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REVIEW

Prediction, assessment, and management of suboptimal GnRH agonist trigger: a systematic review

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Abstract

Purpose This systematic review aimed to identify baseline patient demographic and controlled ovarian stimulation characteristics associated with a suboptimal response to GnRHa triggering, and available options for prevention and management of suboptimal response.

Methods PubMed, Google Scholar, Medline, and the Cochrane Library were searched for keywords related to GnRHa triggering, and peer-reviewed articles from January 2000 to September 2021 included.

Results Thirty-seven studies were included in the review. A suboptimal response to GnRHa triggering was more likely following long-term or recent oral contraceptive use and with a low or high body mass index. Low basal serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol serum levels were correlated with suboptimal oocyte yield, as was a low serum LH level on the day of triggering. A prolonged stimulation period and increased gonadotropin requirements were correlated with suboptimal response to triggering. Post-trigger LH < 15 IU/L best correlated with an increased risk for empty follicle syndrome and a lower oocyte retrieval rate. Retriggering with hCG may be considered in patients with suboptimal response according to post-trigger LH, as in cases of failed aspiration.

Conclusion Pre-treatment assessment of patient characteristics, with pre- and post-triggering assessment of clinical and endocrine cycle characteristics, may identify cases at risk for suboptimal response to GnRHa triggering and optimize its utilization.

Keywords In vitro fertilization (IVF) · GnRH agonist (GnRHa) · Ovulation triggering · Luteinizing hormone (LH) · Review

Introduction

The utilization of gonadotropin-releasing hormone agonist (GnRHa) triggering in in vitro fertilization (IVF) cycles was first introduced in the early 1990s [1]. Although an off-label use of GnRHa, it was shortly reinforced as a potential agent for the induction of the preovulatory luteinizing hormone (LH) surge, with the advantage of ovarian hyperstimulation syndrome (OHSS) prevention [2]. Numerous randomized controlled trials have since assessed the efficacy of GnRHa compared with human chorionic gonadotropin (hCG) triggering in IVF. GnRH agonist triggering has been demonstrated to be as effective as hCG for follicular maturation, with comparable live birth rates achieved in donor-recipient cycles [3]. The risk for severe OHSS was also nearly eliminated with the use of the GnRHa trigger instead of hCG. However, in fresh autologous cycles, the efficacy of GnRHa triggering is probably hampered by a resulting suboptimal luteal phase, leading to significantly reduced ongoing pregnancy and live birth rates [3]. As controlled ovarian stimulation (COS) is becoming increasingly personalized, patient selection and identification of treatment characteristics associated with successful response are of major importance when assigning the safest and most effective triggering option.

The efficacy of GnRH agonist triggering can be assessed in several ways. A complete lack of oocytes (empty follicle syndrome) is an important outcome of interest. It has been described to occur in 0.5–3.4% of IVF cycles following GnRHa triggering [4–7]. Alternative measures of success

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include suboptimal oocyte yield [4], oocyte recovery rate, and oocyte maturation rate [4, 8, 9]. With constant increase in its popularity and widespread use, intensive research on the subject of GnRHa triggering has recently highlighted a combination of demographic, clinical, and endocrine characteristics at different stages of the treatment process, which may affect the efficacy of the GnRHa trigger.

The objective of our review was to systematically assess the current literature regarding the efficacy of GnRHa triggering in IVF cycles. We aimed to review current strategies to predict a suboptimal response to triggering based on baseline patient characteristics, laboratory assessment, and cycle dynamics, and to review available options for the management of cases with suspected suboptimal response.

Materials and methods

Protocol and registration

The protocol of the present study was registered at the PROSPERO registry (http://www.crd.york.ac.uk/PROSPERO), an international database for the prospective registration of systematic reviews in health and social care (PROSPERO ID: CRD42021228275).

This study was exempt from Institutional Review Board approval, as it was a systematic review. The study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10].

Search strategy

We conducted a systematic search of the literature published in the main databases—Medline/PubMed, Google Scholar, Embase, and Cochrane Library, from January 2000 until September 2021. We included all original English, peer-reviewed articles, irrespective of study design. Case reports and conference abstracts were excluded. The search strategy included keywords related to GnRH triggering, so that results were required to include a combination of two words—one from a first predefined list and another from a second. The first list of words included gonadotropin-releasing agonist, gonadotropin-releasing analog, GnRH agonist, GnRHa, GnRH-a, leuprolide, leuprolide acetate, triptorelin, buserelin, and nafarelin. The second list of words included trigger, triggering, oocyte maturation, oocyte maturity, final oocyte maturation, follicular maturation, ovulation triggering, oocyte recovery rate, oocyte maturity rate, and empty follicle syndrome. References were hand-searched to identify additional studies not covered by the literature search.

All citations were screened for eligibility by two authors (authors H.G.H. and A.W.) in a non-blinded fashion. Any discrepancies were resolved by discussion and, when needed, a consensus was reached with the help of third author (A.R.).

For the purpose of this study, we included all studies, in which the efficacy of GnRHa triggering in IVF was assessed. All types of GnRH agonists were eligible for inclusion.

Data collection

The following data were extracted from the selected studies: study design, number of participants, study population, baseline follicle-stimulating hormone (FSH) and LH levels, recent oral contraceptive use, patient age and BMI, stimulation parameters (stimulation duration and total gonadotropin dose number of days of antagonist administration), serum LH, FSH estradiol and progesterone (P) levels on trigger day, time interval between last GnRH antagonist dose and GnRHa trigger, time interval between GnRHa trigger and oocyte retrieval, post-trigger LH and P levels, lack of oocytes (empty follicle syndrome), number of metaphase II (MII) oocytes, suboptimal oocyte yield, oocyte recovery rate, and oocyte maturation rate.

