Empty Follicular Syndrome: Understanding Controversial Entity

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ABSTRACT

Empty follicular syndrome (EFS) is defined as the failure to retrieve oocytes from mature ovarian follicles after controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF). There are two types of EFS—genuine and false EFS. In genuine EFS, there is failure to retrieve oocytes from mature ovarian follicles after COH for IVF after apparently normal follicular development and steroidogenesis in the presence of optimum β-human chorionic gonadotropin (hCG) levels, whereas in false EFS, there is failure to retrieve oocytes in the presence of low β-hCG levels. Whatever may be the cause of EFS, these patients should be counseled regarding its possibility of recurrence and future poor prognosis. However, different IVF treatment methods in subsequent cycles could modulate the response with successful oocyte recovery in such cases.

Keywords: Genetic factor, Human chorionic gonadotropin, Oocyte retrieval, Ovarian follicle, Ovulation induction.

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INTRODUCTION

The nature of empty follicular syndrome (EFS) has been controversial since its description by Coulam et al. in 1986. The condition was defined as the failure to retrieve oocytes from mature ovarian follicles after controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF), even after meticulous aspiration and repeated flushing, despite apparently normal follicular development and estradiol (E2) levels. The EFS is estimated to affect <1 to 7% patients undergoing IVF treatment. Although occurrence of EFS is rare, it is really a frustrating complication of IVF leading to cycle cancellation, which may cause substantial stress and anxiety for both patients and treating physicians. It is, therefore, very important to understand EFS.

In 2008, Stevenson and Lashen categorized EFS into “false” or “genuine” according to β-human chorionic gonadotropin (hCG) levels on the day of oocyte retrieval. In their review, 33% cases were genuine EFS (G-EFS) and 67% were labeled as false EFS. The G-EFS was defined as failure to retrieve oocytes from mature ovarian follicles after COH for IVF after apparently normal follicular development and steroidogenesis in the presence of optimum β-hCG levels on the day of oocyte retrieval, and “false EFS” as failure to retrieve oocytes in the presence of low β-hCG due to an error in the administration of hCG or its bioavailability on the day of oocyte retrieval.

ETIOLOGY AND PATHOGENESIS

The underlying mechanism of EFS remains hypothetical. It has been suggested that it is not a syndrome, but rather a sporadic event that cannot be predicted by the pattern of ovarian response either sonographically or hormonally. Many hypotheses have been put forward ranging from human error to pharmacologic problems. The underlying pathology is unknown; however, it has been earlier suggested that EFS might reflect dysfunctional folliculogenesis with an altered follicular steroid profile. Others have interpreted EFS solely as a drug-related syndrome, resulting from an abnormality in the biological activity of some batches of hCG or human error related to injections. However, these hypotheses fail to explain the recurrence of the syndrome in certain patients.

The underlying mechanism of EFS still remains unresolved. Dysfunctional folliculogenesis and genetic factors have been implicated in the etiology of EFS. Molecular studies using transcriptional profiling showed that genes involved in apoptosis were differentially expressed in the granulosa cells from a patient with recurrent EFS, suggesting a role in the disappearance of the oocyte. The luteinizing hormone/choriogonadotropin receptor (LH/CGR) is a glycoprotein hormone receptor belonging to the G-protein coupled receptor family. Loss-of-function mutations of LH/CGR lead to
The etiology of failed injections is challenging; it may result from human error in either mixing or administering the medication or rapid clearance of the medication resulting from human error in either mixing or administering the medication or rapid clearance of the medication. The GnRH antagonist should be given on cycle day 6 (when the serum E2 level was >1,000 pmol/L) and continued until the day of β-hCG administration. This will help to avoid premature trigger and prevent from aspirating immature oocyte or only follicular fluid (FF).

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The effect of the stimulation protocol on the risk of EFS implantation rates, clinical pregnancy, and live births were detected. However, β-hCG administered. By increasing the time of exposure to β-hCG, no consistent differences in oocyte yield, maturity, fertilization, or embryo quality were detected. However, as age increases, significant trends toward improved implantation rates, clinical pregnancy, and live births were detected by extending exposure to hCG for > 36.5 hours. It may be beneficial in patients aged > 40 years.

