REVIEW
http://dx.doi.org/10.5653/cerm.2012.39.4.132
pISSN 2233-8233 · eISSN 2233-8241
Clin Exp Reprod Med 2012;39(4):132-137

CERM

Empty follicle syndrome

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Empty follicle syndrome (EFS) is a condition in which no oocytes are retrieved after an apparently adequate ovarian response to stimulation and meticulous follicular aspiration. EFS can be classified into 'genuine' and 'false' types according to hCG levels. It is a rare condition of obscure etiology. The existence of genuine EFS has been questioned and is still controversial. The limitation around EFS is that the definition of EFS is obscure. Management of patients with EFS is a challenge to physicians. No single treatment is known to be universally effective. However, patients should be adequately informed regarding the importance of correct hCG administration because improper hCG administration is a common and preventable cause of EFS. EFS is a syndrome that deserves additional study because such investigation could lead to a further understanding of ovarian biology and infertility.

Keywords: Infertility; Ovarian stimulation; Retrieval; Oocyte; Chorionic gonadotropin

Introduction

Empty follicle syndrome (EFS) was first described by Coulam et al. [1]. It is a condition in which no oocytes are retrieved from apparently normally growing ovarian follicles with normal steroidogenesis after ovarian stimulation and meticulous follicular aspiration. The etiology remains enigmatic and some have even cast doubt regarding the existence of the syndrome [2-5].

EFS has been classified into 'genuine' and 'false' types. The former has been defined as a failure to retrieve oocytes despite optimal hCG levels on the day of oocyte retrieval. The latter has been defined as a failure to retrieve oocytes in the presence of low hCG (< 40 IU/L) due to an error in the administration or the bioavailability of hCG, and seems to be more commonly encountered. In a review of EFS by Stevenson and Lashen [6], 33% of EFS cases were labeled as genuine and 67% as false type.

Occurrence of EFS is a rare but frustrating complication of IVF, leading to cycle cancellation. It may cause substantial stress and anxiety for both patients and physicians during assisted reproductive technology (ART). It is therefore of importance to understand EFS. In this review, we thoroughly searched the literature to identify several studies and case reports regarding EFS published to date in PubMed to verify the reality of EFS. The term used for the search was 'empty follicle syndrome'. The references of the articles found in the search were also explored. The papers included were observational studies, scientific reviews, case reports or case series, and letters or comments. The studies that have been published in English were included. The papers have been reviewed and presented in order of their importance or the date of the studies.

Incidence

EFS is an uncommon event, estimated to occur in 0.045% to 7% of patients undergoing ovum pickup (OPU) [2-4,7-12]. This variability may primarily result from different inclusion criteria. In some studies, patients with a poor ovarian response or premature ovulation were included while in others they were not.

Aktas et al. [4] included 3,060 IVF cycles with a regular indication,

Received: Nov 27, 2012 · Revised: Dec 11, 2012 · Accepted: Dec 12, 2012
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and among them, no oocytes were recovered in 25 cycles. They assigned all those cases to an EFS group without any exclusion; thus the prevalence of EFS (0.81%) that they reported seems to be quite overestimated [4].

Reichman et al. [10] confined EFS to cases in which no oocytes were retrieved despite adequate follicular development (≥4 follicles with at least two being >18 mm in mean diameter) and identified seven cases false type EFS, representing 0.045% of the 15,729 cycles. Mesen et al. [11] described the prevalence of genuine and false EFS separately. They strictly excluded the subjects who had fewer than five follicles measuring ≥14 mm to avoid incorrectly designating patients with poor ovarian response as having EFS. Only two cases of genuine EFS (0.016%) and nine cases of false EFS (0.072%) were identified among a total of 18,294 oocyte retrieval cycles.

Castillo et al. [12] reported the incidence of EFS according to the triggering method among 2,034 of donor cycles and 1,433 of IVF cycles. EFS incidence after GnRH agonist and hCG triggering did not differ significantly (3.5% vs. 3.1%). Although EFS after GnRH agonist triggering may represent a different physiology (inducing endogenous LH/FSH surge) as compared to hCG triggering, the incidence was similar. Currently, it seems that no specific stimulation or triggering protocol is related to the occurrence of EFS.

