

A case of empty follicle syndrome who conceived after aspiration of an endometrial cyst

Rieko Tanaka · Mariko Murase · Yoshino Aizawa · Miwa Segino · Yumi Ishidera · Masakazu Kitagawa · Kayo Katayama · Kunitomo Takashima · Yasushi Yumura · Hiroshi Yoshida · Hideya Sakakibara · Fumiki Hirahara

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Abstract Empty follicle syndrome (EFS) has been defined as a condition where no oocytes can be retrieved for in vitro fertilization (IVF) even though ultrasound findings and estradiol (E_2) levels suggest the presence of potential follicles. The EFS is a rare condition with an incidence of 0.5–7 % of women undergoing IVF treatments. Although there are many hypotheses as to the cause of EFS, including advanced ovarian age, drug-related problems, and dysfunctional folliculogenesis, its cause remains unknown. A 37-year-old woman with endometriosis and a 5-year history of primary infertility underwent IVF treatment for 4 cycles. No oocytes were retrieved in 2 cycles and no fertilized eggs were obtained in the other 2 cycles. We assumed that endometriosis adversely affected folliculogenesis and fertilization. Aspiration of an endometrial cyst in the right ovary and subsequent administration of oral contraceptives resulted in successful folliculogenesis and fertilization. Thereafter, she conceived and delivered a 2,662 g female infant at 38 weeks of gestation. Here, we report a case of EFS who conceived in the 5th IVF cycle after aspiration of an endometrial cyst. We assumed that

endometriosis might have been involved in the dysfunction of folliculogenesis and EFS.

Keywords Dysfunction of folliculogenesis · Empty follicle syndrome · Endometriosis · IVF–ET · Oocyte–cumulus complex

Introduction

Empty follicle syndrome (EFS) has been defined as a condition where no oocytes are retrieved from mature ovarian follicles after induction of ovulation for in vitro fertilization (IVF), even though ultrasound findings and estradiol (E_2) levels suggest the presence of many potential follicles [1]. Although EFS is a rare condition, with an incidence of 0.5–7 % of women undergoing IVF treatments [2–4], it is a frustrating condition for both patients and medical staff.

There are many hypotheses regarding the cause of EFS, such as advanced ovarian age [4, 5], drug-related problems [6], inheritance [7–9], and dysfunctional folliculogenesis [1, 4, 10, 11]. Some of these focus on folliculogenesis, and altered folliculogenesis is likely to be involved in the etiology of EFS [12]. Early oocyte atresia or strong attachment of the oocyte–cumulus complex (OCC) to the follicle wall was also suggested [13]. Zreik et al. [4] suggested that hampered granulosa cell function and/or metabolism reflect altered oocyte growth and maturation and consequent EFS. It is also known that endometriosis affects folliculogenesis, fertilization, and embryo development [14].

Here, we present a case of EFS who conceived by IVF after aspiration of an endometrial cyst. We suggest that endometriosis may be involved as a cause of dysfunction of folliculogenesis and EFS.

R. Tanaka · M. Murase · Y. Aizawa · M. Segino · Y. Ishidera · M. Kitagawa · K. Katayama · K. Takashima · H. Yoshida
Department of Obstetrics and Gynecology, Yokohama City University Medical Center, 4-57 Urafunecho, Minami Ward, Yokohama, Kanagawa 232-0024, Japan

Y. Yumura
Department of Urology, Yokohama City University Medical Center, 4-57 Urafunecho, Minami Ward, Yokohama, Kanagawa 232-0024, Japan

H. Sakakibara (✉) · F. Hirahara
Department of Obstetrics and Gynecology, Yokohama City University, 3-9 Fukuura, Kanazawa Ward, Yokohama, Kanagawa 236-0004, Japan
e-mail: sakakih@yokohama-cu.ac.jp

Case report

The patient was a 37-year-old woman who had a 5-year history of primary infertility. We found that she had an endometrial cyst 8 cm in diameter in her right ovary and occult hyperprolactinemia. She underwent laparoscopic cystectomy and synechiotomy. More than two-thirds of the right ovarian cyst adhered strongly to the surrounding tissue, the Douglas' pouch was completely closed, and occlusion of the right fallopian tube was confirmed by hydrotubation. Her revised American Society for Reproductive Medicine score decreased from 42 pre-surgery to 6 post-surgery.

