

Thyroid autoimmunity in adverse fertility and pregnancy outcomes: Timing of assisted reproductive technology in AITD women

Jia-Wei Wang¹, Xiao-Xian Liao², Tuo Li²

¹Department of Obstetrics and Gynecology, Nantong Maternity and Child Health Care Hospital affiliated to Nantong University, Nantong 226018, Jiangsu Province, China;

²Department of endocrinology, Changzheng hospital, Naval Medical University, Shanghai 200003, China

ABSTRACT

Thyroid autoimmunity (TAI) is prevalent in women of live-birthing age and has independently been associated with complications of fertility and pregnancy, in the case of spontaneous conception or after assisted reproductive technology (ART) treatment. However, it remains challenging to identify causation between infertility and TAI, even interventional trials looking at the impact of levothyroxine (LT4) treatment on fertility and pregnancy outcomes due to differences among study results which related to small scales, inappropriate study designs, enrollment criteria of infertility cause and titer/hormone concentration measurements. Furthermore, many questions remain unsettled in ART management in AITD infertile women attempt pregnancy. Therefore, further observational and interventional trials are needed more comprehensive multiple-center, double blinded, and randomized.

Key words: autoimmune thyroid diseases, AITD, Infertility, Assisted reproductive technology, ART

INTRODUCTION

Autoimmune thyroid diseases, AITD, are the most common organ affected by autoimmune disease via T cells,^[1] in which Grave's disease (GD) and Hashimoto's thyroiditis (HT) are common, accompanied with hyperthyroidism or hypothyroidism. AITD is caused by disorders of the thyroid-related autoimmune system, characterized by lymphocytes infiltration, and the appearance of thyroid autoantibodies. Antithyroid antibodies (ATA) mainly include thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb), and thyroid-stimulating hormone receptor antibody (TRAb). The appearance of TRAb has a direct role in the pathogenesis of GD, while TPOAb and TgAb are thyroid autoimmunity (TAI) markers, and their production may be a response to thyroid injury.

TRAb may play a role in fetal and neonatal hyperthyroidism. During early pregnancy,

high concentrations of human chorionic gonadotropin (hCG) are a high-risk factor for hyperthyroidism, and women with high hCG level often develop transient thyrotoxicosis during gestation.^[2-4] Therefore, women at risk are recommended to monitor TRAb titer.^[5-9] The presence of positive ATA throughout pregnancy has a higher risk with subclinical hypothyroidism (SCH) and clinical hypothyroidism than those with negative ATA.^[10-12] However, about 15%–65% of pregnant women with thyroid-stimulating hormone (TSH) higher than the upper limit of normal range present positive ATA,^[13-15] which indicates that there are other causes (such as iodine deficiency, subtotal/total thyroidectomy) that kick in hypothyroidism during pregnancy. Because of the increased risk of hypothyroidism in AITD women during pregnancy, the American Thyroid Association guidelines recommend that women with AITD evaluate TSH concentrations every four weeks in mid-pregnancy. Pregnant women

Address for Correspondence:
Dr. Tuo Li, Department of Endocrinology,
Changzheng Hospital, Naval Medical
University, 450 Fengyang Road, Huangpu
District, Shanghai 200003, China.
E-mail: zoe_leeto@hotmail.com

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with a TSH value of 2.5–10.0 mIU/L should detect the level of TPOAb, and the level of TSH before entering the ART treatment should not exceed 2.5 mIU/L. This information helps determine which patients should receive interventions.^[16]

EPIDEMIOLOGY AND DEVELOPMENT IN AITD FEMALE

The prevalence of AITD in different population usually differs greatly due to differences in age, gender, genetics, environment, iodine intake, ethnicity, *etc.* A general population survey found that the incidence of AITD was (11.3 ± 0.4)%, women were much more than men, and the prevalence was positively correlated with aging^[17]. Positive rates of TPOAb and TgAb in women aged 20–29 were 9.2 and 11.3%, respectively, while those aged 30–39 were 14.5 and 14.2%, respectively. The positive rate of TPOAb in pregnant women is 5%–14%, and the positive rate of TgAb is 3%–18%.^[13, 18, 19] However, due to the differences in analytical methods and diagnostic cutoffs used in each study, there may be differences in the reported thyroid antibody levels and the relationship between antibody levels and pregnancy outcomes. Studies have reported some risk factors for AITD, such as: aging, family history of AITD, iodine deficiency or overdose, and European ancestry, but with no correlation between multiple pregnancies and the occurrence of AITD.^[19, 20]

