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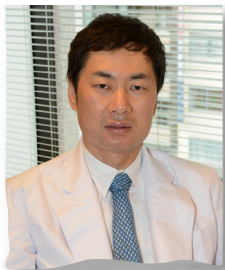
ARTICLE

Cytogenetic analysis of the retained products of conception after missed abortion following blastocyst transfer: a retrospective, large-scale, single-centre study


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Abstract Cytogenetic analysis of the retained products of conception (POC) is the most effective test for identifying miscarriage causes. However, there has been no large-scale study limited to blastocyst transfer. This study retrospectively reports the findings of 1030 cases in which POC analysis was performed after missed abortion following single blastocyst transfer performed at the Shinbashi Yume Clinic. We identified 19.4% as normal karyotypes and 80.6% as aneuploid. These cases broke down into: 62.3% trisomy; 7.8% double trisomy; 0.5% triple or quadruple trisomy; 1.3% monosomy 21; 3.2% monosomy X; 0.1% 47,XXY; 1.0% polyploidy; 1.0% mixed; 1.1% embryonic mosaicism; and 2.4% structural anomalies. In samples with normal karyotypes, 49.5% were female while 50.5% were male. The occurrence of trisomy and double trisomy were both significantly more frequent in the ≥ 38 years group than in the ≤ 37 years group ($P < 0.01$). Trisomy was significantly more frequently associated with fetal heartbeat ($P < 0.01$); double trisomy, polyploidy and normal karyotype were significantly more frequent with no fetal heartbeat ($P < 0.01$). There was no significant difference in the frequency of chromosomal abnormalities between the number of miscarriages or blastocyst quality. Thus, POC cytogenetic testing is highly valuable for ascertaining the cause of miscarriage. 

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KEYWORDS: blastocyst, intracytoplasmic sperm injection, karyotype, missed abortion, products of conception, vitrification

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Introduction

In recent years, the rate of late-in-life pregnancies and the number of infertile patients of advanced age have risen as women's participation in society and the tendency to marry late have increased. Because of recent advances in assisted reproductive technologies, the treatment outcome of these patients has improved. However, as the age of female patients rises, so does the occurrence of chromosomal abnormalities in the embryos, deriving from defects inherent in the gamete itself or arising at fertilization and/or cleavage. As a result, the miscarriage rate has also increased (Angell, 1994; Eiben et al., 1990; Munné et al., 1995; Nybo Andersen et al., 2000). Cytogenetic analysis of the retained products of conception (POC) is therefore thought to be the most effective test for identifying the cause of miscarriage and recurrent abortions.

Some reports are available on the analysis performed for miscarriages following treatment with assisted reproductive technologies. However, most of these studies were mainly concerned with comparisons of the rates of chromosomal abnormalities according to the mode of conception, such as natural pregnancy, IVF and intracytoplasmic sperm injection (ICSI) (Bettio et al., 2008; Bingol et al., 2012; Kim et al., 2010; Kushnir and Frattarelli, 2009; Martínez et al., 2010; Pendina et al., 2014). Qin et al. (2009) carried out a meta-analysis covering 15 studies and found that there was no significant difference in the frequency of chromosomal abnormalities between natural pregnancy, IVF and ICSI groups. In addition, studies on blastocyst transfer have been increasingly reported regarding current assisted reproductive technology treatments, wherein embryos are cultured up to the blastocyst stage, vitrified and then warmed, to be transferred in a later cycle in order to avoid ovarian hyperstimulation syndrome or to improve the pregnancy rate (Cobo et al., 2012; Hill et al., 2013; Lainas et al., 2009). As blastocysts have been further naturally selected than have embryos at the cleavage stage, the frequency of chromosomal abnormalities and the rate of each karyotype are expected to differ between these two groups. However, most published reports have analysed the outcome data without distinguishing between these classes. In a study comparing the frequency of chromosomal abnormalities between POC after cleavage-stage embryo transfer and those after blastocyst transfer, Werner et al. (2012) reported a lower rate of frequency with blastocyst transfer, although their data was too limited to indicate a significant difference. To date, there have been no large-scale studies limited to blastocyst transfer.

The aim of this study was to retrospectively report on the 1030 cases in which cytogenetic analysis of the retained POC was successfully carried out after missed abortion following ICSI and vitrified-warmed single blastocyst transfer performed at the Shinbashi Yume Clinic. The study focused on the relationship of various factors relating to the pregnancy, such as maternal age, to each karyotype found in the analysis of the POC, comparing the frequency of chromosomal abnormalities between groups. The significance of cytogenetic analysis of the retained POC is also discussed.

Materials and methods

Subjects

There were 1236 consecutive cases of Japanese women who had missed abortions during the first 7 – 10 weeks of pregnancy after ICSI and vitrified-warmed single blastocyst transfer at the Shinbashi Yume Clinic during the 6 years between April 2009 and March 2015, during which a total of 11,886 cases underwent embryo transfer at the clinic. All the data were extracted from the database kept at the clinic. Almost all the patients were residents of Tokyo or from its environs. Patients who had miscarriages before 7 weeks and after 10 weeks of gestation were excluded from this study. For the cases with POC of less than 7 weeks of gestation, the placenta was too small for the chorionic tissue to be collected and therefore few analyses were carried out; for cases with more than 10 weeks of gestation, the patients had been moved to other clinics and we were therefore unable to carry out the analysis ourselves. Of the 1236 patients, 1150 (93.0%) had dilatation and curettage (D and C) in the clinic and the remaining 86 (7.0%) had D and C in another clinic according to their wishes. Of the 1150 women who had D and C in the clinic, 1043 (90.7%) underwent cytogenetic analysis of the POC after having given informed consent. The remaining 107 women (9.3%) did not undergo the analysis for financial or other reasons. As a result, 84.4% of all the missed abortions (1043 out of 1236) received POC cytogenetic analysis in the clinic. Of the 1043 cases that underwent POC chromosome analysis, the analysis was cancelled for nine cases (0.9%) because no retained POC was present in the specimen, and for four cases (0.4%) where the cell culture failed. Cytogenetic analysis of the POC was successful in the remaining 1030 cases (98.8%), and were included in the study. Approval of this study was obtained from the independent Institutional Review Board of the Shinbashi Yume Clinic (SYC-2015-8) on 1 November 2015.

IVF and embryo transfer protocols

All the cases underwent the same procedures: oocytes were retrieved during a natural or minimal stimulation cycle; the retrieved oocytes were fertilized by ICSI and cultured until the expanded blastocyst stage; they were then vitrified and warmed in a later cycle and transferred. The methods for ovulation induction, oocyte retrieval, embryo culture and vitrified-warmed embryo transfer were all carried out following the methods reported previously (Kato et al., 2014; Teramoto and Kato, 2007). Blastocyst morphological quality was determined following Gardner's scoring criteria based on inner cell mass and trophectoderm development (Gardner et al., 2000) and the blastocysts were divided into good (grade AA), fair (grades AB and BA) and poor (the remainder) categories.

D and C and POC chromosome analysis

D and C was carried out after performing local anaesthesia by injecting 10 ml xylocaine 0.5% solution and dilating the

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