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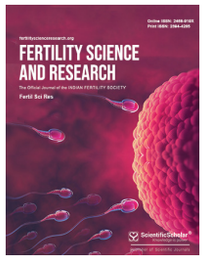

Original Article

Empty Follicle Syndrome in Poly Cystic Ovarian Syndrome Patients After GnRH Agonist Trigger at a Tertiary Level Infertility Centre: A Prospective Cohort Study

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ABSTRACT

Objectives: To analyse the incidence and underlying physiology of Empty Follicular Syndrome (EFS) following gonadotropin-releasing hormone (GnRH) agonist trigger in Polycystic Ovarian Syndrome (PCOS) patients at a tertiary-level infertility centre in India.

Material and Methods: A prospective cohort study was conducted amongst 225 PCOS patients diagnosed as per Rotterdam's criteria during the period between January 1, 2017, and December 31, 2019, at a tertiary care infertility centre in New Delhi, India. Controlled ovarian hyperstimulation (COH) using a fixed GnRH antagonist protocol was followed for all patients, concluding with a GnRH agonist trigger. In cases where no oocytes were obtained during ovum pick-up from the first ovary, serum progesterone (P4) levels were assessed to differentiate between genuine EFS (S. P4 >3.5 ng/ml) and false EFS (S. P4 <3.5 ng/ml). Rescue human chorionic gonadotropin (hCG) trigger was given in cases of false EFS and oocyte retrieval was planned 35 hours after the trigger. Segmentation of the cycle was done, and frozen embryo transfer was scheduled for a subsequent cycle.

Results: EFS following GnRH agonist trigger was seen in 3.11% (7/225) of PCOS patients undergoing in vitro fertilisation (IVF) at our centre. The age, body mass index, parity, and the type and duration of infertility were comparable between the EFS group and the non-EFS group. No significant differences were observed in serum follicle-stimulating hormone, anti-mullerian hormone, or antral follicle count between the two groups. However, patients in the EFS group needed significantly higher doses of gonadotropins (2500 ± 743 IU vs. 1850 ± 690 IU; p = 0.02) and experienced a longer stimulation period (11.6 ± 1.79 days vs. 9.5 ± 1.2 days; p = 0.001) compared to those in the Non-EFS group. Among the seven EFS cases, five cases (71.43%) were determined to be false EFS, while two cases (28.57%) were classified as genuine EFS with no identifiable aetiology. Of the five false EFS cases, four patients had successful egg retrieval following a rescue hCG trigger, and two of these patients (40%) achieved clinical pregnancy. In cases of genuine EFS, the subsequent cycle was managed using a GnRH antagonist protocol with a dual trigger. Egg retrieval was successful in one patient, while the other experienced a recurrence of genuine EFS.

Conclusion: Based on our experience at a specialised infertility care centre in India, EFS appears to be an uncommon event in PCOS patients undergoing IVF after a GnRH agonist trigger. False EFS may yield positive outcomes with the use of a rescue trigger, while genuine EFS is mostly associated with intrinsic ovarian dysfunction.

Keywords: Agonist trigger, Empty follicle syndrome, False EFS, Genuine EFS, PCOS

INTRODUCTION

Empty follicular syndrome (EFS) has been a topic of debate since its first description by Coulam *et al.* in 1986.[1] EFS is characterised by the inability to retrieve oocytes during ovum pick-up from mature ovarian follicles following controlled ovarian hyperstimulation (COH) in patients undergoing in vitro fertilisation (IVF). This occurs despite careful aspiration, repeated flushing, optimum follicular development, and normal oestradiol (E2) levels.[2] EFS is estimated to impact 0.045%–7% of patients undergoing IVF treatment.[3]

Though EFS is a rare entity, it remains a challenging complication in IVF, often leading to the cancellation of the IVF cycle and causing a significant amount of anxiety and stress for both patients and the treating fertility specialists.[4] For this reason, understanding EFS is crucial.

