Recurrent Empty Follicle Syndrome

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We report a case of a recurrent empty follicle syndrome. The patient was admitted to our intracytoplasmic injection program because of her partner's azoospermia. Ovarian stimulation was accomplished using gonadotrophin therapy after treatment with oral contraceptive pills followed by gonadotrophin-releasing hormone agonist. Thirty-six hours after the administration of HCG (human chorionic gonadotrophins), transvaginal oocyte retrieval yielded no oocytes despite the aspiration and flushing of all available follicles. Two years later, a second treatment cycle was started using the same pituitary desensitisation and ovarian stimulation regimens. HCG from a different batch with respect to that used in the first treatment cycle was administered. Aspiration and repeated flushing of all follicles of one ovary failed to yield any identifiable oocyte. The β -HCG and progesterone serum concentrations on the day of retrieval were 181 mIU/mL and 3.79 ng/mL, respectively. New oocyte retrieval was planned 6 h after the first attempt for aspiration of follicles. Again, no ova were obtained at this second trial despite the aspiration of the all follicles. As to our knowledge this is the first report of recurrent EFS (empty follicle syndrome) and managed without repeating the HCG injection on the day of unsuccessful oocyte retrieval.

KEY WORDS: Empty follicle syndrome; human chorionic gonadotrophins; oocyte retrieval; recombinant FSH.

INTRODUCTION

Empty follicle syndrome (EFS) was first described by Coulam and Sculman to indicate the absence of oocytes at the time of aspiration despite normal E₂ serum levels and follicular development (1). The incidence of this syndrome in patients undergoing IVF/ICSI has been estimated to be about 0.5–2% (2,3). A clear explanation of the underlying mechanism of EFS does not exist. It was suggested that it is a sporadic event that cannot be predicted by pattern of ovarian response either sonographically or hormonally (2). Also, the risk of recurrence of EFS in future IVF/ICSI cycles remains an enigma.

We report a case of recurrent EFS, despite the use of different batches of commercially available urinary HCG.

CASE REPORT

A 21-year-old woman presented with a 2-year history of primary infertility. She had oligomenorrhoea. She had usually anovulation alternating with sporadic ovulatory cycles confirmed by mid-luteal plasma progesterone concentrations. Her ultrasonographic scanning revealed the appearance of polycystic ovaries (4). Laboratory tests revealed a basal serum FSH level of 7.5 mIU/mL, an LH level of 9.6 mIU/mL and an E₂ level of 75 pg/mL. Hysterosalpingography of the patient was normal. Her husband's sperm analysis was consistent with azoospermia. Both partners had normal peripheral blood karyotypes. Intracytoplasmic sperm injection treatment was planned. In her first cycle, pituitary desensitisation was achieved with

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triptorelin acetate (decapeptyl[®]; Ferring Pharmaceutical, Kiel, Germany). The oral contraceptive pill was given for 21 days. Triptorelin acetate was started on day 17 at a daily dose of 0.1 mg sc, overlapping the oral contraceptive pills for 4 days and continued until the administration of HCG. Gonadotrophin stimulation of the ovaries was started after 8 days of sc triptorelin acetate when serum estradiol concentration was 40 pg/mL and a vaginal ultrasonographic scan showed an absence of follicles >10 mm in diameter. In that cycle, ovarian stimulation was carried out using recombinant FSH (Gonal-F[®]; Serono). It was administered 225 IU daily for 5 days and then 150 IU daily for 5 days. HCG (Profasi[®]; Serono) 5000 IU was given on day 11 of stimulation when a total of 17 follicles was present, with 12 being ≥ 14 mm in diameter and 7 leading follicles measuring ≥ 18 mm (estradiol concentration 4384 pg/mL, endometrial thickness ≥ 18 mm). Thirty-six hours after the administration of HCG all of the available follicles were transvaginally aspirated and flushed repeatedly under sonographic control but no oocytes were recovered despite the presence of normal follicular fluid and granulosa cells in some follicular samples. The procedure was ended.

