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Case Report

Encountering premature ovulation during controlled ovarian hyperstimulation in IVF/ICSI cycles

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Abstract

Objective: To report successful pregnancy outcomes in three cases of documented premature ovulation in intracytoplasmic sperm injection (ICSI) cycles.
Case Report: Three cases of premature ovulation were noted during the oocyte retrieval procedures in *in vitro* fertilization (IVF)/ICSI cycles with gonadotropin-releasing hormone antagonist protocol. Immature oocytes were aspirated from the remaining small and medium-sized follicles with *in vitro* maturation performed in two cases. All three cases achieved successful pregnancy with documented live birth after ICSI.
Conclusion: This is the first ever report of successful pregnancy outcome after documented premature ovulation. Fertilizable oocytes and successful pregnancies can still be obtained from the remaining small and medium-sized follicles after premature ovulation and used for ICSI.

Keywords: ICSI; pregnancy outcomes; premature ovulation

Introduction

In the early days of *in vitro* fertilization (IVF), premature ovulation was a common problem encountered during controlled ovarian hyperstimulation (COH). Such event almost invariably led to cycle cancellation because of the depletion of limited number of dominant follicles. With the availability of human menopausal gonadotropin (hMG) and recombinant follicular stimulation hormone (rFSH), clinicians were able to synchronize multiple follicular growth thus ensuring higher successful retrieval and fertilization rate per IVF cycle.

Nevertheless, the positive pituitary feedback by rapidly rising estradiol (E_2) levels secreted by the stimulated follicles can augment the risk of an early luteinizing hormone (LH) surge associated with premature ovulation. Although the development of gonadotropin-releasing hormone (GnRH) agonists and antagonists has effectively lower the occurrence of such incidents [1,2], they are still not completely eradicated. Some institutes would propose cancellation of the cycle after premature ovulation, believing that oocytes from the remaining smaller follicles are incapable of fertilization. We here present three cases of successful pregnancy outcome after documented premature ovulation during IVF with intracytoplasmic sperm injection (ICSI) cycles.

Case reports

Case 1

A 28-year-old gravida 2, para 0 woman with a diagnosis of polycystic ovary syndrome (PCOS) by Rotterdam criteria was scheduled for IVF in our clinic after six failed attempts of clomiphene with intrauterine insemination (IUI) treatment. On

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baseline examination, serum FSH, LH, testosterone and anti-Müllerian hormone (AMH) were 4.68 IU/L, 15.46 IU/L, 0.79 ng/mL, and 20.30 ng/mL respectively. Patient was pretreated with combined oral contraceptive pills for one cycle prior to initiation of IVF. An antagonist protocol was selected under the discretion of the attending physician. Controlled ovarian hyperstimulation was initiated on cycle day 2 using hMG (Menopur, Ferring, Italy) 150 IU/day for 4 days. On Day 6, the stimulation was switched to rFSH (Gonal-F, Merck Serono, Geneva, Switzerland) only stimulation at 100 IU/day for 6 days. Serum E_2 level on the Day 10 was 407.05 pg/mL. On Day 12 of the cycle, transvaginal ultrasound revealed several antral follicles in each ovary, with the largest measured 15 mm. She started Cetrorelix acetate 0.25 mg/day (Cetrotide, Merck Serono, Geneva, Switzerland) on the same day for 4 days, and dosages of hMG and rFSH were adjusted. E_2 was decreased to 152.47 pg/mL the day after she started Cetrorelix treatment, 43.22 pg/mL the next day, and 182.42 pg/mL on the third day. On cycle Day 16, 500 mcg of recombinant human chorionic gonadotropin (r-hCG; Ovidrel, Merck Serono, Geneva, Switzerland) was given for the final maturation after two leading follicles reached greater than 18 mm in mean diameter. LH, progesterone (P4), and E_2 level measured on the day of hCG injection was 0.5 mIU/mL, 0.96 ng/mL, and 855.86 pg/mL, respectively. Oocyte retrieval was performed 36 hours later. The nonvisualization of leading follicles and the presence of multiple corpus luteum during the oocyte retrieval process confirmed the occurrence of premature ovulation. Six metaphase I (MI) oocytes from medium-sized follicles ranging from 1.2～1.4 cm in diameter were retrieved and placed in the fertilization medium (Quinn's Advantage Fertilization medium; SAGE IVF Inc. Trumbull, CT, USA) overnight. Four oocytes reaching metaphase II were chosen for micromanipulation with conventional ICSI on Day 1 after ovum retrieval, and assisted hatching with zona thinning by laser was performed on Day 4 when four embryos were obtained. All four embryos were transferred. The profiles of the embryos were as follow: 6-cells-grade 1, 8-cells-grade 2, 8-cells-grade 4, and 6-cells-grade 4 according to the Veeck's classification [3]. The pregnancy with heartbeats was demonstrated on the sixth gestational week. The pregnancy continued until 36 weeks and a live female infant weighing 2452 gm was delivered spontaneously due to preterm labor. No major sequelae were noted for this infant as of the date of manuscript completion.

