Retrospective study	2999 POSEIDON groups 3 and 4	Retrieved oocytes, M2 oocytes, oocyte maturation rate, fertilisation rate, implantation rate, clinical pregnancy rate and live birth rate	• Retrieved oocytes, M2 oocytes, oocyte maturation rate, fertilisation rate, implantation rate, clinical pregnancy rate and live birth delivery rates—significantly higher in dual-trigger group in comparison to hCG-trigger • Quality and number of cryopreserved embryos were higher in dual group, particularly within the POS 3 subgroup thereby increasing cumulative pregnancy rates	• Retrospective study design • Non-randomised case selection • Frozen-thawed cycles were not included in the analyses

(Continued)

Author	Type of study	Study criteria (No. of subjects, type of PR)	Study parameters	Study conclusion	Comments
Zhou, 2022[44]	Randomised controlled trial	Advanced age (aged >= 35 years), 510 women	Good quality embryos and viable embryos	Numbers of good-quality embryos and viable embryos were both significantly higher in the dual trigger group Comparable pregnancy outcomes after fresh embryo transfer (ET) seen between the groups	• Not double blinded • Results could be affected by placebo effect
Sloth et al., 2021[45]	Pooled meta-analysis	2474, POSEIDON criteria	Clinical pregnancy rate; Live birth rate	• 1.62-fold increase in clinical pregnancy rate • 2.65-fold increase in live birth rate in the dual trigger group • No significant difference between the two groups in implantation rate	• Relatively small sample size • Five of seven studies were retrospective, making it likely to be susceptible to both confounding and bias
Maldonado,2019[46]	Case-control within-subject analysis	maternal age >37 years old, and previous low rates of oocyte retrieval, mature oocyte and blastocyst development, 18 patients	Retrieved oocytes, M2 oocytes, oocyte maturation rate, fertilisation rate, blastocyst rate	• Dual trigger is more effective than r-hCG trigger yielding improved response to stimulation, and laboratory and clinical outcomes	• Main limitation is the small sample size
Lu, 2016[47]	Meta-analysis	Low baseline LH, 8,970 IVF/ICSI cycles with previous low response to GnRH agonist trigger	Oocyte retrieval rate	Significant improvement in oocyte retrieval rates	• Dual triggering tends to make up for the unpredictable deficiencies and risks of each trigger and tends to improve the overall outlook of the treatment

MII: Meiosis II, hCG: Human chorionic gonadotrophin, LH: Luteinizing hormone, IVF: In-vitro fertilization, ICSI: Intracytoplasmic sperm injection GnRH: Gonadotrophin-releasing hormone, POSEIDON: Patient-oriented strategy encompassing individualized oocyte number.

dose in these situations, may be useful to maintain oocyte maturation and achieve high ongoing pregnancy and live birth rates without increasing the risk of OHSS.[13,14] The combination of hCG and GnRHa, with or without additional luteal support with oestrogen and progesterone, also tends to minimise the risk of luteal phase deficiencies likely to be induced by the short duration of the LH surge by a GnRHa-only trigger, which affects the life span and quality of the corpus luteum and consequently endometrial receptivity and implantation.[23]

Hence, the dual trigger would be a reasonable and more physiologic approach to enhance oocyte maturity and endometrial receptivity, thereby improving overall IVF/ICSI cycle outcomes in patients with a history of negative results due to low mature oocyte percentage and luteal phase defects after standard hCG or GnRHa triggers.

Weakness

No Consistent Increase in Live Birth Rates in Normo-Responders

Although studies have shown improvements in mature oocytes, fertilisation, and high-quality embryo formation rates, a number of meta-analyses have failed to show consistent improvements in live birth rates in normal responders [24,25] across the key

Table 3: Analysis of studies showing dual triggers in normoresponders.

