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Association of serum autoantibodies with pregnancy outcome of patients undergoing first IVF/ICSI treatment: A prospective cohort study

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ABSTRACT

The relevance of antiphospholipid (aPL), antinuclear (ANA) or antithyroid (ATA) antibodies in women undergoing *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) are controversial. The present study aims to investigate which autoantibodies are associated with the pregnancy outcome of patients undergoing first IVF/ICSI treatment. A total of 3763 IVF/ICSI patients were recruited from January to December 2015. Forty-five patients positive for aPL presenting adverse outcomes in their first cycle received low-dose aspirin treatment before the second transfer. Logistic regression analyses were performed to assess any association between autoantibodies and IVF/ICSI outcomes. The aCL-IgG was significantly associated with live birth rate (OR 0.58, 95% CI 0.36–0.96, $p < 0.05$) and miscarriage rate (OR 2.04, 95% CI 1.23–3.40, $p < 0.01$). The aCL-IgM was associated with miscarriage rate (OR 2.14, 95% CI 1.29–3.54, $p < 0.01$). The aβ_2GPI-IgG was associated with implantation rate and clinical pregnancy rate (OR 0.61, 95% CI 0.24–0.96, $p < 0.05$; OR 0.40, 95% CI 0.13–0.87, $p < 0.05$, respectively). After the low-dose aspirin treatment, the live birth rate (37.0% vs. 19.1%, $p < 0.05$) increased significantly in patients with positive for aPL. In contrary, the aβ_2GPI-IgM, ANA, anti-thyroglobulin (aTG) and anti-thyroperoxidase (aTPO) antibodies had no association with IVF/ICSI outcome. It is suggested that the presence of aCL-IgG, aCL-IgM and aβ_2GPI-IgG might exert a detrimental effect on IVF/ICSI outcomes. Low-dose aspirin treatment could be useful for patients positive for these antibodies. Therefore, it is suggested that these antibodies should be assessed prior to IVF/ICSI treatment.

1. Introduction

Infertility is a disease, defined as the failure to conceive after 12 months of regular sexual intercourses (Practice Committee of American Society for Reproductive, 2013), estimating to affect between 8 to 12% of reproductive-aged couple worldwide (Boivin et al., 2007; Ombelet et al., 2008). The etiology of infertility is thought to be multifactorial. The known risk factors include genetic abnormalities, ovulatory disorders, tubal damage, uterine or peritoneal problems, and male factors (De Ziegler et al., 2010). However, approximately 40% of female infertilities have no identifiable risk etiologies (Cates et al., 1985). Recently, it is suggested that the autoimmune factors may play an important role in pathogenesis of infertility (Matalon et al., 2001; Twig et al., 2012; Akhlaghi et al., 2013). To investigate reproductive failure, several researchers have focused on the association between autoimmune factors and *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) outcome, where the focus was especially directed toward autoantibodies (Ruiz-Irastorza et al., 2010; Zhong et al., 2012). Thus, by examining associations between specific autoantibodies and IVF/ICSI outcome, potentially pathogenic autoantibodies can be unrevealed (Deroux et al., 2016).

The prevalence of antiphospholipid antibodies (aPL), antinuclear antibodies (ANA) or antithyroid antibodies (ATA) was significantly increased in unexplained infertility women (Reimand et al., 2001; Cervera and Balasch 2008). Moreover, a variety of studies have reported on the relationship between autoantibodies and IVF/ICSI outcome. Previous study suggested that the presence of aPL could significantly reduce the delivery rate and increase the abortion rate in women undergoing IVF treatment (Lee et al., 2007). A retrospective study showed a lower rate of embryo implantation in women with

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positive for ANA (Kikuchi et al., 2003). More so, a lower rate of implantation and clinical pregnancy in women with positive ANA was reported (Zhu et al., 2013). In a comparable line, 90 women presenting with ATA had a significantly lower rate of fertilization, implantation and pregnancy than women with negative for ATA in a cohort of 676 infertile women (Zhong et al., 2012). Although previous studies indicated a possible negative impact of these autoantibodies on the IVF/ICSI outcome, controversy exists regarding a possible association between these antibodies and IVF/ICSI failure. The Practice Committee of the American Society Reproductive Medicine reported that aPL abnormalities were not associated with IVF success as estimated by clinical pregnancy rate in seven studies [odd ratio (OR) 0.99, 95% 95% confidence intervals (CI) 0.64–1.53] or by live birth in five studies (OR 1.07, 95% CI 0.66–1.75) (Practice Committee of American Society for Reproductive, 2008). Tan et al. (2014) found that the presence of anti-thyroglobulin (aTG) or anti-thyroperoxidase (aTPO) antibodies did not impair ICSI outcome in women with normal thyroid function. Thus it is clear that the contribution of serum autoantibodies to IVF/ICSI outcome remains debated. It is not yet established which antibodies should be assessed in the evaluation and management of infertility.

Furthermore, in the context of an identified autoimmune disease, particularly for antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE), the risk of infertility is now well reported (Geva et al., 2004; Carp et al., 2012). However, few data exist on serum autoantibodies and its influence on female fertility without clinical or biological criteria for defined diseases (APS, SLE, Sjogren syndrome, etc). The above mentioned limited information does not lead to a definite conclusion on the relationship between IVF/ICSI outcome and aPL, ANA, or ATA.

