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Empty Follicle Syndrome: The Possible Cause of Occurrence

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ABSTRACT

Objectives: Empty follicle syndrome (EFS), although rare, is a disappointing condition in which no oocytes are retrieved from mature follicle after ovulation induction in in vitro fertilization (IVF) cycles. The aim of this study was to estimate the incidence and factors associated with EFS. ***Methods:*** All cycles resulting in EFS from May 2012 to September 2013 were retrospectively identified at a tertiary referral infertility center. Among the 3,356 cycles performed, 58 (1.7%) women who underwent their first IVF cycle and had no oocyte retrieval were enrolled in the study. Three different stimulation protocols (long, antagonist, and miniflare) were mainly used for induction of follicular growth. Data relating to the age, follicle stimulating hormone (FSH) level, anti-Müllerain hormone (AMH) level, and the number of ampules and follicles for each patient was obtained. ***Results:*** Out of 58 individuals, 10 (17.2%) showed false type and 48 (82.8%) showed genuine EFS. The most frequent findings in our study were diminished ovarian reserve, low anti-Müllerian hormone (AMH; ≤0.5 ng/mL), and less than four mature follicles, indicating EFS in 1.7% of the patients. ***Conclusion:*** Low serum AMH levels and a small number of follicles after ovarian stimulation is the manifestation of diminished ovarian reserve. Thus, we suggest that EFS could be a manifestation of low ovarian reserve.

Empty follicle syndrome (EFS) is a condition in which no oocytes are retrieved from the mature follicle after ovulation induction in in vitro fertilization (IVF) cycles. This syndrome was first reported by Coulem et al,[1,2] in 1986. However, the belief that the follicles are empty is under debate.[3] The incidence of this syndrome has been estimated at 0.6–7.0%.[4-7] Stevenson and Lashen described two types of EFS in 2008.[8] Their description was based on the beta-human chorionic gonadotropin (βhCG) level at the time of oocyte retrieval. The authors explained that one type of EFS showed βhCG levels below optimal, identified as false EFS, whereas the other type showed optimal βhCG levels, identified as genuine EFS. The level defined as optimal was βhCG ≥40 mIU/mL on the day of follicular puncture. The mechanism responsible for this syndrome remains obscure.[9,10] However, some believe that early oocyte atresia due to dysfunctional folliculogenesis is one cause of this syndrome.[11] Others believe a longer exposure to human chorionic gonadotropin (hCG) is necessary for detachment of oocyte-cumulus complexes from the follicular wall.[12] Another belief is about ovarian aging in older women presenting with varying growth and function of granulosa, which results in altered oocyte growth and disorder of generation and maturation of follicle.[13] Genetic factors, low bioavailability of hCG,[14-17] a decrease in estradiol (E2) levels before the hCG injection,[3,18] rapid metabolic clearance, intrinsic problems of the drug, and human error[19] are other causes of empty follicle cycles in which no oocytes are retrieved. This leads to psychological and physical trauma for the patients. The aim of this study was to estimate the incidence of EFS and clarify the associated factors.

METHODS

A retrospective analysis of EFS was performed at the Royan Institute, Tehran, Iran, between May 2012 and September 2013. All first IVF cycles resulting in EFS during the study period were included. The study was approved by the Ethics Committee of the Royan Institute. Written informed consent was taken from each patient to use the data for future scientific research.

Three different stimulation protocols were mainly used for induction of follicular growth. These were long, antagonist, and miniflare protocols. In

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the long protocol, the ovary was suppressed with gonadotrophin-releasing hormone analog (GnRH-a) Buserelin (CinnaFact, Laboratory, Cinnagen, Iran) therapy, starting from the mid-luteal phase of the previous menstrual cycles. It was followed by stimulation of the ovary using recombinant follicle-stimulating hormone (rFSH) (Gonal-F; Merk-Sereno, Geneva, Switzerland) or human menopausal gonadotrophin (Menopur; Ferring Pharmaceuticals, Germany), and the follicular growth was monitored by using a transvaginal sonography with an SSD-1000 machine (Aloka, Tokyo, Japan). When the size of the follicle reached 18 mm, recombinant hCG (rhCG) (Ovitrelle; Merck-Serono, Geneva, Switzerland), 250 µg was administered, and follicular puncture was performed after 34–36 hours. In the antagonist protocol, on the second day of the menstrual cycle, two ampules of rFSH or Menopur 150 IU, depending on patient's response, were administered and follicular growth was monitored using transvaginal sonography. Antagonist Cetrorelix (Merk-Sereno, Geneva, Switzerland) 0.25 mg/day was administered when the follicular size was 12 mm. After the follicular size had reached 18 mm, rhCG 250 µg was administered, and follicular puncture was performed after 34–36 hours. In the miniflare protocol, on the second day of menstrual cycle the patient received 0.8 µg Buserelin. On the following day, gonadotropins Gonal-F or Menopur was started. The follicular growth was monitored using transvaginal sonography. When the size of the follicle reached 18mm, rhCG, 250 µg was administered, and follicular puncture was performed 34–36 hours later.