Study	Type of study	Population	Outcomes	Limitations/comments
Gonzalez, 2023[48]	Systematic review and meta-analysis	Six studies	Dual trigger - • Increase in total and mature oocytes and high-quality embryos • Improved pregnancy and live birth rates • No effect on implantation rate or the positive Beta-HCG rate	• Only six studies were eligible for inclusion • Not all studies reported results for all the analysed variables • The quality of the studies were moderate • Not specified if blinding of participants and assessors was performed • The studies used different drugs for dual trigger • Live birth rate was reported in only two of the six studies
Hsia, 2023[49]	Systematic review and meta-analysis	10 RCT, 1638 women	Dual trigger - • Increase in total and mature oocytes and high-quality embryos • Improved clinical pregnancy and live birth rates in subgroup with fresh transfer • Main strength—only randomised studies were included	Heterogeneity of study participants, study design and hCG dose among the included studies—main limitation
Beebeejaun, 2023[24]	Systematic review and NMA	54 RCTs involving 5838 women	No difference in LBR with dual trigger vs hCG trigger	• Abstract only • Limitations on the certainty of the evidence and a high risk of bias due to disconnected networks while stratifying results according to predicted ovarian response
Blockeel, 2023[50]	Retrospective study	8500 cycles	Dual trigger - • Increase in cumulus oocyte complexes, mature oocytes and fertilisation rate • Increased Day 5 embryo transfer • Similar ongoing pregnancy rate	
Chi, 2023[51]	Retrospective cohort study	2649 IVF-PGT cycles	Similar number of oocytes retrieved, blastocysts and euploid blastocysts in both groups	
Hu, 2021[52]	Systematic review and meta-analysis	8 RCT 1048 women	Dual trigger - • Increase in total and mature oocytes and fertilisation rate • Improved clinical pregnancy and live birth rates • Increasing trend in both ongoing pregnancy rate and implantation rate • The main strength - only randomised studies were included, larger number of included studies and larger sample size	• Although it showed a significant increase in LBR, only three studies report this outcome. • Low quality of most studies • Risk of bias in view of supoptimal reporting of methods

hCG: Human chorionic gonadotrophin, RCT: Randomised controlled trial, NMA: Network meta-analysis, LBR: Live birth rate, PGT: Pre-implantation genetic testing, IVF: In-vitro fertiilisation.

outcome parameter in the major bulk of the population undergoing IVF treatment. These studies included the use of both a dual trigger (GnRHa and hCG used simultaneously) or a double trigger (GnRHa and hCG used sequentially within a specified time interval). Therefore, it is not clear which group of patients this trigger is best suited for.

No Consistent Dose and Type of GnRH Agonist Used Across Different Studies

The dose and type of GnRH agonist used were inconsistent in the various studies analysed, making it difficult to make evidence-based recommendations on the ideal drug and dose to be used in dual trigger regimens. This may be related to the heterogeneity of the different GnRha molecules available and the vast spectrum of duration of action due to differing half-lives. Whereas the half-life of endogenous GnRH is 2–4 minutes, by amino acid replacement, those of synthetic GnRHa can vary to a notable extent (triptorelin 4 hours, nafarelin 3–4 hours, leuprolide 1.5 hours, and buserelin 1.3 hours). Several GnRH agonists are effective as triggers of follicular maturation, viz., buserelin (0.2–2 mg), triptorelin (0.2 mg), and leuprorelin (0.5–1 mg), have been used. However, only one study has compared the efficacy and doses of different types of GnRHa currently in use and reported no significant differences.[26] A dose-finding RCT showed that oocyte yield was the same following 0.2, 0.3, or 0.4 mg of triptorelin.[27]

Therefore, further studies are required to identify the optimal drug and dosage for dual triggers, which should ideally also take into consideration the market trends, logistics, and availability of the different preparations across the world. This is particularly important for prioritising the supply of GnRHa drugs for triggering high responders and patients with specific risk factors for OHSS.

Similar Euploidy Rate

A retrospective cohort study conducted in a total of 385 preimplantation genetic diagnoses for aneuploidy (PGT-A) cycles found similar rates of euploidy between the dual trigger and HCG trigger.[28]

Similar Embryological Parameters

Embryo quality, one of the most important outcome parameters in an IVF cycle, can be objectively assessed in modern practice, facilitated by the Time-lapse monitoring system (TMS). Although correlation of morphokinetics by the TMS with live-birth rates are not fully established, as evident by their rating on the HFEA Traffic light system, they have been used to observe the differences in embryo quality in various types of trigger groups.[29]

Oron et al. analysed 3352 embryos formed following ovulation triggering with hCG, dual trigger, and GnRHa-only. The division timing durations (tPB2, tPNf, t2–t7) were found to be much shorter in the GnRH-agonist group compared to the other groups. GnRH-agonist trigger had the highest top-quality cleavage embryo rate when compared to hCG and dual trigger.[30] However, in another study of 4859 embryos, the same authors did not find any significant differences in morphokinetic parameters between embryos formed following dual triggers or hCG-only triggers.[31]

Therefore, the use of dual triggers did not demonstrate any significant differences in objective parameters of embryo quality compared to hCG or GnRHa triggers.

