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SHORT COMMUNICATION

Live birth following early follicular phase oocyte collection and vitrified-warmed embryo transfer 8 days later

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Abstract A 30-year-old woman with premature ovarian insufficiency had two follicles measuring 17 mm and 14 mm on day 3 of her menstrual cycle. Serum oestradiol concentration was 210 pg/ml. Recombinant human chorionic gonadotrophin was given and 5 mg/day letrozole started orally. One metaphase II oocyte was collected 36 h later. A 4-cell embryo was vitrified on the second day after fertilization. Letrozole was stopped on cycle day 8 due to absence of any other visible antral follicles. Oestradiol valerate 6 mg/day was started and the endometrium was 9.2 mm on cycle day 11. The embryo was warmed and transferred on cycle day 13, the 8th day after oocyte retrieval. Luteal phase support with progesterone, oestradiol and low molecular weight heparin was started on the day of transfer and continued until the 10th gestational week. A healthy girl weighing 3200 g was born at term. Early follicular phase oocyte collection did not result in early opening of the implantation window. Apparently secretory transformation was not started until luteal phase support, enabling a cleavage stage embryo transferred 8 days later to implant. Either corpus luteum formation could be disrupted or the endometrium could remain unresponsive to progesterone during the early follicular phase.

KEYWORDS: aromatase inhibitor, endometrial receptivity, implantation, menstrual cycle, premature ovarian insufficiency, random start stimulation

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Introduction

Premature ovarian insufficiency (POI) is early onset ovarian malfunction and affects 1–3% of reproductive age women. Serum follicle stimulating hormone (FSH) concentrations in the postmenopousal range, i.e. ≥40 IU/l, is diagnostic for POI in a woman aged <40 years with normal 46 XX karyotype. Most patients present with irregular spontaneous menstrual cycles; therefore amenorrhoea is not essential for definitive diagnosis of POI (Nelson, 2015).

Women with POI frequently seek fertility-promoting therapies. However, they often respond poorly or do not respond at all to ovarian stimulation, resulting in a poor prognosis. There is no consensus on the optimal stimulation protocol for women with POI. It has recently been shown that follicular growth can be induced at any time of the menstrual cycle, and this is called random start ovarian stimulation (Cakmak et al., 2013). Oocyte donation studies showed that endometrium can be maintained on oestrogen for up to 6 weeks without an adverse affect on implantation (Remohí et al., 1995). Hence, it could be possible to manage ovarian and endometrial cycles separately during an assisted reproductive technology (ART) cycle. Exploiting these two facts, we were able to achieve an ongoing pregnancy with vitrified/warmed embryo transfer 8 days after oocyte retrieval in a woman with POI.

Case report

A 30-year-old woman presented with a 2-year history of primary infertility. Apart from irregular menstrual cycles ranging from 60 to 120 days, her medical history was unremarkable. Her serum FSH values ranged between 49 and 150 IU/l, measured on two occasions >4 weeks apart, and her serum anti-Müllerian hormone value was <0.1 ng/l. She had a normal 46 XX karyotype. There was no other endocrinologic abnormality except for elevated serum thyroid-stimulating hormone concentration at 8.55 IU/l.

Pelvic examination did not reveal any abnormal findings. Transvaginal ultrasound showed only one antral follicle, an apparently normal uterus and a thin endometrial lining. Her partner had a normal semen analysis. She was diagnosed with POI and offered ART following further investigaton and treatment of her hypothyroidism. Her serum free T4 concentration was low and she was given levothyroxin orally. The dose was adjusted to keep serum thyroid-stimulating hormone concentrations below 2.5 IU/l. She refused screening for Fragile X premutation status.

Ovarian stimulation with 5 mg/day letrozole (Femara tablet; Novartis Pharma, Switzerland) and 150 IU/day menotropin (Merional; IBSA Pharmaceuticals, Switzerland) commenced on the third day of a spontaneous period and resulted in the collection of a metaphase II oocyte. Despite normal fertilization with intracytoplasmic sperm injection (ICSI), development was arrested before cleavage. Five similar stimulation cycles were all cancelled due to the absence of follicular growth following 7 days of stimulation.

Three months after the sixth attempt she presented on the third day of a spontaneous period. Transvaginal ultrasound showed two follicles of 17 and 14 mm, a thin endometrium, and her serum oestradiol concentration was 210 pg/ml. Given the possibility of rapidly growing follicles, 250 μg human chorionic gonadotrophin (HCG; Ovitrelle, MerckSerono, Switzerland) was administered subcutaneously and letrozole 5 mg/day was started simultaneously. Thirty-six hours later one metaphase II oocyte was collected and succesfully fertilized with ICSI. A 4-cell embryo was vitrified on the second day after fertilization. Letrozole was stopped on cycle day 8, i.e. 3 days after oocyte retrieval, due to the absence of any visible antral follicles. It was decided to abandon stimulation and proceed with the transfer of the cryopreserved embryo in the same cycle. Oestradiol valerate (Estrofem tablet; Novo Nordisk, Denmark) 2 mg every 8 h orally was started on the same day. Endometrial thickness was 9.2 mm on cycle day 11. Oestradiol dose was increased to 8 mg/day and vitrified-warmed embryo transfer was scheduled for 2 days later. On cycle day 13, all four blastomeres survived warming and the embryo was transferred under ultrasound guidance 8 days after oocyte retrieval. Oestradiol valerate was continued at the same dose of 8 mg/day and luteal phase support (LPS) with 100 mg/day progesterone in oil (Progynex 50 mg/ml; Koçak Farma, Turkey) intramuscularly and 0.4 mg/day low molecular weight heparin (Clexane; Sanofi Aventis Intercontinental, France) subcutaneously, was started on the day of transfer. Management of the cycle is shown in **Figure 1**.

Serum β-hCG concentration was 149 mIU/ml on the 12th day after embryo transfer and 384.1 mIU/ml 2 days later. A singleton intrauterine pregnancy with a heartbeat was visualized 2 weeks later. LPS was continued until the 10th gestational week. The rest of the pregnancy was uneventful and she gave birth to a healthy girl weighing 3200 g at 39 weeks.

Koç University Committee on Human Research approved the publication of this case report on 4 August 2015.

Discussion

POI impairs reproductive function years before normal menopause. Various protocols have been tried to improve ovarian response to stimulation but they fail to do so in the majority of cases (Nelson, 2015). Traditionally stimulation starts in the early follicular phase, when the antral follicles are still small. However, in contrast to the notion of a single follicular recruitment episode during one menstrual cycle, multiple cohorts or 'waves' of antral follicle recruitment have been described (de Bianchi et al., 2010). A follicular wave is defined as the synchronous growth of a group of antral follicles that occurs at regular intervals during the menstrual cycle. Distinct follicular waves have been recently detected in women during the perimenopausal transition (Hale et al., 2007) and in women undergoing ovarian stimulation therapy (Bentov et al., 2010). Elevated circulating FSH appears to precede the recruitment of each follicular wave during the interovulatory interval. High endogenous FSH concentrations during luteo-follicular transition can cause follicles reaching pre-ovulatory status earlier in the subsequent cycle. This is not an uncommon occurrence in POI, as indicated by detection of high serum oestradiol concentrations, i.e. >65–80 pg/ml, as early as the third day of the menstrual cycle. Indeed, elevated serum oestradiol concentrations in the early follicular phase is a sign of 'occult ovarian failure'. While such early growing follicles were regarded as 'functional cysts'