

Case Report

Severe Ovarian Hyperstimulation Syndrome in a Case of Nonmutated Recurrent Genuine Empty Follicle Syndrome

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ABSTRACT

Empty follicle syndrome (EFS) is a rare event in which no oocytes are retrieved from apparently normal growing follicles with normal steroidogenesis despite meticulous follicular aspiration in assisted reproductive technology (ART) cycles. EFS is mainly of two types, genuine EFS and false EFS. Here, we report a case of a 24-year-old woman presenting with primary infertility with normal ovarian reserve and regular menstrual cycles, husband having severe “oligo-astheno-teratozoospermia,” and planned for ART treatment. We could not retrieve any oocytes in successive cycles despite optimum human chorionic gonadotropin (hCG) levels on the day of oocyte retrieval and using different management protocols mentioned until now in the literature. The whole genomic analysis was found to be normal (46, XX). Further, the patient had experienced severe ovarian hyperstimulation syndrome (OHSS) after the second cycle of ovarian stimulation despite no luteal hCG support. We were ineffectual to find the cause of recurrent EFS in this patient and therefore counseled the patient for donor oocytes. This case highlights the difficulty in treating genuine EFS patients and the need for monitoring serum estradiol levels during ovarian stimulation to prevent another serious complication of OHSS.

KEYWORDS: Assisted reproduction, case report, empty follicle syndrome, genes, genuine empty follicle syndrome, in vitro fertilisation, intracytoplasmic sperm injection, ovarian hyperstimulation syndrome

INTRODUCTION

Since the first description by Coulam *et al.* three decades ago, empty follicle syndrome (EFS) remains an enigma for the world. The syndrome represents a rare event in which no oocytes are retrieved despite meticulous aspiration and repeated flushing of follicles in the assisted reproductive technology (ART) cycles.^[1] Its etiology remains obscure and has an incidence rate between 0.6% and 7%.^[2] In 2008, Stevenson and Lashen described two types of EFS based on human chorionic gonadotropin (hCG) level at the time of oocyte retrieval (OR). The “genuine” type of EFS (gEFS) is characterized by an optimal hCG level (>40 mIU/mL), whereas the false type of EFS (fEFS) is characterized by a below optimal level

of hCG (<40 mIU/mL).^[3] The gEFS is reported to be further rare comprising only 33% of all the total cases of EFS.^[2] It is due to the complete failure to retrieve mature oocytes without any issues during the ovulation induction process, whereas fEFS is mainly associated with an error in the administration or the bioavailability of hCG.^[3] The psychological and physical trauma for the patients experiencing this paradox syndrome is huge resulting in cycle cancellations and negative ART outcomes.^[1] It is therefore of importance to study its true existence in recurrent cycles and develop comprehensible and optimal management strategies.

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Recent studies have uncovered inherited mutations of luteinizing hormone/choriogonadotropin receptor (LHCGR), zona pellucida sperm-binding protein 1 (ZP1), and zona pellucida sperm-binding protein 3 (ZP3) genes in patients with EFS.^[4-6] However, the pathogenic mechanism responsible for EFS, including gEFS, remains largely unknown.^[2] Moreover, the occurrence of ovarian hyperstimulation syndrome (OHSS), another major iatrogenic complication of ART,^[7] in the patients experiencing EFS is largely unknown. There exists only a single case report of a woman who had experienced severe OHSS following a rescue of EFS.^[8] The purpose of this case report is to describe a case of recurrent gEFS in the consequent ART cycle of a woman that produced no eggs. The whole-exome sequencing revealed the absence of any genetic variations. Further, the patient had experienced severe OHSS after the second cycle of ovarian stimulation despite no oocyte recovery.

CASE REPORT

A young couple with a married life of 3 years came to our clinic with primary infertility. The wife was 24 years old with regular menstrual cycles. Her baseline ultrasound showed normal uterine and ovarian anatomy. Antral follicle count was 16 with around eight follicles on each side. Her baseline day-3 follicle-stimulating hormone (FSH), luteinizing hormone, and estradiol (E_2) were normal. Anti-Mullerian hormone level was 3.1 ng/ml. She was a known hypothyroid patient for which she was using levothyroxine 25 mcg daily. Her hysterosalpingogram showed bilateral patent tubes. The husband's semen analysis showed severe "oligo-astheno-teratozoospermia" with a total motile sperm count of <1 million. The couple was advised *in vitro* fertilization – intracytoplasmic sperm injection (ICSI) treatment.

In the first cycle, ovarian stimulation was achieved with an antagonist protocol. On cycle day 2, recombinant FSH and human menopausal gonadotrophins administration was started. Their doses were adopted according to the size of ovarian follicles and their growth rates in vaginal ultrasonography. Gonadotropin-releasing hormone antagonist (GnRH antagonist) was initiated when the leading follicles reached 14 mm in diameter in vaginal ultrasonography and continued up to the day when at least three follicles reached a diameter of ≥ 18 mm. Trigger was performed with recombinant hCG (rhCG) and after 36 h, OR was undertaken. A total of 7 follicles in each of the ovaries with a diameter of ≥ 16 mm were found in ultrasonography. Surprisingly, aspiration and repeated flushing of all seven follicles in the right ovary failed to yield an oocyte. We, therefore, suspended

further aspiration, leaving all the follicles intact in the left ovary. A satisfactory response was obtained after careful interrogation of the patient and the nurse who had administered the rhCG injection. Serum hCG and E_2 levels on the day of OR were 182 mIU/ml and 2420 pg/ml, respectively. As the serum levels were assuring, we proceeded with the aspiration of the left ovary after 24 h. Unfortunately, we were not able to retrieve any oocytes. Therefore, we diagnosed the patient as a "genuine" case of EFS. We, then, sent the patient's blood sample to evaluate the gene variants related to the phenotype. Next-generation sequencing was used to perform whole-exome sequence analysis. The sequencing results of the patient's genomic DNA revealed the absence of any genetic variations (46, XX).