Quality assessment

The level of evidence of the included studies was assessed using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system [11].

Results

Search results

Our systematic search generated 4317 results, of which 2945 remained after removal of duplicates, and screened according to title and abstract. The full texts of 48 studies were reviewed, including a review of all reference lists for additional suitable records. A total of 37 studies were selected to be included in the review. The review of reference lists did not yield any additional suitable records for inclusion. A PRISMA flow chart diagram for our search process is presented in Fig. 1. A summary of the selected studies is presented in Table 1.

What are the means available to assess the efficacy of GnRH agonist triggering?

To assess the effect of GnRHa triggering on oocyte yield, and best express the extent of optimal utilization of potential follicles, two measures have been studied: oocyte recovery rate and suboptimal oocyte yield. Oocyte recovery rate was defined as the ratio between the total number of oocytes collected and the number of follicles with a mean diameter

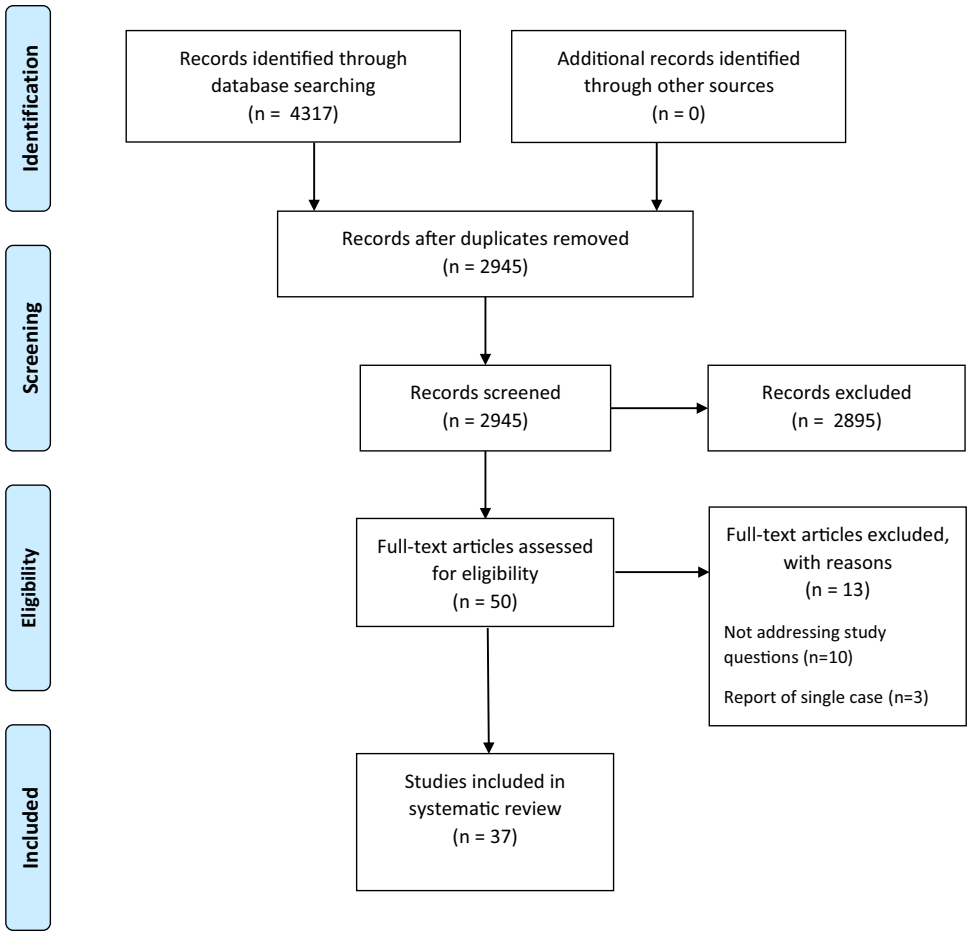

Fig. 1 PRISMA flow diagram of search results

of ≥10–11 mm on the day of the trigger [4, 8, 12], and suboptimal oocyte recovery rate was defined as an oocyte yield below the <10th percentile of oocyte yield [4]. Following retrieval, oocyte maturation rate was defined as the ratio between the number of MII oocytes and the number of oocytes retrieved [4, 8, 9, 12]. Another "endpoint" outcome assessed in many studies was the incidence of empty follicle syndrome, which is a complete lack of oocytes aspirated from follicles. This has been demonstrated to occur in about 1.2% of patients (range 0.5 to 3.4%) triggered with GnRHa [4–7, 13–15] (Table 2).

For the purpose of the review, we will refer to "suboptimal response" to triggering, as any negative endpoint, including suboptimal oocyte recovery and empty follicle syndrome as discussed above, or an LH level following triggering below the anticipated level, as discussed further below. We used this term to address different studies, which employed variable outcome measures, all aimed to express an unsatisfactory result.

In summary—the outcomes available to assess triggering efficacy are oocyte recovery rate, suboptimal oocyte yield, empty follicle syndrome and, for the purpose of the review, suboptimal response to triggering.

What are the background patient characteristics associated with a suboptimal response to GnRH agonist triggering?

