

Empty follicle syndrome: Successful pregnancy following dual trigger

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ABSTRACT

Empty follicle syndrome (EFS) is an uncommon, but the frustrating complication of assisted reproductive technology with failure to obtain oocytes after an adequate ovarian response to stimulation. Most of the reported cases of EFS are drug-related problems which are actually avoidable and do not represent any potential pathology and that the risk of genuine EFS (GEFS) is much smaller than was once thought. Our case is the first report of a pregnancy obtained after management of GEFS with dual trigger in a gonadotropin-releasing hormone (GnRH) antagonist cycle. In this report, we present a patient who underwent two oocyte retrievals, in which no oocytes were obtained. In the third *in-vitro* fertilization cycle, a dual trigger with the combination of GnRH agonist and human chorionic gonadotropin yielded 11 oocytes, which led to the transfer of 2 blastocysts resulting in a live birth. Changing the treatment protocol with dual trigger brought about a successful outcome.

KEY WORDS: Dual trigger, empty follicle syndrome, genuine empty follicle syndrome, gonadotropin-releasing hormone antagonist

INTRODUCTION

Empty follicle syndrome (EFS), a much debated enigmatic syndrome, is annoying and highly stressful causing considerable concern for both the clinician and the patient.^[1] EFS is defined as a condition in which no oocytes are retrieved from mature ovarian follicles following ovulation induction in an *in-vitro* fertilization (IVF) cycle with apparently normal folliculogenesis and steroidogenesis despite meticulous follicular aspiration and flushing. It cannot be predicted by the pattern of ovarian response to stimulation, either sonographically or hormonally. Consequently, the diagnosis of EFS is retrospective. In view of the uncertainty surrounding the causes of this phenomenon, and the mounting evidence that oocytes can, in some instances, be successfully retrieved, the term EFS is considered inappropriate; yet still in use in current medical literature.^[2]

EFS has been classified into two types: "Genuine EFS" (GEFS) and "false" EFS (FEFS). The prevalence of GEFS is 0–1.1%.^[3] GEFS is defined as failure to retrieve oocytes from apparently normal growing ovarian

follicles following stimulation in IVF cycles with normal levels of estradiol and appropriate serum levels of beta human chorionic gonadotropin (β -hCG) on the day of oocyte retrieval (OR). The underlying mechanism of GEFS remains obscure, still questioning the doubtful existence of this syndrome as a discrete clinical entity.^[4] We here report a case of GEFS which was managed successfully with dual trigger.

CASE REPORT

A couple with 6 years of primary infertility was referred to our fertility center for unexplained infertility. The lady was 32 years old with normal menstrual cycles, known case of hypothyroidism and was on thyroxin 50 μ g daily. Her elder sister

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was also a case of unexplained infertility, who had undergone three IVF cycles elsewhere with the retrieval of only 1–2 immature oocytes in all the cycles and was advised donor oocytes. Her physical examination was unremarkable with no acne or hirsutism and body mass index of 22 kg/m². Pelvic sonography was normal and her baseline investigations were all within normal limits with follicle stimulating hormone (FSH)-7.5 IU/L, anti-mullerian hormone - 2.9 ng/ml, and prolactin-17 ng/ml. Her thyroid stimulating hormone (TSH) was 6.6 µIU/ml for which her thyroxine was upgraded to 75 µg/day with repeat TSH 6 weeks later being 1.9 µIU/ml. Diagnostic hysterolaparoscopy revealed normal findings. Patient's husband was 38 years old with normal semen analysis (total count - 69 million/ml, total motility - 68%, and normal forms - 35%) and normal DNA fragmentation index.