EFS is a retrospective diagnosis since it cannot be anticipated through ultrasound or blood hormone levels.[5] The gonadotropin-releasing hormone (GnRH) agonist trigger works by stimulating the pituitary to secrete gonadotropins, resulting in a Luteinising Hormone (LH) surge that lasts for 24–36 hours, resulting in luteinisation of granulosa cells and subsequent progesterone rise. This is in contrast to the human chorionic gonadotropin (hCG) trigger, which induces a surge lasting 8–9 days.[6]

In 2008, Stevenson and Lashen classified EFS into two types: "genuine" and "false," based on the β-human chorionic gonadotropin (β-hCG) levels observed on the day of ovum pick-up. Their review revealed that 33% of cases were genuine EFS, while 67% were categorised as false EFS. Genuine EFS was defined as the failure to retrieve oocytes despite normal follicular development and adequate steroidogenesis with optimal β-hCG levels. In contrast, "false EFS" referred to cases with low β-hCG levels leading to oocyte retrieval failure.[7]

False EFS is primarily caused by human errors related to timing, trigger administration, or issues with manufacturing or cold chain.[8] In the case of genuine EFS, factors such as receptor polymorphisms, the pituitary's failure to secrete gonadotropins, and dysfunctional folliculogenesis associated with Polycystic Ovarian Syndrome (PCOS) are thought to be involved.[9]

Hence, we conducted this study with the aim of analysing the occurrence and underlying physiological mechanisms of EFS following GnRH agonist triggers in PCOS patients undergoing IVF at a tertiary care infertility centre in India.

MATERIAL AND METHODS

A prospective cohort study was carried out at Akanksha IVF Centre, New Delhi, from January 1, 2017, to December 31, 2019, involving 225 patients with PCOS as diagnosed by the Rotterdam criteria. After obtaining ethical approval from the Institutional Review Board and written informed consent from the patients, individualised controlled ovarian hyperstimulation was carried out using a fixed GnRH antagonist protocol. Subcutaneous administration of recombinant follicle-stimulating hormone (FSH) (Injection Folisurge, Intas Pharmaceuticals Ltd., India) or human menopausal gonadotropin (Injection Menotas XP, Intas Pharmaceuticals Ltd., India) was initiated on day 2 of the menstrual cycle while closely monitoring follicular growth using transvaginal ultrasonography. A GnRH antagonist, Cetrorelix (Injection Cetrolix 0.25 mg, Intas Pharmaceuticals Ltd., India), was added on day 6 of ovarian stimulation, followed by a GnRH agonist trigger Injection Leuprolide (Injection Lupride 2 mg, Sun Pharmaceutical Ind. Ltd., India). In cases where no oocytes were obtained from the first ovary during oocyte retrieval, serum progesterone (P4) levels were measured to distinguish between genuine EFS (serum P4 >3.5 ng/ml) and false EFS (serum P4 <3.5 ng/ml). In false EFS cases, a rescue recombinant hCG trigger (Injection Ovitrelle 250 mcg, Merck Ltd., India) was administered subcutaneously, and oocyte retrieval was planned 35 hours later. A freeze-all approach was applied, with embryo transfer planned for a subsequent cycle.

Statistical Analysis

Statistical analysis was conducted using Statistical package for social sciences (SPSS) version 25.0. Continuous variables were reported as mean values with standard deviations, while categorical variables were presented as frequencies and percentages across the EFS and non-EFS groups. Differences in mean values were assessed using the t-test, and the chi-square test was applied for categorical data. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

The occurrence of EFS in PCOS patients after a GnRH agonist trigger was 3.11% (7 out of 225). Both groups, EFS and non-EFS, showed comparable characteristics in terms of age, body mass index, type of infertility and duration of infertility. Additionally, no significant differences were observed in FSH levels, anti-mullerian hormone levels or antral follicle count between the two groups. However, the EFS group required significantly higher gonadotropin doses (2500 ± 743 IU vs. 1850 ± 690 IU; p = 0.02) and a longer stimulation period (11.6 ± 1.79 days vs. 9.5 ± 1.2 days; p = 0.001) compared to the Non-EFS group [Table 1].