In our institute, no oocytes were recovered in 17 (2.4%) of a total of 705 cycles after ovarian stimulation during the period from January 2003 to May 2012. We excluded the women ≥45 years old and with estradiol ≤200 pg/mL on the day of hCG to exclude poor ovarian response. A total of 633 GnRH antagonist cycles and 72 GnRH agonist cycles were included and the incidence of EFS in the two cycles did not differ (2.5% vs.1.4%, $p=1.000$).

Underlying mechanism

In false EFS, hCG-related faults are the main mechanism. Improper hCG administration has been the most common cause of false EFS [4]. According to Aktas et al. [4], among 25 cases of EFS, 9 cases (36%) were related to improper hCG administration. Seven women were administered the hCG injection later than scheduled (11 hours before retrieval), and a failure of the hCG injection occurred in two women hCG, which was confirmed by the undetectable hCG serum concentrations.

Rapid metabolic clearance, manufacturer defects in hCG production, and low bioavailability of hCG are also proposed causes [4,6,13-16]. Zegers-Hochschild et al. [13] showed the reduced *in vivo* biological activity of some batches of commercially available hCG and described EFS as a pharmaceutical industry syndrome. Later, Ndukwe et al. [14] reported the cases in which the serum hCG concentrations never exceeded 10 mIU/mL after 36 hours from hCG administration. The cycle could be salvaged by giving another dose of hCG from a new batch and scheduling another retrieval 36 hours later [15]. Hirshfeld-Cytron and Kim [17] showed that the low bioavailability of hCG after bariatric surgery may induce EFS. Abdominal skin redundancy after bariatric surgery may alter the absorption of subcutaneously administered hCG; thus intramuscular administration is a safe option in those women.

Early oocyte atresia in continued follicular growth has been suggested as the underlying mechanism of EFS [3,18,19]. Awonuga et al. [3] reported a case where cumulus complexes without oocytes were aspirated, and they suggested that this might be evidence of early oocyte atresia. Inan et al. [18] analyzed the whole gene expression of granulosa cells (GC) from a 22-year-old patient with recurrent EFS and found a total of 160 genes that were differently expressed (by at least two-fold) compared to those in patients from which oocytes were retrieved. They supposed that the absence of oocytes might be due to increased apoptotic gene expression and reduction of transcripts whose products are responsible for healthy follicular growth. Desai et al. [19] observed 200 pre-antral follicles with thin zonae and devoid of oocytes through a microscope. They proposed these tiny follicles, if left to grow *in vivo*, would have led to empty follicles and genuine EFS. The presence of a zona in the follicle may be proof that an oocyte has been present and then undergone atresia after the formation of a zona.

Several reports suggest that a significant part of genuine EFS is associated with ovarian ageing [4,8,20-22]. Ovarian ageing is characterized by poorly functioning GC [23]. Hampered granulosa cell function reflects altered oocyte growth and maturation, and consequently causes EFS. In these cases, ovarian GC may respond to exogenous gonadotropins with increasing estradiol concentration, although mature oocytes are no longer retrievable [2].

Some investigators showed that genuine EFS could be a manifestation of low ovarian reserve [8,21,22]. Risk factors for EFS have been suggested: 1) advanced age (37.7±6.0 years vs. 34.2±6.0 years, $p<0.001$), 2) longer infertility duration (8.8±10.6 years vs. 6.3±8.4 years, $p<0.05$), 3) higher baseline FSH levels (8.7±4.7 IU/L vs. 6.7±2.9 IU/L, $p<0.001$), and 4) lower E_2 levels before the hCG injection (499.9±480.9 pg/mL vs. 1,516.3±887.5 pg/mL, $p<0.001$) [22]. The risk factors of EFS are similar to those of low ovarian reserve, and this suggests that ovarian ageing may be involved in the etiology of EFS. EFS may be a gradual biological occurrence related to ovarian ageing.

Other investigators have suggested that some follicles may need longer exposure to hCG for cumulus expansion and detachment of oocyte cumulus complexes from the follicular wall [24-26]. Follicular rupture and oocyte maturation are time-dependent processes being needed at different times in different patients. It might be hypothesized that cumulus expansion and detachment of oocytes from the

follicular wall also requires longer time periods in certain patients. In those cases, the commonly used stimulation protocol may result in EFS.

Genetic causes of EFS have also been suggested [27-29]. Onalan et al. [27] reported an inherited condition of EFS with moderate sensorineural deafness affecting two sisters. This case may represent an inherited condition of EFS with hearing loss with genetic factors affecting both the etiology of EFS and the hearing loss. Vujisic et al. [28] showed the presence of a pericentric inversion of chromosome 2:46, XX,inv(2)(p11q21) in a patient who had multiple failed oocyte retrieval. Recently, an inherited mutation of LH/hCG receptor was identified in two sisters with EFS [29].

