

## Borderline form of empty follicle syndrome treated with a novel dual trigger method combined with delayed oocyte retrieval: A case report

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**Author contributions:** Cao XL reviewed the literature and contributed to manuscript drafting; Sun ZG was responsible for revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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### Abstract

#### BACKGROUND

Borderline form of empty follicle syndrome is a condition in which only a few mature or immature oocytes are recovered after meticulous follicular aspiration, despite adequate ovarian response to stimulation. It is a rare phenomenon with an unclear cause. Currently, the condition still lacks effective treatment.

#### CASE SUMMARY

A patient with secondary infertility who had undergone three cycles of assisted reproductive technique (ART) is described. With regard to good follicular response, two oocytes were obtained in the first two ART cycles, but no embryo was formed. In the third ART cycle, which is the subject of this study, ovulation was induced by dual trigger of a supernormal dose of human chorionic gonadotropin (HCG) combined with a delayed oocyte retrieval approach. The method involved administration of gonadotropin-releasing hormone agonist, recombinant HCG, and urinary HCG 39 h before ovum pick-up. Ten oocytes were recovered, two out of three mature eggs were fertilized after intracytoplasmic sperm injection, resulting in two embryos that were subsequently cryopreserved. The case report guidelines have been used herein to present the first case of this novel dual trigger method.

#### CONCLUSION

This approach provides a new treatment option for patients with a similar condition in the future. This study can also inspire further investigation on the effects of various  $\beta$ -HCG serum levels 36 h after intramuscular HCG administration.

ses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Received:** November 26, 2019

**Peer-review started:** December 10, 2019

**First decision:** January 7, 2020

**Revised:** January 10, 2020

**Accepted:** January 15, 2020

**Article in press:** January 15, 2020

**Published online:** February 26, 2020

**P-Reviewer:** Exbrayat JM

**S-Editor:** Zhang L

**L-Editor:** Webster JR

**E-Editor:** Qi LL



**Key words:** Empty follicle syndrome; Dual trigger; Delayed oocyte retrieval;  $\beta$ -HCG threshold; Case report

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**Core tip:** Although there is still a dispute regarding the existence of a borderline form of empty follicle syndrome, it is undeniable that this phenomenon does exist. Our case study reports a new ovulation triggering approach that involves a dual trigger of a supernormal dose of human chorionic gonadotropin combined with delayed oocyte retrieval. Our study provides a new technique for the treatment of borderline empty follicle syndrome.

**Citation:** Cao XL, Sun ZG. Borderline form of empty follicle syndrome treated with a novel dual trigger method combined with delayed oocyte retrieval: A case report. *World J Clin Cases* 2020; 8(4): 825-830

**URL:** <https://www.wjnet.com/2307-8960/full/v8/i4/825.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v8.i4.825>

## INTRODUCTION

Empty follicle syndrome (EFS) was first described by Coulam *et al*<sup>[1]</sup>. It refers to a condition in which no oocytes are recovered after meticulous follicular aspiration, despite normal follicular development. Failure to recover oocytes from dominant follicles is a rare phenomenon, and the incidence is estimated to be between 0.045% and 3.5%<sup>[2]</sup>. The condition is divided into two types, that is, “genuine” EFS and “false” EFS. The genuine form is a situation in which aspiration produces no oocytes despite a satisfactory ovarian response, whereas the false form can be described as a failure to recover oocytes due to low levels of beta-human chorionic gonadotropin ( $\beta$ -HCG). Low serum  $\beta$ -HCG levels may occur as a result of its erroneous administration or decreased bioavailability<sup>[3]</sup>.

A borderline form of EFS has been described in cases in which only a few mature or immature oocytes are recovered from several mature follicles. The condition was initially thought to be caused by the poor quality of  $\beta$ -HCG or its improper administration<sup>[4-6]</sup>. Until now, the underlying causes of the condition remain a mystery. Also, the optimum threshold level of circulating serum  $\beta$ -HCG is still disputed (reports vary from 5–160 IU/L of exogenous HCG administration after about 36 h)<sup>[7]</sup>. The main reason for these conflicting findings could be because of limited knowledge regarding the pathophysiology of EFS, which has resulted in a lack of practical solutions for the management of these conditions. Currently, it is thought that changing the trigger strategy could be a feasible approach to improve the egg acquisition in EFS patients<sup>[7]</sup>.

## CASE PRESENTATION

### Chief complaints

A couple with six years of secondary infertility visited a reproductive and genetic center in 2019.