Studies have shown that the prevalence and titer of thyroid antibodies have decreased during gestation. These studies also reported that the baseline TSH concentration of AITD women was higher than that of antibody-negative women.^[10, 13, 14, 21] In women with AITD, the TSH level is maintained at high level during pregnancy. Although the ATA decreases during delivery, the TSH concentration will further increase. The decrease or disappearance of the ATA level during pregnancy may be due to the body's immune tolerance state, which is usually due to gestation. However, the physiological changes that occur during pregnancy lead to an increase in the body's demand for thyroid hormone production, which may counteract the beneficial effects of reduced ATA titers. Although thyroid antibodies can pass through the placenta, TPOAb and TgAb have no effect on fetal thyroid function.^[22]

AITD MAY INCREASE INFERTILITY HAZARD

A meta-analysis of four studies showed that among euthyroid women, the risk of unexplained infertility in ATA-positive people is slightly increased (relative risk (RR) 1.47, 95% CI 1.06–2.02).^[23] This goal remains to be demonstrated by larger studies. All in all, people

understand the relationship between thyroid autoimmunity and infertility because the test data of related studies are substituted, and multiple studies are studied. Therefore, it is not recommended in the American Thyroid Association guideline that positive-ATA females with euthyroidism receive LT₄ treatment when trying to conceive normally.^[16]

Because multiple causes lead to infertility in women with TAI, the pathogenic mechanism between AITD and infertility is unclear. The zona pellucida expresses antigens shared by thyroid tissues, and is, therefore, considered a target for thyroid antibodies.^[24] In addition, the Monteleone *et al.*^[25] found that ATA in the follicular fluid of AITD women, and the proportion of these women's fertilization and Grade A embryos, was much lower than that of women without thyroid antibodies. Although, in this study, ATA women had a higher pregnancy success (43% *vs.* 29%, $P < 0.001$), without statistical difference. Thus, they speculated that ATA detected in follicles may reduce the quality and fertilization potential of oocytes through antibody-mediated cytotoxicity.

AITD may induce a high-risk ART

Some studies have explored whether AITD will affect the outcome of assisted reproductive technology. The observation objects included in these studies include infertile women caused by different causes. Some of them have completed the first cycle of assisted reproductive assisted pregnancy, and some have received multiple cycles of assisted reproductive assisted pregnancy. It is, therefore, difficult to compare the results of the research. The two main indicators evaluated are usually the proportion of clinically pregnant women and the proportion of miscarried women. Some small-scale studies have reported the correlation between AITD and the low pregnancy rate among women who received assisted reproductive assistance.^[26, 27] However, most studies have found that there is no significant difference in the pregnancy rate between women with positive thyroid antibody and women with negative antibody among women with normal nail function who received assisted reproductive assist.^[28-30]

A few studies have discussed the risk of miscarriage after assisted reproductive assisted AITD women with normal nail function, but have obtained the opposite results. Two meta-analysis results showed that women with thyroid antibody positive who received assisted reproductive assist treatment had a significantly increased risk of miscarriage.^[31, 32] In one of the meta-analysis,^[32] 12 studies reported that the ratio of miscarriage was 1.44 (95% CI 1.06–1.95, $P = 0.02$) in AITD women compared with the controls, rather than the baseline TSH concentrations. The analysis found that thyroid antibodies had no effect on the average number of eggs harvested, fertilization, and implantation.

Intervention in ART cycle of AITD female

Both the retrospective study and another small-scale randomized controlled trial (RCT) evaluated the therapeutic effect of levothyroxine in euthyroid women with AITD and undergoing ART and infertility treatment.^[33,34] Studies in this area have not found any changes in pregnancy or miscarriage among women receiving LT_4 treatment. In the study, in addition to aspirin and heparin, the group that received intravenous immunoglobulin, and the other group took only aspirin and heparin, found that the intravenous immunoglobulin group had a higher reproduction rate (51% *vs.* 27%; $P = 0.027$).^[35] More small-scale randomized clinical trials have studied the therapeutic effect of glucocorticoids on AITD women and found that the proportion of AITD women taking prednisolone in clinical pregnancy and childbirth is significantly higher than that of AITD women not taking prednisolone.^[36,37]

Although studies have reported that glucocorticoid therapy is effective, larger studies are still needed to further validate these data. In addition, because it is unknown whether corticosteroids are used early in pregnancy, the use of corticosteroids in early pregnancy requires caution. Although there is still insufficient evidence, but considering that the potential benefit is greater than the minimum risk, the American Thyroid Association guidelines recommend that ATA-positive euthyroid women are better for receive low-dose LT_4 supplementation during ART treatment to increase its success.^[16]

AITD INCREASES THE MISCARRIAGE RISK

AITD and recurrent miscarriages (RM)

