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CASE REPORT

Recurrent Empty Follicle Syndrome: A Rare Entity

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ABSTRACT

Failure to aspirate oocytes from apparently normally growing ovarian follicles with normal steroidogenesis after ovarian stimulation and meticulous follicular aspiration is referred to as empty follicle syndrome (EFS). It is a rare event in *in vitro* fertilization (IVF), but the economical consequences and emotional frustration of a cancelled cycle are enormous, as it causes substantial stress for both the patients and the treating physician. Here, we have reported one patient of recurrent EFS who had IVF in view of previous failed intrauterine inseminations, with normal male factor. Two cycles of controlled ovarian stimulation were done using antagonist protocol for this patient. However, as we were unable to retrieve any oocytes in both the cycles, we were offered her oocyte donation as the last resort.

Keywords: Controlled ovarian stimulation, Empty follicle syndrome, Oocyte donation.

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INTRODUCTION

Empty follicle syndrome (EFS) was first described by Coulam et al.[1] It is a condition in which no oocytes are retrieved after apparently successful ovarian stimulation. The etiology remains enigmatic. Empty follicle syndrome is an uncommon frustrating event, with a reported incidence of 0.04 to 7% in patients undergoing ovum pickup .

Literature review has shown that there are two types of EFS: genuine EFS (GEFS) and false EFS (FEFS).[2] The former has been defined as a failure to retrieve oocytes despite optimal human chorionic gonadotropin (hCG) levels on the day of oocyte retrieval. The latter has been defined as a failure to retrieve oocytes in the presence of low hCG (<40 IU/l) due to an error in the administration or the bioavailability of hCG, and seems to be more commonly encountered. In a systematic review of EFS by Stevenson and Lashen[3] in 2008, 33% of EFS cases were labeled as genuine and 67% as false. Here we are reporting a case of recurrent EFS who opted for oocyte donation after undergoing two cycles of COS by antagonist protocol which resulted in empty follicles in both the her cycles.

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CASE REPORT

A couple with 10 years of primary subfertility presented in 2014 to our fertility clinic. Mrs La 30-year-old lady, had previous regular 3/30 days cycles since menarche. Her physical examination was otherwise unremarkable except a body mass index (BMI) of 25 kg/m^2. Her partner was 35 years old, nonsmoker, nonalcoholic with a normal semen analysis. She had undergone several cycles of IUI and one *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) in 2010 at some other center. In her first ICSI cycle, she was stimulated with recombinant follicle stimulating hormone (r-FSH) and 3-hydroxy-3-methyl-glutaryl (HMG), and had six oocytes collected of average quality, and got three embryos that were transferred on day 3. Day 16 β hCG was < 3.5 mIU/ml. She had a history of antinuclear antibody (ANA) profile done in May 2014 following the first ICSI cycle that was strongly positive for ribonucleoprotein (RNP)/Sm; rest of the profile was normal and she was treated for the same. Her anti-Mullerian hormone (AMH) was 1.61 ng/ml in May 2014.

She visited our center in September 2014. Her day 2 blood tests showed FSH of 9.57 mIU/ml, luteinizing hormone (LH) 3.95 mIU/ml, E2 22.5 pg/ml, and prolactin 20.6 ng/ml and antral follicle count was 4/5. Her thyroid-stimulating hormone (TSH) was 6.75 mIU/ml and FT4 was 14.9 Pmol/l, and she was started on tablet eltroxin 25 µg. Hysteroscopy and dummy embryo transfer (ET) done was normal. Her repeat ANA profile done in our center was negative, thus, the rheumatologist's opinion was taken, and according to him, there was no contraindication for IVF in that patient. Her first IVF/ICSI cycle in our center was started in October 2014. She was stimulated with antagonist protocol using r-FSH (starting dose 375 units) and HMG added later (150 units). She was stimulated with gonadotropins for total 13 days, following which her E2 was 1271.2, thus triggered with r-hCG 250 µg. Her ultrasound day of stimulation

had shown two dominant follicles on the right side and four follicles on the left side. Oocyte retrieval was done 35 hours later, and no oocytes were retrieved. Urine pregnancy test (UPT) done with follicular fluid at that time was positive and serum β hCG was 76.4 mIU/ml.

She came for follow-up after 6 months in June 2015, when we did her FSH receptor polymorphism assay, and it came as normal. Her second IVF/ICSI cycle was started in September 2015 at our institute. Her day 2 E2 was 35.7 pg/ml, LH 6.29 mIU/ml, and P4 0.478 ng/ml and AFC of 5/4. We again stimulated her with antagonist protocol starting with r-FSH 375 units and HMG 75 units, for 5 days and finally changing to r-FSH 225 units and HMG 225 units. Total 13 days of stimulation was given; her triggering E2 was 1316.3 pg/ml and the scan done on the day of stimulation had shown three dominant follicles on the right and left side each. Oocyte retrieval was done 36 hours after giving a dual trigger with hCG 7500 IU and decapeptyl 100 µg. Follicular flushing was done. Unfortunately, even this time, we did not get any oocytes. Urine pregnancy test done with follicular fluid on table was positive and serum βhCG was 86.12 mIU/ml. Patient came back to us in October 2015, and after extensive counseling and knowing all the pros and cons of the repeat stimulation cycle, the patient decided to go for oocyte donation.