After post-operative fertility treatment that included 7 episodes of timed intercourse and 4 cycles of intrauterine insemination had failed, IVF was initiated. For the 1st IVF cycle, we chose a long down-regulation protocol. Three oocytes were retrieved 36 h after intramuscular injection of 10,000 units of human chorionic gonadotropin (hCG). Although all oocytes were mature and the sperm condition was suitable for fertilization, none of the oocytes was fertilized and one had malformation of the zona pellucida.

For the 2nd IVF cycle, we chose a short down-regulation protocol, but there were no oocytes in the 7 aspirated follicles although the serum hCG level was 106 mIU/mL. In the 3rd IVF cycle, we used a short down-regulation protocol again, and 3 oocytes were retrieved. Intracytoplasmic sperm injection was performed for two mature oocytes, but neither oocyte was fertilized. For the 4th IVF cycle, controlled ovarian stimulation was altered by clomiphene. No oocytes were retrieved from 2 follicles.

At that point, the right endometrial cyst was growing. We decided to treat the endometriosis before the 5th IVF cycle because we felt that the endometriosis was adversely affecting folliculogenesis and fertilization. So that we could retrieve oocytes that were not affected by endometriosis during their growth process, the endometrial cyst was aspirated and an oral contraceptive (norethisterone/ethinylestradiol) was administered. It is known that early-stage follicular growth is not dependent on gonadotropin [15]. Following the 2-month period of oral contraception, we used a short down-regulation IVF protocol that resulted in retrieval of 3 oocytes, all of which were fertilized. An embryo was transferred and the patient conceived (Table 1). Her prenatal course was uneventful, and at 38 weeks of pregnancy, she gave birth by cesarean section due to a breech presentation to a girl that weighed 2,662 g.

Discussion

The EFS has been defined as a condition where no oocytes are retrieved from mature ovarian follicles after induction

Table 1 Profile of induction of ovulation in a pregnant patient with empty follicle syndrome

No. IVF procedures	No. of aspirated follicles	Stimulation	Hormone levels						No. of retrieved oocytes	Maturity		Fertilization	
			3rd day of retrieval cycle			Day of hCG injection				No. MA	No. IM		
			E2 (pg/mL)	FSH (mIU/mL)	LH (mIU/mL)	E2 (pg/mL)	P4 (pg/mL)	FSH (mIU/mL)					LH (mIU/mL)
1	5	Long	2,100	17.1	2.3	1.1	1,128	0.3	8.7	2.4	3	0	0
2	7	Short	1,725	42.1	9.2	4.5	1,980	0.5	6.7	6.2	–	–	–
3	4	Short	1,725	22.4	11.7	4.2	1,587	0.5	7.6	5.9	2	1	0
4	2	Clomiphene	–	28.8	6.9	5.1	532	0.2	4.1	8.5	–	–	–
5	3	Short	2,175	<5	9.9	4.5	750.7	0.2	7.0	3.7	3	0	3

MA mature eggs, IM immature eggs, hMG human menopausal gonadotropin, hCG human chorionic gonadotropin, E2 estradiol, FSH follicle-stimulating hormone, LH luteinizing hormone, P4 progesterone

of ovulation for IVF, even though ultrasound findings and E₂ levels suggest the presence of many potential follicles [1]. This syndrome was first reported by Coulam et al. [16]. It is said that it is not, strictly speaking, a syndrome but a sporadic unpredictable event [1]. Since factors surrounding it remain obscure, there are no standard criteria for its diagnosis [5]. Its incidence has been estimated at 0.5–7 % of women undergoing IVF [2–4].

Zreik et al. [4] retrospectively extracted cycles as EFS meeting the following conditions: using standard IVF protocols, stimulation with gonadotropins undergoing until E₂ ≥500 pg/ml and at least 2 follicles ≥18 mm, and failed oocyte retrieval. Coskun et al. [5] defined EFS as no oocytes retrieved during follicular aspiration despite performing multiple flushes of the follicles on good responder patients undergoing IVF ovarian stimulation, with at least 5 mature follicles (≥15 mm) seen in the ultrasound scan on the day of hCG. There were various definitions of EFS by researchers. Stevenson et al. reported that approximately 70 % of reported EFS cases occurred as a result of human error, such as with drug dosages, and that “genuine empty follicle syndrome (GEFS)” is an even more rare event than previously presumed [1, 2]. On the other hand, van Heusden et al. [11] suggested that the meta-analysis clearly showed a lack of basic evidence for the existence of GEFS.