As the patient had failed to conceive in four cycles of Intrauterine insemination, IVF was planned with long luteal agonist protocol. Dual suppression was achieved with oral contraceptive pill started from day 5 of the previous menstrual cycle and gonadotropin-releasing hormone agonist (GnRHa) (Lupride, Sun Pharmaceutical Ltd.,) 0.25 mg subcutaneously (s.c.) twice daily from day 21 after a transvaginal sonography confirmed no cysts. On day 2 of cycle, after confirming downregulation: (Estradiol [E2]-41 pg/ml, luteinizing hormone [LH]-1.1 IU/L, progesterone [P4]-0.1 ng/ml), ovarian stimulation was started with recombinant FSH (R-FSH), (Recagon, Organon) 150 IU s.c. daily and GnRHa 0.25 mg once a day was continued till the day of trigger. On day 5 of stimulation with 8 follicles between 7 and 11 mm and E2-230 pg/ml, 75 IU human menopausal gonadotropin (HMG), (Reprogon, Ferring Pharmaceuticals Ltd.,) was added to recagon 150 IU. On day 10 of stimulation with 4 dominant follicles ≥17 mm, endometrial thickness of 9.8 mm with E2-2011 pg/ml, LH-1.9 IU/l and P4-0.2 ng/ml. Recombinant-hCG (R-hCG) (Ovitrelle, Serono) 250 mcg was given as trigger and OR scheduled at 35 h. Before the start of oocyte pickup, transvaginal scan (TVS) showed evidence of intact follicles in both the ovaries. Following aspiration of the mature follicles from the right ovary, as the follicular fluid in the first three tubes did not show any evidence of granulosa cells or oocytes, we decided to flush the remaining follicles. Despite repeated flushing, neither oocytes nor cumulus ± corona complexes were recovered. Follicular fluid tested for β-hCG was found to be positive. A careful interrogation of the patient and the nurse who had administered the hCG injection revealed that there were no drug-or administration-related problems. We also decided to check the serum levels of hCG and P4 and surprisingly, we found it to be 165 mIU/ml and 14 ng/ml, respectively. As the serum levels were assuring and within the expected

range, we proceeded with the aspiration of the other ovary. Unfortunately, no oocytes were retrieved.

A second cycle was planned 4 months later with an antagonist protocol. On day 2 of spontaneous cycle, FSH, LH, E2, and P4 levels were 6.5 IU/L, 4.6 IU/L, 37 pg/ml, and 2.1 ng/ml, respectively, with antral follicle count (AFC) of 6–8 in both the ovaries. Stimulation was started with a combination of R-FSH (Recagon, Organon) 150 IU and 75 IU HMG (Menogon, Ferring Pharmaceuticals Ltd). On stimulation day 5, with lead follicles of 13 mm and 14 mm and E2-456 pg/ml, GnRH antagonist, Ganirelix (Orgalutran, Organon) 0.25 mg s.c. was added which was continued daily till the day of trigger. On day 9 of stimulation with 3 dominant follicles ≥17 mm and peak E2, LH, and P4 levels of 1856 pg/ml, 2.4 IU/L, and 1.01 ng/ml, respectively, R-hCG (Ovitrelle, Serono) 500 mcg was administered s.c. by a qualified nurse and OR was planned at 36 h. TVS at the time of pickup showed intact follicles in both the ovaries and also the LH levels on the day of trigger were reassuring. Even with repeated flushing of the follicles in both the ovaries, neither cumulus complexes nor oocytes were recovered. We were perplexed to find a serum hCG level of 154 mIU/ml and P4 of 19 ng/ml and a repeat problem made us really worry despite taking all the precautions in the second cycle.

After two previous failed IVF attempts, the patient returned only 2 years later for a third cycle. This cycle we choose an antagonist protocol with dual trigger. Her day 2 FSH, LH, E2, P4 levels were 7.9 IU/L, 3.5 IU/L, 43 pg/ml, 1.9 ng/ml, respectively, with an AFC of 5–6 in each ovary. Ovarian stimulation was started with R-FSH, (Gonal F, Serono) 225 IU. On stimulation day 6 with a lead follicle of 13 mm and the rest of the follicles between 9 and 11 mm with E2-301 pg/ml, Recombinant LH, Luveris (Serono) 75 IU along with Gonal F 150 IU and GnRH antagonist, and Ganirelix (Orgalutran, Organon) 0.25 mg s.c., was added which was continued daily till the day of trigger. On day 10 of stimulation with 5 lead follicles 17 mm and E2, LH, and P4: 2415 pg/ml, 2.45 IU/L, and 0.78 ng/ml, respectively. R-hCG (Ovitrelle, Serono) 250 mcg and Triptorelin (Decapeptyl, Ferring) 0.2 mg was administered for final maturation and OR planned at 36 h. Eleven oocytes were retrieved, 10 were mature, 9 fertilized with intracytoplasmic injection, and 9 cleaved further. A total of seven 8-cell good quality embryos were available on day 3 with two 6 celled arrest being discarded. Four 8-cell good quality embryos were cultured to blastocyst and the remaining 3–8 cell good quality embryos were frozen on day 3. Two good quality blastocysts (311, 211) were transferred on day 5. Luteal phase was supported with micronized progesterone 400 mg vaginally twice a day and three doses of hCG 2000 IU every 3 days from the day of