### History of present illness

The 38-year-old patient had experienced irregular menses since menarche (which occurred at the age of 14), with maximal amenorrhea periods of 90 d. Her body mass index was 22.04 kg/m<sup>2</sup>.

### History of past illness

She had undergone induced abortion in 2006 after 40 d of pregnancy (because of an unplanned pregnancy) and had no other pregnancy history. In 2015, she received drug-induced ovulation treatment for three months (clomiphene/letrozole/urinary gonadotropins). Subsequently, she was able to produce dominant follicles monthly and could ovulate naturally; however, she was unable to conceive. In December 2015, she underwent laparoscopic removal of bilateral ovarian endometriosis cysts followed

by hysteroscopic resection of an endometrial polyp, which was conducted in Qilu Hospital based on strict surgical indications. Other than that, she had no surgical or disease history.

### **Physical examination**

Her physical examination results were generally normal. Her husband was a 40-year-old civil servant without a history of smoking or drinking. No apparent abnormalities were found during his physical examination.

### **Laboratory examinations**

The serum concentrations of the following hormones were examined in the laboratory on the third day of her menstrual cycle on May 2019, and the early follicular phase hormone profile was: Follicle-stimulating hormone (FSH) 5.64 U/L; luteinizing hormone (LH) 3.06 U/L; estradiol (E2) 42.13 pg/mL; prolactin (PRL) 10.64 ng/mL; testosterone (T) 0.14 ng/mL. Due to her long-term infertility, her chromosome status was analyzed using peripheral blood. Her chromosomal examination results displayed a 46, XX, 1qh+ karyotype.

Her husband's semen test results revealed oligo-asthenozoospermia (12 mol/mL, 35% motility), which was diagnosed following the 5<sup>th</sup> World Health Organization semen parameter standard and his chromosome karyotype was 46, XY.

### **Imaging examinations**

Hysterosalpingography indicated bilateral obstruction of her fallopian tubes, but the cause could not be determined. Pelvic sonography revealed normal pelvic conditions with a 1.04 mm regular endometrium and 1.6 mm ovarian follicle.

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## **FINAL DIAGNOSIS**

The previous definition of the borderline form of EFS which has been described in cases in which only a few mature or immature oocytes are recovered from several mature follicles. In combination with the history of this case, in her first two *in vitro* fertilization (IVF) cycles, her target number of mature follicles was both more than 10, but only one oocyte was obtained each time. Thus, we have reason to believe that she meets the definition of a borderline form of EFS and was therefore diagnosed as having a borderline form of EFS.

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## **TREATMENT**

In December 2016, IVF was performed in Qilu Hospital using the GnRH-antagonist protocol<sup>[8]</sup> to assist her in conception. Twelve follicles  $\geq$  14 mm, and one M1 egg was obtained; however, embryo formation failed to occur. In March 2017, another IVF was performed in Shandong University using a short protocol<sup>[9]</sup>. Fourteen follicles  $\geq$  14 mm, and one egg was obtained, fertilization of one egg occurred, but embryo formation failed. Unfortunately, the quantitative  $\beta$ -HCG level was not examined at the time. The specific trigger method and medication protocol are described in [Table 1](#).

On June 7, 2019, a third IVF cycle was conducted in our reproductive and genetic center using a flexible luteal phase ovarian stimulation protocol<sup>[9]</sup>. Ovulation was maintained at high progesterone (P) levels by oral administration of dihydroxyprogesterone. On the 24<sup>th</sup> d of her menstrual cycle, a B-ultrasound and serological hormone test was performed. The hormone profile showed that E2 was 64 pg/mL, LH was 1.79 IU/L, and P was 0.82 ng/L. Pelvic sonography revealed normal pelvic conditions (with a 12.1 mm endometrium and 6.5 mm, 6 mm two ovarian follicles, and ten antral follicles). The medication strategy was changed in this study based on her previous two IVF failures.

