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Case Report

Recurrent genuine empty follicle syndrome: a rare case report

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ABSTRACT

Failure to aspirate oocytes from follicles after Controlled ovarian stimulation with apparently normal growing follicles with normal steroidogenesis after meticulous follicular aspiration is called Empty follicular syndrome (EFS). EFS are mainly two types, Genuine EFS & False EFS. Here we report a case of 24 yrs female presenting with primary subfertility with normal ovarian reserve, husband having normal semen analysis, planned for In vitro fertilization for failed Intra uterine insemination (IUI) & underwent two cycles of oocytes retrieval after controlled ovarian stimulation. We couldn't retrieve any oocytes in spite of adequate serum β hCG level in both the cycles. Karyotyping of the patient was normal (46 XX). In this patient we were not able to find out any cause for recurrent genuine empty follicle syndrome. So we advised the couple to opt for oocyte donation program.

Keywords: Oocyte, Controlled ovarian stimulation, EFS, β hCG, Karyotyping

INTRODUCTION

Failure to aspirate oocytes from follicles with meticulous follicular aspiration after Controlled ovarian stimulation (COH) in a patient having apparently normal growth of follicles and steroidogenesis is called empty follicular syndrome. It is a frustrating complication of ART. This could be traumatic for both the couple & the treating clinician. EFS were first reported by Coulam et al.¹ Prevalence of EFS range from 0.045-7%.^{2,3} Empty follicle syndrome (EFS) is mainly two types- Genuine EFS- failure to retrieve oocytes despite optimal Serum β -HCG level on the day of oocytes retrieval and False EFS- failure to retrieve oocytes in presence of low Serum β -HCG level (40Iu/L) due to error in the administration or bioavailability of HCG. Study by Stevenson et al reviewed that 33% of EFS were genuine & 67% were false.⁴

Risk factors for EFS are advanced maternal age, longer duration of infertility, higher base line FSH & lower serum Estradiol (E2) level before HCG injection.⁵

Genuine EFS could be a manifestation of low ovarian reserve. The actual mechanism responsible for EFS is still unknown.

Possible aetiology for EFS

1. Dysfunctional folliculogenesis due to early oocyte atresia with normal hormonal response.
2. Biological abnormality in the supply of mature oocytes despite normal bioavailability of Hcg.
3. Genetic factor in some cases.
4. Drug related abnormality in the in vivo biological activity or rapid clearance of hCG by the live.
5. Advanced ovarian ageing with altered folliculogenesis.^{3,6-8} Onalan et al reported EFS as an inherited disorder found in two sisters affected with moderate sensorineural deafness. Vu Jisic et al showed EFS may occur due to presence of pericentric inversion of chromosome 2:46XX, inv (2)(p11q21) or inherited mutation of LH/HCG receptor identified in two sisters with EFS.⁹⁻¹¹ Risk of recurrence of EFS is 20% & it is higher with

advanced maternal age i.e. 24% at 35yrs & 57% at age > 40yrs.

Some cases of EFS were sporadic with good outcome however in 15-30% cases, recurrent EFS can be anticipated.⁷ Assessment of serum β hCG next day after the trigger is a potential preventive measure against False EFS. hCG has long been used as a surrogate marker for the LH surge. Advantages of GnRH agonist for final oocyte maturation is, simultaneous induction of an FSH surge.¹² The role of the natural mid-cycle FSH surge is not fully clear. FSH was reported to induce LH receptor formation in luteinizing granulosa cells, promote oocyte nuclear maturation and cumulus expansion.¹³ It also has a role in keeping the gap junction open between the oocyte and cumulus cells and thus may have an important role in signalling pathways.¹⁴

METHODS

A 24 yrs old lady with primary sub fertility for 2 yrs with regular menstrual cycle & bilateral patent tubes on Hysterosalpingography (HSG) who failed to conceive after 6 cycles of ovulation induction (OI) & timed intercourse (TIC) presented to OPD. On evaluation the male partner was 29 yrs old business man having normal clinical findings & normal Semen analysis result. Female partner had BMI - 20.63kg/m². Clinical examination revealed no abnormality. Her thyroid profile and serum prolactin, FSH, LH and Estradiol levels were within normal limits. Diagnostic hysterolaparoscopy showed bilateral patent tubes, pouch of Douglas free, there was no evidence of endometriosis & uterine cavity was normal. She underwent 3 cycles of COH followed by IUI. Later on she was planned for IVF due to failed IUI.

