Suboptimal response to GnRH agonist trigger: causes and practical management

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Purpose of review
GnRH agonist products are used extensively worldwide to trigger ovulation and final oocyte maturation in in vitro fertilization cycles. The purpose of this article is to outline possible causes for a suboptimal response to the GnRH agonist trigger.

Recent findings
Risk factors for such a suboptimal response include prolonged hormonal contraceptive use, previous GnRHa-induced pituitary downregulation, a hypogonadotropic/hypogonadal condition, patient error, environmental conditions that may damage the GnRHa product used, GnRH and luteinizing hormone (LH) receptors polymorphisms, low baseline LH and low endogenous serum LH levels on trigger day as well as low BMI. The induction of an adequate LH surge can be ascertained by an LH urine test 12 h post trigger.

Summary
In most cases, GnRHa trigger elicits effective LH+follicle stimulating hormone surges, resulting in mature, fertilizable oocytes. Clinical awareness to conditions that may predispose to a suboptimal response to the GnRHa trigger may prevent failed oocyte retrial.

Keywords
empty follicle syndrome, GnRH agonist trigger, in vitro fertilization, suboptimal response

INTRODUCTION

Off-label use of GnRH agonist (GnRHa) as an ovulatory trigger was first suggested in 1988 as a means to prevent ovarian hyperstimulation syndrome (OHSS). When GnRH antagonists were introduced, this practice gained popularity, and is now extensively used with different products and doses. In most cases, GnRHa trigger elicits luteinizing hormone (LH) and follicle stimulating hormone (FSH) surges sufficient to produce mature, fertilizable oocytes. Suboptimal response to GnRHa trigger is not common. The purpose of the current article is to alert practitioners of clinical hints prior to or during ovarian stimulation that may serve as warning signs for a potential suboptimal response to GnRHa trigger.

GnRH AGONIST FOR OVULATION TRIGGER: THE DOSE AND THE TYPE

In 1977, the Nobel Prize in Physiology and Medicine was divided between Rosalyn Yalow 'for the development of RIAs of peptide hormones' and the other half jointly to Roger Guillemin and Andrew Victor Schally 'for their discoveries concerning the peptide hormone production of the brain' [1]. This discovery in the 1980s led to a race in finding potential agonists, and the development of commercial GnRHa preparations, registered for pituitary downregulation in in vitro fertilization (IVF). In the early days of IVF, prior to the introduction of GnRHa, the occurrence of spontaneous endogenous LH surges led to premature luteinization, oocyte maturation and ovulation in up to 20–25% of cycles, hampering success rates [2]. However, after the introduction of GnRHa and the long GnRHa downregulation protocol to suppress the endogenous LH surge [3], cycle cancellation due to spontaneous ovulation was more or less 'history', leading to significantly improved success rates and facilitating scheduling of IVF.

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KEY POINTS

- Off-label use of GnRHa as a trigger is a common practice, and in most cases results in mature, fertilizable oocytes.
- Suboptimal response to GnRHa trigger may result from prolonged hormonal contraceptive use, previous GnRHa-induced pituitary downregulation, a hypo-hypo patient, patients' error, environmental conditions that may damage the GnRHa product used, GnRH and LH receptors polymorphisms, and low endogenous serum LH levels on the trigger day.
- Self-detection of the LH surge in urine 12 h after GnRHa trigger is an easy, well tolerated, reliable and convenient method to ascertain adequate trigger.

Despite the positive impact of GnRHa on success rates after IVF treatment, the addition of GnRHa to ovarian stimulation regimens in the 1980s also led to a large increase in the incidence of OHSS. A possible explanation for this phenomenon is that the pretreatment blockade of endogenous gonadotropins requires an increased dose of exogenous FSH for adequate ovarian stimulation. Moreover, downregulation of the pituitary may interfere with natural cohort selection, preventing smaller and medium sized antral follicles from becoming atretic. Finally, the long GnRHa protocol introduced not only cyst formation because of the initial 'flare up', but also accompanying menopausal symptoms.

