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Research Paper

Relationship between Antithyroid Antibody and Pregnancy Outcome following in Vitro Fertilization and Embryo Transfer

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Abstract

Objective: To investigate the impact of antithyroid antibody on pregnancy outcome following the in vitro fertilization and embryo transfer (IVF-ET).

Methods: A total of 90 patients (156 cycles) positive for antithyroid antibody (ATA+ group) and 676 infertile women (1062 cycles) negative for antithyroid antibody (ATA- group) undergoing IVF/ICSI from August 2009 to August 2010 were retrospectively analyzed.

Results: There was no significant difference in the days of ovarian stimulation, total gonadotropin dose, serum E2 level of HCG day and number of oocytes retrieved between the two groups. The fertilization rate, implantation rate and pregnancy rate following IVF-ET were significantly lower in women with antithyroid antibody than in control group (64.3% vs 74.6%, 17.8% vs 27.1% and 33.3% vs 46.7%, respectively), but the abortion rate was significantly higher in patients with antithyroid antibody (26.9% vs 11.8%).

Conclusion: Patients with antithyroid antibody showed significantly lower fertilization rate, implantation rate and pregnancy rate and higher risk for abortion following IVF-ET when compared with those without antithyroid antibody. Thus, the presence of antithyroid antibody is detrimental for the pregnancy outcome following IVF-ET.

Key words: thyroid auto-antibodies; in vitro fertilization and embryo transfer; pregnancy outcome

Introduction

The presence of antithyroid antibody (ATA) is frequently encountered in general population and approximately 1/5 of childbearing-age women are positive for the anti-thyroid peroxidase antibody (TPO-Ab) or anti-thyroglobulin antibody (TG-Ab)[1,2]. Previous research showed there were 10.5% of infertility women who were positive for ATA [3]. It has been shown that the TPO-Ab level was associated with the thyroid-stimulating hormone (TSH) level: 1) TPO-Ab positive women had significantly increase TSH level; 2) some women with normal TSH level were found to be positive for TPO-Ab [4,5]. The presence of ATA in euthyroid women may be related to some fertility problems such as increased abortion rate and raised incidence of infertility [6]. In recent years, some researchers speculated that assisted conception women positive for ATA had poor outcome of *in vitro* fertilization, even they were euthyroid [3]. To date, no consensus has been achieved on the impact of ATA on the outcome of in vitro fertilization and embryo transfer

(IVF-ET). Whether to give adjuvant therapy to regulate the thyroid autoimmunity before and during IVF is still controversial. These issues are required to be investigated and clarified.

Materials and methods

Patients

Patients receiving IVF/ICSI in the Center of Reproductive Medicine of the First Affiliated Hospital, Sun Yat-sen University, from August 2009 to August 2010 were recruited, and these patients were divided into two groups, in the ATA+ group, 90 women (a total of 156 cycles) were positive for TG-Ab and/or TPO-Ab, 676 women (a total of 1062 cycles, including 981 embryo transfer cycles and 81 embryo cryopreservation cycles) negative for TG-Ab and/or TPO-Ab served as controls. All patients did not receive any adjuvant treatment, such as glucocorticoids, anticoagulants, or other adjuvants. Patients with other autoimmune diseases, or positive for anticardiolipin antibody, anti-nuclear antibody, lupus anticoagulant, or rheumatoid factor were excluded from this study.

IVF-ET

Long-term pituitary down-regulation was performed in all patients with the following sequential regimen: gonadotropin-releasing hormone agonist (GnRH-a)/gonadotropin (Gn)/ human chorionic gonadotropin (HCG) for ovarian hyperstimulation[7]. The doses of these drugs were adjusted according to the age and the number of antral follicles and sex hormone level at baseline. Transvaginal ultrasonography together with detection of blood estradiol (E2) was used to measure the ovarian response. When at least 2 follicles larger than 18 mm in diameter or more than 3 follicles larger than 17 mm in diameter, HCG (5,000-10,000 IU) was intramuscularly injected on the same day and oocytes were collected about 36 h later. The selection of fertilization program (IVF or ICSI) was based on the semen condition on the day when the oocytes were collected. At 3 days after oocyte collection, at most 3 embryos were transferred into the uterine. The HCG or progesterone was administered from the day of oocyte collection for luteal support. 14 days after embryo transfer, the urine and serum HCG was measured. Once urine and serum HCG examination showed positive, the patients received ultrasonography 2 weeks later.

Collection of clinical information

The clinical information including age, body mass index (BMI), duration of infertility, basal serum levels of follicle stimulating hormone (bFSH) and luteinizing hormone (bLH) were collected. During the IVF treatment, data including days of Gn treatment, total Gn dose, E2 level on the day of HCG, number of oocytes retrived, fertilization rate, number of available embryos, number of embryo for transferring, pregnancy rate, implantation rate and abortion rate were recorded and analyzed.