Baum et al. [9] proposed the hypothesis that EFS was associated with aging, prolonged infertility, lower estrogen levels, and higher gonadotropin levels. Stevenson et al., suggested that 41 % of GEFS couples had male factor infertility, and that there was no underlying pathology in most women who experienced EFS. Coskun et al. [2] and Stevenson et al. [5] suggested that the average age of reported GEFS patients was 33 years and that most patients with this condition had normal ovarian reserve, refuting the hypothesis of ovarian age as a potential cause of EFS.

We investigated all cases of oocyte retrieval by IVF cycles in our institution from January 2005 to December 2010. We extracted those cases with cycles fulfilling the following conditions: (1) use of a standard down-regulation protocol, (2) follicle size ≥18 mm, follicle count ≥4 and estradiol level ≥1,200 pg/mL at the time of hCG injection, and (3) failure in oocyte retrieval. Four EF cycles (4 patients) were identified from a total number of 574 cycles (283 patients). The average age of those 4 EF patients was 38.5 years, which was older than the total population evaluated (mean age: 36.0 years), and the most frequent indication for IVF in these 4 women was endometriosis (Table 2). These 4 patients underwent a total of 13 cycles of oocyte retrieval procedures. However, there were no recurrent cycles.

Baum et al. [9] noted that EFS might recur in about 16 % of patients and these patients might have a variant form of poor response in comparison with those having sporadic EFS. Zreik et al. [4] suggested that the rate of recurrence of EFS increased with patients’ age (24 % in those 35–39 years of age; 57 % in those over 40 years of age), and that ovarian aging might be implicated in the etiology of EFS and its recurrence. Smisha et al. [17] mentioned that EFS did not represent a permanent pathophysiological condition because of its sporadic occurrence, and that it should be investigated whether there is some intrinsic ovarian pathology causing defective follicular development or a possible genetic cause to elucidate the occurrence of GEFS. There were 9 non-EF cycles among our 4 patients with EFS. No significant differences were found between hormonal levels in EF and non-EF cycles on the 3rd day of the preceding cycle and on the day of hCG injection and in the amount of injected human menopausal gonadotropin (hMG) (Table 3). Therefore, it is difficult to predict an EFS cycle according to hormonal levels or amount of hMG administered.

Table 2 Profile of 4 cases of empty follicle syndrome in our institution

Case no.	No. aspirated follicles	Age (years)	Gravida para	Infertility period (years)	Indication for IVF	Down-regulation protocol	Hormone levels				
							3rd day of retrieval cycle			Day of hCG injection	
							E2 (pg/mL)	FSH (mIU/mL)	LH (mIU/mL)	E2 (pg/mL)	P4 (pg/mL)
1	6	37	0G0P	8	Endometriosis Tubal factor	Short	–	–	–	1,980	0.5
2	5	38	0G0P	11	Unexplained Tubal factor	Antagonist	50.2	8.1	6.7	2,175	0.7
3	5	41	2G0P	5	Endometriosis	Long	41.9	8.7	7.5	2,135	0.8
4	5	38	0G0P	9	Endometriosis	Long	33.9	6.6	2	–	–
Average	5	38.5	–	–	–	–	42	7.8	5.4	2,097	0.67

E2 estradiol, FSH follicle-stimulating hormone, LH luteinizing hormone, P4 progesterone

Table 3 Comparison of hormone levels, and amount and duration of hMG injection between empty follicle and non-empty (retrievable) cycles in 4 cases of empty follicle syndrome

	Empty follicle cycles ($n = 4$)	Non-empty follicle cycles ($n = 9$)	<i>P</i>
No. follicles	5.25	4.44	0.304
Third day of retrieval cycle			
E2 (pg/mL)	44.10	63.11	0.807
FSH (pg/mL)	8.37	7.90	0.833
LH (pg/mL)	4.63	3.66	0.441
Day of hCG injection			
P4 (pg/mL)	0.67	0.48	0.087
E2 (pg/mL)	2,096	1,407	0.063
E2/follicle (pg/mL \times follicle)	399.36	316.41	0.461
hMG			
Amount of injection (IU)	2,400	2,122.5	0.404
Duration (days)	10.25	10.44	0.833