Case 2

Patient is a 34-year-old gravida 0, para 0 woman with a diagnosis of primary infertility. The bilateral tubal occlusion was confirmed during surgery for endometrioma. On baseline evaluation, serum E2, P4, and AMH were 13.10 IU/L, 0.79 ng/mL, and 1.75 ng/mL, respectively. Patient was pretreated with combined oral contraceptive pills for one cycle prior to initiation of IVF. An antagonist protocol was selected and controlled ovulation hyperstimulation began on cycle Day 2 using hMG 225 IU/day and rFSH 450 IU/day for 7 days. On Day 9 of the cycle, transvaginal ultrasound revealed several small follicles in each ovary, with only one leading follicle reaching the size of 14 mm. She started Cetrorelix acetate 0.25 mg/day on the same day for 3 days, and ovarian stimulation was maintained with the same dosage of hMG and rFSH. On cycle Day 12, three leading follicles with the sizes of 20 mm, 19 mm, and 17 mm were seen on the ultrasound. The final oocyte maturation was triggered on Day 14 with 500 mcg of r-hCG. The P4, LH, and E_2 levels measured on the day of r-hCG injection were 1.60 ng/mL, 0.64 mIU/mL, and 1125 pg/mL, respectively. The non-visualization of leading follicles and the presence of ample cul-de-sac fluid during the procedure of oocyte retrieval confirmed the occurrence of premature ovulation. Six MI oocytes were obtained, and four underwent rescue *in vitro* maturation over night and micromanipulation with ICSI was performed on the Day 1 after ovum retrieval. Among them only one progressed beyond 2 pronuclear stage (2PN) stage, and a postovum retrieval Day-4 transfer was performed. The profile of the embryo was 8-cells-grade 2. The pregnancy with heartbeats was demonstrated on the 6^{th} gestational week. The pregnancy continued until 37 weeks and a living male infant weighing 4006 g was delivered by cesarean section with the indication of breech presentation.