Detection of serum ATA

Serum ATA was detected with the ARCHITECT Anti-TPO and ARCHITECT Anti-Tg kit (Abbott Laboratories, Abbott Park, IL, USA). It's a Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of the IgG class of thyroid peroxidase autoantibodies and thyroglobulin antoantibodies in human serum and plasma. The positive predictive value for Anti-TPO is ≥5.61 IU/ml, and it's designed to have an analytical sensitivity of ≤1.0 IU/ml, concordance of 92.6%. In addition, the positive predictive value for anti-Tg is ≥4.11 IU/ml, and it's designed to have a limit of detection of ≤1.0 IU/ml, concordance of 92.7%.

Statistical analysis

Statistical analysis was done with SPSS version 13.0 statistic software package. Comparisons of quantitative data were performed with t test or Wilcoxon rank sum test between two groups, and those of qualitative data carried out with chi square test. The significance level (alpha) was defined as 0.05. A value of $P<0.05$ was considered statistically significant.

Results

General Characteristics

There were no marked differences in the age, BMI, duration of infertility, bFSH and bLH between the two groups. (Table 1).

Table 1 General characteristics and basal hormone levels in ATA+ and ATA- group

Variables	ATA+ group	ATA- group	*p*-value
age (year)	32.8±4.5(22～45)	32.4±4.1(22～44)	0.305
BMI (kg/m^2)	20.5±2.2	20.4±2.2	0.108
Duration of infertility (year)	4.9±3.2(1～17)	4.6±3.2(1～19)	0.112
Basal FSH (IU/L)	5.9±2.0	5.8±1.7	0.405
Basal LH (IU/L)	4.1±1.9	4.2±1.5	0.166

Controlled Ovarian Stimulation and IVF-ET Outcome

Statistical analysis showed there were no significant differences in the days of ovarian stimulation, total Gn dose, E2 level on the day of HCG treatment and number of retrieved oocytes. In the ATA+ group, the fertilization rate, number of available embryos, implantation rate and pregnancy rate were dramatically lower but abortion rate remarkably higher than those in the control. (Table 2)

Table 2 Comparison of COS and IVF outcome between ATA+ and ATA- group

Variables	ATA+ Group	Control Group	P-value
Stimulation length(days)	11.0±1.8	10.7±1.7	0.074
Total Gn dose(IU)	2302±864	2246±736	0.885
E2 level on the day of HCG (pg/ml)	2290±1101	2342±1173	0.716
Number of retrieved oocytes	10.9±6.1	11.8±6.9	0.166
Fertilization Rate	64.3%(729/1134)	74.6%(8848/11856)	<0.001
Number of available embryos	5.3±3.9	6.0±4.2	0.01
Number of embryo transferred	2.4±0.6	2.3±0.6	0.086
Pregnancy Rate	33.3%(52/156)	46.7%(458/981)	0.002
Implantation Rate	17.8%(66/370)	27.1%(611/2251)	<0.001
Abortion Rate	26.9%(14/52)	11.8%(54/458)	0.002

Discussion

Thyroid autoimmunity and IVF outcome

In women receiving IVF-ET, the incidence of auto-antibodies is relatively high, which may be attributed to the poor IVF outcome[8-10]. In the present study, we compared the IVF outcome in ATA positive women and ATA negative women. Our results showed the fertilization rate, number of available embryos, implantation rate and pregnancy rate in the ATA positive women were significantly lower than those in ATA negative women. In a previous study, Kin et al also reported that the ATA positive infertile women had a lower pregnancy rate than ATA negative infertile women (26.3% vs 39.3%), which was at least partly consistent with our findings [11]. However, in the present study we not only found the significantly lower pregnancy rate but markedly lower fertilization rate and less available embryos in patients with ATA, which may be due to our relatively larger sample size.

In the another study, Revelli et al [3] found that although there was no significant difference in the proportion of patients positive for ATA between infertile women and normal fertile ones, the ATA positive infertile women had a poorer IVF outcome when compared with ATA negative women. However, Kim et al [11] and Revelli et al[3] did not investigate the mechanism underlying the association between ATA level and IVF outcome, which has never extensively studied so far.

Other researchers also showed women receiving assisted reproductive technology did not have an increased incidence of ATA positivity, and the pregnancy outcome was not closely related to the ATA [12,13], but there are also limitations of these studies including incomplete basic clinical information of patients (lack of patient age, basal hormone levels, etc) and small sample size, which may lead to inaccurate results. According to our findings that ATA positive patients had low fertilization rate, implantation rate, and pregnancy rate and high abortion rate. Regarding the question how ATA could interfere with fertilization, embryo development as well as implantation potential, our study did not resolve the problem also and further studies should still be undertaken to evaluate the immunologic mechanism in this special group. We speculate that ATA may bind to either the surface of the egg and/or embryo and interfere with fertilization and subsequent embryo development. Alternatively, the presence of ATA in endometrial may exert detrimental effect on embryo implantation and induce early pregnancy loss.

