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Original Article

Antithyroperoxidase antibodies increase miscarriage and biochemical pregnancy rates of euthyroid women underwent IVF-ET/ICSI

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Abstract: The effect of thyroid autoimmunity, especially the presence of antithyroperoxidase antibodies (TPO-Ab) on pregnancy outcomes of euthyroid women underwent in vitro fertilization-embryo transfer (IVF-ET) and intracytoplasmic sperm injection (ICSI) treatments was controversial. This retrospective cohort study was performed to measure the cycle outcomes of euthyroid women with positive or negative TPO-Ab underwent IVF-ET/ICSI treatment. The presence of TPO-Ab was found in 153 women among 1262 euthyroid women (12.1%). No significant differences of endometrial thickness, number of oocyte retrieved, number of embryo transferred, implantation rate, clinical pregnancy rate and ectopic pregnancy rate were found between euthyroid women with or without TPO-Ab. Incidences of biochemical pregnancy rate (10.5% vs. 5.9%, $P < 0.05$), miscarriage rate (15.0% vs. 8.7%, $P < 0.05$) were significantly higher among patients with TPO-Ab than those without TPO-Ab. Euthyroid women with TPO-Ab had increased risk of biochemical pregnancy and miscarriage [OR 2.53 (95% CI, 1.37-2.97) and 3.02 (95% CI, 1.62-5.87), respectively]. The presence of TPO-Ab has minimal effect on pregnancy rate, but it is an independent risk factor of biochemical pregnancy and miscarriage of IVF-ET/ICSI women.

Keywords: Euthyroid, TPO-Ab, IVF, miscarriage, biochemical pregnancy

Introduction

Thyroid disease is the second most common endocrine condition in women of childbearing age [1]. Thyroid function and female fertility are closely related. Thyroid hormones are involved in control of menstrual cycle and fertility by regulating the actions of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) on steroid biosynthesis by specific triiodothyronine sites on oocytes. During pregnancy, a high level of estrogen induces elevated level of thyroid binding globulin, which binds more thyroxin and thus less free serum thyroxin. As a result, thyroid stimulating hormone (TSH) would increase to provide sufficient thyroid hormones [2]. The status of pregnancy itself could also induce immune tolerance, which might induce potential thyroid autoimmunity among women with possible risk factors [3, 4]. Abnormal thyroid function has been confirmed to have adverse impact on maternal and fetal outcomes, for instance, pregnancy loss, gestational hypertension, or preeclampsia, pre-term delivery [5, 6].

Thyroid autoimmunity refers to the positive state of anti-thyroid antibodies, mainly, antithyroperoxidase antibody (TPO-Ab) and/or antithyroglobulin antibody (TG-Ab). The presence of thyroid autoimmunity, especially TPO-Ab, could indicate thyroid inflammation and higher possibility of autoimmune thyroid disorders [7]. The presence of TPO-Ab among reproductive age is quite common, which was reported to be between 5.4% and 20% [5]. Its presence was even higher among those with recurrent miscarriage or infertility, which was reported to be between 14% and 33% [5].

For infertile couples, assisted reproductive technologies including intrauterine insemination (IUI), in vitro fertilization-embryo transfer (IVF-

ET), and intracytoplasmic sperm injection (ICSI) are common treatment options. In a very recent report, Unuane et al [8] suggested that compared with euthyroid women without TPO-Ab, euthyroid women with positive TPO-Ab showed no significant differences regarding pregnancy rate, miscarriage rate and liver birth rate during IUI cycles. Some researchers reported that patients having normal range of TSH levels but with thyroid autoimmunity or subclinical hypothyroidism had similar pregnancy rates and cumulative live birth rates during IVF treatment [9, 10]. Another study, in contrast, suggested that thyroid autoimmunity lowered fertilization and pregnancy rates for patients receiving IVF treatment [11]. The effect of thyroid autoimmunity in euthyroid patients on pregnancy outcomes for IVF patients have not reached consensus. It remains controversial if positive thyroid autoimmunity, especially the presence of TPO-Ab, will affect the pregnancy outcomes of euthyroid women, especially women having IVF-ET or ICSI treatment.

