HCG Trigger After Failed GnRH Agonist Trigger Resulted in Two Consecutive Live Births: A Case Report

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Background: Failed gonadotropin-releasing hormone (GnRH) agonist trigger with no oocyte retrieved during aspiration of several follicles is a rare but recurrent situation that can be rescued by the termination of the aspiration procedure, retriggering by human chorion gonadotropin (hCG), and repeated oocyte pickup 36 h later. Failed GnRH agonist trigger is frustrating and unsatisfactory, and fertility doctors must be aware of possible hCG retriggering and retained opportunity for successful cycle outcome.

Objective: In this case report, we present a woman who experienced failed GnRH agonist trigger and rescue hCG retrigger followed by two consecutive live births after frozen-thawed single blastocyst transfers.

Methods: A case report.

Results: Two healthy children were born in 2018 and 2020, respectively as a result of controlled ovarian stimulation for IVF, failed GnRH agonist trigger followed by hCG re-trigger, and successful retrieval of 25 oocytes.

Conclusion: Retriggering with hCG after failed GnRH agonist trigger can result in consecutive live births, and such knowledge can prevent cycle cancellation and patient discouragement. Knowledge on retriggering with hCG and consecutive live births after failed GnRH agonist trigger can prevent cycle cancellation and patient discouragement.

Keywords: empty follicle syndrome (EFS), rescue hCG, failed agonist trigger, re-trigger with hCG, consecutive live births after empty follicle syndrome

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a serious complication to in vitro fertilization (IVF), which is potentially life-threatening. Moderate to severe OHSS has a prevalence of 3–8% (1, 2) being highest for women with polycystic ovarian syndrome (PCOS). The risk of OHSS increases with an increasing number of growing follicles and also high oestradiol levels on the day of ovulation trigger, and it increases with an increased number of retrieved oocytes (3, 4). More than 18 growing
were retrieved (≥ follicles Liest et al. Re-trigger After Failed GnRH-Agonist Trigger predictor of severe OHSS (infertility and unsuccessful intrauterine inseminations. The duration of infertility was 1 year. The female diagnosis was PCOS partner were referred to a tertiary clinic because of combined In 2016, a 29-year old, nulligravida, healthy woman and her CASE DESCRIPTION

In 2016, a 29-year old, nulligravida, healthy woman and her partner were referred to a tertiary clinic because of combined infertility and unsuccessful intrauterine inseminations. The duration of infertility was 1 year. The female diagnosis was PCOS based on secondary amenorrhea and an antral follicle count of 80 corresponding to an antimullarian hormone (AMH) level of 96 pmol/L. Androgen status, prolactin, and thyroid stimulating hormone levels were normal. Follicle stimulating hormone (FSH) and LH levels were 5.8 IU/L and LH 6.7 IU/L, respectively. BMI was 21 kg/m². The sperm volume and count were just within the normal range, but the motility was affected with a lower than a normal number of progressively motile sperm cells according to the recommendation of ICSI.

The woman underwent a total of three controlled ovarian stimulation cycles that are summarized in Table 1. All three were in a flexible GnRH antagonist protocol. In the first two stimulations, final oocyte maturation was triggered with hCG as the risk of OHSS was not pending based on the number of follicles > 11 mm. After the first ovarian stimulation 11 oocytes were retrieved, but none of them developed into blastocysts. In the second stimulation, 12 oocytes were retrieved, one cleavage stage embryo was transferred, and the last embryos did not develop into blastocysts. None of the first two simulations resulted in pregnancy.

In the third ovarian stimulation, a daily dose of human menopausal gonadotropin (Menopur; Ferring Pharmaceuticals) 112–131 IU was administered from cycle day 2 (CD2), and 0.25 mg of GnRH antagonist (Cetrotide; Merck) was added daily when the leading follicles reached 13–14 mm (stimulation day 12). On stimulation day 16, when ~15 follicles reached 17 mm, and a total of 23 follicles were ≥11 mm, the final oocyte maturation was triggered with 0.50 mg of GnRH agonist Suprefact (Buserelin; Orifarm). Elective freeze-all was planned to reduce the risk of OHSS. Oocyte retrieval was performed 36 h after trigger using ultrasound-guided transvaginal needle aspiration after administration of local anesthetic and low-dose intravenous opioids. Approximately 12 follicles from the right ovary were emptied without retrieval of any oocytes, even though flushing was used in several follicles. The procedure was stopped, and five follicles in the right ovary and all the follicles in the left ovary were left untouched. No GnRH antagonist was administered after the oocyte retrieval. Rescue hCG retrigger was performed at 10 pm the same day with chorion gonadotropin-alfa (Ovitrelle; Merck) 250 µg, and 36 h later a second oocyte retrieval was performed. Here 25 oocytes, of which 20 were mature, were retrieved from 30 follicles, 13 were fertilized and five-six days after the second oocyte retrieval, eight good quality blastocysts were vitrified. There were no symptoms of OHSS after rescue hCG retrigger.

The patient used contraceptive pills for 1 month and consecutive frozen-thawed embryo transfer (FET) was planned in artificial hormone replacement cycles (AC). In the fourth AC FET the patient conceived and delivered a healthy girl at gestational age 40+0 weeks, 4 days after initiation of partus provocatus medicamentalis by oral misoprostol. The weight of the girl was 2,155 g (~34%). In the AC FET, the patient took 4 mg oestradiol twice daily for 17 days before the addition of 90 mg of vaginal progesterone gel (Crimone; Orifarm) daily. Single blastocyst warming and transfer were performed on the 6th day of progesterone.