Of the seven EFS cases, five were identified as false EFS (71.43%) and two as genuine EFS (28.57%), where no

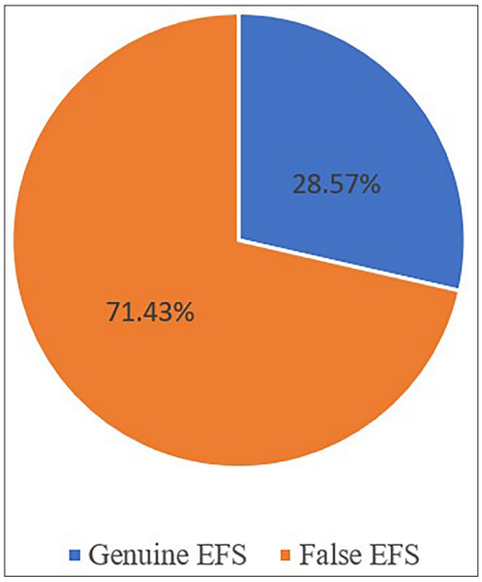

Figure 1: Distribution of study subjects according to the type of EFS (n = 7). EFS: Empty follicle syndrome.

Table 1: Distribution comparison of EFS and non-EFS patients by various study variables (n = 225).

	EFS (Mean ± SD) n = 7	NON-EFS (Mean ± SD) n = 218	p-value
Age (years)	31.02 ± 2.76	30.74 ± 3.22	0.82
BMI (kg/m^2)	23.70 ± 2.45	24.09 ± 2.78	0.54
Primary infertility	5 (71.4%)	167 (76.6%)	0.65
Secondary infertility	2 (28.5%)	51 (23.39%)	0.28
Duration of infertility (years)	6.4 ± 3.14	7.28 ± 3.55	0.90
AMH (ng/ml)	5.73 ± 2.40	6.64 ± 3.26	0.46
AFC	22.94 ± 7.15	24.46 ± 6.72	0.62
FSH (IU/l)	5.54 ± 2.76	5.20 ± 1.95	0.51
Total dose of gonadotropins (IU)	2500 ± 743	1850 ± 690	0.02
Duration of stimulation (number of days)	11.6 ± 1.79	9.5 ± 1.2	0.001

EFS: Empty follicle syndrome, SD: Standard deviation, BMI: Body mass index, AMH: Anti mullerian hormone, AFC: Antral follicle count, FSH: Follicle stimulating hormone.

specific cause could be determined [Figure 1]. Among the five false EFS cases, eggs were retrieved in four patients following a rescue hCG trigger, and two of these patients achieved a clinical pregnancy (40%). For the genuine EFS cases, a GnRH antagonist protocol with a dual trigger (Injection Leuprolide 2 mg + Injection hCG 2000 IU) was planned for the next cycle. Oocytes were successfully retrieved from one patient, while the second patient experienced a recurrence of genuine EFS.

DISCUSSION

Our study was conducted between January 1, 2017, and December 31, 2019, during which the original Rotterdam criteria were applied. The latest PCOS guideline (August 2023) has updated the diagnostic criteria to evidence-based criteria, allowing polycystic ovary morphology to be assessed using transvaginal ultrasound with a bandwidth of 8 MHz (≥20 follicles per ovary) or elevated anti-Müllerian hormone levels (>3.5 ng/ml). This has helped in preventing over-diagnosis and reducing the prevalence of PCOS in the general population from 9.8% (Rotterdam Criteria) to 6.3%.

EFS is a distressing and challenging condition for individuals undergoing IVF and poses a considerable challenge for infertility specialists. The estimated occurrence of EFS ranges from 0.045% to 7% of IVF cycles.[3] Among our study population, the incidence of EFS was 3.11%, which is marginally higher than the incidence reported by Deepika *et al.* (2.38%)[5] and Madani *et al.* (1.7%).[10]

The average age of the patients in our study population was 31.02 ± 2.76 years in the EFS group and 30.74 ± 3.22 years in the non-EFS group. Most prior studies, such as those conducted by Zreik *et al.*[2] and Revelli *et al.*,[11] have identified advanced age as a risk factor for EFS; however, this was not observed in our study population.

