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Early miscarriage rate in lean polycystic ovary syndrome women after euploid embryo transfer – a matched-pair study

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KEY MESSAGE

This is a 1:3 retrospective paired study matched for age, BMI and embryo scores to evaluate whether PCOS contributed independently to early miscarriage after euploid blastocyst transfer. Results showed that PCOS was significantly associated with a higher risk of early miscarriage and a decreased chance of live birth.

A B S T R A C T

The early miscarriage rate is reported to be higher in patients with polycystic ovary syndrome (PCOS) compared with non-PCOS patients. However, whether PCOS is an independent risk factor for early miscarriage is still controversial; to what extent embryonic aneuploidy accounts for miscarriages of PCOS is still unknown. In this 1:3 matched-pair study, 67 lean PCOS patients and 201 controls matched for age, body mass index (BMI) and embryo scores undergoing a single euploid blastocyst transfer in vitrified-warmed cycles were analysed. Clinical pregnancy, early miscarriage and live birth rates were compared. Logistic regression analysis was performed to further evaluate the factors associated with early miscarriage and live birth. Clinical pregnancy rates were 50.7% in PCOS and 55.2% in control groups. Early miscarriage rate was significantly ($P = 0.029$) increased in the PCOS group compared with controls; non-PCOS patients had a significantly higher live birth rate than PCOS patients, $P < 0.001$. Further regression analyses showed that PCOS was significantly associated with a higher risk of early miscarriage and decreased chance of live birth. In conclusion, PCOS in women undergoing pre-implantation genetic diagnosis may, independently from BMI and karyotype, increase the risk of miscarriage.

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http://dx.doi.org/10.1016/j.rbmo.2017.07.010
1472-6483/

Please cite this article in press as: Lu Luo, et al., Early miscarriage rate in lean polycystic ovary syndrome women after euploid embryo transfer – a matched-pair study, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.07.010

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder, affecting 5–18% of women of reproductive age (Asunción et al., 2000; Azziz et al., 2004; March et al., 2010). The clinical features include irregular menses/amenorrhoea, oligoovulation/anovulation, and clinical and/or laboratory signs of hyperandrogenism (Azziz et al., 2004; March et al., 2010). Evidence suggests that pregnancy outcomes in patients with PCOS are less than satisfactory even after treatment with assisted reproductive techniques (Balen et al., 1993; Beydoun et al., 2009; Cardozo et al., 2011). The early pregnancy loss rate has been reported to be 20–50% (Balen et al., 1993; Beydoun et al., 2009; Rai et al., 2000), and complications later in the pregnancy are increased (Roos et al., 2011). However, because a considerable number of women with PCOS are overweight or obese, which is a known risk factor for early pregnancy loss (Jung et al., 2015; Metwally et al., 2008; Rees et al., 2016), it is still controversial whether PCOS is attributed to miscarriage independently.

In addition, embryonic aneuploidy is the most common reason for spontaneous abortion during the first trimester of pregnancy (Bruno et al., 2008; Warren and Silver, 2008). However, there is little information in the literature regarding the karyotypes of embryos from PCOS. Hasegawa et al. (1996) found that elevated LH and/or polycystic ovary may be involved in the genesis of spontaneous abortions that could not be explained by fetal chromosomal abnormality. However, the 41 patients included were not diagnosed with PCOS because there were no uniform criteria for its diagnosis. Another study reported that the percentage of euploid embryos was similar in PCOS women when compared with control women with a pre-implantation genetic diagnosis (PGD) using the FISH method (Weghofer et al., 2007). However, our recent study showed that abortuses from PCOS patients were significantly less likely to have chromosome aneuploidy (Wang et al., 2016). To what extent embryonic chromosomal anomalies account for miscarriages in women with PCOS is still unknown.

Recent high-quality evidence has suggested that the live birth rate could be significantly increased in patients with PCOS after frozen-thawed embryo transfer (FET) (Chen et al., 2016). This study showed that an early miscarriage rate was reduced by 10% after FET (Chen et al., 2016). This brings us to the hypothesis that pregnancy outcome may be increased to a level similar to that of patients without PCOS in FET cycles. However, there is limited research comparing the pregnancy outcome of women with and without PCOS after cryopreserved embryo transfer.