After 18 months, the couple returned with the wish for a second child. There were still four vitrified blastocysts left. In the third and last AC FET cycle (one blastocyst did not survive
In the present case, supplementary GnRH antagonist was not used after the first failed oocyte retrieval. We would not expect premature ovulation to be an issue in cases of genuine EFS. The initial GnRHa trigger is expected to empty the pituitary LH, and if this endogenous LH should reach a circulatory “threshold level” of concern, we would expect a suboptimal endogenous LH surge. Even though a conventional LH trigger was a suboptimal endogenous LH surge. Even though a conventional LH trigger was a suboptimal endogenous LH surge. Even though a conventional LH trigger was a suboptimal endogenous LH surge.

In the current case, there were no issues regarding patient compliance, and most likely the reason for failed GnRHa trigger was a suboptimal endogenous LH surge. Even though gonadotropin levels were measured and found within the mid-normal range as a part of the standard fertility work-up of this anovulatory women (LH 6.7 IU/L), no LH measurement was performed at the initiation (baseline) of this third ICSI treatment, which is a limitation to causal interpretation. However, the patient did use oral contraceptive pills (OCP) to initiate her bleeding, and the baseline LH level may have been suppressed.

As the incidence of EFS is generally low (15–17), and the sensitivity of baseline LH levels to predict EFS is low (15), we would suggest measurement of baseline LH level “on indication” rather than on all patients. Such indications could be the use of OCP or other drugs that induce pituitary downregulation even after a wash-out period and/or anovulation, especially if the anovulation is not a part of a PCOS diagnosis where LH levels are usually normal–high. If baseline LH is low after OCP, postponement of stimulation start could be applied if only small antral follicles (proceeded by another LH measurement), or a cautious gonadotropin dose for ovarian stimulation could be chosen aiming for hCG trigger with a minimal risk of OHSS.

In the present context, supplementary GnRH antagonist was not used after the first failed oocyte retrieval. We would not expect premature ovulation to be an issue in cases of genuine EFS. The initial GnRHa trigger is expected to empty the pituitary LH, and if this endogenous LH should reach a circulatory “threshold level” of concern, we would expect a suboptimal response with at least a few oocytes retrieved at the first retrieval rather than zero oocytes (genuine EFS).

Another question is whether to measure the LH level in blood or urine in the morning after the GnRHa trigger. Interestingly, it has recently been demonstrated that a standard urinary LH test on the morning after GnRHa trigger can be used by patients at home as an easy and convenient way to document a sufficient LH release in response to GnRHa trigger (21). Only three out of

TABLE 1 | Overview of the three controlled ovarian stimulation cycles and associated outcome.

| Treatment number (date of oocyte retrievals) | 1. (16/11 2016) | 2. (15/2 2017) | 3. (1/4+3/4 2017) |
|---|---|---|---|
| Days of stimulation | 21 | 31 | 15 |
| Gonadotropin starting dose | Menopur 75 IU | Purogen 91 IU | Menopur 112 IU |
| Gonadotropin total dose | 1,872 IU | 3,295 IU | 2,051 IU |
| Fertilization method | ICSI | IVF/ICSI 6/6 oocytes | ICSI |
| Number of oocytes | 11 | 12 | (0)/25* |
| Number of mature oocytes | 5 | NA/3 | 20 |
| Number of cleavage stage embryos | 4 | 0/2 | 13 |
| Number of blastocysts** | 0 | 0 | 8 |
| Embryos transferred in the stimulated cycle | 0 | 1 | 0 |
| Number of FET cycles | 0 | 0 | 7*** |
| Pregnancies | 0 | 0 | 2 |
| Live births | 0 | 0 | 2 (2018 + 2020) |

*Zero oocytes were retrieved after GnRHa trigger, after rescue hCG re-trigger 25 oocytes were retrieved.
**Gardner score (on Day 5 or 6) ≥ 3BB.
***One blastocyst underwent atresia after warming.
of 359 (0.8%) urine LH tests were negative; however, in one out of the three cases, an LH measurement in blood showed LH rise consistent with optimal response to the GnRHa trigger (21). Thus, the predictive value of a negative urine LH test does not seem reliable and could have resulted in ovulation if hCG retriggering and rescheduling of the oocyte retrieval had been based on the urine LH testing alone.

In our opinion, insufficient LH rise after GnRHa trigger is too uncommon to justify posttrigger LH measurements. Instead, if no oocytes are retrieved after proper emptying of ~7 preovulatory follicles, we advocate hCG retrigger and a second oocyte retrieval, as presented in this case report.

The diagnosis EFS could be given when no oocytes are retrieved from ~7 preovulatory follicles despite proper emptying and flushing. The risk of OHSS has been suggested to be reduced after failed GnRHa and hCG retrigger due to reduction of the oestradiol level after the first attempt to retrieve oocytes (18) as well as by an elective freeze-all regimen. Moderate to severe OHSS after rescue hCG retrigger has nevertheless been described, and an individual estimation of OHSS risk before hCG retrigger is important in each patient (19, 22). In this case report, we lack data on posttrigger serum LH, progesterone, and oestradiol.

The experience from the presented case report is that rescue hCG retrigger after failed GnRHa trigger can result in a complete family formation. The case is important as knowledge on retriggering with hCG and consecutive live births after failed GnRHa can prevent cycle cancellation and patient discouragement. Correct counseling from clinicians to patients is needed in clinical situations where this unexpected situation appears.

Perspective of the patient: Sharing the knowledge that hCG retrigger after failed GnRHa trigger is possible can prevent cycle cancellation and patient discouragement and result in consecutive live births.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

**ETHICS STATEMENT**

Informed written consent has been obtained from the woman for publication of the case report.

**AUTHOR CONTRIBUTIONS**

IR, LP, JB, NF, AP, and KL helping with literature, references, and reading correture on article. All authors contributed to the article and approved the submitted version.

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