

Case Report

Empty follicle syndrome after GnRH agonist triggering: Is it possible to rescue with hCG? Two cases and review of the literature

Ali Sami Gurbuz¹, Funda Gode², Emel Ebru Ozcimen^{3,*}, Necati Ozcimen¹, Ahmet Zeki Isik²

¹ Novafertil IVF Center, Konya, Turkey

² Irenbe IVF Center, Izmir, Turkey

³ Department of Obstetrics and Gynecology, Baskent University Hospital, Selcuklu, Konya, Turkey

Abstract

Empty follicle syndrome (EFS) is a rare condition characterized by failure to obtain oocytes despite repeated meticulous aspiration from normally growing ovarian follicles during in vitro fertilization (IVF) cycles. Here in we report two cases of empty follicle syndrome after gonadotropin releasing hormone agonist (GnRHa) triggering for final oocyte maturation due to ovarian hyperstimulation syndrome (OHSS) risk. Neither oocytes nor granulosa cells were recovered in both patients during first oocyte pick up procedure despite developing multiple follicles. The patients were successfully rescued by retriggering maturation using hCG and only two and one oocytes could be obtained in patient 1 and 2 respectively after 24 hours. The oocytes were mature (MII) and fertilized normally. Fresh transfer of two embryos and frozen thaw transfer of one embryo was applied to patient 1 and patient 2 respectively. Successful pregnancies were achieved in both patients. Management options of EFS in hyperresponder patients triggered with GnRH agonist might be a rescue protocol including retriggering with hCG, freeze the embryos and also a subsequent frozen thaw transfer in order to avoid from OHSS. Fresh transfer could be an option when the embryos could not be frozen however other prevention strategies such as cabergoline and hydroxethylstarch should be considered in these cases.

Key words:

Empty follicle syndrome, GnRH agonist trigger, ovarian hyperstimulation syndrome

Introduction

Empty follicle syndrome (EFS) is a condition in which no oocytes are retrieved after a meticulous aspiration and repeated flushing of mature follicles after ovulation induction in in vitro fertilization (IVF) treatment. It was first described by Coulam et al. in 1986 [1]. Later it has been classified into 'genuine' and 'false' types by Stevenson and Lashen [2]. Genuine type has been defined as a failure to retrieve oocytes despite optimal hCG levels on the day of oocyte retrieval. Whereas false type has been defined as a failure to retrieve oocytes in the presence of low hCG due to an error in the administration or the bioavailability of hCG [2,3].

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* **Correspondence:** Emel Ebru Ozcimen

Department of Obstetrics and Gynecology, Baskent University Hospital, Selcuklu, Konya, Turkey

Phone: +90 532 4641390

Email: eparlakyigit@yahoo.com

Ovarian hyperstimulation syndrome (OHSS) is a potentially life threatening condition and is the most serious iatrogenic complication of controlled ovarian hyperstimulation cycles. [4]. Early OHSS is related with ovarian response to stimulation however late OHSS is related with the endogenous hCG from implanting embryo. Human chorionic gonadotropin is an excellent trigger for final oocyte maturation due to its LH homology, an extended half life, and simple manufacturing process however OHSS almost always requires either exogenous administration or endogenous presence of this molecule [5]. Triggering with GnRH agonist instead of hCG administration is currently viewed as a new and effective option in GnRH antagonist cycles to prevent especially early OHSS [6]. Also endogenous surge of both follicle stimulating hormone (FSH) and Luteinizing hormone (LH) after agonist triggering was reported to be related with retrieving more mature oocytes (MII) in IVF cycles [7,8]. However empty follicle syndrome might also be seen after GnRH agonist triggering rarely [7]. Since EFS is a very frustrating event for both patient and cli-

nician, management of this complication is extremely important. Here in we report two cases of empty follicle syndrome after gonadotropin releasing hormone agonist (GnRHa) triggering for final oocyte maturation due to ovarian hyperstimulation syndrome (OHSS) risk. Management options of EFS after GnRH agonist triggering were also discussed.