Stevenson *et al.*[7] and Revelli *et al.*[11] classified EFS into "genuine" and "false" types according to β-hCG levels measured on the day of ovum pick-up. In genuine EFS, no oocytes are obtained even with sufficient hCG levels. Conversely, it is considered false EFS when oocytes are not retrieved and the hCG level is below 40 IU/l on the day of ovum pickup. In our study, a GnRH agonist was utilised to induce final oocyte maturation to reduce the risk of ovarian hyperstimulation syndrome in PCOS patients. GnRH agonist trigger leads to an endogenous LH surge lasting for 24–36 hours, resulting in luteinisation of granulosa cells and progesterone rise. Serum P4 levels were assessed to differentiate genuine EFS (serum P4 >3.5 ng/ml) from false EFS (serum P4 <3.5 ng/ml). In instances of false EFS, which is caused due to human error in timing, administration of trigger or manufacturing and cold chain problems, the trigger may fail to induce an LH surge, leading to incomplete luteinisation of granulosa cells, resulting in low serum progesterone levels. This post-trigger serum progesterone level of 3.5 ng/ml aligns with the study published by Deepika *et al.* in 2015.[5]

Research on the incidence and underlying mechanisms of EFS in PCOS patients undergoing IVF with a GnRH agonist trigger is limited. Hence, we conducted this study to evaluate this outcome.

The incidence of genuine EFS amongst our study population was 28.57%, similar to the review done by Stevenson *et al.* (33%).[7] The etiopathology of genuine EFS is not well understood but can be attributed to dysfunctional folliculogenesis commonly seen in PCOS patients. Failure of the pituitary gland to secrete gonadotropins and receptor polymorphism are other causes of genuine EFS.[12] Yuan *et al.* conducted a study identifying a homozygous mutation in the luteinizing hormone/choriogonadotropin receptor gene, c.1345G>A (p.Ala449Thr), as a contributing factor to genuine EFS.[13] GnRH receptor mutations can also lead to genuine EFS.[14]

Contrarily, in false EFS, the issue arises mainly due to procedural or technical errors. Common causes include improper timing of the trigger, incorrect administration of the trigger, or issues with the follicular aspiration technique. Management involves confirming the administration and timing of the hCG trigger, optimising aspiration techniques, and finally, giving a rescue hCG trigger followed by a second ovum pick-up 35 hours later.[8]

Among the five cases of false EFS in our study, eggs were successfully retrieved in four patients after a rescue recombinant hCG trigger, resulting in two patients achieving a clinical pregnancy (40%). In genuine EFS cases, a GnRH antagonist protocol with a dual trigger was implemented for the following cycle. Although oocytes were successfully retrieved from one patient of genuine EFS, recurrence occurred in the other case.

As noted in a study by Baum *et al.*, recurrence occurs in approximately 15% of cases.[15] However, accurately determining this percentage is challenging due to the limited number of studies available. Since only a small number of patients underwent repeat IVF cycles, concluding the recurrence rate of EFS is challenging. Despite being a prospective study, a small sample size is a notable limitation of this study.

CONCLUSION

From our experience at a tertiary infertility centre in India, EFS seems to be an uncommon occurrence in PCOS patients following a GnRH agonist trigger. False EFS may lead to positive outcomes with the use of a rescue trigger, while genuine EFS is likely linked to inherent ovarian dysfunction. Accurate diagnosis and differentiation between true and false EFS are crucial for tailoring appropriate interventions and optimising reproductive outcomes. Regardless of the underlying cause of EFS, it is important to counsel these patients about the potential for recurrence and the likelihood of a poor prognosis in the future.

Author contribution

KDN, SS, SG: Concept; KDN, SG, RB: Design; SS, SG: Definition of intellectual content; SG, MS: Literature search; RB, GK, DN: Data acquisition & analysis; KDN, SG: Manuscript preparation; KDN, MS: Manuscript editing and review.

Ethical approval: The research/study was approved by the Institutional Review Board at Mata Chanan Devi Hospital, C-1, Janak Puri, New Delhi, number MCDH/2016/30, dated 30th December 2016.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

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