embryo transfer. Serum β -hCG 2 weeks later was 426 mIU/l and TVS at 6 + weeks showed a single live intrauterine fetus.

Patient continued well through the first trimester. Thyroid supplementation was altered as per the need for pregnancy and monitored with TSH and free T4 levels. During the second trimester, she developed gestational diabetes and was started on insulin. Elective cesarean section was performed at 38 weeks of gestation delivering a live female baby of 3.1 kg with uneventful intra and postpartum period.

DISCUSSION

EFS was first reported by Coulam *et al.* in 1986.^[5] The incidence of EFS has been estimated to be 0.6–7%,^[6,7] 2–7%,^[4] and 0.5–2%^[4,8,9] of IVF cycles. Unsuccessful OR does not appear to be related to stimulation regimen^[4] as the phenomenon is observed in natural as well as stimulated cycles^[10] and in almost all IVF cycles because the oocyte yield rarely reaches 100%. However, the terminology is usually used to refer to total failure to retrieve any oocytes.^[11] The etiology of EFS is multifaceted, with both procedural factors and ovarian dysfunction contributing as suggested by Bustillo.^[2]

FEFS is defined as a condition where no oocytes are retrieved in the presence of low β -hCG due to human errors^[12] or pharmaceutical problems^[12] or due to reduced bioavailability of hCG.^[11] Indeed, EFS has been described as a “pharmaceutical industry syndrome”^[8] and accounts to about 67% of cases.^[11]

GEFS is presumably related to intrinsic ovarian dysfunction^[10] and various hypotheses have been suggested which include: (1) Dysfunctional folliculogenesis or premature apoptosis of the oocytes that still continued follicular growth.^[4,13] (2) Defective granulosa cell function.^[10] (3) Faulty oocyte development and maturation.^[14] Abnormal oocytes like immature oocytes that were zona-free or that had zona which was lacking in oocytes could be the cause in some cases.^[14] (4) Strong attachment of cumulus cell complexes to the follicular wall. (5) Dysfunctional ovulation induction. (6) Rare cases, follicles may need longer exposure to hCG to undergo cumulus expansion and separate from the follicular wall.^[8,9] (7) Biological abnormality in the supply of mature oocytes.^[7] (8) Genetic factors (a) LH/hCG receptor mutations.^[15] (b) altered expression of genes regulating cumulus expansion. (c) Altered expression of genes involved in cellular processes and apoptosis resulting in increased apoptotic gene expression and reduction in transcripts with loss of oocytes during late folliculogenesis due to apoptosis. (d) Pericentric inversion of chromosome 2.^[15] (9) Advanced ovarian ageing^[4] through

altered folliculogenesis which is considered as a risk factor for EFS recurrence.^[10]

The various reasons for FEFS include: (1) Drug-related causes due to an abnormality in the *in-vivo* biological activity of some batches of commercially available urinary hCG preparations.^[8] (2) Human errors-inappropriate timing, administration, and dosage of hCG.^[7-9] (3) Low bioavailability resulting from variation in the absorption or clearance of hCG with some batches of urinary hCG.^[8,12] (4) Pharmacological problems.^[7] (5) Variation in the threshold for follicular response to hCG. (6) Variation in the time needed from hCG exposure to the maturation of oocyte-cumulus complexes. (7) Rapid breakdown of products that contained desialylated hCG by the liver, resulting in a lack of exposure to biologically active hCG.^[8] (8) As with any other metabolic process, individuals vary in their rate of clearance of hCG and some may metabolize hCG quite rapidly.

