

Case Reports

Successful Rescue hCG Trigger Following GnRH Agonist Failure in an Egg Donor Cycle: Live Birth Case Report

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Introduction

Gonadotropin-releasing hormone agonists (GnRHa) effectively trigger final oocyte maturation while reducing ovarian hyperstimulation syndrome (OHSS) risk compared to human chorionic gonadotropin (hCG). However, empty follicle syndrome (EFS) occurs in a subset of patients, potentially resulting in complete cycle loss. Rescue hCG protocols may salvage these cycles.

Materials and methods

Case report of GnRHa trigger failure in an oocyte donor with successful hCG rescue and literature review.

Results

A 26-year-old oocyte donor with a history of prolonged oral contraceptive use experienced EFS following GnRHa trigger (0.2 mg triptorelin). Initial aspiration of the right ovary yielded no oocytes despite normal follicular development. Rescue triggering with hCG (250 mcg) was performed, resulting in successful retrieval of 12 oocytes from the left ovary 36 hours later (10 metaphase II). Ten high-quality blastocysts were vitrified (5 grade 4BB, 5 grade 3BB). Frozen embryo transfer in the recipient resulted in a successful pregnancy and live birth at 37 weeks with no complications.

Discussion

This case demonstrates the effectiveness of rescue hCG in salvaging donor cycles after GnRHa trigger failure. The recurrence of EFS with GnRHa may reflect inter-patient variability in pituitary responsiveness, potentially linked to genetic or hormonal factors such as prolonged oral contraceptive use. Rescue protocols are essential for optimizing outcomes in oocyte donation programs.

INTRODUCTION

Human chorionic gonadotropin (hCG) administration for triggering final oocyte maturation has long been considered the gold standard in controlled ovarian hyperstimulation protocols for *in vitro* fertilization (IVF). However, the prolonged hCG luteotropic effect compared to endogenous luteinizing hormone (LH) favors the formation of multiple corpora lutea, raising the risk of ovarian hyperstimulation syndrome (OHSS).¹

As an alternative to hCG, Nakano *et al.* pioneered in 1973 the use of GnRH agonists (GnRHa) to trigger final oocyte maturation in women who underwent intrauterine insemination,

which resulted in two pregnancies.² More recently, the GnRHa trigger has been used in GnRH antagonist cycles to induce the final stage of follicular maturation while reducing the risk of OHSS.³ However, some clinical trials that included normo-responsive patients reported unacceptable rates of early gestational loss after fresh embryo transfer, probably associated with corpus luteum insufficiency secondary to the desensitization of the GnRH receptors.⁴

Some protocols use luteal support by bolus injection of 1,500 IU hCG on the day of oocyte retrieval, in combination with estradiol and progesterone, to improve pregnancy rates and reduce the incidence of OHSS.⁵

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The administration of GnRHa to trigger oocyte maturation may prevent OHSS in hyper-responsive patients, that is, women with polycystic ovary syndrome (PCOS), history of OHSS, and those under treatment for fertility preservation. The GnRHa trigger also offers other benefits such as decreased pain, less abdominal distension, and shortening of the menstrual bleeding interval.^{1,6,7}

However, in some patients, a suboptimal pituitary response to GnRHa results in failed oocyte maturation, a phenomenon known as empty follicle syndrome (EFS). This syndrome has an incidence between 0.045 and 7%.⁸ It is a condition in which no oocytes are obtained during follicular aspiration after ovarian hyperstimulation despite normal follicular development and without evidence of technical failure during the oocyte retrieval procedure performed after GnRHa or hCG trigger.⁹

There are two types of EFS, genuine (gEFS) and false (fEFS). The gEFS is characterized by hCG or LH levels consistent with the proper administration of the stimulus, whereas in fEFS, gonadotropin levels are low due to human or pharmacological errors during medication administration.⁸ The recurrence of EFS with GnRHa may reflect inter-patient variability in pituitary responsiveness, potentially linked to genetic or hormonal factors.

