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Original Article

The relationship between the *CYP19* alleles rs727479A/C, rs700518A/G, and rs700519C/T and pregnancy outcome after assisted reproductive technology in patients with polycystic ovary syndrome in a Chinese population: A population-based study

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Abstract This study investigated the relationship between the *CYP19* alleles, rs727479A/C, rs700518A/G, and rs700519C/T, and pregnancy outcome after assisted reproductive technology (ART) in patients with polycystic ovary syndrome (PCOS). Between January 2012 and September 2015, 293 PCOS patients undergoing ART were randomly selected for the study. According to pregnancy outcome after ART, the patients were assigned to pregnancy and non-pregnancy groups. *CYP19* rs727479A/C, rs700518A/G and rs700519C/T genotypes were determined using the denaturing high-performance liquid chromatography (DHPLC) method. Haplotype frequencies of the *CYP19* alleles rs727479A/C, rs700518A/G and rs700519C/T were estimated using the SHEsis platform. Logistic regression analysis was employed to analyze the factors influencing the pregnancy outcome after ART. The frequency of the AC + CC genotype of rs727479A/C was higher in the pregnancy group than in the non-pregnancy group. The frequency of the CT + TT genotype of rs700519A/G was also higher in the pregnancy group than in the non-pregnancy group. Haplotype analysis indicated that the AAC and AGT haplotypes both exhibited unfavorable influence on the pregnancy outcome after ART. The AAT and CGT haplotypes were favorable to the pregnancy outcome after ART. Logistic regression analysis suggested that the rs727479A/C AA genotype, the rs700519C/T CC genotype and body

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mass index (BMI) might exert unfavorable influence on the pregnancy outcome after ART for PCOS patients. These findings indicated that the *CYP19* alleles rs727479A/C and rs700519C/T might be associated with the pregnancy outcome after ART in patients with PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is the most frequent female endocrinopathy and the most common cause of anovulatory infertility, affecting as many as 10% of women of reproductive age [1]. Although hyperandrogenism (HA) and oligo-anovulation are two major factors, metabolic abnormalities, including insulin resistance, hyperinsulinemia and dyslipidemia, are also closely connected with PCOS [2]. Moreover, metabolic comorbidities often occur in PCOS patients for the interaction between androgen excess and abdominal adiposity [3]. A chronic androgen excess of ovarian and adrenal origin would result in abdominal adiposity and android obesity, which further promote androgen excess due to a direct response of the ovaries and adrenals to inflammatory mediators or indirectly by the development of insulin resistance and compensatory hyperinsulinemian [4,5]. PCOS patients commonly require assisted reproductive technology (ART) to conceive, and ART represents a cornerstone of clinical treatment for approximately 10% women of child-bearing age who are involuntarily infertile [6,7]. In the past two decades, ART has revolutionized the treatment of infertility, accounting for up to 3% of births in many western countries each year [8]. There are enough studies that advocate the continued surveillance of infertile women undergoing ART due to incidence of spontaneous abortion in pregnancies and birth defect risk in infants born [9,10]. Interestingly, genetic causes have been implicated in infertility. Well-known examples are sex-chromosomal abnormalities as well as Y-chromosome deletions or some chromosomal translocations [11]. Therefore, we believe that there is a close correlation between genetic conditions and the pregnancy outcome after ART.

The conversion of androgens to estrogens is catalyzed by the enzyme P450 aromatase, which is encoded by the *CYP19* gene [12]. The human *CYP19* gene is located on the q arm of chromosome 15 and consists of nine coding exons, II-X, and its transcripts are expressed in the placenta and adipose tissue, Leydig cells in the testes, granulosa cells in the ovary, and sites of the brain including hippocampus, amygdala and hypothalamus [13,14]. It has been reported that several mutations including rs4646, rs10046, rs700519, rs700518, rs727479, rs4775936, rs10459592, rs1062033, rs749292, rs6493497, rs7176005, rs700519, rs2414096, rs2470152 and rs2899470 in the *CYP19* gene may lead to an autosomal recessive form of female pseudohermaphroditism as well as virilization of the mother in pregnancy because of impairment or absence of aromatase activity [15—17]. Lto et al., in their study, provide a molecular basis of deficiency of aromatase in an adult female with PCOS as well as sexual infantilism [18]. Specifically, Jin et al. support the positive association between rs2414096 in the *CYP19* gene and hyperandrogenism, which is a clinical manifestation of PCOS [19], and Lazaros et al. confirm that a possible relationship of the *CYP19* (TTTA)7 allele with an ovarian response to standard gonadotrophin stimulation and with the pregnancy outcome after ART exists in PCOS women, potentially as a result of androgen/estrogen ratio changes [20]. Many alleles (rs1870049, rs936306, rs700518, rs700519, and rs4646) in the *CYP19* gene are studied for their correlation with preeclampsia and gestational hypertension, and the investigators find that rs700518 is associated with an increased risk of the disease [21]. Also in a study reported by Wang et al., rs700519, a common polymorphism in the *CYP19* gene, alters the risk of PCOS [22]. At the same time, rs727479, rs700519 and rs700518 in the *CYP19* gene have been more commonly investigated for their relationship with breast cancer [23—25]. Therefore, in this study, we explored the relationship between *CYP19* alleles, rs727479A/C, rs700518A/G, and rs700519C/T, and the pregnancy outcome after ART in patients with PCOS.

Materials and methods

Study subjects

Two hundred ninety-three female PCOS patients between January 2012 and September 2015 were randomly included in this study. Inclusion criteria for recruitment of PCOS patients were in accordance with the diagnostic criteria issued by the Rotterdam European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM)-Sponsored PCOS consensus workshop group (2004) [26]: (1) ovulation induction or anovulation; (2) elevation of androgen and/or hyperandrogenemia; (3) polycystic ovary. A patient was diagnosed as PCOS when one showed at least two of the above symptoms. A patient with hyperandrogenemia caused by hyperprolactinemia or Cushing's syndrome was excluded from subject recruitment. Infertile couples were excluded for male factor infertility using semen analysis. All female patients, with a mean age of 28.22 $\pm$ 4.40 years, underwent assisted reproductive technology (ART). The present study was approved by the ethics committee of our hospital. Informed consent was obtained from each participant.

Data and sample collection

Age at menarche (AAM), and the height and weight of patients were recorded and body mass index (BMI) was calculated. Fasting peripheral blood were obtained from each subject in the morning at day 3—5 during their menstrual period. For postmenopausal patients, fasting peripheral