MANAGEMENT

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, whereas others suggested that the occurrence of EFS in IVF can be attributed to a failure in (a) accurate timing of induction of final oocyte maturation, (b) properly scheduled ovarian hyperstimulation, or (c) instruction of patients and doctors.

However, by differentiating between the false and genuine types, these suggestions become less relevant. A second, rescue dose of β-hCG in the setting of false EFS was first proposed by Ndukwe et al, and this has persisted as the consensus solution in the literature since that time. Although isolated case reports have described pregnancies from this approach, the largest single case series shows a limited prognosis.

Live-birth pregnancies are a realistic possibility after administration of a rescue course of β-hCG and repeat oocyte retrieval in the setting of false EFS. The risk of recurrence of EFS is 20%, the risk being higher with advancing age: 24% recurrence rate for age 35 to 39 years and 57% for age over 40 years. The failure to retrieve the oocyte during the follicle phase may be attributed to EFS, but it cannot be excluded completely that not enough time was allowed before retrieval. In G-EFS, dysfunction of the folliculogenesis seems to be the most plausible etiology. In fact, when they analyzed the etiology of infertility in the IVF patients group, they found a higher proportion of polycystic ovarian syndrome with low response and a lower percentage of unexplained infertility, which supports the concept of dysfunctional folliculogenesis.

As previously mentioned, in contrast to hCG triggering, the action of a bolus of GnRH agonist is indirect via the endogenous release of LH and follicle stimulating hormone (FSH) from the pituitary after binding to and activation of the GnRH receptor. As the pituitary is the target organ for GnRH agonist, one might assume that under temporary or permanent dysfunctions of the pituitary, a sufficient flare-up effect will not be achieved, resulting in a deficient final follicular maturation and EFS.

An example of this is the hypogonadotropic/hypogonadal patient (World Health Organization type I) who is characterized by endogenous levels of LH and FSH below 1.2 IU/L. The GnRH agonist triggering in this type of patient will invariably result in EFS due to the induction of an insufficient surge of gonadotropins. Patients who could be hypothesized to develop EFS after GnRH agonist triggering are patients with a GnRH receptor polymorphism, necessitating a higher dose of GnRH agonist to activate the receptor in line with the FSH receptor polymorphism (Ser680 FSH-R). The same would account for patients with an LH receptor polymorphism. Patients with a variant LH beta gene polymorphism, specifically in the homozygous form, resulting in a less bioactive LH molecule might be at risk to have a blunted response after GnRH agonist triggering. The incidence of EFS seems to be similar after GnRH agonist and β-hCG triggering. As in EFS cases seen after
β-hCG, the exact reason for failure after GnRH agonist triggering remains uncertain. If the oocytes are present but failed to mature in the follicles during stimulation, it may be more effective to remove the immature oocytes and apply the maturation process in vitro. Although the β-hCG was negative, this case could lead to an alternative approach to G-EFS. Most cases of EFS after either β-hCG or GnRH agonist trigger are related to human error, and, thus, a meticulous counseling and instruction of the patient prior to oocyte retrieval is of utmost importance.

CONCLUSION

Ovarian follicles of patients with so-called EFS may not actually be devoid of viable oocytes. The problem seems to be that of inadequate preovulatory follicular changes arising from either poor bioavailability of LH or β-hCG or too short an interval between the onset of these changes and follicular aspiration. Premature lutenization due to a premature LH surge and high P levels on the day of β-hCG injection can also affect the oocyte recovery. The EFS does not predict a reduced fertility potential in future cycles. Nevertheless, whatever the cause of EFS, these patients should be counseled regarding its possibility of recurrence and future poor prognosis. However, different IVF treatment methods in subsequent cycles could modulate the response with successful oocyte recovery in such cases.

REFERENCES