DISCUSSION

Empty follicle syndrome, first reported by Coulam et al in 1986,[1] is not strictly a syndrome, but a sporadic unpredictable event. The diagnosis of EFS is always retrospective and it cannot be predicted by the pattern of ovarian response to stimulation, either sonographically or hormonally. Empty follicle syndrome has been classified into "genuine" and "false" types. Genuine EFS is defined as a failure to retrieve oocytes from mature follicles after apparently normal folliculogenesis and steroidogenesis with optimal βhCG levels on the day of oocyte retrieval. Such patients are unlikely to respond to a rescue protocol.

False EFS is defined as a failure to retrieve oocytes in the presence of low βhCG due to an error in the administration or bioavailability of hCG. Such patients are more likely to respond to a rescue protocol. False empty follicle syndrome is unlikely to recur if all precautionary measures are taken in the subsequent cycles. Two classes of EFS can be differentiated by hormone levels on the oocyte retrieval day; in genuine EFS, the levels of either hCG or luteinizing hormone (LH)/progesterone are concordant with the correct administration of the triggering drug, while in FEFS, they are low. However, the exact meaning of "concordant" has not been defined. Literature survey has shown that when hCG is used as a triggering agent, the minimum hCG concentrations consistent with adequate triggering range are from 5 to 161 mIU/ml.[4] However, in the case of triggering with a GnRH agonist (GnRHa), no cut-off levels of LH or progesterone on the day of the oocyte retrieval have been quoted so far.

It was initially suggested that EFS might arise from the same cause that is responsible for the patient's infertility.[1] But now, various hypotheses have been put forward ranging from human error[5-7] to pharmacological problems.[7-9] Possible causes for EFS include: (1) Dysfunctional folliculogenesis, in which early oocyte atresia occurs with apparently normal hormonal response,[10] (2) Biological abnormality in the supply of mature oocytes that can be retrieved, despite normal bioavailability of hCG,[7] (3) Genetic factors in some cases, [11] (4) Drug-related causes due to an abnormality in the *in vivo* biological activity of some batches of commercially available hCG[6] or GnRH agonist, inappropriate timing of hCG,[8] or rapid clearance of hCG by the liver[6] and (5) Advanced ovarian aging through altered folliculogenesis.[11]

Oocyte maturation is commonly induced by hCG following LH surge, resumption of meiosis occurs about 18 hours later and the second metaphase occurs within 28 to 38 hours.[12] Another important function of hCG is to soften the connective tissue that facilitates the detachment of the oocyte cumulus complex from the wall of the follicle.[13] The oocyte cumulus complex will usually drop into the follicular fluid and will be aspirated during the oocyte retrieval. This is often the underlying pathology of FEFS. Improper hCG administration has been the most common cause of FEFS. Rapid metabolic clearance, manufacturer's defects in hCG production, and low bioavailability of hCG are the other proposed causes. The reduced *in vivo* biological activity of some batches of commercially available hCG is described as pharmaceutical industry syndrome.

Studies have shown that genuine EFS could be a manifestation of low ovarian reserve.[11,14,15] Risk factors for EFS have been suggested such as advanced age, longer infertility duration , higher baseline FSH levels, and lower E2 levels before the hCG injection.[15] The risk factors of EFS are similar to those of low ovarian reserve, and this suggests that ovarian aging may be involved in the etiology of EFS. Other investigators have suggested that some follicles may need longer exposure to hCG for cumulus expansion and detachment of oocyte cumulus complexes from the follicular wall,[13,16,17] and in those cases, the commonly used stimulation protocol may result in EFS.

Genetic causes of EFS have also been suggested.[18-20] Onalan et al[18] reported an inherited condition of EFS with moderate sensori neural deafness affecting two sisters. Recently, an inherited mutation of LH/hCG receptor

was identified in two sisters with EFS.[20] Luteinizing stimulation induces the transient and sequential expression of epidermal growth factors, which seem to mediate the LH action, including cumulus expansion and oocyte maturation.[21,22] These growth factors induce expression of prostaglandin synthase 2, tumor necrosis factor alpha induced protein, and hyaluronan synthase 2. Altered expression of these genes regulating cumulus expansion might result in EFS, but this remains to be determined.

The prospects of future fertility have to be kept in mind when we are counseling the couples of EFS. The prognosis after EFS occurrence is variable. Aktas et al[2] reported that there was no recurrence of unsuccessful oocyte retrieval in subsequent treatments. Baum et al[15] suggested the recurrence rate of 15%. On the contrary, some suggest that the occurrence of EFS would indicate a poor outcome in subsequent cycles. Lorusso et al[23] reported in their case series that poor quality oocytes were obtained after an EFS cycle and suggested that the empty follicle could be a predictor of an unfavorable outcome in the subsequent stimulated cycle.