Increased Cost of Treatment

It is well-known that one of the main barriers deterring patients from seeking and health authorities from offering IVF treatment is the cost burden. Despite being a significant determinant of the choice of protocol and specific medications, there is a paucity of literature on the cost-benefit analysis of various novel interventions in IVF, including the dual trigger. A recent abstract presented that the dual trigger incurred a higher net cost of 175 US dollars, compared to the hCG trigger, but also delivered 13% higher live birth rates.[32] The authors showed that for every $13 extra cost of a second GnRHa trigger added to the conventional hCG trigger, there was an increase of 1% in the LBR. However, these costs will vary between health systems, and the benefits may vary depending on the population studied.

Opportunities

Possibility of Individualised Trigger Strategy

The use of GnRHa trigger in IVF allows for a 'tailored' approach to trigger, taking into account the ovarian response to stimulation of each individual patient, according to their clinical background, ovarian response, and risk of OHSS. It looks beneficial specifically for patients with a risk of inclusion within the following groups:

Empty Follicle Syndrome

Empty follicle syndrome (EFS) is defined as no retrieved oocytes after meticulous aspiration of follicles after ovarian stimulation in IVF treatment. Stevenson and Lashen classified these cases in a systematic review into genuine and false types, in a ratio of occurrence of 1:2.[33] In the genuine type (33% of cases), optimal hCG levels were present on the day of oocyte retrieval, whereas in the false type (67% of cases), serum hCG levels were found to be low due to either error in the administration or poor bioavailability of the triggering agent.[33]

In their review article, Kim and Jee suggested the use of GnRH agonist trigger as a remedial measure to induce an endogenous LH surge to boost oocyte maturation and release[34] based on published case reports of successful oocyte recovery in an antagonist cycle.[35] This was reiterated in a retrospective study by Noushin et al. in 13 patients with a history of

Table 4: Analysis of studies showing dual trigger in high responders.

Study	Type of study	Population	Outcome	Comments/limitations
Hu, 2021[52]	Systematic review and meta-analysis	Three studies, unselected population, OHSS per started cycle	• No OHSS in two studies[53,54] • OHSS rate similar in both dual trigger and HCG-only groups[55]	No clear definition of OHSS in any of the three studies used for OHSS review in this meta-analysis
Shapiro et al., 2008[13]	Retrospective comparative study with fresh blastocyst transfers	High ovarian responders	• Only 1 of 182 (0.05%) patients developed OHSS in the dual trigger group compared to the agonist-only (0.0%) groups, but higher implantation and ongoing pregnancy rate • A low dose of hCG (650 IU) possibly prevents rapid luteolysis, especially if stimulated by pregnancy	• Dual trigger does not increase the risk of OHSS significantly • Low dose hCG formulations may be difficult to procure or standardise
Li et al., 2017[56]	Retrospective cohort study, 226 women	High ovarian responders	Dual trigger is capable of preventing severe OHSS while still maintaining optimal embryo quality and IVF outcome	Can reduce cycle cancellation in high responders, however, further large prospective studies are needed
Chung et al., 2021[57]	Retrospective cohort study	Normal vs high responders, 290 fresh IVF cycles	• No cases of ovarian hyperstimulation syndrome • Comparable clinical pregnancy rate and live birth rates • Dual trigger probably recuperates the detrimental effects of an overresponse and allows fresh embryo transfer	Hormone profiles were not done undertaken and could have been a confounding factor

OHSS: Ovarian hyperstimulation syndrome, IVF: In-vitro fertilisation, hCG: Human chorionic gonadotrophin, IU: International units.

genuine empty follicle syndrome over a period of 6 years, where the dual trigger and delayed oocyte recovery resulted in a significant improvement ($P < 0.01$) in the number of mature oocytes retrieved, oocyte maturation index, number of fertilised oocytes, and number of embryos available for embryo transfer in the dual trigger group.[36]

