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ARTICLE

Retrospective analysis of reproductive outcomes in women with primary ovarian insufficiency showing intermittent follicular development

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Abstract The aim of this retrospective study was to explore the reproductive outcomes of IVF treatment in women with primary ovarian insufficiency (POI) showing intermittent follicular development. A total of 44 POI women with normal karyotype and absent autoimmunity, attending the centre for fertility treatment at Nanfang Hospital, Guangzhou from March 2009 to March 2011, were identified as suitable for inclusion in this study. Out of 44 women, 20 (20/44; 45.5%) had growing follicles and 13 underwent 27 oocyte retrievals. The empty follicle rate per oocyte retrieval was 70.4% (19/27); eight oocytes were recovered: one (12.5%) germinal vesicle (GV), two (25.0%) metaphase I (MI), one (12.5%) metaphase II (MII), and four (50.0%) atretic. One MI oocyte matured *in vitro* and two women had embryo transfer. Only the woman with the MI oocyte matured *in vitro* conceived, giving birth to a healthy baby at term. These results suggest that intermittent follicular development is common in women with POI but most of the developed follicles are empty or contain atretic oocytes. The pregnancy rate remains very low for IVF treatment.

KEYWORDS: Empty follicle, In vitro fertilization, Primary ovarian insufficiency

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Introduction

Primary ovarian insufficiency (POI) is diagnosed when women, before the age 40 years, have amenorrhoea for 4 months or more and two elevated serum FSH concentrations in the menopausal range at intervals of at least 1 month apart (Nelson, 2009). It affects about 1% of women under 40 years old and 0.1% of women under 30 years old (Laml et al., 1999). The causes include 45X, autoimmunity, chemotherapy and ovarian surgery but remain unknown in many patients.

POI is usually associated with infertility, but the phenomenon of intermittent follicular development is commonly seen in these women. Bidet et al. (2011) reported that the cumulative incidence of resumption of follicular growth was 22.5% in 12 months and 25% in 48 months in a cohort of 358 women with POI. About 3–10% of these women may conceive spontaneously after the diagnosis (Bidet et al., 2011). Oocyte donation is usually advised (Shah and Nagarajan, 2014) but is strictly regulated in China, leading to very limited availability. Moreover, the great majority of Chinese women want to have their own genetic children because a couple without their own child may end up in divorce. Therefore, many women with POI strongly request IVF treatment in order to get pregnant as soon as possible, before the depletion of the few follicles remaining in the ovaries.

In literature, only a few reports described IVF treatment in patients undergoing autotransplantation of frozen-thawed ovarian tissue to orthotopic or heterotopic sites for fertility preservation (Biasin et al., 2015; Burmeister et al., 2013; Dolmans et al., 2009; Donnez et al., 2011; Kim, 2012; Revel et al., 2011; Revelli et al., 2013; Schmidt et al., 2011). To date, there is no information regarding reproductive outcomes of IVF treatment in POI women with intermittent follicular development. The aim of this retrospective study was to report the reproductive outcomes of these women.

Materials and methods

This is a retrospective analysis of all POI women with normal karyotype and absent autoimmunity attending the Centre for Reproductive Medicine, Department of Gynecology and Obstetrics, Nanfang Hospital from March 2009 to March 2011. They were followed up until pregnancy and delivery or for 48 months if they did not conceive. Patients gave their informed consent for the treatment given. The Medical Ethics Committee of Nafang Hospital, Southern Medical University approved this study in December 2015, indicating that subject-informed consent was not required for this retrospective analysis of anonymized patient data.

Briefly, clinical evaluations included age at POI diagnosis, clinical presentation, family history, history of autoimmunity, ovarian surgery, chemotherapy or pelvic radiotherapy. They were screened for thyroid antibody, antinuclear antibody, antiendometrium antibody, and antiovarian antibody. Laboratories in Nanfang hospital use chemiluminescence to measure the thyroid antibody (Roche Diagnostics [Shanghai] Ltd., China), immunofluorescence to measure the antinuclear antibody (Roche Diagnostics [Shanghai] Ltd.) and enzyme-linked immunosorbent assay (ELISA) to measure the antiendometrium antibody (Dade Behring Inc., USA) and the antiovarian antibody (Dade Behring Inc.). Serum FSH, LH, oestradiol and progesterone concentrations were checked using electrochemiluminescence immunoassay (Roche Diagnostics (Shanghai) Ltd.). The inter-assay coefficients of variation (CV) for FSH, LH, oestradiol and progesterone were 4.5, 2.2, 4.9 and 4.8%, respectively. The intra-assay CV for FSH, LH, oestradiol and progesterone were 2.8, 1.2, 3.3 and 2.9%, respectively. Anti-Müllerian hormone (AMH) concentrations were measured using ELISA with the Beckman Coulter assay. The inter-assay CV for AMH was less than 14.2% and the intra-assay CV for AMH was less than 12.3%. The sensitivity was 0.14 ng/ml.

POI was diagnosed when a woman who was less than 40 years old had amenorrhoea for 4 months or more, with two serum FSH concentrations (obtained at least 1 month apart) above 40 IU/l, a normal karyotype and absence of thyroid antibody, antinuclear antibody, antiendometrium antibody and antiovarian antibody. Women who had a history of autoimmunity or of chemotherapy or pelvic radiotherapy were excluded from the study group.

All women received 4 mg/day of oestradiol valerate (Tablet Progynova, Bayer Healthcare Co. Ltd., China) for 4 weeks. Transvaginal ultrasounds were performed once a week in order to check the presence of growing follicles. If no growing follicle was detected for 3 weeks, in the last week they were supplemented with oral dydrogesterone (Tablet Duphaston, Solvay Pharma China Ltd.) 10 mg daily for withdrawal bleeding, followed by another cycle of hormone replacement and ultrasound monitoring.

When the diameter of a follicle exceeded 10 mm, the women were scanned daily with the transvaginal ultrasound in the morning. Once the follicle exceeded 14 mm in diameter, serum FSH, LH, oestradiol and progesterone concentrations were measured. The scheduling strategy is summarized in **Table 1**. When serum hormone concentrations met one of the following three conditions: (i) progesterone > 1.0 ng/ml; (ii) progesterone < 1.0 ng/ml and LH > 30 IU/l; or (iii) progesterone < 1.0 ng/ml, LH was 25–30 IU/l and oestradiol > 250 pg/ml, 10,000 IU human chorionic gonadotrophin (HCG) (Livzon pharmaceutical group inc., Zhuhai, China) were given instantly and oocyte retrieval was scheduled the next morning between 15 and 24 h after the HCG injection. Others were given 10,000 IU HCG at night and oocyte retrieval was scheduled 36 h later. A 16-gauge double-lumen–needle (Cook Ireland Ltd., Limerick, Ireland) was used and 20 ml flush medium was re-injected for more than five times and re-aspirated for each punctured follicle. When the aspirated oocyte was mature, intracytoplasmic sperm injection (ICSI) was performed. Three days after ICSI, an early cleavage embryo was transferred into the uterine cavity. Luteal phase was supported by 6 mg of oestradiol valerate (Bayer Healthcare Co. Ltd., China) daily, 40 mg daily of intramuscular progesterone (Shanghai General Pharmaceutical Co. Ltd., Shanghai, China) and 2000 IU HCG (Livzon pharmaceutical group inc., Zhuhai, China) every 2 days from the day of oocyte retrieval to 12 days after embryo transfer, and continued in case of pregnancy diagnosed by serum β-HCG concentration >50 IU/l 12 days after embryo transfer.