In assisted reproductive technology (ART) for decades, a bolus of hCG is commonly used as a surrogate of the mid-cycle LH surge as its actions are similar to those of endogenous LH. The LH surge initiates a cascade of events resulting in mucification of cumulus cells, facilitating the detachment of the oocyte-cumulus complex from the follicular wall, resumption of meiosis with extrusion of first polar body and subsequent ovulation.^[16] The threshold amplitude to define an LH surge is still a matter of debate, but levels more than 10 IU/L are commonly reported although a doubling from basal level could be a more appropriate definition, particularly for patients with high basal LH levels.^[12] The LH concentration must be maintained above a threshold for 14–27 h in order to maximize oocyte maturation with metaphase II oocytes obtainable within 28–38 h after the onset of the LH surge.^[12] Thus, it is easy to understand those cases of EFS that occur due to faulty techniques. In such cases, a repeat hCG from a different batch or the use of R-hCG with OR scheduled 24 h,^[4] 36 h^[9] later would yield mature oocytes from the intact ovary.^[4,10] Thus, it is important for the clinician to differentiate the two types of EFS and if FEFS has been identified, rescue protocol should be used to salvage the cycle. GEFS patients are unlikely to respond to a rescue protocol. FEFS should not recur, provided caution is taken to minimize its recurrence in the subsequent cycles.^[2]

Optimal serum concentrations of hCG to predict EFS and a successful yield of mature oocytes are still not unequivocally defined. Various authors have reported various levels of serum β -hCG as the threshold cut-off value on the day of OR; 106 mIU/ml,^[17] 40 mIU/ml,^[11] 100 mIU/ml,^[8] and 98–161 IU/l.^[18] A serum hCG levels <10 mIU/ml as reported

by Ndukwe *et al.* could predict EFS with a sensitivity and specificity of 100%.^[12] Driscoll *et al.* reported a median serum hCG concentration of 117.1 IU/l (range: 48–249) after R-hCG 250 µg and 83.6 IU/l (range: 32–99) with 5000 IU urinary hCG^[19] due to the immunoassays used to measure serum hCG. Urinary hCG may contain dissociated and oxidized subunits that would be detected by immunoassay but may have no biological activity. R-hCG, due to the absence of contaminant urinary proteins and the exacting standards applied during the production process, may make it possible to predict the risk of unsuccessful OR more accurately.^[19]

Various strategies suggested to prevent the occurrence of EFS in a subsequent ART cycle are: (1) Changing the batch of hCG.^[7,9,12] (2) Using R-hCG to trigger an endogenous LH surge. R-hCG with its high purity (≥99%) and consistency between batches, may be a better choice than urinary hCG, which contains miscellaneous urinary proteins and the biological activity of which may be affected by missing peptide bonds and alterations of the glycosylation profile.^[19] (3) shifting from an agonist to antagonist protocol.^[11] (4) Use of recombinant LH as trigger. (5) Using GnRHa as trigger in an antagonist cycle. (6) Prolonging the interval between ovulation trigger and OPU. Drosch *et al.* reported that retrieval of oocytes at 35–36 h is superior to retrieving at <24 h.^[20]

In our case report, the serum levels of hCG and progesterone were confirmatory of the correct timing, dose of R-hCG administered in both the IVF cycles. On the day of OR, the serum β-hCG in the first and second IVF cycles was 165 mIU/ml and 154 mIU/ml respectively. Since the threshold values of β-hCG on the day of OR were assuring and in concordance to the levels reported above by various authors, we did not find it necessary on a second occasion to administer GnRHa as trigger.

In both the IVF cycles, folliculometry showed good follicular development and normal steroidogenesis. On the day of trigger, the LH and P4 levels in the first and second cycles were 1.9 IU/l, P4=0.2 ng/ml and LH = 2.4 IU/l, P4 = 1.01 ng/ml, respectively. Also, sonography on the day of oocyte pickup documented intact follicles in both the cycles with assuring peak LH levels precluding premature LH surge and ovulation as a cause of EFS.

