A borderline form of empty follicle syndrome. Case report

N. Nikolettos[1], B. Asimakopoulos[1], M. Simopoulou[1], S. Al-Hasani[2]

[1]Lab. of Reproductive Physiology-IVF, Faculty of Medicine, Demokritus University of Thrace, Dragana, Alexandroupolis (Greece)
[2]Department of Obstetrics/Gynecology, Medical University of Lübeck, Lübeck (Germany)

Summary

Background: Empty follicle syndrome is known as the failure of oocyte retrieval despite the adequate response to ovarian stimulation. It is a rare phenomenon in in-vitro fertilization and borderline forms of this syndrome have also been described.

Materials and methods: Two cycles in the same patient were stimulated with GnRH agonist/hMG and recFSH; the first followed the long and the second followed the short protocol.

Results: There was a sudden drop in estradiol levels while the ovaries contained a large number of small and medium sized follicles. hCG was administered and oocyte retrieval was performed 36 hours later. There was no indication of low hCG levels. For the first cycle two oocytes were collected: one degenerated and one of poor quality. The second cycle resulted in total failure of oocyte retrieval.

Conclusion: The two cycles were classified as borderline forms of empty follicle syndrome. The possible aetiology is discussed.

Key words: Empty follicle syndrome; Human chorionic gonadotrophin; Failed oocyte retrieval; IVF.

Introduction

Empty follicle syndrome (EFS) is a rare phenomenon in assisted reproduction having an incidence of 2% to 7% [1, 2]. This syndrome has been defined as the failure of oocyte retrieval after repeated aspiration and flushing, despite a normal response to ovulation induction and the existence of mature follicles of adequate size [3]. The retrieval of very few mature or immature oocytes from the aspiration of several follicles after satisfactory ovarian stimulation has been described as a borderline form of EFS [4]. The underlying physiological mechanisms of the syndrome are not exactly known but it is believed that most patients with EFS will have successful oocyte retrieval in a subsequent cycle.

Here, we report a case of a patient demonstrating a non-typical form of EFS during two subsequent IVF cycles. The possible aetiology is discussed.

Case Report

A 34-year-old female suffering infertility for five years due to polycystic ovarian syndrome was referred to the In Vitro Fertilisation (IVF) program of "Otmar Bauer" Assisted Reproduction Centre, Alexandroupolis, Greece. Ovarian stimulation was carried out according to the long protocol with administration of 31 amploules of recFSH (Gonal-F®, Serono International S.A., Geneva, Switzerland). Pituitary suppression was performed with the GnRH-agonist leuprorelin (Elityran® 3.75, Takeda Chemical Industries, Japan). During the stimulation, there was a continuous increase of estradiol levels up to the 10th day (976 pg/ml). However, the follicles, ranging in size between 12-13 mm at maximum, did not progress satisfactorily. On the 12th day, when there was a large number of follicles with a maximum size of 12-14 mm the estradiol level decreased (572 pg/ml). The estradiol level was recorded twice on the same day and since a further decrease in estradiol level was possible, even though the follicles did not show any further increase of their size, it was decided to proceed with ovulation induction. Ovulation was induced by injection of 10,000 I.U. hCG (Pregnyl, N.V. Organon, Oss, Holland) on day 12 of stimulation. Oocyte retrieval was performed 36 hours following hCG injection. According to our long-standing experience, performing a urine pregnancy test just before the oocyte retrieval helps exclude mistakes in the administration of hCG. The test was positive. All follicles of a size > 10 mm (29 in total) were punctured, aspirated and flushed. There were no cumulus cells present in the follicular fluid samples apart from two of the samples. Consequently, two oocytes were retrieved: one degenerated and another of poor quality. Intracytoplasmic sperm injection was performed with the only available oocyte, but there was a failure of fertilization.

A second IVF cycle was attempted following a six-month interval. According to the short protocol of ovarian stimulation with triprorelin (Arvekap® 0.1, Ipsen Biotech, France), 18 ampoules of recFSH (Gonal-F®, Serono International S.A., Geneva, Switzerland) and 11 ampoules of human menopausal gonadotrophins (Menogon®, Ferring Arzneimittel GmbH, Kiel, Germany) were administered to the patient. The estradiol levels were closely monitored, along with the progesterone levels, in order to avoid an incidence of premature luteinization. On day 10 of stimulation, the levels of estradiol and progesterone were 2,630 pg/ml and 0.75 ng/ml, respectively. The representation of the ovaries this time resembled their appearance during the first attempt, with numerous small and medium sized follicles. On the next day, there was a drop in the estradiol level (1,168 pg/ml) without significant change in the progesterone level (0.86 ng/ml). Following a confirmation of the above results, it was decided to proceed with ovulation induction. The patient received 10,000 IU of hCG (Pregnyl, N.V. Organon, Oss, Holland) when there were 35 follicles of a maximum size of 13 mm. HCG was from a different batch than that of the last time. Thirty-six hours later, the pregnancy test was positive; all available follicles were punctured and aspirated with immense attention, thoroughly flashed and aspirated again. Despite all efforts and great attention to detail, no oocytes were found. In fact it is important to note that no cumulus cells were present in any of