Subsequently, from the 24<sup>th</sup> to 29<sup>th</sup> d of her menstrual cycle, she was administered a daily dose of 75U of urinary gonadotropin (HMG, Zhu hai Li zhu group Libao Biochemical Pharmaceutical Co., Ltd., Zhuhai, China, specification: 75 u/PC), 200U of recombinant human FSH (rFSH, Merck Serono SA Aubonne Branch, specification: 75 u/PC), 75U recombinant LH (rLH, Merck Serono S.A, 75 u/PC) and 40 mg of dydrogesterone. Administration of the gonadotropin (Gn) continued for three days (from 29<sup>th</sup> to 32<sup>nd</sup>) depending on growth of the follicles. After nine days of medication, the serum E2 level was 2357 pg/mL, LH was 1.42 IU/L, and P was 0.78 ng/L. B-ultrasound indicated normal follicle growth. To obtain more eggs, the dose of HMG was doubled to 300U a day for the next three days while maintaining the dosage of

**Table 1** Assisted reproductive technique cycle description

Date	Gonadotrophin	Daily dosage	Total	GnRH analog	Ovulation trigger	Protocol	Estrogen level (pg/mL)	Oocyte no
December, 2016	HMG	225U	2475U	GnRH-ant (0.25 mg)	HCG 1000U	Antagonist, fixed	3101	M I × 1
March, 2017	rFSH + HMG	75U+225U	900U + 2700U	GnRH-a (0.1 mg)	HCG 2000U + rHCG 250U	Agonist, short	4870	M I × 1
June, 2019	rFSH + HMG + rLH	200U+75U+75U	2200U+ 825U + 825U	GnRH-a (0.05 mg)	GnRH (0.2 mg) rHCG + HCG 10000U	Agonist, long	3623	M I × 2 M II × 3

GnRH-a: Gonadotropin-releasing hormone agonist; GnRH-ant: Gonadotropin-releasing hormone antagonist; HCG: Human-chorionic gonadotropin; HMG: Human menopausal gonadotropin; rFSH: Recombinant human follicle stimulating hormone; rHCG: Recombinant human chorionic gonadotropin.

other medications. The treatment lasted for 11 d with a total dosage of rFSH, HMG, and rLH of 2200U, 825U, and 825U, respectively. On the 12<sup>th</sup> d of Gn administration, which was the 35<sup>th</sup> d of her menstruation, all the drugs were stopped. The serum E2 level was 3623 pg/mL, LH was 1.03 IU/L, and P was 1.48 ng/L at this time. To avoid the recurrence of a borderline form of EFS, her trigger protocol was carefully evaluated and administration of 10000U of HCG, 250 µg of recombinant HCG (rHCG) (Choriogonadotropin alfa, Ovitrelle 250 µg, Serono), and 0.2 mg of GnRH-antagonist (Ipsen Pharma Biotech, diphereline, Triptorelin acetate, decapeptyl 0.1 mg × 2) was finally decided upon. At this point, ten follicles were greater than 1.4 mm. Oocyte pick-up (OPU) was delayed for 3 h due to her situation. Eventually, five oocytes (M I × 2, M II × 3) were obtained, two of them were fertilized and later formed two embryos (embryo rating, 6C II × 1, 9C II × 1). To prevent ovarian hyperstimulation syndrome, embryo cryopreservation was performed in this cycle. At present, she is undergoing preparation for frozen embryo transfer. A detailed record is provided in [Table 2](#).

## OUTCOME AND FOLLOW-UP

Eventually, three mature oocytes were obtained in this study, which later formed two embryos after intracytoplasmic sperm injection. The patient decided to rest for a few months before undergoing frozen thawed embryo transfer.

## DISCUSSION

Despite the low incidence of a borderline form of EFS, the condition causes a great burden to patients and doctors who spend a lot of time and other resources on these patients. Predisposing factors for the condition include ovarian dysfunction and factors related to dosage, time of administration, bioavailability, and metabolism of HCG<sup>[10]</sup>. Presently, the main treatment to ensure final oocyte maturation involves administration of HCG 10000 IU (most common), rHCG 250 µg<sup>[11]</sup> and a double-trigger GnRH-a (0.2 mg) + rHCG (250 µg) + HCG 2000 IU<sup>[12]</sup>. In addition, prolonging the interval between ovulation is effective<sup>[10]</sup>.

Triggering and inappropriate OPU could be a contributory factor in some cases of EFS, because it may affect the number or quality of oocytes<sup>[13,14]</sup>. Most studies on EFS are limited in sample size, and this casts doubt on the reliability of their findings.