Case presentation

Case 1: The patient was a 25-year-old woman with polycystic ovary syndrome who had 3 years of infertility duration and two prior failed IVF cycles. The patient's body mass index (BMI) was 27. In her first cycle conventional long protocol beginning with 150 IU recombinant FSH (rec FSH) (Gonal F, Merck Serono) was used. But only 2 follicles were obtained and the cycle was cancelled. The next cycle was stimulated with 225 IU recombinant FSH (Puregon; MSD). GnRH antagonist (Cetrotide® 0.25 mg Merck Serono) was commenced on 6th day of stimulation. Cycle was monitored by both estradiol (E2) levels and transvaginal ultrasound scanning. After 14 days of gonadotropin stimulation, the patient reached a peak estradiol level of 6937 pg/ml and more than 30 follicles above 12 mm in diameter was observed on ultrasound on the day of trigger. First of all coasting (four days) was applied but the level of E2 was not decreased. Therefore when at least two follicles reached a diameter of 17 mm, final oocyte maturation was triggered by administering 1 mg leuprolide acetate (Lucrin, Abbot) instead of hCG. Thirty-six hours later, the patient underwent oocyte retrieval and ultrasound guided puncture and aspiration of 18 follicles in the right ovary yielded no oocytes. Also granulosa cells were not detected in the follicular fluid. After aspiration of 10 follicles without oocyte, aspiration suction pressure and proper function of the pump were also confirmed (Aspiration suction pressure was 120 mmHg.) Then the oocyte pick up was stopped and 5000 IU hCG (Pregnyl® MSD) i.m. was administered. Informed consent was taken from the patient and thirty-six hours later, the patient underwent oocyte retrieval again. In rescue pick up oocytes were obtained from both ovaries. Besides 20 follicles, only 2 oocytes were obtained. Intracytoplasmic sperm injection (ICSI) was performed. Two grade 1 embryos with 4 cells were transferred on day 2 to the patient. Cabergoline was administered for 8 days after oocyte pick up for OHSS prevention. Vaginal progesterone gel, (Crinone Merck Serono) was given twice daily for luteal phase support. At 13th day of embryo transfer β -hCG

was 59 IU/ml. No OHSS was observed. At the 38th weeks of her gestation, she was delivered a healthy 3500 gr baby. **Case 2:** A 33-year-old woman had a 3 year history of polycystic ovarian syndrome-related infertility. She had previously undergone two unsuccessful treatment cycles involving gonadotropin administration plus intrauterine insemination. Her gynecologic examination revealed a normal uterus and polycystic ovaries on both sides. Hysterosalpingography showed normal patency of both tubes. Her body mass index (BMI) was 23.9. The cycle was carried out with a GnRH antagonist down-regulated cycle using cetrotirelix (Cetrotide®; Merck Serono, Turkey). Ovarian stimulation was started on menstrual cycle day 2 with 150 IU of recombinant FSH (rec-FSH) (Puregon®; MSD). Cycle monitoring was performed using both ultrasound scanning and hormonal blood analysis of E2 and LH. GnRH antagonist was started on cycle day 6 when the leading follicle diameter was 14 mm. After 13 days of stimulation the patient reached a peak E2 level of 4600 pg/mL accompanied with more than 20 follicles above 12 mm in diameter. When at least two follicles reached a diameter of 17 mm, final oocyte maturation was triggered by administering 0.2 mg triptoreline acetate (Decapeptyl, Ferring) Thirty six hours later, oocyte pick up was performed. Intraoperatively the number of dominant follicles visualized by ultrasound was consistent with follicular monitoring during controlled ovarian hyperstimulation. Neither oocytes nor granulosa cells were recovered after aspiration of 18 follicles. Aspiration suction pressure was 120 mmHg. The procedure was stopped and 5000 IU hCG (Pregnyl, MSD) i.m. was administered. The patient underwent oocyte retrieval from both ovaries after 24 hours again. And only one oocyte could be obtained. The oocyte was mature (MII), fertilized normally and cryopreserved on third day. A successful pregnancy was achieved by transfer of this frozen-thawed single embryo in a subsequent cycle.

Discussion

The incidence of EFS has been reported as 0.6–3.5% in GnRH agonist trigger cycles, which is similar to that reported (0.1–3.1%) after an hCG trigger in all patient groups including hypo-normo and hyperresponders [7,9-14]. However when the subjects who had fewer than five follicles were excluded, the incidence of genuine EFS was reported to be 0.016 after hCG triggering [13]. Therefore EFS is an extremely rare condition in hyper-