In 3,356 cycles with a follicular puncture, no oocytes were recovered from 58 patients even after extensive flushing. The serum βhCG level of these patients were measured on the day of follicular aspiration. The data, including age, follicle stimulating hormone (FSH) level, anti-Müllerain hormone (AMH) level, the number of ampules, and follicles, and βhCG level at the time of puncture were collected from patients' medical records and analyzed using SPSS Statistics (SPSS Inc., Chicago, US) version 18.0. Appropriate statistical analysis was made by using chi-square or Fisher's exact tests for categorical variables and one-way analysis of variance (ANOVA) for continuous factors. A *p*-value less than 0.050 was considered statistically significant.

RESULTS

Among the 3,356 cycles performed, 58 (1.7%) women who underwent their first IVF cycle and had no oocyte retrieval were enrolled in the study. Their βhCG level was measured on the puncture day. Ten (17.2%) women showed false type and 48 (82.8%) women showed genuine EFS (βhCG level ≥40 mIU/ml).

The age of the patients ranged from 21 to 43 years, and their body mass index (BMI) ranged from 22 to 28 kg/m^2. Indications of infertility treatment were diminished ovarian reserve 37.9% (n=22), male infertility factor 31.3% (n=18), ovulatory dysfunction 12.0% (n=7), unexplained 8.6% (n=5), endometriosis 5.1% (n=3), and tubal and uterine factors 5.1% (n=3).

The variation of protocols in these patients were approximately the same. According to our analysis, the standard long protocol was applied for 32.7% (n=19) of women, the antagonist for 32.7% (n=19) of women, and the miniflare for 34.5% (n=20) of women.

Patients' characteristics and their clinical information were compared according to the stimulation protocols applied [Table 1 and 2]. Most patients were below the age of 40 years (65.5%). Cycles of empty follicles were observed more in patients with baseline FSH levels below 12 mIU/mL (74.1%), AMH levels below 1 ng/mL (79.3%)

Table 1: Comparison of the patients' characteristics according to the stimulation protocols applied.

Variable	Long (n=19)	Antagonist (n=19)	Miniflare (n=20)	Total (n=58)	*p*-value
Age (years)*					
<40	78.9 (15)	57.9 (11)	60.0 (12)	65.5 (38)	0.321
≥40	21.1 (4)	42.1 (8)	40.0 (8)	34.5 (20)	
BMI (kg/m^2)**	24.5±1.1	26.0±2.6	27.6±5.6	26.2±3.8	0.322
Infertility duration**	7.7±2.3	8.6±5.9	7.6±6.2	7.9±5.3	0.879

Data presented as percentage (n number).
**Data presented as mean±SD.*

Table 2: Comparison of the patients' clinical information according to the stimulation protocols applied.

Variable	Long (n=19)	Antagonist (n=19)	Miniflare (n=20)	Total (n=58)	*p*-value
FSH level (IU/mL)					
<12	94.7 (18)	63.2 (12)	65.0 (13)	74.1 (43)	0.043
≥12	5.3 (1)	36.8 (7)	35.0 (7)	25.9 (15)	
AMH level (ng/mL)					
≤0.5	26.3 (5)	47.4 (9)	80.0 (16)	51.7 (30)	0.018
0.6–1	42.1 (8)	26.3 (5)	15.0 (3)	27.6 (16)	
>1	31.6 (6)	26.3 (5)	5.0 (1)	20.7 (12)	
Ampules					
<44	57.9 (11)	73.7 (14)	65.0 (13)	65.5 (38)	0.591
≥44	42.1 (8)	26.3 (5)	35.0 (7)	34.5 (20)	
Follicles					
<4	31.6 (6)	84.2 (16)	90.0 (18)	69.0 (40)	<0.0001
≥4	68.4 (13)	15.8 (3)	10.0 (2)	31.0 (18)	

FSH: follicle stimulating hormone; AMH: anti-Müllerian hormone.
Data presented as percentage (n number).

and who had less than four follicles (69.0%). As seen in Table 3, the empty follicle rate was significantly higher in women who received the miniflare protocol than when they received the antagonist or the standard long protocols.