In 1990, Stagnaro *et al.*^[38] firstly described the relationship between AITD and miscarriage in euthyroid women that the rate of abortion in antibody-positive population was twice those in antibody-negative population (17.0% *vs.* 8.4%, $P = 0.01$). A meta-analysis involved 12 case-control studies, and 19 prospective cohort studies found that the combined odds ratio (OR) of miscarriage in women with positive thyroid autoantibodies was 1.8 (95% CI: 1.25–2.60) in the case-control studies, and in the cohort studies was 3.9 (95% CI: 2.48–6.12), which suggests that AITD can definitely increase risk of spontaneous abortion.^[39] Relatively, there are still doubts about the correlation between TAI and recurrent miscarriages (RM). Some studies have revealed that AITD may cause multiple abortions,^[40,41] while it has not been universally confirmed.^[42] A meta-analysis of eight clinical researches found out that, compared with positive-ATA women with normal thyroid function, negative ones have an increased RM risk (OR = 2.3, 95% CI: 1.5–3.5).^[23]

Pathogenesis of pregnancy loss in AITD female

Aging is considered as an independent risk factor for spontaneous abortion.^[43] Thus, this meta-analysis excluded no age-matched studies and found that the risk of miscarriage in ATA-positive women was higher than that of ATA-negative women.^[23] High level of TSH is also considered as a risk factor for miscarriage.^[44] Chen *et al.*^[45] included a total of 22 clinical analyses on AITD and miscarriage risk and showed that in euthyroid women, the mean TSH level in ATA-positive patients was 0.61 mIU/L higher than that of ATA-negative controls ($P < 0.0001$). Besides, the presence of ATA should be an indirect sign of mild thyroid dysfunction, especially the thyroid abnormal response to increased thyroid hormone demand during pregnancy. A prospective cohort study showed that mild increases in TSH and positive ATA have a superimposed effect on the risk of miscarriage, with normal FT_4 and FT_3 values, whereas an upper normal range of TSH values in these subjects with RM and AITD.^[45] Therefore, it is believed that LT_4 supplementation treatment cannot only control the level of TSH but reduce the risk of autoimmune antibodies exposure as well, thereby effectively suppressing the risk of spontaneous miscarriage in such patients.^[46]

Another potential reason for the increased risk of miscarriage in AITD women is that AITD has comorbidities with other autoimmune diseases, such as systemic lupus erythematosus and antiphospholipid antibody syndrome. There is relationship with AITD and non-organ-specific antibodies. In RM women, the value of $CD3^+/CD4^+$ (Th1/Th2 helper cells expressing cytokines) in ATA-positive individuals is higher than that in ATA-negative ones, suggesting that the appearance of ATA may be part of systemic immune dysfunction.^[47] In women with reproductive failure, the number of $CD5^+/CD20^+$ B lymphocytes increases significantly, which are involved in the development of autoimmune diseases.^[48] It was further found that an immune response dominated by Th1 in cases of RM and embryo transfer (ET) failure.^[49] It has been confirmed that $INF-\gamma$, $IL-2$, and $TNF-\alpha$, secreted by Th1 cells, trigger the thrombosis and inflammatory process of maternal uterine placental blood vessels and may directly migrate into the uterus through T lymphocytes or NK cells, thus finally cause miscarriage.^[50] All the above-illustrated thyroid autoimmunity maybe non-specific to autoimmune diseases and has an indirect connection with reproductive failure.

By contrast, some hypothesize that ATA plays a direct pathogenic effect on pregnancy failure; $TPOAb^+/TgAb^+$ mouse models showed climbing prevalence of fetal absorption, which need further studies to confirm this phenomenon.^[51,52] Besides, TRAb is also believed

to have interaction with hCG receptors, for TRAb may inhibit the LH/hCG receptors to reduce the production of progesterone and estrogen, thus lead to miscarriage.^[24]

Prevention of potential miscarriage in AITD euthyroid women

The current methods of prevention from miscarriage in AITD women are to supplement levothyroxine or intravenous immunoglobulin. Exogenous supplementation of synthetic thyroid hormone analogs to help to reduce the miscarriage risk in AITD female is based on the consideration of the correlation between AITD and hypothyroidism during pregnancy. RCTs and retrospective observational studies have found that euthyroid pregnant women with AITD received LT_4 supplementation has a lower spontaneous abortion than the control group.^[53, 54] However, there are still doubts whether LT_4 treatment has an obvious effect on reproductive success. A randomized study found that supplementation with levothyroxine can reduce the spontaneous abortion rate in TPOAb⁺ women (14.9% toward 11.6%), but without statistical significance.^[55] Another RCT on euthyroidism or SCH (TSH \leq 10 mIU/L with normal FT₃ and FT₄ level) with AITD women also published that LT_4 treatment had no protect effect on live birthing (3.6% of miscarriage rate in treatment *vs.* 3.4% in observational control).^[21] And, a meta-analysis also reported that insignificant decline in miscarriage rate in ATA-positive euthyroid women who received LT_4 treatment.^[56] Thus, it is now not clearly recommended or opposed whether ATA-positive women with normal thyroid function need levothyroxine during pregnancy.^[16, 57] We also need more multi-center clinical randomized trials to further clarify the intervention effect of thyroid hormone on spontaneous abortion, such as TABLET study^[58] and T4-LIFE study.^[59]