responder patients during in vitro fertilization cycles. Similar etiological factors could be related with EFS after both triggering agents, such as human error and abnormalities in the in vivo biological activity of some batches of commercially available products, rapid metabolic clearance, manufacturer defects and low bioavailability [8]. However in some instances the mechanism of EFS might be different in GnRH agonist and hCG triggered cycles. The most probable mechanisms of EFS is hypothalamic dysfunction after agonist triggered cycles [7,11,14-15]. It was reported that a suboptimal LH surge could result in lower oocyte yields when maturation was triggered with GnRHa [16]. Therefore Chen *et al.* suggested a threshold serum level of LH as 15 IU/L 12 hours after agonist triggering [16]. Honnma *et al.* reported two cases in which failure to trigger oocyte maturation was due to severe down-regulation of the pituitary-hypothalamus-axis. They suggested a LH-RH test on cycle day 3 [17,18]. However, Asada *et al.* reported a case with a weak LH reaction to GnRHa which was sufficient to mature oocytes [18]. In most patients little LH surge amplitude are also sufficient for oocyte maturation. Thus 5% of the normal LH surge was found to be necessary for oocyte maturation in rats [19]. Therefore an alternative explanation for EFS after GnRH agonist triggering is GnRH receptor polymorphism, necessitating a higher dose of GnRH agonist to activate the receptor with the FSH or LH receptor polymorphism [20, 21]. LH β gene polymorphism specifically in the homozygous form may cause less bioactive LH molecule and a blunted response after GnRH agonist trigger [22, 23]. Also it was suggested that cumulus expansion and detachment of oocytes from the follicular wall might require longer time periods or longer exposure to LH in certain patient groups [3]. Management of patients with EFS is a challenge for physicians. Unfortunately no single treatment is known to be universally effective [24]. The most important preventive intervention should be the confirmation of the correct application of the triggering agent by the healthcare professional or the patient. Stevenson and Lashen reported that false type of EFS was detected nearly twice as genuine EFS during IVF cycles [2]. In our cases we confirmed the applications of both patients. Nevertheless we can't be sure about the other potential factors related with false EFS such as manufacturer defects and low bioavailability. The suggested management option of false EFS after hCG triggered cycles is

readministration of hCG and retrieval of oocytes 24 hours later [2,3,14,24]. It was reported that 42.8% of cycles in which hCG was readministered in the setting of suboptimal or absent serum hCG resulted in liveborn healthy fetus [2,3]. On the other hand Reichmann suggested that fewer oocytes could be obtained than subsequent cycles of the same patient groups during rescue EFS cycles. Failure of implantation was associated with unintended coasting period of 72 hours and postmaturity of oocytes [24]. In our cases fewer oocytes (two and one oocytes in patient 1 and 2 respectively) could be obtained 24 hours later however the implantation potential of the embryos was not deteriorated. Although there is no information about the exact time of second retrieval, 24 hour might be a better option in these cases to avoid postmaturity of the oocytes. Retriggering with a higher dose of GnRh agonist might be another solution in EFS cases after GnRH agonist triggering. However inadequate response of our patients might be related with severe down regulation of the hypothalamus or GnRH receptor polymorphism. Therefore a rescue with hCG might be a better option in EFS cases after agonist triggering when the exact mechanism is unclear. Potential preventative solutions were also suggested as measurement of LH the day after trigger or prolonging the interval between ovulation triggering and OPU [16,25]. Kummer *et al.* investigated the predictors of the total number of oocytes and mature oocytes during IVF cycles in a retrospective study recently. Since all cases of EFS occurred in patients with post-trigger LH<15 IU/l and progesterone \leq 3.5 ng/mL, they suggested to measure LH and progesterone in GnRHa trigger cycles [9]. However these solutions should be confirmed by larger studies to be recommended to clinicians in routine IVF cycles. GnRH agonist triggering combined with freezing all embryos (segmented approach) has been suggested to completely prevent OHSS and result in OHSS free clinics [26,27]. Although rare OHSS cases were reported with this strategy, freezing all embryos prevent both early and late OHSS in majority of cases. In our second case we also preferred segmented approach for the prevention of OHSS. As it has been described in our first case, other prevention strategies such as cabergoline and hydroxethylstarch should be considered in hyperresponder patients even in EFS cases when the embryos could not be frozen. Another point in these cases is the dose of hCG used for retriggering. Although we

preferred 5000 IU hCG for retriggering in case 1, it might be risky in a setting where cryopreservation was not available. Since the case 1 had previous two failed IVF cycles, we preferred to transfer two embryos. However, when the conditions are not appropriate for cryopreservation, retriggering with 1500 IU hCG and a single embryo transfer might be better options in patients with a high OHSS risk.

As a conclusion management options of EFS in hyperresponder patients triggered with GnRH agonist might be a rescue protocol including retriggering with hCG, freeze the embryos and also a subsequent frozen thaw transfer in order to avoid OHSS. Fresh transfer might also be an option when the embryos could not be frozen taking into account that all of the other prevention strategies should be considered in these cases.

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