Since its definition in 1986 by Coulam, EFS was initially related to the hCG trigger in assisted reproductive cycles. Therefore, the GnRHa trigger was introduced as an alternative for patients at high risk of OHSS; however, EFS still occurs despite these new approaches.⁸ Although hCG and GnRHa are similar in the effect they have on final oocyte maturation, the pathophysiological mechanisms underlying the failed response to each of them are entirely different.¹⁰

The GnRHa induces oocyte maturation by binding to the GnRH receptor in the adenohypophysis that stimulates the gonadotropin release (flare-up effect), allowing the resumption of oocyte meiosis, rupture of the dominant follicle, oocyte release, luteinization of the theca cells, and formation of corpus luteum.¹¹ Therefore, the higher endogenous LH levels resulting from the administration of a GnRHa could set an optimal response to the trigger and even allow the identification of patients with pituitary dysfunction whose LH levels are insufficient to support the maturation of at least 70% of the oocyte population.¹²

On the other hand, due to its structural and biological similarities to LH, hCG can stimulate oocyte maturation by binding to LH receptors on the granulosa cells that leads to the loss of the gap junctions between oocyte and cumulus cells, favoring the expansion of the latter, the resumption of oocyte meiosis, and the luteinization of granulosa cells.¹³

It is important to note that some risk factors of EFS secondary to GnRHa trigger have been identified and include low body mass index (BMI), prolonged use of oral contraceptives (OCPs), and irregular menstrual cycles. Also, it has been suggested that down-regulated pituitary GnRH receptors are insufficient to stimulate oocyte maturation.^{7,14,15}

Due to limited scientific evidence, we reported the case of an oocyte donor who presented failed oocyte maturation

after the GnRHa trigger but did respond to the hCG rescue protocol. Interestingly, the re-triggering with hCG allowed substantial oocyte retrieval, adequate embryo development, successful frozen-thawed embryo transfer, and the birth of a live newborn to the recipient woman.

MATERIALS AND METHODS

STUDY DESIGN AND ETHICS

This case report describes the successful management of empty follicle syndrome (EFS) following gonadotropin-releasing hormone agonist (GnRHa) trigger in an oocyte donation cycle. The study was approved by the Medical and Research Ethics Committee of the Instituto de Fertilidad Humana InSer, and written informed consent was obtained from both the oocyte donor and recipient.

PATIENT 1: OOCYTE DONOR

A 26-year-old healthy female oocyte donor with a body mass index (BMI) of 18.5 kg/m², regular menstrual cycles, and a history of oral contraceptive pill (OCP) use for 5 years underwent controlled ovarian stimulation using a flexible GnRH antagonist protocol. The donor met all institutional screening criteria for oocyte donation and had discontinued OCP use 3 months prior to cycle initiation.

Ovarian Stimulation Protocol: Controlled ovarian stimulation was initiated with human menopausal gonadotropin (HMG) 150 IU daily (Merional®, IBSA) and continued for 11 days with a total cumulative dose of 2,250 IU. Dose adjustments were made based on ovarian response as assessed by transvaginal ultrasound monitoring every 2-3 days and serum estradiol measurements. GnRH antagonist 0.25 mg ganirelix (Orgalutran®, MSD) was initiated when the leading follicle reached 14 mm in diameter and continued daily until final oocyte maturation trigger.

Trigger and Initial Retrieval: Final oocyte maturation was triggered with 0.2 mg triptorelin (Gonapeptyl®, Ferring Pharmaceuticals) when at least three follicles reached ≥17 mm diameter. A total of 24 follicles were monitored during ovarian stimulation (12 from each ovary). Follicular aspiration of the right ovary was performed 36 hours after the GnRHa trigger using standard transvaginal ultrasound-guided technique. Despite normal follicular fluid volume and appearance, no oocytes were retrieved after thorough aspiration and flushing of all mature follicles.