1st IVF cycle- Base line hormone levels were within normal limits. Antimullerian hormonal (AMH) level was -2.24ng/ml and antral follicle count (AFC) were- 4 & 5 in Rt & Lt ovary respectively. Antagonist protocol was used. Controlled ovarian stimulation started with inj. Recombinant FSH 375 units, cycle was monitored by serum E2 & LH & folliculography. Inj. Cetorelix was given from day 5 of Gonadotropin stimulation till the day of HCG trigger. She was stimulated for 9 days. On the day of trigger serum E2- 888.28 pg/ml, LH- 0.933 mIU/L & progesterone-1.29 ng/ml. Ovulation was triggered by Rec-HCG 250 μ g administered subcutaneously when at least 3follicles had a size of > 18 mm diameter, oocyte retrieval was done after 35 hrs of HCG trigger. Total 7 good follicles were aspirated but there was no cell or cumulus obtained after repeated flushing. Serum β -hCG level was checked and the value was 95.5IU/L.

Patient was planned for 2nd IVF cycle of after 4 months. On day 2 of cycle Serum E2 - 33.41miu/L, LH - 4.10 mIU/L, progesterone- 1.67ng/m and FHS was 9.37mIU/L which was boarderline level. Antral follicle count showed Right Ovary of 7 & Lt ovary 5. Inj. Cetorelix 0.25 mg was given SC for 2 days & stimulation started from day 3

with Rec- FSH 375 units (Inj Newmon-R) & cycle was monitored by serum Estradiol, LH & Folliculography. Stimulation was done for 9days. On the day of trigger Serum E2-1413.2mIU/L, LH - 3.8 mIU/L & Progesterone- 2.09ng/ml. Ovulation trigger was done with inj HCG-10,000 units when at least 3follicle were >18mm size. Oocyte retrieval was done after 35 hrs. On next day of hCG trigger, serum β -HCg value was - 88.97miu/ml. On oocyte retrieval 8 follicles were aspirated, only few cells were obtained but no oocytes collected. Later, on investigation for FSH receptor polymorphism showed FSHR 2039AG (Heterozygous genotype) which might have affected fertility. So a higher dose of FSH was suggested for subsequent COH.

Although the serum β hCG level in both the IVF cycle was more than the expected range, we could not retrieve any oocyte on follicular aspiration. So we diagnosed it as a case of genuine recurrent EFS.

DISCUSSION

Diagnosis of EFS is mostly retrospective. It cannot be predicted sonographically or by hormonal assay during controlled ovarian stimulation. Can occur due to human error in administration of hCG, inappropriate dosage & timing. In management of EFS, HCG measurement is mandatory to assess the reality & effectiveness of HCG injection. Treatment of EFS ranged from rescheduling of oocyte retrieval, using of additional dose of urinary hCG from a different batch, using recombinant hCG or using GnRH agonist trigger in antagonist cycle.¹⁵ Most of EFS cases reported are GnRH agonist down regulated cycle with urinary HCG trigger. Only few cases were reported using of GnRH antagonist protocol. But in our patient we used antagonist protocol & Rec hCG as trigger but our result was negative. R. Beck Fruchter & A. weiss published a case report where they succeeded with a full term delivery in last cycle (8 th Cycle of stimulation) by using GnRH agonist trigger 40 hrs before ovum pick up & Rec-HCG 34 hrs before ovum pick up (OPU).

Assessment of serum β hCG, the day after the trigger is a potential preventive measurement against False EFS. A rescue protocol can be used to salvage the cycle when the β -hCG concentration is <100 mIU/ml (Zegers-hochschild); Ndukwe et al, trying to predict EFS, stated that serum hCG levels were < 10 mIU/ml in cases of EFS but Stevenson and Lashen in a comprehensive review, offered that hCG levels of 40 mIU/ml should be the cutoff between normal to low hCG levels on the day of ovum pickup (OPU).^{4,8,16} But In our patient in both cycles serum β hCG level was > 40 mIU/ml. Patients with EFS present a challenge to the treating physician. No single treatment is universally effective. Some authors, relying on the low frequency of recurrence, recommend repeating the standard ART cycle, regardless of the treatment protocol.

CONCLUSIONS

The case reported here is a recurrent genuine empty follicle syndrome as we could not retrieve any oocyte from the patient in spite of her serum β hCG levels being more than 40mIU/L on two consecutive stimulated cycles. We could not find any definite cause in our patient & we advised her for oocyte donation program.

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