In 1988, a conference abstract was the first to suggest that a single bolus of GnRHa could also be used instead of hCG as an agent for ovulation trigger in IVF patients, resulting in the retrieval of mature competent oocytes; furthermore, it also appeared that GnRHa trigger (Buserelin) might reduce the incidence of OHSS [4]. The findings were subsequently followed by a publication, including 14 patients, in whom two different buserelin trigger doses were used, either 250 or 500 μg. Again, the authors reported good oocyte maturity rates as well as ongoing pregnancies, and no OHSS seen in that small cohort [5]. Unfortunately, after the worldwide introduction of the long GnRHa downregulation protocol for standard use in IVF patients [3], the GnRHa trigger concepts was more or less forgotten as the simultaneous use of GnRHa for downregulation and triggering of final oocyte maturation is not possible.

Only when the GnRH antagonist protocol was introduced for the prevention of a premature LH surge [6–8], did the idea of triggering ovulation with a single bolus of a GnRHa as an alternative to hCG become an option again.

Interestingly, GnRHa trigger has more or less always been a practitioner-driven initiative, with very little support from the pharmaceutical industry. As such, over the years, different types and doses of GnRHa have been used and of note, not all GnRHa preparations are available worldwide; hence, the specific GnRHa preparation used in a certain location is subject to availability. Therefore, it is not surprising to see a single early study, in which different GnRHa preparations and different doses were used, depending on location [9].

The use of triprorelin 0.2 mg for trigger has been popular in certain parts of the world, but this specific dose is a mere educated guess [10–12], which only recently was supported by a formal dose-finding study [13]. In other parts of the world, a wide range of GnRHa preparations and doses have been used in clinical trials: buserelin 0.2 [14], 0.5 [15–19] or 1 mg [20]; leuprolide acetate 0.5 [9], 1 [21] or 1.5 mg [22]; nafarelin 400 μg [23], and intranasal administration of buserelin 0.2 mg [24].

As mentioned, the first large sized formal dose finding study was performed only recently, investigating three doses of triptorelin: 0.2, 0.3 and 0.4 mg. A total of 165 oocyte donors were randomized and the authors reported no significant differences between dosing regarding number of oocytes, number of embryos or top-quality embryos. Moreover, no difference was seen as regards to the reproductive outcome in recipients [13]. Moreover, a small randomized controlled trial (RCT) in 20 oocyte donors was performed by Castillo *et al.*, unpublished data), exploring the possible difference between 0.1 and 0.2 mg triptorelin used for trigger. Again, the authors saw no difference in the early luteal steroid profile, the oocyte number, maturity rate, embryos and pregnancy rates in recipients (Castillo, data on file), supporting the notion that a 0.1 mg triptorelin trigger might be sufficient in the young lean patient.

Taken together, the use of triptorelin in doses of 0.1–0.4 mg seems to result in comparable outcomes in terms of oocyte and embryo quality in patients. However, the most optimal GnRHa trigger dose might be impacted by BMI and polymorphisms of the endogenous LH molecule and its receptor.

GnRH AGONIST TRIGGER: SUBOPTIMAL RESPONSE AND EMPTY FOLLICLE SYNDROME

GnRHa acts directly on the level of the pituitary and as such, a temporary or permanent dysfunction of the pituitary would result in an insufficient flare of LH after administration, resulting in either a suboptimal oocyte yield or an empty follicle syndrome (EFS). The literature describes two subtypes of EFS;

the so-called genuine EFS – related to intrinsic factors – and false EFS, mainly related to pharmacological problems or human error [25▪].