Diagnosis of Empty Follicle Syndrome: The procedure was stopped after unsuccessful retrieval from the right ovary, and serum hormone levels were immediately assessed. Post-trigger hormone levels revealed luteinizing hormone (LH) 1.9 IU/L, progesterone 0.51 ng/mL, and estradiol 3,711 pg/mL. The LH level of 1.9 IU/L, well below the expected threshold of ≥15 IU/L, indicated suboptimal pituitary response consistent with EFS.

Rescue Protocol: Rescue triggering was immediately performed with human chorionic gonadotropin (hCG) 250 mcg (Ovidrel®, Merck Serono) administered subcutaneously. Oocyte retrieval from the left ovary was

rescheduled for 36 hours after hCG administration. The rescue retrieval successfully yielded 12 oocytes at different meiotic stages: 10 at metaphase II (mature), 1 at metaphase I, and 1 at prophase I.

Laboratory Procedures: All mature oocytes underwent intracytoplasmic sperm injection (ICSI) using sperm from the recipient's partner. Embryos were cultured in sequential media under standard laboratory conditions (37°C, 6% CO₂, 5% O₂). Blastocyst formation was assessed on day 5-6, and embryo quality was evaluated using standardized morphological criteria. Ten high-quality blastocysts were successfully developed and vitrified using standard protocols.

PATIENT 2: OOCYTE RECIPIENT

A 40-year-old woman diagnosed with primary ovarian insufficiency underwent endometrial preparation for frozen embryo transfer. The recipient had no significant medical history and met all criteria for oocyte recipient treatment.

Endometrial Preparation: Endometrial preparation was performed using an artificial hormone replacement therapy protocol. Pituitary suppression was achieved with a single dose of GnRHa 3.75 mg triptorelin (Decapeptyl®, Tecnofarma) administered during the mid-luteal phase of the preceding cycle. Estradiol valerate (Progynova®, Bayer) was initiated on cycle day 2, starting at 2 mg daily and gradually increased to 6 mg daily based on endometrial response. Serial transvaginal ultrasound monitoring confirmed adequate endometrial development, achieving a 9.5-mm-thick trilaminar pattern suitable for embryo transfer.

Embryo Transfer and Luteal Support: Progesterone supplementation with 800 mg daily (Utrogestan®, Biopas) was administered intravaginally for 5 days prior to embryo transfer to ensure adequate luteal phase support. Two vitrified-warmed blastocysts of 4BB quality were transferred under ultrasound guidance using standard catheter technique.

Pregnancy Outcomes: Serum beta-hCG was positive 14 days after embryo transfer. Transvaginal ultrasound at 4 weeks post-transfer confirmed a viable singleton intrauterine pregnancy. The pregnancy progressed normally throughout gestation, and a healthy live newborn was delivered by cesarean section at 37 weeks of gestation with no maternal or neonatal complications.

LITERATURE REVIEW METHODOLOGY

A comprehensive literature search was conducted to compare the findings, diagnosis, and management of the present case with similar reports. The search was performed using the following terms: "empty follicle syndrome" AND "GnRH-releasing hormone" AND "failure" AND "stimulation" in PubMed, ScienceDirect, ClinicalKey, and Medline Ovid databases. The search yielded 259 publications, of which 254 were excluded because they did not report EFS following GnRHa trigger or lacked clinical outcome data. Five studies were selected for analysis: three retrospective cohort studies and two case reports, all of which described

rescue protocols and clinical outcomes in patients with GnRHa trigger failure.

DISCUSSION

PATHOPHYSIOLOGY OF EMPTY FOLLICLE SYNDROME AFTER GNRH AGONIST TRIGGER

In assisted reproduction treatments, the GnRHa trigger has been an alternative to hCG in patients with risk factors for OHSS.³ However, some studies found a subgroup of patients that showed failure to endogenous response to gonadotropins, resulting in poor oocyte maturation and absence of oocytes during follicular aspiration; this condition is known as EFS.⁸

Although the specific mechanism underlying EFS is unclear, the GnRHa induces oocyte maturation by binding to the GnRH receptor in the adenohypophysis that stimulates the gonadotropin release (flare-up effect), allowing the resumption of oocyte meiosis, rupture of the dominant follicle, oocyte release, luteinization of the theca cells, and formation of corpus luteum. The short-lived LH surge induced by GnRHa may be insufficient in amplitude or duration to complete oocyte maturation in some patients, necessitating hCG's prolonged receptor stimulation.