Thyroid autoimmunity and natural abortion

In the present study, the ATA positive women had significantly higher abortion rate than ATA negative women did. Previous study revealed TPO-Ab positive women had advanced age and high BMI and were largely pluripara when compared with TPO-Ab negative women [14]. There was evidence that the 22.5% of women with natural abortion were positive for ATA, 19.2% of women who received ART, and which was found only in 14.5% of healthy women[15]. In addition, about 13.8% of TPO-Ab positive patients had increased TSH level which was only observed in 2.4% of TPO-Ab negative women. After adjusting the age and TSH, ATA positivity is still an independent risk factor of natural abortion [1,16]. In our study, there were no significant differences in the age, BMI, duration of infertility, bFSH and bLH, which exclude the influence of age, body weight and endocrine factors on the results. In the present study, however, we could not collect TSH level for all patients, so patients with abnormal TSH level may be included. This is one limitation of the present study.

Our results were consistent with those reported recently. In euthyroid mice actively immunized with thyroglobulin, those positive for TG-Ab had significantly higher abortion rate after pregnancy[17]. In the early stage of pregnancy, the presence of ATA has been found to be associated with increased abortion rate. This association can not be influenced by the thyroid hormone and anticardiolipin antibody [2]. The mild thyroid dysfunction is related to increased abortion rate, which may be attributed to the impaired regulation of thyroid function resulting in the increased abortion rate [18]. The findings above suggest abnormal thyroid autoimmunity is closely related to the increase of abortion, but the specific mechanism is still poorly understood. The following explanations may involve in the relationship between ATA and pregnancy loss: 1) ATA positive women have potential mild hypothyroidism [19]; 2) abnormal thyroid autoimmunity may delay the time of conception. The women with advanced age have correspondingly increased abortion rate, which may be a main cause of impaired fertility [19]; (3) ATA is a marker representing the activation of autoimmunity which may be as a result of heredity or result from early immune response leading to the rejection of embryos by mother's immune system [2,15]; 4) ATA is a secondary biomarker of autoimmune disease trend, but not a real cause of abortion [19].

Thyroid autoimmunity and infertility

There is controversy on the relationship between thyroid autoimmunity and infertility. Analysis of available studies shows the infertility due to female factors often involves autoimmunity, and ATA can be used as a marker of abnormal autoimmunity [6]. The proportion of ATA positive women and ATA level in women with implantation failure and infertility of unknown cause are markedly higher than those in controls [20]. Detection of TPO-Ab in euthyroid patients is beneficial for the identification of patients having high risk for hypothyroidism. In particularly, in women preparing for pregnancy and those having high risk for hypothyroidism following pregnancy, detection of TPO-Ab can be used to predict hypothyroidism in the early stage of pregnancy and postpartum thyroid dysfunction. However, in some TPO-Ab positive patients, they have no obvious thyroid lesions. Whether the different antibodies or these autoantibodies together with other risk factors contribute to this phenomenon is still unclear [4]. There is evidence that controlled ovarian stimulation (COS) has influence on the thyroid function, especially in patients with abnormal thyroid autoimmunity. Thus, we recommend the evaluation of thyroid function and thyroid autoimmunity before assisted reproduction, especially for women with recurrent failure of IVF-ET, recurrent abortion, autoimmune diseases or related diseases (such as endometriosis). Although the changes in the thyroid function following COS can not be used to predict pregnancy outcome, the thyroid function of autoimmune thryoid disease (AITD) patients should be closely monitored after COS and during the pregnancy, and treatment should be performed if necessary [21]. Abbassi-Ghanavati et al [14] found 6% women undergoing obstetric examination were positive for thyroid peroxidase antibody, and they had three times higher incidence of placental abruption than those negative for this antibody (1.0% vs 0.3%). However, this evidence is not strong enough to recommend detection of thyroid function as a routine examination during the pregnancy. Hill et al also proposed that detection of ATA and evaluation of "reproductive immunology phenotype" were not of clinical importance for women receiving IVF-ET [22]. In the present study, patients who were positive for ATA had a significantly lower fertilization rate and pregnancy rate and a higher abortion rate than those negative for ATA did. Thus, further studies are needed to explore specific treatment for women with abnormal thyroid autoimmunity to improve their IVF and pregnancy outcome.

Conclusion

The present study reveals patients with antithyroid antibody showed significantly lower fertilization rate, implantation rate and pregnancy rate and higher risk for abortion following IVF-ET when compared with those without antithyroid antibody. Thus, the presence of antithyroid antibody is detrimental for the pregnancy outcome following IVF-ET, thus further studies should investigate appropriate treatment to regulate immune function of ATA positive patients to improve IVF outcome.

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Conflict of Interest

The authors have declared that no conflict of interest exists.

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