Most studies defined euthyroid women with TSH levels at 0.01 to 4.5 or 5.0 mIU/L. For instance, in Unuane's study [10], IVF women with TSH ranged 0.01 to 5.0 mIU/L were recruited and comparable cumulative live birth rate were found between women with or without thyroid autoimmunity. Even though some researchers suggested that taking different cutoff values of TSH either at 2.5 mIU/L, 4.5 mIU/L or even 5.0 mIU/L, clinical pregnancy rate and miscarriage rate did not differ significantly, approximately five times more women were defined as hypothyroid if taking the TSH cutoff value at 2.5 mIU/L [12]. Decreased conception rate were observed from infertile women whose TSH were above 2.5 mIU/L even with thyroxine supplement [13]. Endocrine Society from America also recommended that women who want to conceive a baby would better to keep the TSH levels lower than 2.5 mIU/L [14]. Among those women, if abnormal thyroid autoimmunity and other infertility disorders concomitantly present, it is not surprising that increased adverse pregnancy outcomes can be observed. Therefore, to avoid the interference of slightly increased levels of TSH, the present study recruited euthyroid women with basal TSH less than 2.5 mIU/L and tried to explore the effect of thyroid autoimmunity, especially with positive antibody against TPO on pregnancy outcomes of "euthyroid" IVF women by a more strict criteria.

Materials and methods

Patient recruitment

This retrospective cohort study reviewed 6321 infertility women who underwent IVF-ET or ICSI treatment at Reproductive Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University between January 2014 and March 2016. Approval from the institutional review board was also obtained.

Women who met the following criteria were included in this study, 1) aged 20 to 35 years old; 2) underwent the first fresh IVF-ET/ICSI cycle in our center; 3) with normal thyroid hormone levels (THS level between 0.01 to 2.5 mIU/L); 4) not received treatment against thyroid dysfunction in the past 6 months; 5) not complicated with other autoimmunity diseases, for instance, systemic lupus erythematosus, anti-phospholipid antibody syndrome, rheumatoid, rheumatism; 6) did not take any hormones or anti-coagulation medications in recent 6 months. Women with anti-TPO antibodies more than 60 IU/mL were defined as antibody positive cases, regardless of autoimmune status of anti-TG antibodies.

Data collection

Clinical data including age, gravity, parity, body mass index (BMI), duration of infertility, causes of infertility, smoking status, basal steroid hormone levels, ovarian function assessment and TSH levels, as well as pregnancy outcomes including clinical pregnancy, biochemical pregnancy, miscarriage, ectopic pregnancy results of women with positive and negative anti-TPO antibodies were collected and recorded in a electronic database. Routine evaluation of sex hormone profile and thyroid hormone profile were made by electrochemiluminescence immunoassay (ECLIA) before the commencement of IVF-ET/ICSI treatment.

Ovarian stimulation protocols were determined individually. Most women had GnRH agonist protocols (n=820), and the remaining women received GnRH antagonist protocols (n=329) and minimal stimulation protocols (n=113). Recombinant FSH (Puregon, MSD, US; Gonal F,

Table 1. Comparisons of clinical characteristics of women underwent IVF/ICSI with positive or negative TPO-Ab

	TPO-Ab (+) N=153	TPO-Ab (-) N=1109
Age (years old)	33.2 ± 4.6	32.6 ± 5.3
BMI (kg/m^2)	22.1 ± 1.6	23.3 ± 2.0
Duration of infertility (year)	4.3 ± 2.5	3.8 ± 2.1
Infertility type		
Primary infertility	79/51.6%	560/50.5%
Secondary infertility	74/48.4%	549/49.5%
Causes of infertility		
Tubal factor (n/%)	52/34.0%	338/30.5%
Ovulation disorder (n/%)	31/20.2%	223/20.1%
Male factor (n/%)	26/17.0%	216/19.5%
Combined factors (n/%)	33/21.6%	260/23.4%
Unknown factors (n/%)	11/7.2%	72/6.5%
Basal FSH (IU/L)	6.5 ± 2.9	7.0 ± 2.6
Basal LH (IU/L)	4.1 ± 1.8	3.8 ± 1.7
AMH (ng/ml)	2.3 (0.06-12.0)	2.7 (0.06-12.0)
AFC	7.6 ± 3.1	7.0 ± 3.5
TSH (mIU/L)	2.3 ± 1.5	2.1 ± 1.2
Stimulation protocol		
GnRH agonist protocol	95/62.1%	725/65.4%
GnRH antagonist protocol	41/26.8%	288/26.0%
Minimal stimulation	17/11.1%	96/8.6%

TPO-Ab, antithyroperoxidase antibody. BMI, body mass index. FSH, follicle stimulating hormone. LH, luteinizing hormone. AMH, anti-Mullerian hormone. AFC, antral follicle counting. TSH, thyroid stimulating hormone. GnRH, gonadotropin releasing hormone.