Poor Responders

Poor responders (PR) comprise 5.6–35.1% of the patient population undergoing IVF, with a risk of suboptimal outcome, based on a wide spectrum of definitions to delineate this group of patients.[37] The European Society of Human Reproduction and Embryology (ESHRE) defined poor responders by the Bologna Criteria, defined as women having at least two of the following three criteria: (1) advanced maternal age above 40 or any other risk factor for poor ovarian response; (2) a previous poor ovarian response (cycles cancelled or less than 3 oocytes retrieved with a conventional protocol); (3) an abnormal ovarian reserve test (antral follicle count <5–7 follicles or anti-Mullerian hormone (AMH) <0.5–1.1 ng/mL).[38] Subsequent criticism of this definition led to the development of the POSEDION criteria to predict the different clinical classes of poor responders.[39]

Noushin et al. had observed in their study of 'genuine empty follicle syndrome' that, women with reduced ovarian reserve are expected to be poor responders to stimulation as well as at a higher risk of empty follicle syndrome.[36] Consequently, the use of dual triggers in this group of patients represents a remarkable opportunity for improving their IVF performance and outcome. The first study of a dual trigger in poor responders was done by Chen et al.,[40] showing a significantly higher number of total as well as mature oocytes collected from patients who had the dual trigger compared to those who had hCG but with no differences in fertilisation rate, number of viable embryos, implantation rate, clinical pregnancy, or miscarriage rates.

Since then, different authors have tried to establish the benefit of a dual trigger in poor responders; however, the results are diversified and depend on the exact definition of the poor responder and the outcome parameters chosen by the respective authors, as summarised in Table 2.[41-47]

Women of advanced age are a heterogeneous population and overlap with poor ovarian responders or patients with diminished ovarian reserve.

However, despite the potential selection bias in these groups of patients, the dual trigger seems to improve varying aspects of the outcome consistently in poor responders across all the studies.

Normoresponders

The term 'normoresponder' or normal responder commonly refers to a patient who is expected to have an average response to ovarian stimulation; in other words, they are expected to produce a reasonable number of eggs without an increased risk of OHSS.

The evidence around the use of dual triggers in normoresponders is heterogeneous. Most studies show an increase in oocyte retrieval rate, rate of mature oocytes, and fertilisation rate across the entire population [Table 3].[48-52]

Dual trigger treatment offers better outcomes compared with conventional hCG trigger without significant increase in the risks and could be potentially considered for all normal responder patients, as a universal trigger.

Threats: OHSS and High Responders

High Responders

The term 'high responder' refers to patients who are clinically at risk for having OHSS (ovarian hyperstimulation syndrome) or a significantly high number of oocytes collected. GnRH antagonist protocol with GnRH agonist for trigger has emerged as one of the most effective methods of inducing oocyte maturation and, simultaneously, preventing early onset OHSS in this group of women. Due to its short half-life, the GnRH agonist leads to impaired corpus luteal function, unlike traditional HCG trigger. In a combination, therefore, a dual trigger has been recognised to be an effective way to maintain the optimal luteal phase function while reducing significant OHSS risks.

While dual trigger has considerable benefits, the main concern looming over the high responders is the risk of OHSS. It may seem that the blanket application of dual trigger for all patient groups could increase the overall risk of ovarian hyperstimulation syndrome, especially in high responders. A few studies, including some in this specific group of patients, show that the dual trigger does not necessarily confer an additional risk over the HCG trigger alone [Table 4].[52-57]

CONCLUSION

Research to investigate novel ways to improve outcomes has improved knowledge and appreciation of the complex mechanisms of oocyte maturation and their effects on fertilisation, the luteal phase, and endometrial receptivity—all of which are relevant to a successful outcome in an IVF cycle.

Dual trigger, as a combination of GnRH agonist and a lower dose of HCG, aims to provide a more physiological alternative to HCG-only trigger while obviating some of the problems associated with GnRHa alone. Clinical evidence now supports the value of dual trigger where there has been a previous low proportion of mature eggs or where there is a suboptimal LH response to GnRHa alone.

In poor responders, dual triggers could be considered as an effective first line. It appears that some current data possibly supports the wider use of a 'dual trigger for all' approach; however, many uncertainties remain about the dose and timing of both components. The evidence is stronger for the number of oocytes and mature oocytes, less so for pregnancy and live birth rates. While more large-scale studies are required to establish the role of dual triggers in the modern practice of assisted reproduction, special caution must always be exercised in women at increased risk of hyperstimulation.

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