A case of genuine empty follicle syndrome presented as primary infertility

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Abstract

Background: Empty follicle syndrome (EFS) is a condition in which no oocytes are retrieved after adequate ovarian response to stimulation and meticulous follicular aspiration. The etiology remains enigmatic and its occurrence is a frustrating complication of IVF, leading to cycle cancellation.

Case Report: A case of 32 years female presented with her 35 years old husband to our infertility clinic, married for 7 years and unable to conceive since 4 years. Before presenting to our clinic she has undergone ovulation induction and four cycles of IUI. She has a history of hypothyroidism and is now in euthyroid state with Tab thyroxin 50mcg since 1 year.

Conclusion: EFS is a rare complication of IVF. It may cause substantial stress and anxiety for both patient and physician. It is therefore of importance to understand EFS and help counsel the couple.

Keywords: Infertility, ovarian stimulation, oocytes, ovulation induction, IVF, trigger

Introduction

Empty follicle syndrome (EFS) was first described by Coulam et al. [1]. It is a condition in which no oocytes are recovered from apparently normally growing ovarian follicles with normal steroidogenesis after ovarian stimulation and follicular aspiration. It occurs in 0.045% to 7% of patients undergoing ovum pick up (OPU) [2,3,4].

EFS has been classified into genuine and false types. The Genuine EFS has been classified as a failure to retrieve oocytes despite optimal hCG 10065vels on the day of oocyte retrieval. The False EFS has been defined as a failure to retrieve oocytes in the presence of low hCG (< 40 IU) due to error in the administration or the bioavailability of hCG and seems to be more common.

The underlying mechanism of GEFS remains obscure, some considerable causes are mentioned in literature. We here present a rare case of GEFS with no oocytes retrieved on two ovarian stimulation. Very less reports have been reported on GEFS and we are enlightening on this topic.

Case Report

A couple presented to our clinic, with difficulty in conceiving since 4 years and married since 7 years as a primary infertility case. The lady was 32 years old with normal menstrual cycles. The detailed history was taken and on medical history, she was a known case of hypothyroidism and is now in euthyroid state with Tab thyroxin 50mcg since 1 year. She has tried ovulation induction and follicular study with Siphene with planned cycles for 6 months and 4 cycles of IUI before presenting to us.

Her physical examination was unremarkable and body mass index was24.9kg/m2.

On investigation, hormonal tests and pelvic sonography were done. On Pelvic sonography both ovaries were normal and follicle stimulating hormone (FSH) - 4.29IU/L, Leutinizing hormone (LH)- 4.01 IU/L, anti mullerian hormone (AMH) -4ng/ml, S. Prolactin- 14.13ng/ml and thyroid stimulating hormone (TSH)-2.72 uiU/L. Patient’s husband was 35 years old with semen analysis done according to WHO criteria 2021. Total count- 68 million/ml, total motility- 46%,
and normal forms -1% and diagnosed as teratozoospermia. As the patient had failed to conceive in four cycles of intrauterine insemination, IVF was advised. On day 2 of cycle, baseline hormonal levels were checked. S.FSH - 5.73 IU/L, S.LH- 4.63 IU/L and S. Estradiol- 32.57pg/ml and baseline scan was done with AFC of 5-6 in each ovary and no ovarian cyst present. Patient was enrolled for IVF stimulation and was started with recombinant FSH (Gonal F, Merk Serono, Germany) 225 IU subcutaneously daily from Day 3. On stimulation day 6, with lead follicle of 14mm and S.E2 -1450.41pg/ml, GnRH antagonist (Cetrorelix) 0.25mg subcutaneously was added which was continued daily till the day of trigger.

On day 11 of stimulation when around 7-8 follicles of > = 17mm were seen ml, Leupride 1mg subcutaneously was administered by a trained nurse and ovum retrieval under general anaesthesia was planned at 35 hours. On the day of OPU, as a routine protocol of our centre, urine LH were checked and it was positive. TVS at the time of pickup showed intact follicles in both the ovaries. Following follicular aspiration, no oocytes retrieved in any tubes from both ovaries. Only cumulus cells were recovered in follicular fluid (figure 1). We also checked with nurse who had administered the trigger revealed that there was no drug related issues like storage, batch or administration- related problems and were reassured. Patient was counselled for second stimulation with a different protocol with different drugs and trigger for ovarian stimulation. A second cycle was planned 6 months later with long GnRH agonist protocol. Dual suppression was achieved with oral contraceptive pill started from day3 of the previous menstrual cycle and gonadotropin- releasing hormone agonist (GnRHa, leuprolide acetate) 0.5mg subcutaneously (s.c.) start on daily from day 19 for 3 days and then reduced to 0.3mg once daily till the day of trigger. On day 2 of cycle, after confirming downregulation: (S. Estradiol [E2] - 25.92pg/ml, S. leutinizing hormone [ LH ] — 1.23 IU/L and S. follicle stimulating hormone [ FSH]- 2.79 IU/ L) and baseline scan showed no ovarian cysts and AFC of 5-6 in each ovary, ovulation stimulation started with recombinant FSH (Recagon, Organon) 225 IU/L daily subcutaneously. On day 6 of stimulation, 150 IU/ L HMG was added with R-FSH 150 IU/L continued. On day 10th of stimulation when 6-7 follicles with size > = 17mm were reached, highly purified hCG 10,000 IU/L was given, ovum retrieval under general anaesthesia was done at 35hours. On the day of OR, urine LH were checked as a routine protocol and it was reassuring and on TVS follicles were intact in both ovaries. On aspiration of few follicles from both ovaries, no oocytes retrieved in both ovaries. Only empty cumulus cells were recovered in follicular fluid. Follicular fluid LH was checked in LH kit and was weak positive. The case was abandoned and repeat trigger with high dose of highly purified hCG 20,000 IU was given and OPU was planned after 24 hours.

Next day, serum levels of beta hCG were checked and was around 72.76IU/L, which was optimum and ovum retrieval was done and no oocytes retrieved in both ovaries from all follicles.

Patient was explained the situation and discussed about empty follicle syndrome. Blood sample was sent for FSH and LH receptors polymorphism. Patient was advised for donor oocytes IVF program for future childbearing.

**Discussion**

GEFS is presumably related to intrinsic ovarian dysfunction. Inan et al. observed that the granulosa cells of patients with recurrent EFS have an increased expression of some proapoptotic genes and a significant reduction in transcripts, whose products are responsible for normal follicular growth (eg. PAPP-A, MAPK 3) than normal patients [5]. As a result, oocytes may be lost in the late folliculogenesis due to apoptosis.

Genetic causes of EFS have also been suggested. Novel mutation in LH/hCG receptor (LHCHR) was identified in two sisters with GEFS which is inherited as a recessive trait by Yariz et.al. [5]. A mutation (p.N400S) in the gene coding for LHCHR was detected causing an irreversible block in the transmission pathway of LHCHR signal, and so even repeat administration of hCG would be ineffective [6]. Vujisic et al. [7] showed the presence of a pericentric inversion of chromosome 2:46, XX, inv (2) (p11q21) in a patient who had multiple failed oocyte retrieval.

Several reports suggest that a significant part of genuine EFS are associated with ovarian ageing characterised by poorly functioning granulosa cells [8, 9]. Altered oocyte growth and maturation.

In our patient we checked FSH receptor (rs6166) and LH receptor (rs4539842) polymorphism and found no such polymorphism.

**Conclusion**

Empty follicle syndrome can be a challenging case for clinician leaving many questions unansered and for patients it is an emotional turmoil going through IVF and ending with no result.

**References**


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