Empty Follicle or Not? A Case Report

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Empty follicle syndrome is characterized by retrieving no oocytes in despite of achieving multiple follicle development in an IVF cycle. We report a case having a presumed empty follicle syndrome at 36th hour of human chorionic gonadotrophin (βhcg) administration and rescued by a second oocyte pick-up procedure performed at 42nd hour, without the need of a second dose of the drug. Intrauterine transfer of three good quality embryos resulted in a singleton pregnancy which ended with a healthy girl.

Key Words: Empty follicle syndrome, Oocyte retrieval, Human chorionic gonadotrophin, BMI

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Introduction

Empty follicle syndrome (EFS) is one of the controversial situations of in vitro fertilization and there is still no absolute explanation about its reasons. It is first described by Coulam et al. in 1986 and defined as retrieving no oocytes after aspiration and repeated flushing of multiple follicles at controlled ovarian stimulation cycles. Two types of EFS are mentioned in the literature; classified as 'genuine' (GEFS) and 'false' (FEFS) empty follicle syndrome. GEFS could be defined as failure to retrieve oocytes from mature ovarian follicles after ovulation induction for IVF after normal follicular development and steroidogenesis in the presence of optimal βhCG levels; whereas FEFS could be defined as failure to retrieve oocytes in the presence of low βhCG levels due to an error in the administration or the bioavailability of βhCG on the day of oocyte retrieval. GEFS patients are unlikely to respond to a rescue protocol and mostly undergo cancellation. However; FEFS patients are more likely to respond to a rescue protocol.[1]

Some of the reasons of this rarely seen condition are postulated to be ovarian aging with the advanced maternal age, bioavailability of beta-human chorionic gonadotrophin (bhCG) in patients' blood at 35 h after hCG administration, mistiming or rapid clearance of hCG , premature ovulation, and poor ovarian response.[2-4] Besides; strong attachment of the oocyte-cumulus complex (COC) to the follicle wall (described as oocyte disintegration) was mentioned as one of the possibilities of EFS by Tsuiki et al. in 1988.[5]

The recurrence of the syndrome in the same patient is seen very occasionally and up to date; no absolute treatment has been reported in such cases.[6,7]

Case Report

Our patient was 36 years old and she admitted to our university hospital IVF center with the complaint of secondary infertility. She had an etiology of unexplained infertility and gave birth to a healthy girl after an artificial insemination treatment nine years ago. Two years ago; she had an unsuccessful IVF attempt resulted with no pregnancy in another IVF center. In that ICSI treatment, ovulation induction was done with a long protocol that started with a 225 IU dose of rFSH (Gonal F, Serono,) after downregulation with a GnRH analogue. Three embryos (8-cell, 10% fragmented; 6-cell, %5 fragmented; 5-cell, 5% fragmented) had been transferred at that cycle. The patient has also used metformin during the treatment.

In our center; stimulation of ovaries was achieved by a microdose flare up protocol. Menotrophin (Menopurâ) was administered i.m. to the patient at a daily constant dose of 300 IU with 40 mg of GnRH analogue (Lucrin 3.75 Depot, Abbott Laboratories) administered two times a day (in the morning and evening). At the cycle day 14 transvaginal ultrasound, more than 15 follicles were detected. Recombinant hCG (oVitrelle 10000 IU; Serono Laboratories) was planned to be administered at 10 p.m. when the dominant follicle has reached 20.7 mm. At cycle day 14; 10 of her follicles were more than 17mm in mean diameter. Transvaginally ultrasound guided oocyte pick up procedure was scheduled after 36 hours post hCG administration. No oocytes were obtained after aspiration and several flushing of eight follicles from left ovary and it was suspected the patient could have misused recombinant hCG although it was confirmed by the experienced IVF