The classical example of a genuine EFS is the hypogonadotropic/hypogonadal patient (WHO type I), who although a general consensus has not been achieved as regard the endogenous LH cut-off level, it is usually defined by a baseline level of LH level below 1.2 IU/l. GnRHa triggering in this type of patient is very likely to result in an EFS due to the induction of an insufficient LH surge after trigger. In line with this, one might expect that a 'borderline' patient with low baseline LH levels would also run the risk of a suboptimal response or EFS after GnRHa trigger. Other examples of patients who run the risk of developing a suboptimal response and even EFS after a GnRHa trigger are patients with the presence of GnRH receptor polymorphisms [26], necessitating a higher dose of GnRHa to activate the receptor in line with the FSH receptor polymorphism (Ser/680 FSH-R) [27]. Moreover, patients with LH receptor polymorphisms [28] and patients with the presence of a variant LH β gene polymorphism specifically in the homozygous form, resulting in a less bioactive endogenous LH [29], could also be at risk of a blunted response to GnRHa trigger.

Genuine EFS occurrence is quite rare [30], but deserves special attention when using different preparations for ovulation trigger. Although EFS cases post GnRHa trigger are seen in daily clinical practice and have been reported in the literature [31,32], it is important to emphasize that in the largest retrospective study until now comparing GnRHa trigger and hCG trigger, including a total of 2034 oocyte donors and 1433 IVF patients the incidence of EFS post GnRHa trigger was nonsignificantly different from that of hCG trigger, 3.5 versus 3.1% [25▪]. Interestingly, GnRHa trigger has been reported to overcome EFS encountered in previous hCG triggered cycles [33], most certainly secondary to the endogenous FSH elicited during GnRHa trigger. This highlights the beyond OHSS prevention advantages associated with GnRHa trigger [34].

RISK FACTORS FOR A SUBOPTIMAL RESPONSE TO GnRH AGONIST TRIGGER

Although suboptimal response to GnRHa trigger is not a common feature, clinical hints prior to, or during ovarian stimulation may serve as warning signs for a potential suboptimal response. To be mentioned are long-term hormonal contraception usage before ovarian stimulation, low baseline LH levels less than 2 IU/l at stimulation start, low endogenous serum LH levels on the trigger day, LH levels of 15 IU/l or less 12 h after trigger, prolonged stimulation, high gonadotropin consumption and BMI less than 22 [35–37,38▪].

THE INTERVAL BETWEEN THE LAST GnRH ANTAGONIST DOSE AND THE GnRH AGONIST TRIGGER

GnRH antagonist cotreatment for ovarian stimulation is intended to prevent a premature LH rise and luteinization by competitive inhibition at the level of the GnRH receptors of the pituitary. GnRHa used for trigger must displace the residual GnRH antagonist activity in order to elicit an adequate LH+FSH surge. This potential conflict could raise clinical concerns as to the time interval between the administration of the last GnRH antagonist injection and the subsequent GnRHa trigger. Reassuringly, a recent retrospective analysis of 55 normogonadotropic patients, having a mean time interval between the last GnRH antagonist administration and the GnRHa trigger bolus of 4.6 ± 2.7 h (range 1–12 h), showed that the GnRHa trigger successfully induced an effective LH surge and oocyte maturation, irrespective of the time interval between the last GnRH antagonist dose and the GnRHa trigger [39▪].

PATIENT ERROR AND ENVIRONMENTAL FACTORS

Ovarian stimulation for IVF must meticulously follow instructions, involving different medications, doses, mode of self-administration and timing. Not surprisingly, human error is quite frequent, and in fact, as many as 27% of patients do not comply with or have doubts as regards to the injection schedule and dosing. Physicians often underestimate compliance problems, as usually very high levels of patient compliance are reported (94%) [40▪]. Therefore, treatment instructions must be clear, conveyed both orally and in writing, and with proactive verification of the understanding. Specifically, for failed response to ovulation trigger, the patient must be questioned about dosing and timing of the injection.