PREDICTIVE FACTORS AND RISK ASSESSMENT

LABORATORY PREDICTORS

Kummer et al. observed that in patients with suboptimal response to the GnRHa trigger, LH values less than 15 IU/L at 12 hours post-trigger predicted failed oocyte maturation with a sensitivity of 97.4%, specificity of 100%, and an area under the ROC curve of 0.985.¹⁶ Although a threshold LH level at 12 hours post-triggering is suggested to predict the EFS, the syndrome was diagnosed 36 hours after triggering based on the absence of oocytes on follicular aspiration, regardless of gonadotropin levels.

PATIENT-SPECIFIC RISK FACTORS

Several risk factors have been identified for EFS following GnRHa trigger:

Body Mass Index: Some studies consider that a BMI < 22 kg/m² is a risk factor that increases twice the probability of failed response after GnRHa trigger ($p = 0.039$).¹⁷ In patients with low BMI, reduced leptin levels related to decreased body fat percentage may change the frequency of the GnRH pulses, altering gonadotropin release and causing dysfunction in the hypothalamus-pituitary axis.¹⁸ Conversely, Kummer et al. observed that endogenous LH levels at 12 hours after GnRHa trigger were frequently lower in women with BMI > 28.7 kg/m², possibly due to the dilutional effect on medication absorption.¹⁶

Oral Contraceptive Use: Meyer et al. observed that the long-term use of OCPs had an association 20-times higher with suboptimal endogenous LH levels (OR = 20.97; 95% CI = 5.29-83.14; $p < 0.0001$), compared with patients who had not previously used OCPs.¹⁵ In the current case, the

Table 1. Risk Factors for GnRH Agonist Trigger Failure

Risk Factor	Definition/Threshold	Odds Ratio (95% CI)	Reference
Low BMI	<22 kg/m ²	2.0 (1.1-3.6)	Chang et al. ¹⁷
Prolonged OCP use	>6 months prior to cycle	20.97 (5.29-83.14)	Meyer et al. ¹⁵
Irregular cycles	Self-reported	2.3 (1.2-4.4)	Meyer et al. ¹⁵
Low LH at 12h	<15 IU/L post-trigger	Sensitivity 97.4%	Kummer et al. ¹⁶

*BMI = Body Mass Index; mechanism likely related to altered leptin levels affecting GnRH pulse frequency

**OCP = Oral Contraceptive Pills; prolonged use may cause pituitary desensitization to GnRH

***Irregular cycles defined as cycle length <21 or >35 days, or variation >7 days between cycles

****LH = Luteinizing Hormone; measured 12 hours after GnRH agonist administration

donor had prolonged use of OCPs, which could cause partial desensitization of pituitary receptors and insufficient gonadotropin levels for oocyte maturation. The persistent inhibitory effect of the estrogenic component of OCPs on GnRH pulses may be associated with a temporary pituitary hyposensitivity state to GnRHa.

Menstrual Cycle Irregularities: Meyer et al. observed that among patients with failed oocyte maturation, 43.5% presented irregular and 20.7% regular menstrual cycles ($p = 0.007$), suggesting that irregular cycles may predispose to GnRHa trigger failure.¹⁵

MOLECULAR MECHANISMS OF TREATMENT FAILURE

Although suboptimal LH levels could favor follicular development and initiate follicle luteinization, they are not sufficient to stimulate the expression of growth factors, prostaglandin synthase 2, and tumor necrosis factor- α , which are needed to complete the cumulus cell expansion and the release of the oocyte from the follicular wall at the time of oocyte retrieval.¹²

Other less common causes of failed GnRHa trigger include LH receptor mutations and LH beta-subunit polymorphisms. In these cases, the impaired post-receptor signaling pathways are responsible for the reduced biological LH activity and the lack of oocyte maturation-inducing mechanisms¹⁵ (Table 1).