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nurse that she had the injection 36 hours before the procedure. After two hours, the blood hCG test result was 658 IU/ml and confirmed correct dose administration by the patient. After taken the result; a secondary aspiration was performed at 42nd hour of hCG injection under local anesthesia. Five oocytes (one from the left ovary, four from the right ovary) were collected after the aspiration of 10 follicles. Endometrial thickness was 14.2 mm at the day of retrieval. Three of oocytes (one from the left, two from the right ovary) yielded MII phase. These three mature oocytes were injected with the husband's sperm two hours after the oocyte collection. The sperm count parameters were 32 million/cc in number and %95 total motile/cc in motility. Fertilization of all mature oocytes was confirmed at 18th hour of intracytoplasmic sperm injection (ICSI). Embryo transfer was planned on the second day. Two of three embryos cleaved to 4 cells and one of them cleaved to 2 cells on day 2 and all the cleaved embryos were grade 1 (with even blastomeres and no fragmentation). After 12 days; her pregnancy was confirmed by the blood hCG level of 133 IU/ml. She had a singleton live pregnancy without any problems and had taken a healthy girl home.

Discussion

In the literature, many approaches are presented in order to explain and rescue EFS. A systemic review of these cases has shown that most of EFS cases were actually avoidable and didnot represent any potential pathology in the relevant patients and that the risk of GEFS is much smaller than thought. There is a value of making a clear distinction between FEFS and GEFS. Since FEFS is accepted as a result of a human or pharmacological error, reporting GEFS cases has much more value in understanding the condition and identifying potential risks and etiological factors.[1] In most of FEFS cases, partial follicular aspiration after a second dose administration of hcg had rescued many patients from cycle cancellation.[2,7,8,9] In addition to that; it was also reported that for overcoming EFS, there may be other alternatives to urinary hcg such as recombinant hcg and GnRH agonist for final maturation of the oocytes and cumulus-oocyte complex detachment.[10-11]

As our patient did not face this kind of problem at her first IVF attempt; it was questioned if bioavailability of the drug may be decreased because of the increased body mass index of the patient.[12] Since the blood hCG dose measured after the first follicular aspiration gave a high result; it was thought that the recombinant hCG used in our protocol had a desired bioavailability. Hassan et al. suggested that some patients need longer exposure to hCG for the efficient detachment of the cumulus-oocyte complexes from the follicular wall.[13] Taking this suggestion in account and since at 42nd hour of hCG injection oocytes were obtained in our case, it was thought that a delayed response of the ovaries to the administered dose might have occurred.

Another issue in this case was that; the ovarian stimulation was done with human menopausal gonadotrophin; differing from the first treatment with recombinant FSH. In this cycle, preferrence of hmG might have altered the LH receptor expression of granulosa cells and this seems to support the hypothesis that folliculogenesis in the absence of sufficient amounts of LH activity leads the granulosa cells more quickly to luteinization.[14]

Uygur et al. had experienced a similar case which was continued with a secondary follicular aspiration six hours after the first one. Since the blood hCG level showed no improper patient use , they didn't need to readminister hCG; however, the second aspiration was also resulted with no oocytes.[15]

Although it has ended with a few viable oocytes, we'd like to classify our case into the 'genuine' empty follicle syndrome cases since we couldn't retrieve any oocyte from most of the follicles within oocyte retrieval time. As to our knowledge; this is the first 'genuine' empty follicle case in the literature resulted with viable oocytes and pregnancy afterwards. In these kind of cases, our next step will be studying biochemical composition of follicular fluid and granulosa cell receptor expression levels in detail.

Boş Folikül Ya Da Değil? Bir Olgu Sunumu

Boş folikül sendromu; bir IVF siklusunda çok sayıda folikül gelişimi sağlanmasına karşın hiç oosit elde edilememesi ile karakterize edilir. Biz; insan koryonik gonadotropin verilmesinden 36 saat sonra boş folikül sendromu olarak varsayılan ve 42. saatte, ikinci doz ilaca gerek kalmadan ikinci oosit toplama işlemi ile kurtarılan bir vakayı sunmaktayız. Bu vakada; iyi kalitede üç embriyonun intrauterin transferi sağlıklı bir kız çocuğu ile sonuçlanmıştır.

Anahtar Kelimeler: Boş folikül sendromu, Oosit toplama, İnsan koryonik gonadotropin, BMI

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