Our patient was 32 years old with primary infertility which seems to be a typical profile in these cases as described by Levran *et al.*^[21] Her ovarian reserve tests were within normal limits which refutes the hypothesis of ovarian aging as a potential cause of the condition. She was a case of unexplained infertility and in the original report by Coulam *et al.*, all patients were diagnosed as having unexplained infertility where the authors suggested that EFS itself might

be a cause of infertility.^[5] Though, later studies have shown that EFS could occur in different categories of infertility.^[10] Stevenson and Lashen have shown that about 41% of the GEFS couples had male factor infertility, indicating that most of the women who experienced EFS had no potential underlying pathology.^[11]

In patients with EFS, an altered steroid profile has been suggested to be a sign of dysfunctional ovulation induction.^[13] The follicular fluids in these patients showed high levels of estradiol (E2) and androstenedione with low progesterone levels. On the contrary, Zreik *et al.* reported low levels of estradiol concentrations due to hampered granulosa cell function and/or metabolism.^[11] In our case, the peak E2 and P4 concentrations in the first and second IVF cycles were: E2-2011 pg/ml; P4-0.2 ng/ml and E2-1856 pg/ml; and P4-1.01 ng/ml, respectively, with no demonstrable alterations as reported by few authors.

We concluded it as case of GEFS and the probable cause was within the cumulus-oocyte complex. Hence, it is possible to assume that a more physiologic induction of final follicular maturation with natural LH and FSH activity directly from the hypophysis and in terms of gonadotropin surge duration may optimize the signaling mechanisms from the surrounding cumulus and the oocyte, resulting in adequate OR and maturation.^[22] This can be achieved by the use of GnRHa as a trigger in GnRH antagonist cycles, the simultaneous induction of an FSH surge being an added advantage resembling a natural cycle. This FSH surge induces LH receptor formation in luteinizing granulosa cells, promotes oocyte nuclear maturation and cumulus expansion, opens the gap junctions between the oocyte and cumulus cells which are important in signaling pathways, allowing the oocyte-cumulus cell mass to detach from the follicular wall before ovulation. This might explain why some studies have reported retrieval of more mature oocytes after GnRHa trigger compared with hCG trigger. The FSH surge and the direct action of the agonist on the ovarian GnRH receptor might explain the favorable results in our patient.

We may assume that a GnRHa trigger alone in the third cycle may have resulted in adequate oocyte maturation and might have prevented EFS. We decided to give dual trigger so as to mimic the physiological FSH and LH surge and at the same time the addition of hCG would bring LH activity for luteal support to counteract the luteolytic effect seen after GnRHa trigger, “rescuing” the luteal phase insufficiency for a successful outcome.^[23]

In patients who experience an empty cycle, EFS should be considered as a borderline form of poor response to ovarian stimulation and could be a recurrent event. If EFS

has occurred once, the risk of recurrence is 20%.^[10] As age advances, the risk of recurrence increases and is about 24% in patients between 35 and 39 years of age whereas it is about 57% for those >40 years of age.^[10] In this subset of population, empty cycle could be a good predictor that a subsequent stimulated cycle will be an unfavorable one and such patients need to be counseled regarding the risk of recurrence and might benefit with oocyte donation.

The relatively small risk of GEFS and the even smaller risk of recurrence indicate that it is a chance occurrence and does not represent a permanent pathophysiological condition^[4] as is evident in our case.

It can also not be excluded that the 2 years, which passed between prior treatment failures and the successful treatment, could have influenced the outcome. Thus, EFS may be self-limiting phenomena with most cases occurring only sporadically.^[4] If EFS has been encountered in the previous cycles, different IVF treatment methods in the subsequent cycles like the use of dual trigger using GnRH α and hCG could modulate the response with successful oocyte recovery, pregnancy and term delivery, as proven in our case.

It is also the first case, whereby a combination of GnRH α and R-hCG was used as trigger for the treatment of GEFS, thereby adding a new management option in the armamentarium to this uncommon, yet distressing, and challenging condition.

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Conflicts of interest

There are no conflicts of interest.

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