Merck Serono, Swiss) and human menopausal gonadotropin (HMG, Lizhu Pharmaceuticals, China; Menopur, Ferring, Germany) were administrated based on the growth trend of follicles and economic status of individual patient. Transvaginal ultrasound scan and blood test of estrogen, progesterone, FSH and LH, were performed on a regular basis to monitor the follicular growth. When at least one follicle reach 18-20 mm in diameter were observed, 10,000 IU of human chorionic gonodotrophin (HCG, Lizhu Pharmaceuticals, China) or 0.1 mg GnRH agonist (Ipsen Pharma Biotech, France) were applied for trigger of ovulation. Selection of either IVF or ICSI was determined based on the semen quality on oocyte retrieval day. One to three embryos were transferred based on the embryo quality, patient's age and her medical history. Luteal phase support was routinely prescribed with daily progesterone. Fourteen days following embryo transfer, serum HCG was detected to confirm pregnancy status. Transvaginal ultrasound scan was provided for those with elevated HCG levels 2 weeks later. For patients with ultrasonic confirmed intrauterine gestational sac, they were followed up for at least 12 weeks by telephone to confirm the pregnancy status.

Biochemical pregnancy was determined as elevated serum levels of HCG but no gestational sac indicated by transvaginal ultrasound scan at 6 weeks' gestation. Clinical pregnancy was defined as presence of intrauterine gestation sac and fetal heart beat by transvaginal ultrasound scan. Miscarriage was determined as fetal loss occurred before 28 gestational weeks. Implantation rate was determined as the number of gestational sacs detected by transvaginal ultrasound scan by 8 weeks' gestation out of the number of embryos transferred.

Statistical analysis

Data are presented as mean ± SD for normally distributed continuous variables, median (range) for continuous variables which did not follow normal distribution and number (percentage) for discrete variables. All analyses were performed with two-side tests by SPSS (version 18.0; SPSS Inc., Chicago, IL, USA). Student's *t*-test, and Fisher's exact test were performed when appropriate to compare continuous variables, and chi-square test was performed to compare categorical variables. Logistic regression model was used to determine the predictive values of pregnancy outcomes. $P < 0.05$ was considered as statistically significant.

Results

Among 6321 infertility women, clinical data of 1262 euthyroid women who fulfilled the criteria above were recorded and compared in this study. All those women had been assessed of thyroid hormones and thyroid autoimmunity. Among them, 153 women were shown to have positive TPO-Ab (153/1262, 12.1%).

Clinical characteristics of women enrolled with either positive or negative TPO-Ab are present-

Table 2. Comparisons of cycle outcomes of euthyroid women underwent IVF/ICSI with positive or negative TPO-Ab

	TPO-Ab (+) N=153	TPO-Ab (-) N=1109
Endometrial thickness (mm)	10.5 ± 2.5	11.6 ± 2.1
Number of oocytes retrieved	8 (0-21)	9 (0-20)
Number of embryos transferred	2.1	2.1
Implantation rate [% (n)]	21.2% (68/321)	21.7% (504/2326)
Clinical pregnancy rate (n/%)	64/41.8%	472/42.3%
Biochemical pregnancy rate (n/%)*	16/10.5%	65/5.9%
Miscarriage rate (n/%)*	23/15.0%	96/8.7%
Ectopic pregnancy rate (n/%)	2/1.3%	13/1.2%

TPO-Ab, antithyroperoxidase antibody. *$P < 0.05$.

Table 3. Positive TPO-Ab as a risk factors of adverse pregnancy outcomes of euthyroid women underwent IVF/ICSI

	Adjusted OR	95% CI	*P* value
Biochemical pregnancy	2.53	1.37-2.97	< 0.05
Miscarriage	3.02	1.62-5.87	< 0.01

OR, odds ratio. 95% CI, 95% confidential index.

ed in **Table 1**. The average age, BMI, duration, type and causes of infertility, basal levels of FSH, LH, anti-Mullerian hormone, and antral follicle counting were comparable between women with positive or negative TPO-Ab. Besides, no significant difference was observed of TSH levels between the two groups of patients (2.3 ± 1.5 vs. 2.1 ± 1.2 mIU/L, $P > 0.05$).

