Recurrent genuine empty follicle syndrome

ABSTRACT

Failure to aspirate oocytes after ovarian stimulation for an in vitro fertilization cycle, after confirming normal folliculogenesis and steroidogenesis occurs in about 0.2–7% of the cycles. This condition is known as empty follicle syndrome. Most of the time, it may be due to human or pharmacological error, but rarely there is an entity called genuine empty follicle syndrome where no known cause can be identified.

KEY WORDS: Beta human choriongonadotrophin, genuine empty follicular syndrome, in vitro fertilization

INTRODUCTION

Empty follicle syndrome (EFS) means failure to aspirate or retrieve mature oocytes from mature ovarian follicles following ovulation induction for in vitro fertilization (IVF) treatment in spite of meticulous aspiration and repeated flushing. EFS was first reported by Coulam et al. in 1986.[1,2] Etiologically, this entity can be classified into two groups:

1. Genuine empty follicle syndrome (GEFS)
2. False empty follicle syndrome (FEFS).

GEFS is defined as a failure to retrieve oocytes from mature follicles after controlled ovarian stimulation for IVF with a normal follicular development and steroidogenesis in the presence of optimal beta human chorionicgonadotrophin (βhCG) levels on the day of oocyte retrieval. This could be due to dysfunctional folliculogenesis, and it does not respond to the rescue protocol.

FEFS is defined as a failure to retrieve oocytes in the presence of a low βhCG level on the day of oocyte retrieval. It is basically due to human error or pharmaceutical reasons[3-5] and FEFS benefit from the rescue protocol. In about 67% cases, human error was the cause.[6,7] Here, we are reporting a case of recurrent GEFS.

CASE REPORT

A 34-year-old lady and 38-year-old gentleman with primary sub-fertility for 10 years with normal male factor, irregular menstrual cycle had undergone four cycles of failed intrauterine insemination with controlled ovarian stimulation and two cycles of IVF/ICSI. She underwent the first cycle of IVF/ICSI abroad using the long luteal phase GnRH agonist protocol. She underwent gonadotrophin stimulation for 9 days and oocyte retrieval was done 36 h after administering inj. hCG 10,000 IU. Twenty-five cumulus complexes were obtained but did not show presence of oocytes.

The second cycle of IVF was completed using donor oocytes but the patient failed to conceive. The couple was evaluated at our center. There was no significant past medical or surgical history for both partners. Her BMI was 19.1 kg/m², and systemic and pelvic examination did not reveal any abnormality. Her GTT, lipid profile, screening for viral markers and hemogram were within normal limits. The day 2 hormone profile for follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone (P4), and prolactin (PRL) were within normal limits; thyroid function tests (TFTs) were also normal. Hysteroscopy revealed a normal uterine cavity. Semen analysis showed moderate oligoasthenoteratozoospermia.

The third cycle of IVF/ICSI using the GnRH agonist long protocol was scheduled. The conventional long protocol was used as this was her first IVF cycle at our center. Oral contraceptive was given from day 5 to day 25 of the cycle after the baseline scan which
did not reveal any abnormality. Oral contraceptives were only used so that there would be no folliculogenesis in that cycle. This is important to prevent the presence of corpus luteum on the day of using gonadotrophins. A mock embryo transfer was done on day 19, and the down regulation was started with the GnRH agonist in a dose of 1 mg daily from day 21 of the menstrual cycle. On day 2 of the menstrual cycle, hormone levels were checked. The levels were as follows: E2 – 14.2 pg/ml, LH – 0.54 mIU/ml, P4 – 0.6 ng/ml. Ultrasound showed an antral follicle count of 12 on the left side and 10 on the right side. The dose of the GnRH agonist was reduced to 250 mcg/ml and gonadotrophins were started (inj. FSH 150 units [Recagon] + inj. HMG 75 units [Menopure]). Serum E2 and LH level on day 6 of administering gonadotrophins was 265 pg/ml and 0.76 mIU/ml, respectively. On day 8 of administering gonadotrophins, serum E2 and LH level was 1687 pg/ml and 0.65 mIU/ml, respectively. On day 10 of stimulation, folliculogram showed 7 follicles with a ≥17 mm diameter, and the endometrium was triple lined with a thickness of 9.8 mm. The E2, LH, and P4 level on the same day was 3217 pg/ml, 0.54 mIU/ml, and 0.65 mIU/ml, respectively. As there were more than three follicles of 17 mm diameter, she was given inj. hCG 10,000 IU for final follicular maturation. After 36 h of inj. hCG, oocyte retrieval was done and no oocytes were retrieved. All the follicles were flushed, but no cumulus oocyte complexes were obtained. On scanning the follicular fluid under a stereo microscope, granulosa cell masses were seen. Serum βhCG level on the day of oocyte retrieval was 196 mIU/ml and the P4 level was 8.4 ng/ml. The other subjects who had undergone oocyte pick-up on the same day or in the same week did not show any features of EFS.