Another possibility is a yet-to-be-discovered genetic cause of the syndrome. LH stimulation induces the transient and sequential expression of epidermal growth factor family members such as amphiregulin, epiregulin, and betacellulin. These growth factors seem to mediate the LH action, including cumulus expansion and oocyte maturation [30,31]. These growth factors induce expression of prostaglandin synthase 2 (Ptgs2), tumor necrosis factor alpha-induced protein (Tnfaip6), and hyaluronan synthase 2 (Has2), which are necessary for cumulus expansion and subsequent oocyte release. Altered expression of these genes regulating cumulus expansion might result in EFS, but this remains to be determined.

Does genuine EFS really exist?

Debates about the existence of genuine EFS have continued. Some suggest that genuine EFS does exist and that it might be a real cause of infertility. Desai et al. [19] recently showed microscopic evidence of genuine EFS with a case of borderline EFS. A borderline form of EFS was also suggested in which very few mature or immature oocytes are recovered from several mature follicles [19,26,32-34]. The genetic basis for EFS provides strong evidence for the existence of genuine EFS in some patients [27-29].

Nevertheless, some still question the presence of genuine EFS. Aktas et al. [4] argued that genuine EFS is virtually nonexistent by demonstrating that unsuccessful oocyte retrieval occurs in about 0.8% and recurrent EFS was absent in their study. van Heusden et al. [5] argued that EFS is just a matter of mathematical coincidence. The reported oocyte recovery rate in natural cycles is approximately 80% [35,36]. Assuming that the chance to recover one oocyte per follicle is similar in conventional IVF, the mathematical chance for failure to recover any oocyte is considerable. If there are two to six dominant follicles present before oocyte retrieval, the calculated chance for failure to recover at least one oocyte is 0.064% to 4%. They suggested that this mathematical chance is similar to the reported incidence of EFS and thus EFS may be a phenomenon caused by this mathematical coincidence. Beck-Fruchter et al. [37] also denied the existence of genuine EFS, reporting successful treatment in a recurrent EFS case as a proof. Furthermore, they argued that EFS is a misnomer since the follicles are not actually empty, but rather the oocytes are not aspirated or identified utilizing standard ART methods.

Prognosis

Important factors to consider when counseling of couples who have EFS might be the significance of this event to their future fertility. However, prognosis after EFS occurrence varies from just sporadic events to being an unfavorable predictor. Aktas et al. [4] reported that there was no recurrence of unsuccessful oocyte retrieval in subsequent treatments. Baum et al. [22] suggested that EFS should be seen as a sporadic event with good clinical outcomes in most of the cases except the 15% that are recurrent cases. On the other hand, some suggest the occurrence of EFS would indicate a poor outcome in subsequent cycles. Lorusso et al. [20] reported in their case series that poor quality oocytes were obtained after an EFS cycle and suggested that the empty cycle could be a predictor that a subsequent stimulated cycle will be an unfavorable one. Later, Coskun et al. [9] also reported poor outcomes after genuine EFS. In their study, EFS was defined as no oocytes retrieved in good responder patients undergoing ovarian stimulation with at least five mature follicles ($\geq$15 mm) on the day of hCG. Incidence of EFS was 1% (26 women out of a total of 3,023 patients). Thirteen women went through 32 further IVF treatment cycles following the diagnosis of EFS, yielding only two clinical pregnancies (12%), giving a clinical pregnancy rate of 6.25% per started cycle. In addition, four patients (31%) had recurrence in a total of 15 cycles. In contrast to a previous study [8], patients in this study who experienced recurrence were significantly younger than those with single EFS (27.3$\pm$3.8 vs. 34.7$\pm$6.1, p=0.023). This difference may arise from different underlying mechanism of EFS. Zreik et al. [8] included patients with poor ovarian response while Coskun et al. [9] excluded.