Some investigators have estimated the risk of recurrence. Zreik et al[11] estimated that women with one EFS cycles had a 20% risk of recurrence in later IVF cycles and those with recurrent EFS had a poor success rate. The chances of recurrence of EFS increase with the age of women (24% recurrence rate for women aged 35–39 years, and 57% for those aged >40 years). Recently, it was reported that recurrent EFS occurred in 15.8% (16 cases out of 101 cycles) of subsequent cycles,[15] consistent with a previous study.[11] There were nine clinical pregnancies (10.6%) among patients with sporadic occurrence of EFS in the subsequent IVF cycle. In contrast, among those with two consecutive cases of EFS, no further pregnancies or successful oocyte retrieval were reported. Women with recurrent EFS had significantly prolonged infertility (10.4 ± 5.7 *vs* 6.3 ± 5.4 years, $p = 0.05$) and lower E2 levels (411.1 ± 200.3 *vs* 925.1 ± 784.2 pg/ml, $p < 0.05$) than those with sporadic EFS. Eighty percent of recurrent EFS were in women ≥36 years old. These data suggest that the risk factors of recurrent EFS are advanced age, prolonged infertility, and lower E2 levels, which are consistent with the risk factors of poor ovarian response. Recurrent EFS may be a variant phenotype of poor response.

Prognosis after EFS depends on its etiology. Some cases of EFS were a sporadic event with good clinical outcome; however in about 15 to 30% of the cases, recurrent EFS can be anticipated.[11,15,24]

These patients should be consulted regarding their lower chances of pregnancy.

Treating EFS is a challenge to every physician. No single treatment is universally effective. Some authors rely on the low frequency of recurrence and thus they recommend repeating the previous treatment protocol.[11] As in most EFS cases, downregulation was achieved by GnRH agonist, shifting from an agonist to antagonist protocol was suggested.[25] In cases wherein no oocytes are aspirated from one ovary and hCG levels are low, some have suggested readministering hCG from a different batch and aspirating the second ovary or even reaspirating the same follicles.[13,16,26] Others suggested changing the hCG from a urinary to a recombinant preparation.[27] Hourvitz et al[28] presented two women with EFS who were successfully treated with *in vitro* maturation. The two other treatment remedies that have been suggested were using GnRH agonist for final oocyte maturation[29] and prolonging the interval between ovulation triggering and ovum pickup.[30]

Human chorionic gonadotropin has long been used as a surrogate for the LH surge. Later on, it was demonstrated that ovulation triggering may be achieved by GnRH agonist.[31-33] Among the possible advantages of GnRH agonist for final oocyte maturation is the simultaneous induction of an FSH surge.[32,34] Follicle stimulating hormone was reported to induce LH receptor formation in luteinizing granulosa cells, promote oocyte nuclear maturation, and cumulus expansion.[35,36] FSH also has a role in keeping the gap junctions open between the oocyte and cumulus cells and thus may have an important role in signaling pathways.

Our patient had a low ovarian reserve, her AFC was 4/5 (AFC 3–10 is a low range), and FSH was 9.57 mIU/ml. Although she had oocytes collected in the previous cycle, but it was almost 5 years back and they were of average quality and she had only three embryos transferred of unknown grade. It is well known that so far, there is no definitive treatment for EFS and all the therapeutic approaches that can be offered have only level D evidence. Till 2003, EFS was only reported in GnRH agonist downregulated IVF cycles. Lok et al in 2003[29] were the first to report EFS in an antagonist IVF cycle, in which u-hCG failed to trigger ovulatory changes permitting successful recovery of oocytes using both agonist and antagonist protocols.

CONCLUSION

Genuine EFS prevalence is 0 to 1.1%. Recurrent GEFS cases are scarce; hence, they escape even large studies and thus might be erroneously regarded as nonexisting. False EFS was excluded in our patient, as the serum levels of hCG were assuring and within the expected range.

There is insufficient evidence to support the use of any particular intervention either for pituitary downregulation or ovarian stimulation in the management of poor responders.[37] Although our patient does not fit into the definitive criteria of poor responder, but she is definitely

an expected poor responder, and antagoinst protocol would be ideal in this situation.

The cause of GEFS in our patient most likely was within the cumulus oocyte complex, so a more physiological induction of follicular maturation with GnRH agonist would be ideal.[38] Keeping that in mind, we gave a dual trigger to our patient in the second cycle. It is also one of the therapeutic options mentioned for the treatment of GEFS . In our patient, the two treatment options were combined, using GnRH agonist for final oocyte maturation and prolonging the time between ovulation triggering and oocyte retrieval, but none of the strategies showed any improved outcome, thus oocyte donation was offered to the patient as a last resort.

Hence, we ascertain the existence of GEFS by providing this case report as a proof and suggest oocyte donation as one of the last treatment option for such patients.

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