As the βhCG level on the day of oocyte retrieval was 196 mIU/ml, which we label as a case of GEFS, the couple was counseled. Considering her age, long duration of subfertility with the occurrence of recurrent EFS, she was counseled for oocyte donation or for one more IVF cycle using a GnRH antagonist instead of the GnRH agonist.

DISCUSSION

EFS is reported to occur in about 0.2–7% of IVF cases and most of these cases are sporadic. The incidence is higher in GnRH agonist downregulated cycles. GEFS is reported to recur in subsequent IVF cycles with a recurrence rate of about 20% and the risk increases with age as the chance of recurrence after the age of 40 is found to be about 57%. Various therapeutic strategies are reported in the literature to overcome this condition but the success of obtaining oocytes may not be guaranteed. The treatment option consists of rescheduling of oocyte retrieval 24–36 h after the second dose of hCG, if the hCG level is low on the day of oocyte retrieval. One can also administer the GnRH agonist for the final follicular maturation in a GnRH antagonist cycle. One could try using a different batch of urinary hCG or use recombinant hCG or LH for the trigger. At times, an oocyte retrieval few hours after the first retrieval may be of help.

The effect of the stimulation protocol on the risk of EFS is not known. Some have postulated that EFS is a drug-related problem rather than a clinical dysfunction. Others suggested that the occurrence of EFS in IVF can be attributed to the failure in the accurate timing of the induction of final oocyte maturation, improper controlled ovarian hyperstimulation or inadequate instruction given to patients by the doctors.

An ovarian agent may also result in altered folliculogenesis and granulosa cell dysfunction with resultant altered oocyte growth and maturation. At times, it could be due to a genetic factor or low bioavailability of hCG administered.

The low biological activity of hCG may be due to an inadequate dosage or timing, individual variation in the threshold for the follicular response to urinary hCG, or rapid clearance of urinary hCG. A rescue hCG using a second dose or different batch of urinary hCG or recombinant hCG can be used if the βhCG concentration is <100 mIU/ml or <40 mIU/ml and oocyte retrieval is done 24–36 h later. Some cases of genuine EFS might arise because of a delayed maturation of oocyte cumulus complexes in response to hCG. The situation is similar to oocyte retrieval from immature follicles. The lower number of immature oocytes in the aspirates and the difficulty in identifying them could lead to a mistaken diagnosis of GEFS.

Making the diagnosis of GEFS and FEFS in the same or subsequent cycle for management is of a definite value. At present, there is evidence to support success with a repeat administration of hCG only in cases of false EFS. One would use the same or a higher dose depending on whether a dose error was identified. The oocyte retrieval could be rescheduled if there was an error in the timing or a repeat administration of hCG from a different batch was done. The largest case series regarding the repeat administration of hCG in “false” EFS cycles indicates that patients should be counseled regarding the low likelihood of cycle success after the repeat administration of hCG.

GEFS can be managed in subsequent cycles by using recombinant hCG, recombinant LH, or triggering oocyte maturation with the GnRH agonist in an antagonist cycle.

For the occurrence of GEFS, some intrinsic ovarian pathology causing defective follicular development or a probable genetic cause needs to be evaluated. Till date, no genetic
or ovarian markers are available for the diagnosis of GEFS. EFS does not represent a permanent pathophysiological condition, as many a time it occurs sporadically.

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