Several background patient characteristics have been studied regarding their effect on GnRHa triggering. Patient age was found non-associated with triggering efficacy by some [16, 17], while others have noted a higher average age in the group of suboptimal responders [4, 18, 19]. Similarly, BMI was not found correlated with triggering efficacy by some [4, 15, 18], while others have noted a correlation between the two. Lu and colleagues found a lower average BMI among women with an adequate response to triggering (LH > 15 mIU/mL following triggering) [16], in line with Lainas et al., who noted a comparable retrieval rate but higher number of MII oocytes when patient BMI was lower than 25 kg/m^2 [12]. In contrast, Chang et al. noted that the failure rate, defined by laboratory parameters (post-trigger serum LH level <15 mIU/m and serum P <3 ng/m) or failed retrieval, was twice as high when patient BMI was <22 kg/m^2 [17]. However, one must note that the total number of failures with triggering in the latter study

Table 1 Assessing the efficacy of the GnRH agonist trigger—characteristics of the included studies

Study	*N*	Population	Design	Parameter examined	Quality of evidence[a]
Abbara et al. [23]	151	Oocyte donors	Retrospective cohort study	Post-trigger endocrine characteristics	Low
Aflatoonian et al. [34]	120	PCOS	RCT	Repeat GnRH-a administration	Moderate
Asada et al. [46]	8	PCOS, unexplained infertility, male factor	Case series	HCG administration after failed retrieval	Very low
Blazquez et al. [15]	12483	Oocyte donors	Retrospective cohort study	Incidence of empty follicle syndrome HCG administration after failed retrieval	Low
Castillo et al. [7]	3467	Oocyte donors IVF patients < 35	Retrospective cohort study	Incidence of empty follicle syndrome	Low
Chang et al. [17]	1878	High responders	Retrospective cohort study	Background, cycle base line, stimulation, and post-trigger characteristics HCG administration after failed retrieval	Low
Chen et al. [24]	91	High risk of OHSS—PCOS or previous OHSS/high response	Prospective cohort study	Post-trigger characteristics	Low
Christopoulos et al. [14]	322	High risk of OHSS—E2/follicles	Case series	Incidence of empty follicle syndrome HCG administration after failed retrieval	Very low
Cozzolino et al. [45]	359	Oocyte donors	Prospective cohort study	HCG/dual triggering after failed retrieval	Low
Deepika et al. [35]	125	PCOS	RCT	Repeat GnRH-a triggering	Moderate
Deepika et al. [13]	271	PCOS	Retrospective cohort study	Incidence of empty follicle syndrome Cycle base line, stimulation, and post-trigger characteristics HCG/repeat GnRH-a triggering after failed retrieval	Low
Dunne et al. [44]	97	High risk of OHSS—E2/follicles, previous OHSS, PCOS, and oocyte donors	Retrospective cohort study	Post-trigger endocrine characteristics	Low
Fauser et al. [32]	32	18–39 Y/O, ovulatory, normal BMI	RCT	GnRH-a type for triggering	Low
Griffin et al. [43]	102	Age < 40, peak E2 < 4000 pg/mL, previous OHSS/cancellation d/t OHSS risk, >13 follicles > 11 mm	Retrospective cohort study	Dual trigger in high responders	Low
Gülekli et al. [29]	21	PCOS, male factor, tubal	Case-control study	GnRH-a dose for triggering	Very low
Gunnala et al. [41]	10427	Fresh cycles for which a sliding scale of HCG was used according to E2 levels	Retrospective cohort study	Dual trigger with partial HCG dose	Low
Hershkop et al. [33]	220	ICSI cycles	Retrospective cohort study	Trigger to ovum pick up interval	Low
Honnma et al. [47]	2	PCOS	Case series	HCG triggering after failed retrieval	Very low

Table 1 (continued)

Study	*N*	Population	Design	Parameter examined	Quality of evidence[a]
Horowitz et al. [8]	53	Normogonadotropic	Retrospective cohort study	Trigger to ovum pick up interval	Low
Itskovitz-Eldor et al. [9]	8	High risk of OHSS—E2/follicles	Case series	Maturation rate	Very low
Kummer et al. [26]	316	High risk of OHSS—follicles, previous OHSS	Retrospective cohort study	Peak E2 levels	Low
Kummer et al. [6]	508	High risk of OHSS—follicles, previous OHSS	Retrospective cohort study	Incidence of empty follicle syndrome Stimulation and post-trigger characteristics	Low
Lainas et al. [12]	113	High risk of OHSS—follicles	Prospective cohort study	Body mass index	Low
Lainas et al. [27]	131	High risk of OHSS—follicles	Retrospective cohort study	GnRH-a dose for triggering	Low
Lu et al. [16]	8970	Not limited	Retrospective cohort study	Background, cycle base line, stimulation, and post-trigger characteristics Dual trigger in suboptimal responders	Low
Maslow et al. [25]	959	Planned oocyte cryopreservation, baseline LH > 2.5 IU/L	Retrospective cohort study	Peak E2 levels	Low
Meyer et al. [18]	500	Not limited	Retrospective cohort study	Background and stimulation characteristics	Low
O'Neill et al. [5]	114	High responders	Retrospective cohort study	Effect in PCOS patients	Low
Orvieto et al. [21]	34	High risk of OHSS, with E2 > 2000 pg/mL	Retrospective cohort study	Stimulation protocol	Low
Orvieto et al. [22]	32	E2 > 10000 pmol/L, >15 follicles > 10 mm, or planned freeze all	Retrospective cohort study	Stimulation protocol	Low
Pabuccu et al. [30]	77	High risk of OHSS—E2, follicles	Retrospective cohort study	GnRH-a dose for triggering	Low
Pereira et al. [42]	156	Prior fertilization rate < 40% in fresh ICSI cycle with HCG trigger	Retrospective cohort study	Dual trigger with partial HCG dose	Low
Popovic-Todorovic et al. [4]	3334	Not limited	Retrospective cohort study	Background, cycle base line, and stimulation characteristics	Low
Shapiro et al. [19]	252	High risk of OHSS—E2, follicles, history	Retrospective cohort study	Post-trigger endocrine characteristics	Low
Şükür et al. [31]	137	High risk of OHSS—E2	Retrospective cohort study	GnRH-a type for triggering	Low
Vuong et al. [28]	165	Oocyte donors	RCT	GnRH-a dose for triggering	Moderate
Zarcos et al. [20]	40	Oocyte donors	RCT	GnRH-a dose for triggering	Low

RCT, randomized clinical trial; *PCOS*, polycystic ovary syndrome; *OHSS*, ovarian hyperstimulation syndrome; *E2*, estradiol; *Y/O*, years old

[a]According to the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system

(38/1878 cycles) further sub-analyzed according to BMI was inadequate for conclusion.

