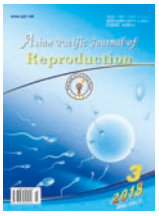

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Missed estradiol determination resulting in oocyte retrieval and embryo development following controlled ovarian hyperstimulation at early pregnancy: Case report

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ABSTRACT

This paper is a case report on the success of oocyte retrieval and good quality embryo development following controlled ovarian hyperstimulation at early pregnancy. A 30-year-old patient underwent controlled ovarian hyperstimulation by gonadotropin-releasing hormone agonist long protocol. On the day of oocyte collection, a 5-week gestational sac was observed by exact sonography monitoring. However, via ultrasound guided follicle puncture, 7 oocytes were collected. After intarcytoplasmic sperm injection, 3 developed good quality embryos were cryopreserved. Moreover, the natural pregnancy was continued and finally a healthy live birth was achieved. Despite physiological hormonal changes during pregnancy, the follicular growth occurred and followed by oocyte retrieval and embryo development, subsequently.

1. Introduction

Generally, the process of folliculogenes is initiated with recruitment of several antral follicles in both ovaries through the late luteal phase of the preceding menstrual cycle. Then, during the initial or middle stage of follicular phase, only one follicle is matured[1]. Moreover, it is mentioned that small antral follicles in luteal phase may not certainly be in atresia status, though may rather be in the primary stages of follicular development. This shows the follicular developmental waves during a single interovulatory period. Typically, standard regimens for ovarian stimulation commences on the early follicular phase of the menstrual cycle[2]. However, there are some studies on oocyte retrieval during the luteal phase with competency of maturation and fertilization[3]. To the best our knowledge, this is the first case report on ovarian stimulation cycle during early pregnancy in a patient with the misdiagnosed natural pregnancy.

2. Case history

A 30-year-old nulliparous woman with primary infertility of 12 years' duration was observed in the study. Infertility investigations revealed an unexplained subfertility. Endocrine profile of the woman before ovarian stimulation was detailed as: follicle-stimulating hormone: 6.00 mIU/mL, luteinizing hormone: 5.00 mIU/mL, anti mullerian hormone: 2.30 ng/mL, thyroid stimulating hormone: 2.65 mIU/mL, prolactin: 14.00 ng/mL, and anti-thyroid peroxidase antibody: 32.04 IU/mL. Her husband's semen analysis showed normozoospermia. The sperm parameters included 45×10^6/mL concentration, 35% progressive motility, 5% non progressive motility, 4% normal morphology and 45% vitality. The signed written consent was obtained from the patient.

The first *in vitro* fertilization (IVF) attempt was performed in December 2016. Pituitary down-regulation was achieved by gonadotropin-releasing hormone agonist protocol. Follicular monitoring by vaginal ultrasonography at 13th day of cycle revealed 13 dominant follicles in both ovaries, and a single bolus of 10 000 IU human chorionic gonadotropin (hCG) *i.m.* (hCG, Pregnyl, NV Organon, Oss, the Netherlands) was administered 36-38 h before the planned time of oocyte retrieval. On the day of hCG triggering, progesterone was not in the normal range (16.5 ng/mL), and also estradiol (E2) level was 3 200 pg/mL. Furthermore, following ultrasound examinations, the endometrium was unusually thick (16 mm). Hence, due to high level of progesterone and unsuitable

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thick endometrium, all embryos freeze program was planned.

Surprisingly, on the time of oocyte collection, a 5-week gestational sac was observed by exact sonography monitoring. However, via ultrasound guided follicle puncture, 7 cumulus-oocyte complexes were collected and cultured in standard IVF media at 37 ℃ and 6% CO_2. The surrounding cumulus cells were detached using 80 IU/mL hyaluronidase, leaving 7 mature oocytes. Thereafter, the woman's husband sperms were injected into these metaphase Ⅱ oocytes that showed the first polar body extrusion. Intracytoplasmic sperm injection (ICSI) was performed despite a good sperm count. Five injected oocytes (71.4%) showed normal fertilization on the next day and finally 3 good quality day-2 embryos were cryopreserved. Luteal support in the form of intravaginal progesterone (Organon; 200 mg, twice daily) was given from the day of oocyte retrieval. The pregnancy was continued until 32 weeks and finally a preterm live birth (1 550 g boy) was achieved. However, the infant was under care in a neonatal intensive care unit one week without intubation. After one week, the infant was discharged with Apgar score of 8/9.

3. Discussion

We report, to our knowledge, the first occurrence of oocyte retrieval and good quality embryo development following controlled ovarian hyperstimulation in an undetected early pregnancy. Generally, the ovarian stimulation at pregnancy isn't performed in any infertility center. In a unique study, Ben-Haroush *et al*[4] reported the aspiration of small follicles during cesarean section in a 38-year-old pregnant patient. Following *in vitro* maturation of collected germinal vesicle oocytes, ICSI was performed and the resulting 4 zygotes were cryopreserved[4]. Also, Goeckenjan *et al*[5] performed ovarian stimulation in the days following an induced abortion regarding fertility preservation in a breast cancer patient. They succeed transvaginal oocyte aspiration and cryopreservation of zygotes in spite of high levels of hCG[5].

In the present case, the agonist long protocol was started on 21th day of preceding menstrual cycle, approximately the time that an embryo was implanted in a natural pregnancy case. Routinely in agonist protocol, ovarian stimulation was started by gonadotropin administration on the second day of menstruation. Probably in this case, the bleeding due to threatened abortion was confused by bleeding caused by menstruation. In fact, this time was one week after the implantation and the gestational sac could not be detected; so, stimulation protocol was continued. In this view, the patient should be asked to prevent getting pregnant by using mechanical contraception or refraining from intercourse during her periovulatory phase[6].

In the gonadotropin-releasing hormone agonist long protocol, the stimulation began after occurrence of down regulation. Down-regulation was verified by serum E2 measurement >30 pg/mL. On the other hand, it was shown that the mean concentration of E2 had gradually increased from 180 pg/mL to 3.5 ng/mL at the third to the thirteenth week of pregnancy[7]. In the present case, the measurement of E2 was missed by the patient before commence of stimulation. This possibility remains open if serum E2 level was checked in the patient, and the protocol would stop before beginning the stimulation due to high level of serum E2. There is evidence for negative effects of supraphysiologic elevated progesterone on endometrial receptivity resulting in premature closure of the implantation window. Recently, one study showed a lower pregnancy rate regarding elevated progesterone levels on the day of hCG triggering in IVF/ICSI cycles[8]. In this condition, freezing all embryos followed by frozen-thawed embryo transfer may increase the pregnancy rates. Moreover, we planned all embryos freeze program due to a high level of serum progesterone (16.5 ng/mL) on the day of hCG triggering. Besides, the mean value for the plasma progesterone concentration was reported from 13.8 ng/mL in the third week of pregnancy to 44 ng/mL at the thirteenth week of pregnancy[7]. Furthermore, the endometrium was unusually thick (16 mm) on the day of hCG triggering. Although the higher clinical pregnancy rate was reported when endometrial thickness $\geqslant$8 mm, but no adverse pregnancy outcome was observed when endometrial thickness >14 mm[9].

In conclusion, despite hormonal changes during pregnancy, administration of ovarian stimulation at an undetected early pregnancy resulted in development of good quality embryos, and a healthy live birth.

Conflict of interest statement

All authors declare that they have no conflict of interest.

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