For these reasons, a prospective cohort study with large sample size was performed. The two aims were to investigate whether the anticardiolipin antibody (aCL), anti-β_2 glycoprotein I antibody (aβ_2GPI), ANA, aTG, and aTPO are associated with the pregnancy outcome following IVF/ICSI treatment. The second aim was to elucidate whether these autoantibodies should be routinely assessed in the evaluation and management of women undergoing first IVF/ICSI treatment.

2. Materials and methods

2.1. Subjects and study design

A prospective cohort study of infertile women with the accepted indication for IVF or ICSI who attended the Fertility Center in Shenzhen Zhongshan Urology Hospital was conducted. All patients included in this study had tubal disorder and/or male factor or unexplained factor. All participants had primary infertility without any prior live births. The period of recruitment of participant was from January 2015 to December 2015. The study was approved by the Research Committee of Shenzhen Zhongshan Urology Hospital, and written informed consent was signed by each participant. Inclusion criteria were: (i) age < 40 years; (ii) normal karyotypes; (iii) no infectious diseases, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), rapid plasma regain (RPP), *Treponema pallidum* particle assay (TPPA), toxoplasma, rubella virus, cytomegalovirus, or herpes virus; (iv) normal basal levels of hormones, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL) or progesterone (P), which were measured on the third day of the menstrual period; (v) normal uterine anatomical. Patients were excluded from the study if they: (i) had endometriosis; and (ii) had autoimmune diseases (including APS, SLE, autoimmune thyroid disease, Sjogren syndrome, etc). During December in 2016, a survey to find out whether the patients had actually started IVF/ICSI or not, and whether the patients delivered or not, was performed. The reasons were registered if the patients who could not start IVF/ICSI.

2.2. IVF/ICSI protocol

Long-term pituitary down-regulation protocol was used in all the patients. Triptorelin injection started from the mid-luteal phase of the preceding cycle to the day of human chorionic gonadotropin (HCG) administration. The daily dose of triptorelin was 0.05–0.1 mg s.c. administered in the upper leg. After 16 days of triptorelin injection when pituitary down-regulation was established (i.e. serum estradiol < 50 pg/ml and luteinizing hormone < 5 mIU/ml), ovarian stimulation was started by daily injection of follicle stimulation hormone (FSH) (112.5–300 IU) according to the age and the number of antral follicles and the basal serum hormones. The following daily dose of FSH could be adjusted and individualized per patient based on the follicular growth as observed by ultrasonography and the detection of serum estradiol. HCG (7500–10,000 IU) was administrated when at least 2 follicles larger than 18 mm in diameter. On the day of HCG administration, no treatment with FSH was done. About 34–38 h after HCG administration, oocyte retrieval was performed followed by IVF or ICSI program. Three days later at most 3 embryos were transferred into the uterine. Progesterone was administered from the day of oocyte retrieval for luteal support. Thirteen days after embryo transfer, the serum HCG was measured. Once serum HCG examination showed positive (> 5 mIU/ml), ultrasonography was done 17 days later.

2.3. Anticoagulant treatment

One hundred and forty-six of patients with positive aCL-IgG, aCL-IgM and/or aβ_2GPI-IgG had poor IVF/ICSI outcomes in their first treatment cycles (Fig. 1). Of these, 25 patients did not start subsequently transfer. The remaining 121 patients were retested for those antibodies before the subsequently transfer. Of the remaining, 45 patients (37.2%) became negative, and 76 patients (62.8%) remained positive. Forty-five patients with positive for aCL-IgG, aCL-IgM and/or aβ_2GPI-IgG received a daily oral dose of 50 mg of aspirin treatment according to the guideline (Ruiz-Irastorza et al., 2010). Treatment was started at one month before the frozen-thawed embryo transfer and to be continued three months if they were pregnant. Thirty-one patients with positive for aCL-IgG, aCL-IgM and/or aβ_2GPI refused the treatment for known reasons and served as control group.

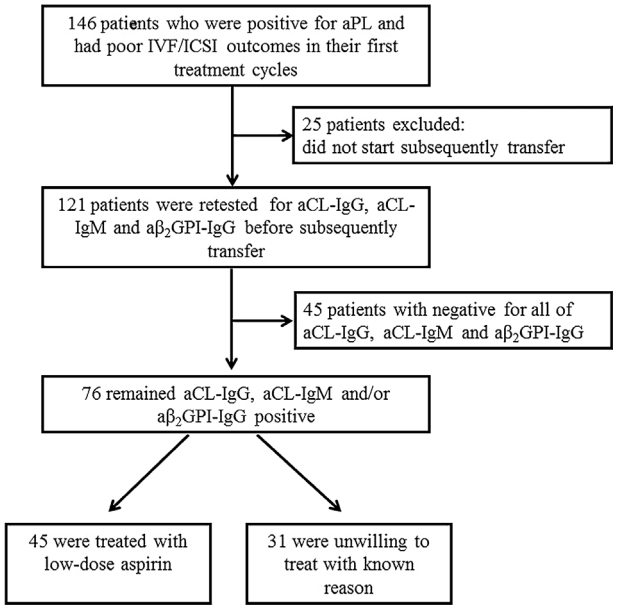

Fig. 1. The anticoagulant treatment flow diagram.

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