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the samples. Due to the exceptional circumstances two clinical embryologists were employed to perform the procedure adding to the precision and validity of the results.

Discussion

It is suggested that the two cycles presented here are not cases of "typical" EFS. There was an unexplained drop of estradiol, without an indication of premature luteinization, as the progesterone levels remained low. At the same time, the patient's ovaries contained an extensive number of small and medium sized follicles. In the first cycle, only two oocytes were recovered of which one degenerated. Therefore, these cases are advised to be considered as "borderline" forms of EFS.

The pattern of ovarian response to stimulation is not sufficient to predict EFS [1, 5]. Instead, hCG serum levels < 10 mIU/ml, 36 hours after hCG administration, have been proposed to be a useful marker for predicting EFS [5, 6]. In the two cycles of our patient the hCG serum level on the day of follicle puncture was higher than 20 mIU/ml, that is the detection threshold of the pregnancy test. Ubaldi *et al.* [7] have also reported serum hCG concentrations higher than 10 mIU/ml after hCG administration. Therefore, the threshold of 10 mIU/ml for serum hCG should be considered as unreliable for the prediction of EFS.

The etiology of EFS remains obscure although several scientists have tried to explain this peculiar situation and elucidate the possible pathophysiological mechanisms. According to some authors, EFS represents a cause of infertility per se, relating to luteal phase defects [3, 8, 9]. It has also been suggested that it may reflect oocyte resorption, disintegration, or tight attachment of the oocyte-cumulus complex to the follicle wall [10]. Ben-Shlomo *et al.* [1] hypothesized that the failure of oocyte development is the underlying cause of EFS. On the other hand, the follicular fluids in EFS are characterized by low progesterone, high androstenedione and high or normal estradiol concentrations [2, 6, 10]. As the ovulation induction is triggered by the administration of exogenous hCG, the attention was focused on this drug and its biological actions. The administration of hCG results in granulosa cell luteinization, decrease of estradiol and increase of progesterone synthesis, resumption of meiosis and oocyte maturation, enlargement and dispersion of the cumulus complex, as well as softening of the connective tissue elements of the follicle. Several investigators refer low bioavailability of hCG as the most possible cause for EFS and they have reported a number of cases with successful oocyte retrieval after a second dose of hCG [5, 7, 11-13].

A number of reasons have been proposed to explain the possible low or inadequate bioavailability of hCG. Abnormalities of biodisposition of some batches of the drug [6], mistakes in the dose and the time of the administration [4, 11, 13], very rapid metabolic clearance by the liver, as well as insufficient ovarian response to biologically active hCG [7, 12]. In the cycles described here, the abnormalities of hCG batches and the human errors in the administration of the drug have to be excluded as the pregnancy tests on the days of oocyte retrievals were positive. In addition to the above, for the second cycle, a different batch of the drug was used. The types of GnRH agonist or gonadotrophins can not be implicated as different types were used in the two cycles. On the other hand, the appearance of the stimulated ovary with a very large number of medium sized follicles leads to the hypothesis that for these cases the failure to retrieve oocytes arouse from a failure of follicular and oocyte development.

For the time being, only speculations can be expressed on the etiology of either "typical" or "borderline" EFS. We believe that the cases described here indicate that low or inadequate bioavailability of hCG may not be the sole underlying cause of this condition. EFS could also be a result of other causes, possibly related to the type of infertility of the patient. Finally, the recurrence of EFS in two subsequent cycles could indicate that this pathophysiological condition might not be transitory but permanent for certain patients.

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Address reprint requests to:
N. NIKOLETTOS, M.D.
Assoc. Professor
Lab. of Reproductive Physiology-IVF
Faculty of Medicine,
Demokritus University of Thrace
Ktirio Proklinikon, Dragana
68100 Alexandroupolis (Greece)