CASE REPORT

Successful treatment of empty follicle syndrome by triggering endogenous LH surge using GnRH agonist in an antagonist down-regulated IVF cycle

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To date, empty follicle syndrome (EFS) has only been reported in GnRH agonist down-regulated IVF cycles. Some cases have been successfully treated by changing the batch, or by repeating the dose of hCG. A case of EFS was observed in both GnRH antagonist and GnRH agonist down-regulated IVF cycles when final oocyte maturation was triggered using urinary hCG (u-hCG). Failure to retrieve oocytes occurred, despite administration of a further dose of u-hCG from a different batch and a delayed repeated oocyte recovery performed in the second GnRH agonist down-regulated cycle. A successful oocyte recovery cycle was achieved after triggering of an endogenous gonadotrophin surge using GnRH agonist in an antagonist down-regulated cycle. Nine oocytes were readily retrieved from 10 follicles, at 36 h after GnRH agonist administration, and eight of these fertilized normally. Two good quality embryos were used for fresh transfer and four were cryopreserved for future use. EFS can occur in GnRH antagonist down-regulated IVF cycles, and can be successfully treated by triggering a natural gonadotrophin surge using GnRH agonist in the absence of any response to previous treatment methods. This represents a novel therapeutic modality for this uncommon but frustrating condition.

Key words: empty follicle syndrome/GnRH agonist/GnRH antagonist/IVF/oocyte retrieval

Introduction

Failure to retrieve oocytes from mature ovarian follicles following ovulation induction for IVF treatment despite meticulous aspiration and repeated flushing has been previously described and coined ‘empty follicle syndrome’ (EFS) (Coulam et al., 1986). This is an uncommon event which has been reported to occur in 0.2 to 7% of cases (Ben-Shlomo et al., 1991; Quintans et al., 1998). The mechanisms responsible for EFS remain obscure, though many hypotheses have been put forward ranging from human error (Meniru and Craft, 1997; Quintans et al., 1998; Papier et al., 2000) or pharmacological problems (Zegers-Hochschild et al., 1995; Ndukwe et al., 1997; Ubaldi et al., 1997) to dysfunctional folliculogenesis (Ben-Shlomo et al., 1991). Most, if not all, of the cases so far reported occur in GnRH agonist down-regulated cycles. Methods reported to overcome the condition have ranged from rescheduling oocyte retrieval (Meniru and Craft, 1997), administering a further dose of urinary hCG (u-hCG) from a different batch (Ndukwe et al., 1997; Ubaldi et al., 1997), and using recombinant hCG (rec-hCG) (Peñarrubia et al., 1999). Here, a case is reported of EFS which occurred in both GnRH agonist and GnRH antagonist down-regulated cycles where final oocyte maturation was triggered using u-hCG. A successful oocyte recovery cycle was achieved following triggering of an endogenous LH surge using GnRH agonist in an antagonist cycle.

Methods and Results

The patient was a 34-year-old woman with a 6-year history of secondary infertility, having had two previous first-trimester miscarriages and an ectopic pregnancy. Severe tubal disease was diagnosed as the cause of her infertility. She underwent three cycles of IVF, the outcomes of which are summarized below.

The first cycle was carried out with a GnRH antagonist down-regulated cycle using ganirelix (Orgalutran®; Organon, UK). Ovarian stimulation was carried out starting on menstrual cycle day 2 with 200 IU of recombinant FSH (rec-FSH) (Puregon®; Organon, UK). Cycle monitoring was carried out using both ultrasound scanning and LH and estradiol (E₂) assays. The GnRH antagonist was administered on cycle day 6 (when the serum E₂ level was ≥1000 pmol/l) and continued until the day of hCG administration. Final oocyte maturation
was triggered by administering 10 000 IU u-hCG (Pregnyl®; Organon, UK) at 35 h prior to oocyte retrieval. The criteria for administering hCG were the presence of a lead follicle ≥18 mm and at least two more follicles measuring ≥16 mm. Oocyte retrieval was carried out using ultrasound-guided transvaginal needle aspiration while the patient was receiving sedation and analgesia.

No oocytes were recovered from a total of 15 follicles, even after extensive flushing. No cumulus mass or immature oocytes were seen, and few granulosa cells were identified upon analysis of the aspirates and flushes. The serum level of hCG measured on the day of follicular aspiration was 548 IU/l, confirming correct dose administration by the patient.

The second IVF cycle was performed 5 months later using a ‘long GnRH agonist down-regulation protocol’. Pituitary down-regulation was achieved using GnRH agonist (buserelin; Suprefact®; Shire Pharmaceuticals Ltd, UK) (0.5 mg daily, s.c.) which was started at the mid-luteal phase of the cycle preceding the stimulation cycle and continued until the day of hCG administration. Upon confirmation of adequate down-regulation (endometrium <5 mm thickness and inactive ovaries), rec-FSH 200 IU was given daily for ovarian stimulation. The final oocyte maturation and oocyte retrieval were carried out as described above.