Recent oral contraceptive use was more common in suboptimal responders to triggering [4, 18], although not in cases of empty follicle syndrome [15]. Menstrual regularity was inconclusively tied to triggering efficacy [4, 18]. One study found that suboptimal responders were more likely to be oocyte donors [18], but another found otherwise [19]. Finally, in a study by O'Neill and colleagues, the response to GnRHa triggering in polycystic

Table 2 Incidence of empty follicle syndrome in cycles triggered with GnRH agonists

Study	*N* (%)
Blazquez et al. [15]	74/12483 (0.5%)
Popovic-Todorovic et al. [4]	20/3334 (0.6%)
Kummer et al. [6]	7/508 (1.4%)
Christopoulos et al. [14]	6/322 (1.8%)
O'Neill et al. [5]	3/114 (2.6%)
Deepika et al. [13]	9/271 (3.3%)
Castillo et al. [7]	118/3467 (3.4%)
Overall	237/20499 (1.2%)

ovary syndrome (PCOS) patients and controls was equally effective, according to both post-triggering laboratory parameters and oocyte maturation rate [5].

In summary—a high or low BMI and recent or prolonged oral contraceptive pill use have been found correlated to a suboptimal response to triggering, while PCOS has not.

Quality of evidence: low.

What are the pre-treatment characteristics (upon cycle initiation) associated with a suboptimal response to GnRH agonist triggering?

A number of laboratory parameters at initiation of stimulation have been investigated in regard to triggering efficacy. Lower baseline LH and FSH [4, 16–18] and estradiol levels [4, 17] were noted as correlated with inadequate response to triggering. In a study by Popovic-Todorovic et al., the risk for an inadequate oocyte yield following triggering was stratified according to basal LH—patients with immeasurable levels (<0.1 IU/L) had a 45.2% risk of suboptimal response, while a basal LH of up to 5 IU/L was associated with 13.6% risk [4]. This linear correlation between basal LH and triggering failure was reaffirmed by Chang et al. and Meyer et al. [17, 18]. Lu et al. further noted basal LH to be the single most valuable marker for identifying suboptimal responders [16]. Notably, in a study by Deepika et al. comparing PCOS patients triggered with GnRHa with empty follicle syndrome ($n = 9$) to normal responders ($n = 262$), no correlation was found with basal FSH, antral follicle count, and anti-Mullerian hormone level [13]. However, basal serum LH levels were not included in the assessment and the numbers were too low to allow for sufficient power to draw firm conclusions.

In summary—low basal serum LH levels have been found correlated to a suboptimal response to triggering.

Quality of evidence: low.

Does the type of stimulation protocol affect GnRHa triggering efficacy?

GnRHa triggering would seem applicable to four main stimulation protocols: classic antagonist cycles, stimulation cycles without any form of pituitary suppression, cycles with progesterone primed pituitary suppression (PPOS), and cycles in which GnRHa is stopped at an early stage of stimulation (ultrashort/stop protocol). Thirty-five of the 37 studies included used GnRH antagonists for pituitary suppression, while one study did not specify [20], and one used PPOS (medroxyprogesterone acetate or utrogestan) [16]. While a direct comparison of GnRHa trigger efficacy between antagonist and PPOS treatment cycles is not available, it appears that suboptimal response characteristics are comparable for both protocols. Notably, two studies included ultrashort GnRHa administration with subsequent GnRH antagonist administration [21, 22], and both proved effective for GnRHa triggering with similar clinical outcomes as compared to dual (hCG and GnRHa) triggering.

In summary—stimulation protocol type does not seem to influence the efficacy of GnRHa triggering.

Quality of evidence: low.

Which stimulation variables and trigger day characteristics are associated with a suboptimal response to GnRH agonist triggering?

The duration of stimulation and cumulative dose of gonadotropins administered have repeatedly been found to be correlated with triggering efficacy, so that a longer stimulation with higher doses of gonadotropins is more likely associated with a suboptimal response [4, 13, 15–19]. Chang et al. noted a failure rate of more than 3.5-fold among patients treated with >3800 IU of gonadotropins as compared with those treated with <3800 IU—5.0% versus 1.4% [17].

LH and FSH levels on the morning before triggering were found to be correlated with triggering success [18, 23], so that lower levels of both were associated with an inadequate response to triggering. Meyer et al. reported that patients with an undetectable serum LH level on the day of trigger had a 25% chance of a suboptimal LH surge [18]. In their study, limiting the use of the GnRHa trigger alone to patients with a trigger day serum LH >0.5 mIU/mL would have reduced the rate of suboptimal response from 5.2 to 0.2%. However, this conclusion was not supported by all [4, 16, 24].

With regard to peak serum estradiol levels, results are conflicting. Some have noted an inverse relation between the two, so that lower estradiol levels are associated with a higher risk of suboptimal response to triggering [4, 6, 16], although in a small cohort investigating empty follicle syndrome occurrence in PCOS patients, the opposite was found [13]. In contrast,

several authors have failed to demonstrate a significant association between peak estradiol and triggering outcome [17–19, 25, 26]. Finally, no definitive correlation to follicle size on triggering was noted [17, 19], although an inverse relationship may exist between the number of intermediate follicles and empty follicle syndrome in PCOS patients [13].

In summary—a longer stimulation with higher gonadotropin requirements has been correlated to suboptimal response to triggering. A low baseline LH level is correlated to suboptimal response to triggering, while peak estradiol levels are not.