Majority of the patients, either in women with positive or negative TPO-Ab, had received GnRH agonist protocol for ovarian stimulation. The proportions of patients received GnRH agonist or antagonist protocol, as well as minimal stimulation protocol did not show any statistical significances.

The cycle characteristics of women underwent IVF/ICSI were also compared in **Table 2**. The endometrial thickness of patients with positive TPO-Ab were slightly thinner than those without TPO-Ab, but no significance was found (P=0.082). The number of oocytes retrieved, number of embryos transferred were also similar between the two groups of patients. The implantation rate, clinical pregnancy rate and ectopic pregnancy rate of euthyroid women without TPO-Ab were 21.7%, 42.3% and 1.2% respectively. Similar rates of implantation, clinical pregnancy and ectopic pregnancy (21.2%, 41.8% and 1.3%) were also observed in euthyroid women with TPO-Ab.

Notably, the incidences of biochemical pregnancy rate, miscarriage rate were significantly higher among patients with TPO-Ab than in those without (biochemical pregnancy rate, 10.5% vs. 5.9%; miscarriage rate, 15.0% vs. 8.7%, $P < 0.05$, **Table 2**).

To determine whether TPO-Ab could be an independent risk factor of predictive adverse pregnancy outcomes of euthyroid women underwent IVF/ICSI, a multivariate regression model was established. And indeed, the odds ratio of TPO-Ab for predicting biochemical pregnancy and miscarriage were 2.53 (95% CI, 1.37-2.97, $P < 0.05$) and 3.02 (95% CI, 1.62-5.87, $P < 0.01$), respectively, as shown in **Table 3**.

Discussion

This retrospective cohort study included more than one thousand patients, and demonstrated increased biochemical pregnancy rate and miscarriage rate in euthyroid IVF women with positive anti-TPO antibodies. TPO-Ab is an independent risk factor of increased biochemical pregnancy rate and miscarriage rate of euthyroid women who try to conceive a baby through IVF-ET or ICSI treatment.

Thyroid autoimmunity might be the most common cause of hypothyrodism and also autoimmunity disorders among reproductive age women [15]. Among infertile population, the presence of thyroid autoimmunity is much more common than the fertile counterparts [15]. This phenomenon also indirectly support the possible effect of thyroid autoimmunity on IVF women's outcomes [16]. The two antibodies, TG-Ab and TPO-Ab has been reported to be critical for a normal pregnancy. In particular, anti-TPO antibodies represent the activities of thyroiditis and development of thyroiditis, since it is strongly associated with autoimmune cytocoxicity, even in euthyroid patients [17]. Anti-TG antibodies, on the contrary, barely involved in immune reaction and destruction in thyroiditis

and cannot indicate the progress of thyroiditis [17]. Bellver et al [18] also reported that the presence of TPO-Ab with or without TG-Ab in women was related with unexplained infertility and implantation failure. The presence of anti-TPO antibodies could slightly increase the risk of infertility (OR 1.5, 95% CI 1.1-2.0) [19]. Therefore, among several thyroid autoimmune antibodies, anti-TPO antibodies might be of higher clinical significances and were chosen for investigation in this study.

Several other studies also indicated increased miscarriage risk in the presence of thyroid autoimmunity [11, 20], as well as reduced fertilization rate, implantation rate and pregnancy rate [21, 22]. Besides, one meta-analysis of observational studies confirmed an elevated risk of spontaneous miscarriage among euthyroid IVF women with thyroid autoimmunity [23]. Therefore, thyroid autoimmune disorder could lead to some adverse outcomes, including spontaneous miscarriage, regardless of assisted or naturally pregnancy. In contrast to the results of this study, several investigators noted a comparable miscarriage rate between women with thyroid autoimmunity or not [24, 25]. Unuane also report that thyroid autoimmunity showed minimal impact on cumulative delivery rate of infertility women following six cycles of IVF/ICSI treatment [8]. However, different thyroid hormone ranges were used in those studies, which might account for the discrepancies with our data. Interestingly, as also suggested by Toulis [23], even though the miscarriage rate was higher in women with thyroid autoimmunity than controls, the difference was still small enough to lead to differences of clinical pregnancy and live birth rate. Our results are in agreement with the above conclusion and showed a comparable clinical pregnancy rate between women with and without TPO-Ab.