Case 3

A 41-year-old gravida 0, para 0 woman of primary infertility with endometriosis and the male factor who had underwent three unsuccessful IVF/ICSI cycles that showed poor ovarian response after COH began her fourth cycle of GnRH antagonist protocol. Patient was pretreated with combined oral contraceptive pills for one cycle prior to initiation of IVF. Controlled ovulation hyperstimulation began on cycle Day 3 using hMG 150 IU/day and rFSH 450 IU/day for 4 days. On Day 7 of the cycle, ultrasound revealed several small follicles in each ovary. She started Cetrorelix acetate 0.25 mg/day on Day 10 for 4 days, and ovarian stimulation was maintained with adjusted dosage of hMG and rFSH. On Day 13 of the cycle, 500 mcg of r-hCG was given when the leading follicle reached 20 mm. P4 and E_2 level measured on the day of hCG injection was 1.88 ng/mL and 1198.85 pg/mL. Three leading follicles disappeared and ample peritoneal fluid was noted during oocyte retrieval. Microscopic examination of the aspirated fluid from the posterior cul-de-sac revealed a postmature oocyte, confirming ovulation. The other five oocytes were retrieved from medium and small-sized follicles; among them, four were metaphase II (MII) stage. ICSI were performed on the MII oocytes and only two progressed beyond 2PN stage. The profiles of the transferred embryos were as follows: 6-cells-grade 1, and 8-cells-grade 2. The pregnancy with heartbeats was demonstrated on gestational Week 7. The pregnancy continued until 38 weeks and a living male infant weighing 3264 g was delivered by elective cesarean section.

Discussion

The literature regarding the outcome after premature ovulation has been scarce. Rather, most research has been

dedicated on the topic of "premature luteinization," which is the occurrence of increased serum P4 levels on the day of hCG administration with conflicting results. In a study by Cunha-Filho and colleagues [4] that analyzed the factors related to premature LH and progesterone rise in intrauterine insemination cycles, the authors concluded that these events cannot be predicted utilizing clinical parameters normally employed, such as ultrasound, serum E_2 assay, or stimulation protocol. Although many studies indicated that there is no direct relationship between P4 levels and pregnancy rates [5−10], others have demonstrated that the pregnancy rate is negatively correlated to serum progesterone levels [11−15]. A possible explanation is that after premature luteinization, elevated serum P4 may lead to a state of asynchrony between embryo and endometrium for implantation [16], resulting in reduced pregnancy rate. The same mechanism may be applied to the events after premature ovulation. A recent large scale meta-analysis by Bosch and others [17] has designated serum P4 levels greater than 1.5 ng/ml at the day of hCG administration to be the threshold associated with lower ongoing pregnancy rates following IVF/ICSI cycles, regardless of the type of GnRH analogue used. A note of interest is that two out the three cases in our study had a P4 level above such value (1.60 ng/mL and 1.88 ng/mL).

Another scenario is when premature ovulation occurred during early phase of ovarian stimulation. There are reported cases of premature ovulation with continued ovarian stimulation followed by successful retrieval and cryopreservation of collected mature oocytes [18,19] in cancer and advanced-aged patients, since time is the utmost important for such patient population. Several authors have proposed a "LH receptor theory" [19,20], which stated since the granulosa cells of the small antral follicles do not express sufficient LH receptors to be affected by patient's premature LH surge, the cycle can be rescued if ovarian stimulation was continued.

Occasionally, premature ovulation was noted close to or during oocyte retrieval. It is unknown exactly how long the human oocytes can remain "fertilizable" after ovulation, but mouse models have demonstrated oocytes can retain their fertilization capacity for as long as 4−6 hours post-ovulation [21]. Therefore the aspiration of the free fluid within the pelvic cavity can theoretically offer a chance of collecting the ovulated oocytes. Previous studies have demonstrated that ovulated oocytes collected from cul-de sac shared similar fertilization rates as the ones collected from intact follicles, as well as documented live birth resulting from embryo developed from the oocytes collected from cul-de-sac [22,23]. Therefore, another plausible management when encountering premature ovulation is to aspirate the cul-de-sac fluid thoroughly in the hope of recovering the ovulated oocytes.

Conclusion

To the best our knowledge, this is the first ever report addressing the pregnancy outcome from the oocytes of the remaining small and medium-sized follicles after documented premature ovulation during controlled ovarian hyperstimulation. In the face of such event, some institutes would opt for cancellation of the ovum retrieval, fearing that oocytes from the remaining small and medium sized follicles do not possess the ability to undergo fertilization. From the present report, it is evident that fertilization, even live birth, is attainable from the oocytes of the smaller follicles after premature ovulation of the leading follicles.

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