Quality of evidence: low.

Is there an optimal GnRHa dose for triggering?

Five studies have directly evaluated different GnRHa doses for triggering—four compared different doses of triptorelin (0.1 to 0.4 mg) [20, 27–29], and an additional study compared two doses of leuprolide (1 and 2 mg) [30]. A small comparison of fresh cycles triggered with 0.1 mg ($n = 7$) and 0.2 mg ($n = 14$) triptorelin did demonstrate less immature oocytes with the 0.1 mg dose but comparable oocyte recovery rate and number of mature oocytes in both groups [29]. Overall, most studies, with more adequate sample size, did not find a correlation between GnRHa dose and oocyte maturation rates and doses of triptorelin of 0.1–0.4 mg appear to be equally effective. To further support this conclusion, in a comparison of suboptimal responders (post-trigger LH < 15 mIU/mL) to adequate responders, no difference was found in the rate of patients triggered with 2 or 4 mg leuprolide [18].

In summary—different GnRHa doses are not correlated to triggering efficacy.

Quality of evidence: low.

Is there a preferred GnRHa type for triggering?

Our systematic search yielded two studies evaluating the type of GnRHa used for triggering [31, 32]. In both studies, patients were administered 0.2 mg of triptorelin or 0.5–1 mg of leuprolide and were compared to controls triggered with hCG. No difference in the number of MII oocytes retrieved was noted between the triptorelin and leuprolide groups.

In summary—different GnRHa types are not correlated to triggering efficacy.

Quality of evidence: low.

Is there an ideal time interval between GnRH antagonist administration and GnRHa triggering, and between triggering and oocyte retrieval?

As GnRH antagonists occupy the pituitary GnRH receptors by competitive inhibition, it has become common practice to maintain a minimum time interval between the last antagonist dose and the agonist trigger so that the antagonist molecules can be displaced by the GnRHa and an effective trigger can occur. Horowitz and colleagues investigated the effect of the interval between the last antagonist dose and agonist trigger on treatment outcomes, in four study groups which varied from >2.5 to <7 h [8]. They did not find a correlation between the interval, oocyte recovery rate and MII oocyte rate.

In a study by Hershkop et al., patients triggered with GnRHa were compared based on the lag time between triggering and oocyte aspiration, which varied from 34 to 41 h [33]. While the authors did note a slight difference in the number of MII oocytes aspirated between the two intermediate interval groups in favor of a longer interval, overall, no difference was demonstrated in the proportion of MII oocytes and the number of cycles with >70% MII oocytes.

In summary—different time intervals between GnRH antagonist and GnRHa administration, and GnRHa and oocyte retrieval are not correlated to triggering efficacy.

Quality of evidence: low.

Does a repeat dose of GnRHa trigger improve outcomes?

Two randomized controlled trials have explored the efficacy of administering a repeat dose of GnRHa trigger, in an attempt to mimic the amplitude and duration of the gonadotropin surge, and consequently affect oocyte maturation. Both randomized PCOS patients to receive 0.2 mg triptorelin 35 h prior to oocyte retrieval, versus 0.2 mg triptorelin and an additional 0.1 mg dose 12 h later. In the first, the results of 100 patients randomized were analyzed [34]. Despite a trend for more MII oocytes with repeat trigger, no differences were noted in maturity rate. In the second, the results of 100 cycles analyzed did demonstrate a significantly lower maturity rate with a single dose of GnRHa administration (OR 0.47, 95% CI 0.38–0.57, $p < 0.001$) [35].

In summary—the evidence regarding the efficacy of repeat GnRHa triggering is conflicting.

Quality of evidence: moderate.

Does dual triggering (GnRHa and hCG) offer an advantage over triggering with GnRHa?

While the quality of evidence is currently low, dual triggering with both GnRHa and full dose hCG has been demonstrated by several authors to be associated with improved maturation and fertilization rates [36–38], and a higher rate of clinical pregnancies and live births [39]. Recently, the addition of a reduced dose of hCG to the GnRHa trigger has been suggested as a means of improving the efficacy of the GnRHa trigger. Lu et al. examined 229 suboptimal responders to trigger (LH < 15), of whom 198 were triggered with

GnRHa and three different doses of hCG—1000, 2000, and 5000 IU, and 31 only with GnRHa alone [16]. The oocyte retrieval rate in the dual trigger group was significantly higher than the GnRHa group, and no difference was noted between the different doses of hCG. Notably, two cases of severe OHSS were noted with dual trigger with 5000 IU of hCG. The concept of incorporating a partial dose of hCG with GnRHa trigger is further supported by additional studies—Shapiro et al. noted improved implantation and pregnancy rates with dual triggering, with an hCG dose adjusted according to the patient's BMI [40]. Only one case of clinically significant OHSS was noted in the group of 182 who received dual trigger. In addition, a sliding scale hCG trigger was investigated in a cohort of 10,427 cycles, triggered with a dose of 3300–10000 IU of hCG or with a dual trigger of GnRHa and 1500 IU hCG, according to serum estradiol levels [41]. The authors found a higher rate of mature oocytes with dual trigger as compared to low dose hCG, although no differences in pregnancy and live birth rates were noted. Four patients (0.03%) developed severe OHSS, who were triggered with 4000–5000 IU of hCG. Pereira et al. retrospectively compared 156 patients with <40% fertilization rate in a prior ICSI cycle with standard hCG trigger who underwent another ICSI cycle with a combined 2 mg leuprolide and 1500 IU hCG ovulatory trigger [42]. Significantly more mature oocytes were retrieved in the dual trigger group compared with the hCG trigger group. The fertilization, clinical pregnancy, and live birth rates were all improved in the dual trigger group. It was suggested that combined GnRHa and hCG trigger in ICSI cycles may increase oocyte maturity, thereby increasing fertilization and improving ICSI cycle outcomes in patients with a history of poor fertilization after standard hCG trigger alone. Finally, in a report by Griffin and colleagues, high responders at risk for OHSS were triggered with either GnRHa alone or GnRHa with 1000 IU hCG [43]. Live birth, clinical pregnancy, and implantation rates were significantly higher in the dual trigger group, with only one case of mild OHSS in this group.