Results from several studies can support the notion that TPO-Ab might lead to adverse pregnancy outcomes of women underwent IVF treatment. Using a short thyrotropin releasing hormone (TRH) stimulation test, Lazzarin et al [26] found that recurrent miscarriage patients who were also with thyroid autoimmunity had abnormal response by showing elevated levels of TSH above 15 mIU/L. The presence of thyroid autoimmune could also lead to relatively reduced concentration of thyroid hormones at different gestational weeks, even though the women were actually euthyroid. TPO-Ab above 2000 IU/mL could also increase the risk of hypothyroidism [15]. Therefore, an impaired thyroid function was indeed present in euthyroid patients with thyroid autoimmunity. Thyroid autoimmunity was involved in reproductive failure not only through thyroid function abnormality, but it can also be accompanied with other immune imbalance. In pregnant women with elevated anti-thyroid antibodies, T helper-1 (Th1)/T helper-2 (Th2) ratio may shift to a Th1-type immune response. These activated T lymphocytes may lead to implantation failure [27]. TPO-Ab can also impair embryo quality in euthyroid women [1]. Because a higher level of TSH could also negatively affect embryo quality, the effect of TPO antibodies is more apparent for euthyroid patients with low-normal TSH (no more than 2.5 mIU/L) [1]. Moreover, levels of anti-thyroid antibodies in follicle fluid were strongly correlated with their serum concentrations [11]. Even though the direct relationship is not clear, number of embryos with good quality, oocyte fertilization rate and pregnancy rate was indeed decreased in IVF women with thyroid autoimmunity [11]. Some researchers also suggested that thyroid autoimmunity is more prevalent among women with endometriosis and ovarian dysfunction, including polycystic ovarian syndrome, premature ovarian failure [8, 28-31], which might be due to shared autoimmune disorders in those subfertile women. However, underlying mechanisms of those association were still largely unknown.

For women with positive TPO-Ab, supplement of selenium, an critical trace mineral which involved in the synthesis of thyroid hormones and modulation of immune function, seemed to be beneficial [32]. Although low-dose selenium (60 μg/day) in pregnant women had minimal effect on the levels of TPO-Ab, it might help to improve thyroid function in those women [32]. In another study, 200 μg/day selenium was provided for TPO-Ab positive women during pregnancy and postpartum period to lower TPO-Ab titers, and showed an reduction of incidences of hypothyroidism and postpartum thyroid disorders [33]. However, iodine status was not taken into consideration in this study, which might influence the relationship of TPO-Ab levels and relevant management. Since the presence of TPO-Ab might uncover an potential thyroid dysfunction, it was proposed that supplement of levothyroxine might correct the subtle thyroid deficiency, and thus improve pregnancy outcomes [5, 34]. One meta-analysis

including two randomized studies with 187 women reported 52% reduction of relative risk of miscarriage with supplement of levothyroxine [20]. However, whether infertility women following IVF treatment could benefit from levothyroxine with or without selenium treatment is not confirmed, and requires more prospective randomized studies.

One major strength of this study is that we included a relatively large population of women underwent IVF-ET/ICSI treatment, among whom, more than 150 euthyroid women with positive TPO-Ab were included. However, the study is limited by several weaknesses. First of all, this study is a retrospective, single centered study, which is the major drawback of the present study. Further, the live birth rate, one critical pregnancy outcome was not included in this study, since this part of data was incomplete by the time of drafting this manuscript. Besides, whether the adverse pregnant outcomes were dose-dependent on the titers of TPO-Ab was not investigated in this study or any other studies. In the future, a dose-dependent pattern of adverse pregnancy outcomes might further imply a direct association of thyroid autoimmunity and pregnancy outcomes.

In conclusion, the presence of positive TPO-Ab is an independent risk factor of the occurrence of biochemical pregnancy and miscarriage for women underwent IVF-ET/ICSI treatment. It is necessary to screen thyroid autoimmunity for women undergo IVF-ET/ICSI, especially those with repeated miscarriage.

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Disclosure of conflict of interest

None.

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