In this study, we designed a retrospective matched-pair study to assess whether PCOS was independently associated with an increased risk of early miscarriage and a decreased chance of live birth after a single euploid embryo transfer in PGD FET cycles.

Materials and methods

Participants

The design of our study was a retrospective 1:3 matched-pair study. The patients recruited were followed up at the Centre of Reproductive Medicine, the First Affiliated Hospital of Sun Yat-sen University, between January 2010 and September 2015. The study was approved by the Hospital Ethics Committee on 29 June 2016 (reference no. 2016 [119]). All patients were undergoing PGD cycles because either one of the couple had been diagnosed with chromosome translocation (sex chromosome translocations were excluded). Patients diagnosed with endometriosis, intrauterine adhesions or thin endometrium (endometrial thickness less than 8 mm on the day of progesterone initiation), uterine malformation or abnormal thyroid function were excluded. For each patient, a single euploid blastocyst diagnosed using single nucleotide polymorphism (SNP) array with a morphological score of 3BB or above was selected and transferred in a vitrified-warmed cycle with a hormone replacement method for endometrium preparation. A total of 268 lean women (BMI 18–25 kg/cm^2) were analysed. Among these patients, there were 67 patients with PCOS (study group) and 201 non-PCOS controls. The definition of PCOS was based on the Rotterdam Criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Two out of the following three criteria had to be fulfilled: oligoovulation and/or anovulation, excess androgen activity and polycystic ovaries, as well as no other endocrine secretion diseases including thyroid disease, adrenal hyperplasia or androgen-secreting tumour. All the patients in the control group had no evidence of PCOS. For each patient in the PCOS group, three control cases were selected. The control group was matched by age (exactly the same), BMI (differences no more than 0.5 kg/cm^2) and embryo scores (exactly the same). Baseline characteristics were compared between the study group and the control group (**Table 1**).

Ovarian stimulation in PGD cycles

Before PGD cycles, all couples underwent genetic counselling, understood the advantages and limitations of PGD therapy, and provided written informed consent.

All the patients received a standardized ovarian stimulation regimen in the PGD cycles. In brief, recombinant FSH (Gonal-F; Merck-Serono, Geneva, Switzerland; Puregon; NV Organon, Oss, the Netherlands) was used for ovarian stimulation in gonadotrophin-releasing hormone agonist (GnRH-agonist) protocols or gonadotrophin-releasing hormone antagonist (GnRH-antagonist) protocols. Human menopausal gonadotrophin (Menopur, Ferring; hMG, Lizhu, China) could be added if needed. The doses of the medications were adjusted according to the ovarian response. Human chorionic gonadotrophin (HCG, Pregnyl; Merck) at a dose of 4000–10,000 IU was given to induce oocyte maturation when three or more follicles reached 18 mm or more. Oocyte retrieval was performed 34–36 h after HCG injection.

Fertilization, embryo culture and biopsy

Oocytes were retrieved and fertilized by intracytoplasmic sperm injection (ICSI). Normal fertilization was identified 16–18 h after ICSI according to the presence of two pronuclei and two polar bodies. If the number of viable D3 embryos was too low (usually fewer than 6–8, according to the embryo scores), patients chose whether they would like to proceed to biopsy or to receive one more ovarian stimulation cycle. For patients who chose one more PGD cycle, D3 embryos were vitrified immediately and stored until enough D3 embryos were gained after the next oocyte retrieval cycle. Embryos for biopsy were cultured in sequential media to blastocyst stage (G1/G2 medium with 5% HSA, Vitrolife, Goteborg, Sweden). Modified Gardner and Schoolcraft grading was used to assess developing blastocysts (Gardner and Schoolcraft, 1999). Trophectoderm (TE) biopsy was performed for genetic diagnosis on D5 or D6 after fertilization. Blastocysts in which

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