In summary—dual trigger with a full or partial dose of hCG improves laboratory and clinical outcomes but has been associated with case reports of OHSS.

Quality of evidence: low.

Which post-trigger endocrine characteristics predict a suboptimal response to trigger?

One of the most studied variables in correlation with GnRHa triggering efficacy is post-triggering serum LH level. The correlation between the two has become a natural assumption by many, so that many studies investigating GnRHa triggering efficacy have used post-triggering LH level as a reflection of the extent of response to triggering [6, 16–19, 24].

Two studies to date have failed to demonstrate an association between post-triggering serum LH levels and oocyte maturation. In the first by Abbara et al., LH rise following triggering was not associated with the number of mature oocytes in general, except for patients with lowest and highest LH levels, 4 h following triggering [23]. Similarly, in a cohort of 97 patients, Dunne and colleagues did not find LH level or post-trigger rise as predictive of oocyte maturation [44].

In contrast, several studies have established a clear correlation between post-triggering LH, commonly assessed 12 h following administration, and treatment outcomes. One study found a lower LH level post-triggering in patients with empty follicle syndrome [13], while another found that in patients with a LH <15 IU/L, the incidence of empty follicle syndrome was as high as 18.8%, as compared with no cases when LH was >15 IU/L, $p < 0.01$ [6]. Three independent groups demonstrated a higher oocyte yield when LH post-triggering was >15 IU/L [16, 24] or >52 IU/L [19]. Two studies demonstrated an increase in the total number of oocytes and MII oocytes retrieved when LH post-trigger was >15IU/L, although the oocyte maturation rate was similar [6, 16]. Overall, a LH <15 IU/L post-trigger was demonstrated in 2.7% (range 2.0–5.4%) of patients triggered with GnRHa (Table 3).

Post-triggering P level has also been studied. While one study did not demonstrate a lower P level in suboptimal responders [6], three studies noted a significantly higher P level in optimal responders [13, 17, 23]. Abbara et al. found the rise in P level following triggering to be the strongest laboratory predictor of the number of mature oocytes retrieved [23].

In summary—a low post-trigger LH is correlated to suboptimal response to triggering, with a common cutoff of 15 IU/L. Low progesterone is also correlated to suboptimal response to triggering.

Quality of evidence: low.

Table 3 Incidence of suboptimal response to trigger—LH < 15 IU/mL following triggering

Study	*N* (%)
Chang et al. [17]	38/1878 (2.0%)
Lu et al. [16]	243/8970 (2.7%)
Kummer et al. [6]	16/502 (3.1%)
Meyer et al. [18]	26/500 (5.2%)
Chen et al. [24]	5/91 (5.4%)
Overall	328/11941 (2.7%)

Can a suboptimal response to the GnRH agonist trigger be corrected?

Retriggering based on LH rise

Chang et al. described 22 cycles retriggered with hCG based on suboptimal LH rise following triggering (<15 IU/mL) [17]. These patients subsequently had an average 17 oocytes retrieved, and half delivered. Kummer et al. described five cases of lack of a LH rise, of which two were retriggered—retriggering with hCG yielded 15 oocytes in one case, while retriggering with GnRHa was unsuccessful the other [6].

Self-monitoring for the presence of LH secretion in urine post-triggering, to identify cases of lack of response, has been suggested by some [28, 45]. This approach potentially offers a non-expensive and accessible screening tool, to select patients who require further assessment with serum LH measurement, in case of a negative urine test. In a prospective study of 359 oocyte donors, post-triggering assessment of serum LH was required in only three patients with a negative urine LH test 12 h following triggering [45]. Two subsequently received dual triggering with GnRHa and hCG and underwent successful oocyte retrieval. In an additional report [28], only one of 165 patients required serum LH evaluation due to a negative urine test 4 h following triggering. Serum LH was found satisfactory, so that no additional triggering was administered and the patient underwent successful oocyte retrieval.

Retriggering following failed retrieval

Blazquez et al. described 17 cases of failed retrieval, who were retriggered [15]. Four cases with a LH level < 8 IU/L on retrieval day were retriggered with GnRHa, one successfully, and 13 cases with a LH > 8 IU/L on retrieval day were retriggered with hCG, 12 for whom oocytes were retrieved. Chang et al. reported 16 cycles in which oocyte retrievals were attempted but aborted after aspiration of several follicles without successful recovery of oocytes [17]. These patients were then retriggered with the use of hCG and underwent a second retrieval attempt 36 h later. In all cases, oocytes were successfully recovered. Notably, aspirating more than seven follicles prior to abandoning retrieval (and retriggering) was associated with less optimal outcomes [17]. Similarly, others have described successful retrieval after retriggering with hCG after initial failed trigger [13, 14, 46, 47].

In summary—retriggering with hCG following insufficient LH rise post-triggering or failed aspiration may be beneficial.

Quality of evidence: low.

Discussion

Since its initial introduction in IVF, the use of GnRHa for oocyte maturation triggering has become a popular choice in a variety of clinical indications. Its widespread use most probably stems from its comparable efficacy to hCG and its improved safety profile, as it virtually eliminates the risk for severe OHSS [48]. However, it is possible that not all patients are equally responsive to GnRHa triggering in terms of oocyte yield and maturation. Therefore, early identification of variables associated with suboptimal response can facilitate the decision-making process by physicians, and potentially optimize treatment results. Currently, there is no agreement on a protocol to determine the adequacy of the GnRHa trigger.

