CASE REPORT

The Empty Follicle Syndrome

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Summary

The empty follicle syndrome (EFS) is a rare complication of in vitro fertilization (IVF) treatment, leading to cycle cancellation. Low human chorionic gonadotropin (hCG) bioavailability and ovarian dysfunction have been implicated with this condition. This case report illustrates a typical case of EFS and several strategies suggested to overcome this problem.

Key Words: Empty follicle syndrome

Introduction

Failure to retrieve oocytes from mature ovarian follicles following ovulation induction for IVF treatment despite meticulous aspiration and repeated flushing has been previously described and termed 'empty follicle syndrome' (EFS) by Coulam and Sculman[1]. The reported incidence is estimated at 0.6- 7% of all IVF cycles[2]. There is no exact explanation for this problem and prediction using ultrasound or serum hormonal levels is difficult. We report a case of EFS and discuss the various hypotheses, clinical implications and useful strategies to overcome this problem.

Case report

A 35- year old nulliparous woman was referred to the infertility clinic, Universiti Kebangsaan Malaysia for unexplained subfertility of five years duration. Both her fallopian tubes were patent and she had regular menstrual cycles. Her husband's semen analysis was normal. The couple had three unsuccessful cycles of gonadotropin stimulation with intrauterine insemination before. She claimed that her previous response to gonadotropin was good with three mature follicles.

Subcutaneous follicle stimulating hormone (FSH) 200iu daily was started from Day 2. There were 13 follicles measuring 10-14mm by Day 9 and subcutaneous Gonadotropin Release Hormone (GnRH) antagonist, Cetrorelix 0.25mg daily was added. Intramuscular human Chorionic Gonadotropin (hCG) 10,000 unit was administered on Day 12 when there were more than three follicles of >18mm and the endometrial thickness was 13.9 mm. Oocyte retrieval was scheduled 36 hours later. Despite repeated flushing, there was no oocyte aspirated except for some cumulus- corona complex cells found in the follicular fluid. The urine pregnancy test was positive, indicating adequate hCG level. Her IVF cycle was cancelled.

Three months later, she had a second IVF cycle using the same GnRH antagonist protocol. This time the oocyte retrieval yielded 14 mature oocytes with ten embryos formed. Three embryos were transferred on the Day 3 post oocyte retrieval and the rest were cryopreserved.

Discussion

The failure of hCG to induce follicular maturation leading to EFS is an uncommon, but frustrating

This article was accepted: 2 May 2006

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complication of IVF treatment. It is also associated with cycle cancellation resulting in loss of time and effort besides emotional consequence to the couple as well as the IVF personnel. Luteinizing hormone (LH) surge is an essential step towards follicle maturation and rupture. It causes the reactivation of meiosis in oocytes together with important changes in cumulus, including enlargement by mucification and dispersion of the cumulus cells. These changes soften the connective tissue and facilitate the detachment of oocytes- cumulus complex (OCC) from the granulose cells and follicle wall. In IVF cycles, administered hCG serves as surrogate LH surge to induce similar effects on follicular development. It usually takes 34- 38 hours for the hCG to trigger follicle rupture.

There is currently no accepted explanation for the underlying mechanism of EFS but a low bioavailability of administered hCG and dysfunctional folliculogenesis have been proposed[3]. EFS associated with altered folliculogenesis leads to early atresia of oocytes or strong attachment of OCC to the follicle wall. This latter condition is associated with advanced stage ovarian aging where the oocytes fail to develop adequately. Another postulate is the possibility of an underlying post- receptor signaling system –cAMP that induces early expression of apoptosis genes, leading to rapid apoptosis before ovulation[4]. Alternatively, human error in administrating the hCG (wrong timing, inadequate dosages), variation in individual hCG thresholds and increased plasma clearance contribute to poor bioavailability. The intrinsic defects in the in-vivo biological activity of some batches of commercially available hCG has been reported. A low serum hCG assay (<10 IU/ml) and/ or progesterone taken on the day of oocyte retrieval would confirm low bioavailability.

In this patient, her response to ovulation hyperstimulation was within the expected limits, although serum estrogen level was not measured. The timing of hCG administration and dosage were re-confirmed and found to be adequate. Although low hCG bioavailability remains the commonest cause of EFS, it was excluded by a positive urine pregnancy test. All these point towards a possibility of inadequate softening up of OCC. The presence of cumulus cells during oocyte retrieval was highly suggestive of the abnormal folliculogenesis. Although the patient could have a repeat hCG with reschedule oocytes retrieval[3], this was not done as it was not a routine practice then. It is critical for IVF physicians to have a contingency plan when faced with this rare condition. Low drug bioavailability can be excluded by immediate hCG assay or urine hCG test, although EFS can occur in the presence of normal hCG concentration on the day of oocyte retrieval. A repeat hCG injection 5000-10000 unit followed by second oocyte retrieval after 24 hours would be another option[2] as these follicles were not empty after all. In the majority of cases, EFS does not predict a reduced fertility potential in future cycles and rarely recur as in this patient.

References

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