No oocytes or cumulus cells, and few granulosa cells were detected in the follicular fluid collected from the left ovary. Serum hCG and progesterone levels were found to be 199 IU/l and 13.2 nmol/l respectively. The procedure was abandoned and a further 5000 IU u-hCG from a different batch was administered. The second oocyte retrieval was performed 24 h later, and no oocytes were obtained. Serum hCG and progesterone levels of 300 IU/l and 30.5 nmol/l respectively were recorded on the day of the second oocyte retrieval.

In the third cycle, a GnRH antagonist protocol was used as described for the first cycle. However, final oocyte maturation was triggered using 200 μg buserelin s.c., instead of u-hCG. Serum LH and progesterone levels, measured at 24 h after buserelin injection, were 91.1 IU/l and 21.6 pmol/l respectively. When follicular aspiration was conducted 36 h later, nine metaphase II oocytes were retrieved from nine follicles. Eight of the nine oocytes fertilized normally at 20 h post insemination. Two 7-cell embryos were transferred at 72 h after oocyte collection using a Sydney IVF catheter (Cook Ireland Ltd, Ireland), and four embryos were considered of sufficiently high quality to be cryopreserved.

Vaginally administered progesterone (200 mg) pessaries (Cyclogest®, Shire Pharmaceuticals Ltd) were used for luteal phase support. No pregnancy was achieved in that cycle, and the patient is currently being followed up for a frozen embryo replacement cycle.

Discussion

The failure of hCG to induce follicular maturation leading to EFS is an uncommon, but frustrating, complication of IVF treatment that in turn leads to a failure to collect oocytes in IVF cycles. A low bioavailability of administered u-hCG is perhaps the most common and most well-documented cause of EFS (Zegers-Hochschild et al., 1995; Ubaldi et al., 1997), and reasons for this include human error in either the timing (Meniru and Craft, 1997; Quintans et al., 1998) or dosage (Papier et al., 2000) of u-hCG administration, individual variation in thresholds for follicular response to u-hCG (Abdalla et al., 1987) or body clearance of u-hCG (Zegers-Hochschild et al., 1995). In addition, low bioavailability may be linked to intrinsic defects in the in-vivo biological activity of some batches of commercially available u-hCG (Zegers-Hochschild et al., 1995; Ndукwe et al., 1997).

In this case report, the serum levels of hCG and progesterone were confirmatory of the correct timing and doses of hCG administered. As there were no published reports on the occurrence of EFS with the GnRH antagonist protocol, the present authors resorted to the use of a more familiar long GnRH agonist down-regulation protocol in the second cycle of treatment. However, in this second cycle no oocytes were retrieved at 35 h after triggering with 1000U u-hCG from a different batch. The incidence of occurrence of EFS in two successive cycles is not known, especially in a patient with a history of three spontaneous pregnancies.

It has been suggested that some patients may need a longer exposure to hCG in order for their cumulus–oocyte complex (COC) to detach from the follicular wall (Hassan et al., 1998), and especially in those patients where GnRH agonist and gonadotrophin are used in combination (Tarlatzis, 1992). Indeed, oocytes could be recovered when retrievals were repeated 24 h after the first failed recovery in the presence of both normal serum hCG and progesterone (Ubaldi et al., 1997; Hassan et al., 1998). Nonetheless, the repeated failure despite a 24-h delay and further dose of u-hCG in the presence of luteinization suggested a problem which was specific to COC detachment. As this patient had conceived previously on three occasions, spontaneous ovulation must have occurred, thereby excluding the presence of an intrinsic defect in the LH receptor or ovulation.

Despite the recent report of successful oocyte retrieval using rec-hCG in a similar case (Pepiarrubia et al., 1999), there is a lack of theoretical rationale to explain how this approach would work differently with the already proven bioavailability of u-hCG administered. The utilization of endogenous ovulatory gonadotrophin surges (as proven effective from the patient’s history) using either a natural cycle IVF or a stimulatory cycle that allows for a natural LH surge, was seen as a more logical approach. Triggering an endogenous gonadotrophin surge has become a possibility with the introduction of the antagonist regime into IVF programmes. GnRH antagonists provide an immediate, but reversible, inhibition of a premature LH surge. The inhibitory effect on gonadotrophin release can be competitively overridden by exogenous administration of either GnRH or a GnRH agonist. The substitution of u-hCG administration by a single dose of GnRH agonist for triggering ovulation has been used successfully in IVF cycles for patients at high risk of developing ovarian hyperstimulation syndrome (Itskoitz-Eldor et al., 1993).

The present case is the first to be reported of EFS in an antagonist IVF cycle, in which u-hCG failed to trigger
ovulatory changes permitting successful recovery of oocytes using both agonist and antagonist protocols. It is also the first case whereby GnRH agonist was used to trigger ovulation instead of the traditional hCG for the treatment of EFS, thereby adding a new management option to this uncommon yet distressing and challenging condition.

References


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