The objective of our systematic review was to identify and summarize, in a step-by-step manner, clinical and laboratory parameters that may affect the efficacy of GnRHa triggering and to suggest potential treatment strategies in cases with suboptimal response. We identified 37 studies eligible for inclusion and described their findings above. The majority of studies available were of low quality, as further discussed. However, based on the existent data to date, we propose the following four-step strategy for optimizing the efficacy of GnRHa triggering (Fig. 2).

Identification of the patient at risk for suboptimal response to triggering

Expect possible suboptimal response to GnRHa triggering in patients with recent/long-term oral contraceptive use [4, 18], and patients with high [12, 16] or low BMI [17].

Low serum LH levels at beginning of stimulation have been repeatedly and significantly associated with suboptimal response and a higher risk of failed retrieval [4, 16–18]. It is suggested that a LH cutoff level of <1 mIU/mL can define the patient at high risk for suboptimal response to GnRHa triggering.

Triggering

On the day of triggering—suspect a higher risk for suboptimal response in cycles with prolonged stimulation and high cumulative gonadotropin dose administered [4, 13, 15–19]. Patients with low or undetectable LH levels on the day of the trigger are also at risk for a suboptimal response [18, 23]. It is suggested that an LH cutoff level of 0.5 IU/L can define the patient at high risk for suboptimal response to GnRHa triggering.

There is paucity of data comparing the efficacy of different GnRHa types for triggering ovulation. In addition, except

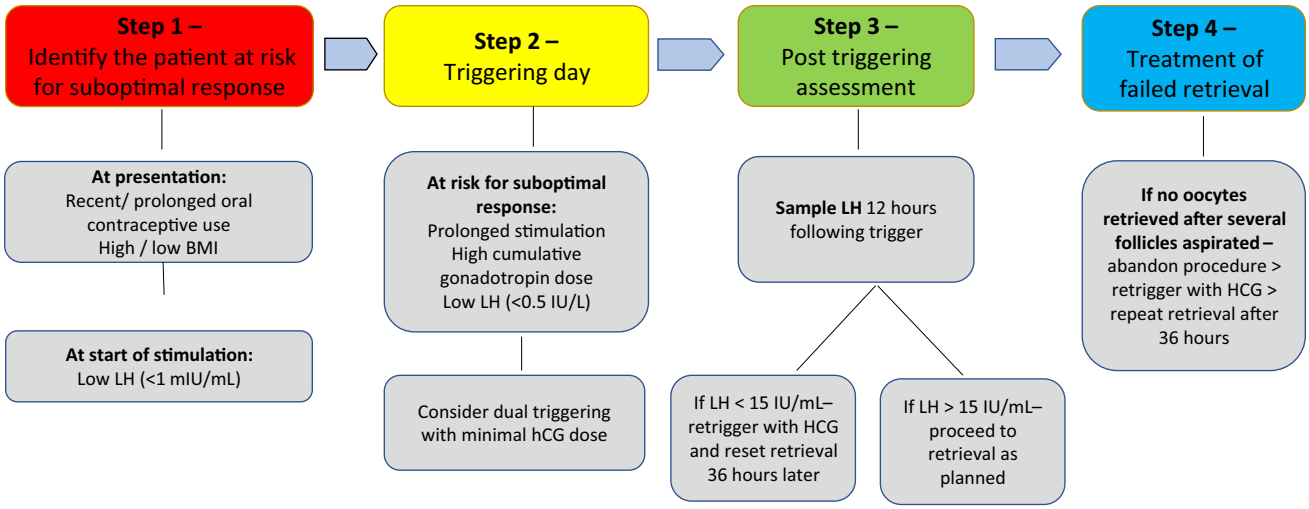

Fig. 2 Proposed four-step strategy for optimizing the efficacy of GnRHa triggering

for triptorelin, dose-finding studies for the GnRHa preparations that are commonly used for triggering (leuprolide and buserelin) rarely exist. There appears to be no advantage for any of the GnRHa types [31, 32] and different doses [20, 27–30]. Doses of 0.1–0.4 mg of triptorelin or 1–2 mg of leuprolide appear to be equally effective.

In normogonadotropic patients, a GnRH agonist trigger can successfully induce an effective LH surge and oocyte maturation and release, irrespective of the time interval between the last antagonist dose and the agonist trigger [8].

There is insufficient data regarding the optimal interval from GnRHa triggering to oocyte retrieval. A single retrospective study has found an interval of 34–41 h to be equally effective [33].

There is insufficient data to support retrigger with a second dose of GnRHa 12 h following the initial trigger.

Post-triggering assessment

Past research has evaluated the expected serum concentration of LH and P following GnRHa triggering [17, 23, 32]. LH levels have been demonstrated to rapidly rise following GnRHa administration, peak at 4 h and return to baseline on the day of oocyte retrieval [32]. The increase in serum P levels, on the other hand, was found to be less pronounced and relatively stable from triggering to oocyte retrieval [32].

Blood sampling for serum LH and P levels 12 h after triggering has been suggested as an effective clinical tool to assess the response to the trigger. Due to a large diurnal variability of timing the triggering according to the scheduled time of oocyte retrieval, blood sampling 12 h post-trigger is not always feasible. In order to compensate for that, an exponential decay model to estimate LH values at 12 h post-trigger has been suggested [19], but is not widely used. It is our recommendation to assess serum LH levels 12 h following triggering, although earlier assessment may be considered in select cases, as LH peak occurs earlier.

The role of post-trigger P levels in the assessment of GnRHa trigger efficacy awaits further clarification. No clear threshold for adequate P level following triggering was demonstrated [13, 17, 23]. Progesterone levels reflect the degree of luteinization of the follicles in response to the GnRHa trigger but may be subjected to variability by the time interval from the trigger to blood sampling and from the number of corpora lutea present, a fact which makes the results difficult for interpretation. The higher the number of follicles, the greater the serum P level [17]. Therefore, unless used for research purposes, routine post-trigger blood sampling for P cannot be recommended.