E2 estradiol, FSH follicle-stimulating hormone, hCG human chorionic gonadotropin, hMG human menopausal gonadotropin, LH luteinizing hormone, P4 progesterone

Table 4 Comparison of IVF outcomes in patients with retrievable oocyte cycles who did and did not have empty follicle syndrome (EFS)

	Retrievable oocyte cycles in EFS patients ($n = 9$)	Retrievable oocyte cycles in Non-EFS patients ($n = 561$)	<i>P</i>
Average no. oocytes retrieved	4.11	8.47	0.0070
Immature eggs rate (IM/no. oocytes retrieved)	43.78 %	18.11 %	0.0007
Fertilization rate per cycle	56.88 %	77.20 %	0.0099
ET cancellation rate per cycle	33.00 %	5.10 %	–
Frozen embryo rate per cycle	0.00 %	11.60 %	–
Pregnancy rate per cycle	0.00 %	20.74 %	–

IM immature eggs, ET embryo transfer

Table 4 shows a comparison of the outcome in retrievable cycles of IVF between patients with and without EFS. In the EFS patients versus the non-EFS patients, average number of retrieved eggs was 4.11 versus 8.47, the fertilization rate was 56.9 versus 77.2 %, and the rate of embryo transfer cancellations per cycle was 33.0 versus 5.10 %, respectively. As for our 4 patients with EFS, the fertility and normal embryogenesis rates were low, and there was no pregnancy. There were no recurrent cases, even when the same protocols were used, which is understandable because of the rarity of EFS in IVF [1]. However, there were significant differences between our 4 patients with EFS and the 279 non-EFS patients in the rate of immature eggs, fertilization, canceled embryo transfer, pregnancy, and denaturation of ova. Since 3 of our 4 patients with EFS had endometriosis, we suggest that a cause of EFS may be dysfunctional folliculogenesis affected by endometriosis.

It has been proposed that endometriosis may prevent maturation of eggs and folliculogenesis because expression

levels of estrogen receptor β was low in those with endometriosis; in contrast, levels of estrogen receptor α and progesterone receptor were high in the luteinized granulosa cells in patients with endometriosis [18]. Kuroda et al. [19] suggested that patients with endometrial cysts had significantly higher rates of oocyte retrieval failure and significantly fewer oocytes retrieved than those without endometrial cysts. In addition, they found that the rate of confirmed fetal heartbeat was low, although there was no difference in the clinical pregnancy rate [19]. Lin et al. reported that the clinical pregnancy rate in an endometriosis group was significantly lower than in the control group. Also, they found that the numbers of oocytes retrieved, fertilized oocytes, cleaved embryos, and high-quality embryos per cycle as well as the fertilization rate in the endometriosis group were markedly lower than in the control group. However, the cleavage rate, high-quality embryo rate, and implantation embryo/high-quality embryo ratio were similar in both groups [20].

Ovarian surface epithelium structural changes and deterioration of the ovarian environment are caused by endometrial cyst formation. Therefore, it has been suggested that endometrial cysts were related to decreasing numbers of primordial follicles and the quality of oocytes [18]. Follicular growth and rupture lead to OCC detachment from granulosa cells and connective tissue of the follicle. Since oocyte retrieval is performed just before follicular rupture, either early oocyte atresia or strong attachment of the OCC to the follicle wall was previously suggested as possible. The mechanism whereby the OCC has difficulty in detaching from the follicle wall is due to changes in the structure and environment of the ovary related to endometriosis [2, 4, 12]. Since we could impregnate patients by treating endometriosis prior to IVF, we suggest that in these cases EFS is related to dysfunction of folliculogenesis due to endometriosis. On the other hand, Tocci et al. [21] suggested that removal of endometrial cysts might not be beneficial to controlled ovarian hyperstimulation.

In conclusion, although EFS is rare in IVF and its cause remains unclear, we suggest that endometriosis might be involved as a cause of EFS, and that treatment of endometriosis could improve outcome in IVF. We propose that continued identification and investigation of EFS are needed and can lead to an understanding of this syndrome.

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