DISCUSSION

EFS is an infrequent event in assisted reproductive technique (ART) cycles, but the economic consequences and emotional frustration of the syndrome are enormous.[20] The incidence of EFS has been estimated at 0.6–7.0% of ART cycles.[5,6,18] This variation may be due to different inclusion criteria. In some studies, poor responders or patients with premature ovulation were enrolled while in others they were not.[3] In our study, the occurrence of EFS was 1.7%, which was similar to another study that recorded 8,292 IVF cycles[18] and a study by Zreik et al.[20]

The high percentage of empty follicles in the miniflare protocol (12.1%) may depend on ovarian reserve and protocol itself. Our data showed that the incidence of diminished ovarian reserve was more than other causes of infertility (37.9%). The applied stimulation protocol for this type of infertility was either miniflare or antagonist, and our findings revealed that the incidence of empty follicle was more in the miniflare protocol compared to the antagonist protocol. Therefore, the type of protocol may have a role in the occurrence of this syndrome. However, based on the fact that the clinician chooses the stimulation protocols based on age, AMH levels, the number of antral follicles etc, of the patient,[21] it may be more reasonable to conclude that this syndrome could be a manifestation of low ovarian reserve than the GnRH agonist flare protocol. This finding is close to the estimate of some investigators,[3,18,20,22] suggesting that genuine EFS could be a variant form of low ovarian reserve. According to the study by Zreik et al,[20] poor ovarian response was found in 29% of the stimulated cycles. Various authors argue that the EFS phenomenon could be clarified by premature ovulation, low ovarian reserve, or hCG-related errors.[2,13] In diminished ovarian reserve, our data indicated that not only the number of antral follicles decreased, but also that the quality of folliculogenesis was impaired. Therefore, the selection of a stimulation protocol for better oocyte recovery is suggested. This finding is similar to the report by Bustillo,[23] in which he pointed out that the syndrome might be related to underlying ovarian dysfunction resulting in impaired follicular maturation and ovulation. In a study conducted by Zreik,[20] he also maintained ovarian aging, through altered folliculogenesis may be involved in the etiology of this syndrome and its recurrence. Another study indicated the syndrome was related to the underlying cause of the women's unexplained infertility,[1] but our findings showed

Table 3: Comparison of empty follicle rate according to stimulation protocols applied.

Protocol	Empty follicle rate	*p*-value
Long	0.7 (19/2677)	
Antagonist	3.7 (19/514)	
Miniflare	12.1 (20/165)	<0.0001

Data presented as percentage (n number).

that only 8.6% of patients with empty follicle had unexplained infertility. Our results also showed that 51.7% of women had AMH levels ≤0.5 ng/mL, whereas 25.9% of women had FSH levels ≥12 IU/mL. This finding may imply the stronger role of AMH than FSH in EFS.

In line with these results, there are still some questions about the existence of genuine EFS. Strong evidence suggests that genuine EFS does exist and it is likely a cause of infertility, including microscopic evidence of genuine EFS with a case of borderline EFS, very few mature or immature oocytes obtained from several mature follicles, and the presence of the genetic basis for EFS.[3,24] On the other hand, other authors denied the existence of genuine EFS because of successful treatment in a recurrent EFS case[25] and by giving reasons that EFS is just a matter of mathematical coincidence.[3,26,27] In aggregate, this study shows that EFS is a misleading term and that its occurrence is associated with either hCG-related errors or low ovarian reserve.

CONCLUSION

Low serum AMH levels and a small number of follicles after ovarian stimulation is the manifestation of diminished ovarian reserve. Thus, we suggest that EFS could be a manifestation of low ovarian reserve.

Disclosure

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