It remains to be determined whether post-trigger assessment should be reserved for patients suspected to be at risk for suboptimal response or should be universally applied. Although patient friendly and potentially cost saving, insufficient data exists to suggest performing post-trigger urinary LH testing and subsequent serum testing as indicated. A post-trigger serum LH level >15 IU/mL should be used as the threshold to define an adequate response and in most of the limited studies available lower levels have been correlated with inferior retrieval results [6, 13, 16, 24]. In the event of an LH < 15 IU/mL, retriggering with hCG seems reasonable, with subsequent retrieval differed to 36 h following retriggering [17]. The increased risk for OHSS associated with hCG triggering should be taken into consideration before the final decision is made. The minimal effective dose of hCG for this indication has yet to be determined.

Treatment of patients with failed retrieval

In light of the limited number of studies investigating retriggering following failed retrieval with hCG (52 patients in all of the aforementioned studies) as compared to GnRHa (7 patients), and relatively higher success with hCG retrigger as described, retriggering with hCG may be considered. Concerns regarding the risk of OHSS seem justified, as suboptimal responders to triggering may display similar peak estradiol levels during stimulation [4, 6, 16], and GnRHa triggering is commonly applied to reduce the risk for OHSS. Indeed, the authors identified one case of severe OHSS following retriggering with hCG which has been so far described [14]. Yet, in freeze-all cycles, the risk for severe OHSS is further reduced since no embryo transfer is performed. The minimal effective dose of hCG that should be given for retriggering has yet to be determined, with special attention to the resulting risk for OHSS. Partial aspiration from one ovary (prior to abandoning the procedure) may also reduce the risk for severe OHSS [49].

Identification of the patient at risk for suboptimal response to triggering

A suboptimal LH surge has been observed under a variety of clinical situations described in our study such as previous oral contraceptive use, prolonged ovarian stimulation with increased gonadotropin requirements, deviation from optimal BMI indices, and decreased basal and trigger day serum LH levels. Common to all of the above conditions in the event of a suboptimal trigger is the lack of an adequate response of the pituitary gonadotrophs to the GnRHa bolus which results in failure to elicit an effective endogenous LH surge. In addition, although not addressed in past studies, patients with "induced" hypogonadotropic hypogonadism such as those with recent long-acting use of a GnRH agonist products or continuous hormonal treatment for endometriosis should be also considered at risk for suboptimal response to GnRHa triggering. The pathophysiology of suboptimal response to the GnRHa trigger in normogonadotropic patients is currently unknown. Evaluation of pituitary function during COS is limited by the administration of exogenous gonadotropins and high serum level of ovarian steroids. Dynamic testing of pituitary function, for example, by means of the GnRH test [50], is not possible during COS, and performing the GnRH test during pre-treatment evaluation is most probably cumbersome and not cost effective. Honnma et al. reported on two patients with PCOS with multifollicular development who had a normal response to a GnRH test at the pre-treatment phase but empty follicles during oocyte retrieval [47]. Retriggering with hCG resulted in a successful retrieval of oocytes in both cases, suggesting that different conditions may prevail during COS and that normal pituitary response to a GnRH test does not ensure subsequent optimal response to a GnRHa trigger. More research should be directed to developing methods for the assessment of pituitary function during COS.

Our study is not without limitations, the major of which being the lack of high-quality randomized controlled trials addressing the review questions. Most studies included were retrospective cohorts, with several case series. This, unfortunately, precluded us from conducting a meta-analysis and certainly limits the validity of our conclusions. In addition, many studies compared different variables associated with suboptimal response, and presented them as averages [6, 16, 24]. While this did allow for our understanding of the influence of these variables on cycle outcomes, it did not allow the authors to establish clear cutoff values on which to base specific recommendations (for example, which duration of stimulation or gonadotropin consumption should raise suspicion of potential suboptimal response to triggering). Notably, further information was not available for all outcomes investigated, included the important differentiation between genuine empty follicle syndrome and false cases, such as those following improper administration of medication. The incidence of genuine empty follicle syndrome is probably lower than the overall incidence depicted, and needs to be weighed against the low but clinically significant risk for ovarian hyperstimulation syndrome.

The strength of the current review is that it provides clinicians with a comprehensive step by step approach to identify patients at risk for a suboptimal response to GnRHa triggering, and strategies for prevention or correction once a suboptimal response has been identified. With the increased utilization of the GnRHa trigger that we are currently witnessing, increasing physicians' awareness and providing them with a simplified tool for optimizing outcomes in cycles with GnRHa triggering is of utmost importance.

In conclusion, the utilization of GnRH agonists for triggering final oocyte maturation in IVF cycles is effective and safe. It may, however, be associated with suboptimal results in some patients and under certain clinical circumstances. Early identification of patients at-risk, proper post-trigger assessment and individualized management with hCG retrigger, may improve cycle outcome. By employing this approach, our patients can benefit from OHSS risk reduction in most cases, with a carefully selected small subgroup of patients who require dual or repeat hCG triggering. Considering the effective vitrification techniques available today [51], even in the event of hCG administration, the risk for severe OHSS is significantly reduced with the freeze-all approach, without risking cycle cancelation and the need for repeat unplanned stimulated cycles. Yet, the majority of our findings and the application of our proposed model remain to be proven in a prospective, preferably randomized setting. We strongly encourage future standardization of trigger

efficacy assessment in future studies, adhering to select outcome measures such as oocyte recovery and maturity rate.

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Code availability Not applicable.

Declarations

Conflict of interest The authors declare no competing interests.

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