GnRH agonists are short peptide chains, and as such are susceptible to harsh environmental conditions, especially excessive heat. Maintaining a strict cold chain from manufacturer to the patient is imperative, especially in hot climate countries. Any cold chain breach can lead to a defective product.

THE SPECIAL CASE OF LONG-TERM DOWNREGULATION AND THE HYPO-HYPO PATIENT

Long-acting GnRHa is often used in IVF patients, either to induce pituitary downregulation before

ovarian stimulation, or in the treatment of endometriosis. Although the manufacturers guarantee at least 1-month effectiveness, patients may be downregulated for many months. If stimulated for IVF shortly after the downregulation and using GnRH antagonist cotreatment, the patient is not likely to respond to the GnRHa trigger due to a low endogenous LH; therefore, medication withdrawal must be ascertained, preferably by documenting a spontaneous ovulatory cycle before embarking on ovarian stimulation with the intention of triggering final oocyte maturation with GnRHa.

In the case of a genuine hypogonadotropic hypogonadism patient, the origin of the endocrine failure must be documented before IVF treatment, to detect if a GnRHa trigger in some cases could still be used. The intravenous GnRH stimulation test has previously been the gold standard test for the evaluation of the hypothalamic-pituitary-gonadal axis. However, this test is time-consuming, costly and uncomfortable for the patient. In contrast, a single bolus of GnRHa may substitute the lengthy intravenous test and in this simplified GnRHa 'challenge test', LH is measured at baseline and 90 min after the GnRHa injection [41].

RESPONSE TO GnRH AGONIST TRIGGER: DETECTION OF THE LH SURGE IN SERUM AND URINE

The endogenous response to a GnRHa trigger can be monitored in serum as well as in urine. After a bolus of GnRHa, LH reaches a peak of approximately 140 IU after 4 h, comparable in amplitude to that seen during the natural ovulatory cycle. Subsequently, LH levels decrease and 12 h after the trigger, the LH level is approximately 40 IU, reaching baseline 24 h after trigger [13,42]. As the trigger is administered in most cases in late evening, a blood test in the very early morning hours (2–4 a.m.) is not practical. However, to assess the efficacy of the GnRHa trigger, a serum sample after 12 h has been the standard until now in several IVF units. At this time point, LH should be more than 15 IU/l and progesterone more than 3 ng/ml to ascertain a sufficient response to the trigger [37,43].

More elegantly, a very recent study in 359 oocyte donors showed that self-detection of the LH surge in urine 12 h after trigger is an easy, well tolerated, reliable and convenient method [44]. In this study, the patient was asked to check the LH surge in morning urine at home, using a standard ovulation stick. To avoid any misinterpretation by the patient, a WhatsApp picture was sent to the staff in the IVF clinic, who confirmed if ovulation had taken place or not. Only three out of 359 (0.2%) of tests were negative, and only those three patients were asked to visit the unit for a serum sample. Subsequently, the serum analyses proved one urine test to be false negative, whereas two tests were true negative. These two patients were retriggered with a bolus of hCG and had a successful oocyte retrieval 36 h later [44].

CONCLUSION

The use of GnRHa as an ovulation trigger agent is a practitioner-driven initiative, not officially endorsed by regulatory agencies, although extensively used worldwide with different products and dosing. In most cases, GnRHa trigger elicits effective LH+FSH surges, resulting in mature, fertilizable oocytes. Rarely, suboptimal response to a GnRHa trigger may result in EFS. Risk factors for a suboptimal response include prolonged hormonal contraceptive use, previous GnRHa-induced pituitary downregulation, hypogonadotropic/hypogonadal conditions, GnRH and LH receptors polymorphisms, low baseline LH and low LH on day of trigger, patient error and environmental conditions that may damage the GnRHa product used. Self-detection of the LH surge in urine 12 h after GnRHa trigger is an easy, well tolerated, reliable and convenient method to ascertain an adequate response to GnRHa trigger.

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Conflicts of interest

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