RESCUE HCG PROTOCOL: MECHANISM AND EFFICACY

BIOLOGICAL RATIONALE FOR RESCUE TREATMENT

The present case of EFS shows similarities with previously reported cases in which rescue hCG successfully compensated for the initial insufficiency by directly interacting with receptors on follicular cells. This interaction promoted cumulus cell expansion, resumption of meiosis, and detachment of oocytes from the follicular wall, ultimately enabling successful oocyte retrieval. Due to its structural and biological similarities to LH, hCG can stimulate oocyte maturation by binding to LH receptors on granulosa cells, leading to the loss of gap junctions between oocyte and cumulus cells, favoring the expansion of the latter, the resumption of oocyte meiosis, and the luteinization of granulosa cells.¹³

CLINICAL OUTCOMES OF RESCUE PROTOCOLS

Although there is no agreement on the management of EFS, Ndukwe et al. suggested the rescue hCG trigger as a “cure” for EFS.¹⁹ According to literature, the rescue hCG trigger has allowed the retrieval of mature oocytes in up to 92.3% of patients, increasing the possibility of obtaining good-quality embryos and future pregnancies.^{9,19,20} In the present case report, approximately 50% of the oocyte cohort was retrieved; specifically, 12 oocytes at different maturation stages gave rise to 10 good quality blastocysts after rescue triggering with hCG (Table 2).

PREGNANCY AND LIVE BIRTH OUTCOMES

A few published studies on rescue triggering have reported the resulting pregnancies and live newborns: Asada et al. reported 8 patients with failed GnRHa trigger achieving oocyte retrieval after rescue hCG. All 8 patients underwent frozen-thawed embryo transfer with results: 5 live newborns, 2 ongoing pregnancies, and 1 negative case.¹⁴ Christopoulos et al. published a retrospective cohort study of 322 patients with six reported cases of failed trigger. After rescue with hCG, mature oocyte retrieval was achieved in five of the 6 cases, but pregnancy outcomes were limited.²⁰ Deepika et al. studied 271 women with PCOS and reported 9 cases of failed GnRHa trigger. Oocyte retrieval was successful in 8 patients with rescue hCG, but pregnancy outcomes were poor (2 pregnancies with losses)⁹ (Table 3).

Unlike most reports, which focus on autologous cycles or lack data on live birth outcomes, this case demonstrates the effective use of rescue hCG in a donor cycle, culminating in a frozen embryo transfer (FET) and the birth of a healthy child.

CLINICAL MANAGEMENT STRATEGIES

FREEZE-ALL STRATEGY

The studies reviewed showed a trend towards frozen-thawed embryo transfer with better outcomes in terms of clinical pregnancy and live births compared to fresh embryo transfer. These results may be related to institutional policies of each clinical center or higher recruitment of hyper-responsive women in the studies. For these patients, the strategy of freeze-all is a measure that avoids the effect of supraphysiological hormone levels on the endometrium,

Table 2. Comparison of Trigger Methods

Parameter	hCG Trigger	GnRH Agonist Trigger	Rescue hCG
OHSS Risk	High	Low	Moderate
Failure Rate	<1%	0.045-7%	N/A
Luteal Support	Standard	Intensive	Standard
Fresh Transfer	Preferred	Contraindicated	Possible
Cost	Low	Moderate	High

*OHSS = Ovarian Hyperstimulation Syndrome; risk varies by patient factors (PCOS, young age, high AMH)