Indeed, the existence of EFS remains controversial<sup>[10]</sup>. The condition can still occur in cases in which correct administration and high bioavailability of HCG have been achieved. Also, EFS could be caused by the low availability of HCG in the ovary, and this condition has been described as “pharmaceutical industry syndrome”<sup>[15]</sup>. In the present study, a trigger method that involved a dual trigger of a supernormal dose of HCG combined with delayed oocyte retrieval prevented HCG-related faults and ensured adequate HCG action time and a relative increase in HCG concentration in the ovary. However, this study had some limitations: (1) The dosage of HCG used was higher than the conventional dosage, and this might increase the risk of ovarian hyperstimulation syndrome; (2) Oocyte retrieval was performed 39 h post HCG injection which might lead to excessive maturation of oocytes or spontaneous ovulation; and (3) This study did not determine whether increased dose of HCG and delayed oocyte retrieval affected the fundamental aspects of oocyte or embryo quality.

**Table 2** Introduction to the third *in vitro* fertilization

Date	June 7, 2019	June 12, 2019	June 15, 2019	June 17, 2019	June 18, 2019	June 20, 2019
D (Gn)	24 (1)	29 (6)	32 (9)	34 (11)	35 (12)	
E2 (pg/mL)	64	1120	2357	4146	3623	
LH (IU/L)	1.79	2.19	1.42	1.49	1.03	
P (ng/L)	0.82	1.01	0.78	1.28	1.48	
RF (cm)	0.65, 0.2 × 10	1.2, 1.1 × 3, 1.0, 0.9 × 3	1.35 × 2, 1.25 × 3, 1.2 × 4, 0.95 × 3	1.7, 1.65, 1.55, 1.3 × 3, 1.15 × 3, 1.05 × 3, 0.9	1.9, 1.7 × 2, 1.6, 1.45, 1.4, 1.35, 1.3, 1.25 × 3, 1.15, 1.0	Total 10, ≥ 1.4
LF (cm)	0.6, 0.2 × 10	1.25, 1.15, 1.1, 0.8 × 2, 0.75 × 2, 0.6	1.65, 1.45, 1.25, 1.05, 0.95 × 2, 0.9, 0.85, 0.75, 0.6	1.7, 1.55, 1.5, 1.15 × 3, 0.95, 0.9, 0.7 × 2	1.75 × 2, 1.7, 1.4, 1.35, 1.2 × 3, 1.0 × 2	
EM (cm)	1.21A-B	1.2B	1.38B	1.29B	1.13B	
HMG	75U × 5	75U × 3	150U × 2	150U × 1		
rFSH	200U × 5	200U × 3	200U × 2	200U × 1		
rLH	75U × 5	75U × 3	75U × 2	75U × 1		
Dydrogesterone	20 mg Bid	20 mg Bid	20 mg Bid	20 mg Bid		
Ovulation trigger					rHCG 250U + GnRH-a 0.2 mg + HCG 10000U	39 h oocyte retrieval

Gn: Gonadotropin; RF: Right follicle; LF: Left follicle; EM: Endometrium; HCG: Human chorionic gonadotropin; HMG: Human menopausal gonadotropin; rFSH: Recombinant human follicle-stimulating hormone; rHCG: Recombinant human chorionic gonadotropin; rLH: Recombinant luteinizing hormone; P: Progesterone, E2: Estradiol.

In the present study, the serum  $\beta$ -HCG level was 389.47 U/L, 3 h before OPU, which was higher than the  $\beta$ -HCG threshold previously mentioned in borderline forms of EFS<sup>[16]</sup>. Therefore, a standardized  $\beta$ -HCG threshold level and time of its detection in serum is still needed for EFS diagnosis<sup>[17]</sup>. The results of this study suggested that patients who have been diagnosed with EFS multiple times should have a more rigorous final oocyte maturation approach in the next IVF cycle to avoid the recurrence of EFS.

## CONCLUSION

The patient in the present study received three cycles of ART in three different reproductive centers, and the oocytes collected in the first two cycles were of poor quality, despite adequate ovarian response. In the third cycle, a high *P* level controlled the ovarian hyperstimulation protocol, and was applied to obtain more oocytes. A dual trigger of a supernormal dose of HCG combined with a delayed oocyte retrieval approach was selected after careful evaluation of the patient's medical history. Dual trigger involves using a single bolus of GnRH agonist combined with a reduced or standard dosage of HCG to trigger ovulation<sup>[18]</sup>. Eventually, three mature oocytes were obtained in this study, which later formed two embryos after intracytoplasmic sperm injection.

This case study reports a new ovulation triggering approach that involves a dual trigger of a supernormal dose of HCG combined with delayed oocyte retrieval. The method can be applied in the treatment of a borderline form of EFS.

## ACKNOWLEDGEMENTS

The authors wish to thank the patient for supporting this study and Zhen-Gao Sun for assisting in manuscript preparation.

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