Some investigators have estimated the risk of recurrence. Zreik et al. [8] estimated that women with one EFS cycles had a 20% risk of recurrence in later IVF cycles (7 out of the 35 patients) and those with recurrent EFS had a poor success rate. The chances of recurrence of EFS increase with the age of women (24% recurrence rate for women aged 35 to 39, and 57% for those aged >40). Recently, it was reported that recurrent EFS occurred in 15.8% (16 cases out of 101 cycles) of subsequent cycles [22], consistent with a previous study [8]. There were 9 clinical pregnancies (10.6%) among patients with sporadic occurance of EFS in the subsequent IVF cycle. In contrast, among those with two consecutive cases of EFS, no further pregnancies or successful oocyte retrieval were reported. Women with recurrent EFS had significantly prolonged infertility (10.4$\pm$5.7 years vs. 6.3$\pm$5.4 years,

http://dx.doi.org/10.5653/cerm.2012.39.4.132

$p = 0.05$) and lower E_2 levels (411.1 ± 200.3 pg/mL vs. 925.1 ± 784.2 pg/mL, $p < 0.05$) compared with those of sporadic EFS. Eighty percent of recurrent EFS were in women ≥ 36 years old. These data suggest that the risk factors of recurrent EFS are advanced age, prolonged infertility, and lower E_2 levels, which are consistent with the risk factors of poor ovarian response. Recurrent EFS may be a variant phenotype of poor response.

In our institution, among sixteen women with EFS (17 cycles), 9 women (56.3%) chose to continue the IVF treatments and performed subsequent IVF cycles with the same or a different protocol. EFS recurred in one woman (11.1%) and oocytes were successfully obtained in the remaining women. Clinical pregnancy was noted in 5 women (55.6%), but one ended in a missed abortion.

Prognosis after EFS varies and depends on its etiology. EFS itself should not discourage patients. Some cases of EFS were a sporadic event with good clinical outcome. However, in about 15% to 30% of the cases, recurrent EFS can be anticipated [8,9,22]. These patients should be consulted regarding their lower chances of pregnancy.

Therapeutic approach

Attempts to rescue the IVF cycle in case of false EFS have been suggested: readministering hCG and reaspiration [10,15,16,38-40]. A second, rescue dose of hCG in the setting of false EFS was first proposed by Ndukwe et al. [15] in 1997, and successful IVF cycles have been reported [38-40]. A recent literature review indicated that 42.8% of cycles (6 out of 14) in which hCG was readministered in the setting of suboptimal or absent serum hCG resulted in a healthy liveborn fetus [6]. Thus this has been the reasonable solution for false EFS.

Reichman et al. [10] presented a less optimistic picture regarding rescue hCG administration. This study is important in that it is the largest single case series to date. In their cycle-matched study in the same patients, fewer oocytes were obtained than in subsequent cycles and no implantation occurred in seven rescue false EFS cycles. The etiologies proposed for these limited results included a 72-hour unintended "coasting" period and postmaturity of some oocytes. In spite of this less optimistic study, considering successful cases, readministration of hCG can be an option for rescuing the cycle. However, the success rates should be further investigated and patients should be given careful counseling.

Reichman et al. [41] has recently proposed a potential preventative measurement against false EFS through the assessment of serum hCG the day after the trigger and a second bolus of hCG administration. According to their report, failed initial hCG injection occurred in 44 patients (0.25%) of the 17,298 fresh IVF cycles. Of the 41 patients undergoing retrieval who received a second injection of hCG approximately 24 hours after the first, the live birth rate was 39.0%. Compared with matched controls, there were no statistical differences in oocyte maturity, fertilization, implantation, clinical pregnancy, or live birth rates. Given the rarity of this occurrence in our practice, some clinicians may hesitate to adopt such a policy as a uniform practice. However, in donor cycles, monitoring of hCG should be taken to minimize the risk of unsuccessful oocyte retrieval.

Uygur et al. [42] suggested prolonging the interval between ovulation triggering and OPU. However, the strategy regarding prolonging the interval between triggering and OPU has little evidence to be generally recommended.

One successful outcome has been reported using two combined strategies, prolonging the interval between ovulation triggering and OPU and inducing ovulation using GnRH agonist [37]. GnRH agonist triggering to induce an endogenous LH surge in a GnRH antagonist cycle has been suggested as one strategy to prevent the occurrence of EFS [43,44]. A patient had undergone seven repetitive borderline EFS cycles. In the treatment cycle, ovulation was triggered using GnRH agonist 40 hours prior to OPU and hCG was added 6 hours after the first trigger. That resulted in aspiration of mature oocytes, pregnancy, and delivery. However, it is impossible to differentiate whether the two strategies exerted the desired outcome.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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