**Failure defined as empty follicle syndrome or <50% expected oocyte yield

***N/A = Not applicable; rescue hCG is used only after initial trigger failure

****Standard luteal support = progesterone + estradiol; Intensive = progesterone + estradiol + low-dose hCG

*****Fresh transfer timing depends on endometrial receptivity and hormone levels

*****Contraindicated due to inadequate luteal phase and risk of luteal phase defect

*****Cost includes medication, monitoring, and potential cycle cancellation/rescue procedures

Table 3. Summary of Rescue hCG Studies for GnRH Agonist Trigger Failure

First Author (Year)	Study Type	Cases (n)	Rescue Success Rate	Live Birth Rate
Asada (2013)	Case series	8	100%	62.5% (5/8)
Kummer (2013)	Retrospective	7	28.6%	0% (0/7)
Blazquez (2014)	Retrospective	13	92.3%	Not reported
Christopoulos (2015)	Case series	6	83.3%	0% (0/6)*
Deepika (2018)	Retrospective	9	88.9%	0% (0/9)**
Present case (2024)	Case report	1	100%	100% (1/1)
TOTAL	Mixed	44	81.8% (36/44)	13.6% (6/44)

*One pregnancy achieved but miscarried at 11 weeks

**Two pregnancies were achieved but both resulted in early pregnancy loss

thus improving endometrial receptivity and implantation rates.

MONITORING AND PREVENTION

It is important to note that LH levels are not necessary to diagnose EFS during follicular aspiration. However, the LH level at 12 hours post-triggering is clinically helpful in predicting EFS in patients with risk factors such as low BMI, use of OCPs, or irregular menstrual cycles to avoid failed aspirations and ensure oocyte retrieval.

IMPLICATIONS FOR OOCYTE DONATION PROGRAMS

This case has particular relevance for oocyte donation programs, as donor cycles represent a significant investment of time and resources. The successful rescue protocol prevented complete cycle loss and ultimately resulted in a live birth for the recipient. The case reinforces the hypothesis of a transient dysfunction of the hypothalamic-pituitary axis, likely associated with prolonged use of oral contraceptive pills prior to the initiation of controlled ovarian hyperstimulation.

LIMITATIONS AND FUTURE DIRECTIONS

While this case report demonstrates successful rescue with hCG, several limitations should be acknowledged. As a single case report, the findings have limited generalizability to

broader patient populations. Additionally, this study lacks comparison with alternative management strategies and provides limited long-term follow-up data on both maternal and neonatal outcomes.

Future research should focus on developing standardized protocols for rescue triggering to ensure consistent clinical application across different centers. There is also a critical need for identifying additional predictive biomarkers beyond current LH thresholds to better predict which patients are at risk for trigger failure. Cost-effectiveness analyses comparing rescue protocols versus cycle cancellation would provide valuable guidance for clinical decision-making and resource allocation. Furthermore, prospective studies examining optimal timing and dosing of rescue hCG administration are essential to maximize success rates while minimizing patient burden and treatment delays. Large-scale multicenter studies would be particularly valuable to establish evidence-based guidelines for managing GnRHa trigger failure in both autologous and donor cycles, ultimately improving outcomes for patients undergoing assisted reproductive technologies.

CONCLUSION

GnRH agonists (GnRHa) are commonly used to trigger oocyte maturation while minimizing the risk of ovarian hyperstimulation syndrome (OHSS). However, in certain cases—particularly in patients with specific risk

factors—GnRHa triggers may fail to induce adequate oocyte maturation. In such situations, re-triggering with rescue hCG has proven to be an effective strategy to enable the retrieval of mature oocytes. These observations support the importance of routinely monitoring post-trigger LH levels and maintaining readiness to administer rescue hCG in GnRHa cycles, especially in oocyte donors with identifiable risk factors, to optimize both oocyte yield and pregnancy outcomes.

The present case, along with previously published reports, reinforces the hypothesis of a transient dysfunction of the hypothalamic–pituitary axis, likely associated with prolonged use of oral contraceptive pills (OCPs) prior to the initiation of controlled ovarian hyperstimulation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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