The patient, however, returned to us only after 5 months. In her second cycle, ovarian stimulation was achieved similarly to the first cycle with an antagonist protocol. On day 12 of stimulation, a total of 8 follicles in the right ovary and 7 follicles in the left ovary with a diameter of ≥ 18 mm were found. This time we used a dual trigger with GnRH agonist and rhCG. The trigger was administered in the fertility center by the fertility nurse and was additionally supervised by the resident doctor. After 36 h, OR was undertaken. During the next second cycle also, we were not able to retrieve any oocytes even after repeated flushing and aspiration of follicles in both of the ovaries. We were completely perplexed to find a serum hCG level of 227 mIU/mL. Serum E_2 and progesterone levels were found to be >3000 pg/ml and 1.3 nmol/l, respectively. We advised the patient for good hydration and a high protein diet. Besides, cabergoline and GnRH antagonist injections were administered to her for 3 days post the OR.

Two days later, the patient complained of severe abdominal distension, nausea, vomiting, dyspnea, and decreased urine output. Blood tests confirmed leukocytosis (WBC count = 21,000 cells/cum), hemoconcentration (hematocrit = 46.8%), and hypoosmolality (serum osmolality = 283 mOsm/kg). Ultrasonography revealed the presence of enlarged ovaries and abundant ascites measuring 12 cm \times 15 cm. A diagnosis of severe OHSS was made.^[9] She was admitted to the hospital and managed conservatively according to the standard OHSS protocol. Her condition improved over the next 4 days following admission and she was discharged on the 5th day. On the 3rd day after her discharge, the clinical parameters were almost normalized and her ascites completely resolved. Her serum osmolality was 290 mOsm/kg and her hemoconcentration had resolved (hematocrit = 34%).

After detailed counseling, the couple opted to use donor oocytes for further treatment.

DISCUSSION

The current understanding for EFS is much debated and it stands as a mysterious event of the ART cycles.^[2] Our patient had two cycles of ovarian stimulation for ICSI, though none were able to yield any oocytes. Both of the cycles were performed with an antagonist protocol and had optimal serum levels of hCG and progesterone on the day of OR, and hence, a diagnosis of gEFS was made. Inherited mutations in LHCGR, ZP1, and ZP3 genes have been found by authors Yariz *et al.*, Sun *et al.*, and Chen *et al.*, respectively, in patients experiencing EFS.^[4-6] However, despite recurrent gEFS in our patient, the genetic analysis revealed the absence of any genetic variations for the phenotype. Although the literature suggests the occurrence of EFS in women with a diminished ovarian reserve and that of recurrent gEFS in the older age woman,^[2,3] our case is a 24-year-old woman with good ovarian reserve.

As suggested by Deepika *et al.*,^[10] we had given a dual trigger with GnRH agonist and rHCG during the second ovarian stimulation. However, despite trying all the possible strategies mentioned in the literature till now including the use of an antagonist protocol, correction of hCG administration, aspiration of the second ovary, re-aspiration of same follicles, and use of dual trigger,^[2,10,11] none of them had worked for our patient. Kaluarachchi *et al.* also reported difficulty in the management of EFS with any of the suggested management options.^[12]

OHSS is a serious complication of ovarian stimulation. It can occur either during the luteal phase or early pregnancy.^[7] The primary risk factors for OHSS are the use of exogenous hCG for triggering, young age, polycystic ovary syndrome (PCOS), extremely high preovulatory estradiol concentrations, and numerous OR.^[13] Since there was no PCOS, or luteal hCG support in our patient, we speculate that high levels of serum estradiol and rhCG given for the trigger might be responsible for the development of severe OHSS. Although serum E₂ levels in EFS patients were previously reported to be either normal or low,^[4,6] our patient had conflicting findings along with acceptable follicle size and number. It is being hypothesized that the low serum E₂ levels before the hCG injection could contribute to the development of EFS.^[3,6] However, our case emphasizes that even the higher levels of serum E₂ levels before the hCG injection may not prevent the development of EFS but, in addition, may predispose the patient to an increased risk for OHSS. The mechanism

by which elevated estrogen can cause OHSS is multifaceted and includes the release of chemical mediators responsible for its development.^[13]

To date, there exists only a single case report of a woman with EFS experiencing OHSS due to luteal hCG support.^[8] In concordance with this, the present case highlights that OHSS can occur in patients with gEFS. Therefore, it becomes crucial to consider the possibility of OHSS even in such patients and individualise their doses of ovarian stimulation drugs with the serum E₂ levels.

In conclusion, an optimum management strategy for gEFS patients is very much desired. Moreover, our observations of higher E₂ levels and OHSS development in a patient experiencing recurrent gEFS without any genetic alterations challenge the previous description of EFS and advance understanding of the disease. Future studies should aim to explore its pathophysiologic nature and develop comprehensive treatment guidelines.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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