Two years later, the couple was admitted to our clinic with the same complaint. A second treatment cycle was planned. In that treatment cycle, we used the same pituitary desensitisation and ovarian stimulation regimens. But pituitary desensitisation was achieved with leuprolide acetate 1 mg sc daily (Lucrin[®]; Abbot). Once the pituitary-ovarian suppression was achieved, recombinant FSH (225 IU daily for 6 days and then 150 IU daily for 2 days) (Gonal-F[®]; Serono) was used again for ovarian stimulation. After 8 days of ovarian stimulation, the estradiol serum concentration was 2300 pg/mL in association with the presence of 13 follicles of 10 were ≥ 14 mm in diameter and the three leading follicles were 18 mm. Endometrial thickness was 14 mm. HCG (Profasi[®]; Serono) from a different batch with respect to that used in her first treatment cycle was administered (im 5000 IU) on day 8 of stimulation. Follicular aspiration was performed transvaginally 36 h later by ultrasound-guided puncture. No oocytes were recovered despite the aspiration and flushing of all the follicles in the right ovary. The procedure was suspended. The β -HCG and progesterone serum concentrations measured just after the failed oocyte retrieval were 181 mIU/mL and 3.79 ng/mL, respectively. A new oocyte retrieval procedure was planned 6 h after the first attempt for aspiration of follicles.

Again, no ova were obtained at this second trial despite the aspiration of the all the follicles (follicles in the left ovary and refilled follicles of the right ovary).

DISCUSSION

There is no universally accepted explanation of the underlying mechanism of EFS. But a number of possible mechanisms have been proposed. Altered folliculogenesis is likely to be involved in the etiology of EFS (5). Early oocyte atresia or a strong attachment of the oocyte-cumulus complex (OCC) to the follicle wall were previously suggested (6) as possibilities. Follicular growth and rupture lead to OCC detachment from the granulosa cells and connective tissue of the follicle. In IVF cycles, oocyte retrieval is performed just before follicular rupture. If the number and growth of developing follicles as well as plasma estrogen concentrations show a normal response, one could speculate that failed oocyte retrieval may be due to dysfunctional intrafollicular events, such as the softening of OCC anchoring elements (5,7).

Administration of HCG plays a crucial role in intrafollicular events such as softening of the connective tissue elements of the follicle, which facilitates the detachment of the OCC complex from the follicle wall (5). So the time between HCG administration and oocyte retrieval is important. Inappropriate timing of HCG administration may thus result in iatrogenic EFS (8).

There are reports suggesting that a low bioavailability of administered HCG may be the cause of this syndrome (9,10).

The possibility of an intrinsic defect in the *in vivo* biological activity of some batches of the commercially available HCG is favoured (9,10). Zegers-Hochschild *et al.* demonstrated that EFS was caused by rapid clearance of the batch of HCG that was injected (9). This was explained by some defects arising during the production, packaging, or storage of the drug. Thus, the rapid clearance of the drug by the liver would prevent adequate exposure of relevant follicular processes to the action of HCG.

Ndukwe *et al.* reported that serum β -HCG levels 36 h after im HCG in empty follicle syndrome were all <10 mIU/mL, whereas in cycles in which oocytes were retrieved, serum β -HCG levels ranged from 106 to 291 mIU/mL (10). But recent reports have shown that

in patients having detectable immunoreactive HCG in serum and elevated progesterone serum concentrations on the day of the failed oocyte retrieval, salvage of the cycle was achieved after giving a second ovulatory dose of HCG and repeating the oocyte retrieval for 24–36 h later (11,12). Serum β -HCG and progesterone concentrations were not investigated in first treatment cycle in our patient. However, in the second treatment cycle serum β -HCG and progesterone concentrations were 181 mIU/mL and 3.79 ng/mL, respectively, on the day of oocyte retrieval. Thus, the present case also shows that normal bioavailability of β -HCG does not exclude the possibility of EFS. Unlike the general approach to the EFS, that repeats the HCG injection 24–36 h later (11,12), we did not repeat the HCG injection. Instead, in the second treatment cycle since we have approved the bioavailability of the HCG injection with the serum β -HCG and progesterone concentrations, we repeated oocyte retrieval only 6 h after the failed procedure, without administering the second dose of HCG. With this approach, we have tried to gain more time for possible further softening of the connective tissue elements of the follicle, which can lead to the detachment of the OCC from the follicle wall. As to our knowledge, this is the first case that was treated as such. In present case, EFS was recurrent in the second treatment cycle despite the use of HCG from a different batch with respect to the previous cycle. This also supports that the underlying mechanism of EFS might be a permanent pathologic condition rather than an event related to the HCG preparation itself. Whatever the underlying cause of the EFS, possibility of the recurrence of the event should be kept in mind in future cycles of the patient.

Overall, the etiology of this syndrome remains an enigma. There is a great need for randomised clinical

studies to find out the cause of the EFS and most importantly a way of predicting it.

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