In addition, intravenous immunoglobulin is another potential treatment method to suppress the titers. If the pregnancy loss in euthyroid women with ATA is due to the potential systemic autoimmune activation, intravenous immunoglobulin may effectively regulate the cellular response of transformation of Th1 to Th2 and eventually avoid abortion in these population.^[60] Unfortunately, this method has application limits.^[61, 62] One of the clinical trials observed and compared the livebirth rate of LT_4 supplementation and intravenous immunoglobulin for ATA-positive female and found out that the delivery outcomes in those with LT_4 supplementation were generally improved than those with immunoglobulin injections.^[62] Due to lack of sufficient evidence, it is not recommended for RM women with TAI and euthyroidism to undergo LT_4 treatment.^[16]

AITD MAY INCREASE THE RISK OF PREMATURE DELIVERY (PTD)

The incidence of preterm birth is 6%–10% in China, in which induced abortion (44.6%), premature rupture of the membranes (PPROM, 44.2%), and unknown reasons (21.0%) are the main causes of preterm birth.^[63] In 1994, Glinoe^[10] discovered that women with AITD had a doubling premature delivery (PTD) rate (16% in AITD *vs.* 8% in controls, $P < 0.005$). A meta-analysis of five cohort studies confirmed that the appearance of ATA was clearly related to the PTD risk (OR = 2.07, 95% CI: 1.17–3.68, $P = 0.01$).^[39] Another meta-analysis of 11 prospective cohort studies showed that the overall RR of preterm birth in euthyroid women with AITD was 1.98 (95% CI 1.29–3.04, $P = 0.002$).^[64] At present, the pathophysiological mechanism of the correlation between TAI and premature birth is not clear, slight damage to thyroid function, direct action of ATA, systemic non-specific autoimmune hyperactivity, or all of the above reasons may have played roles in PTD.^[65]

Management of PTD risk in AITD euthyroid women throughout pregnancy

Some randomized clinical trials have found that PTD risk in ATA-positive female can be reduced via levothyroxine supplementation,^[21, 66] in which Nazarpour *et al.*^[21] reported reducing of preterm delivery, however, mainly present in TPOAb⁺ women with TSH over 4 μ IU/ml. Meanwhile, the impact of LT_4 treatment in preterm delivery rates in another RCT^[55] revealed no beneficial effect. In this trial, the enrolled women with TPOAb⁺ and TSH less than 2.5 mIU/L were randomly selected to treatment group, LT_4 replacement as 0.5 μ g/(kg·d) for pregnant women with TSH between 0.5 and 1.5 mIU/L and 1.0 μ g/(kg·d) for those at 1.5–2.5mIU/L, and control group untreated in the first trimester of pregnancy and received LT_4 intervention if TSH exceeded 3.0 mIU/L from the second trimester. In conclusion, the present studies are insufficient to prove that levothyroxine intervention has an impact on the PTD rate in euthyroid thyroid antibody-positive women.^[16]

WOMEN WITH AITD MAY BE AT INCREASED RISK OF OTHER ADVERSE PREGNANCY AND DEVELOPMENTAL OUTCOMES

TAI impact on other adverse neonatal outcomes

Current controversies are focused on the relationship between maternal TAI and fetal neurodevelopmental disorders.^[67-70] Wasserman *et al.*^[71] found that the mother-to-be with TPOAb⁺ in the third trimester eventually gave

birth to lower IQ score, in which the gap peaked in the IQ scores at the aged of four, and then narrowed after the age of seven. Furthermore, sensorineural hearing loss turned out to be related to intelligence, with an OR of 7.5 in risk of sensorineural hearing loss in children whose mothers occurred gestational AITD (95% CI: 2.4–23.3).^[72] Hence, it remains to be further studied whether the development of the fetal nervous system is interacted with maternal TAI, gestational SCH, or direct systemic autoimmune disorders, or both.

It is reported that mothers who were TPOAb⁺ more often had intrauterine growth retardation (IUGR) infants than TPOAb⁻ mothers and thus might lead to the climbing incidence of PTD,^[73] while the correlation has not been confirmed generally by evidence-based medicine.^[74] Besides, the offspring of ATA-positive mothers had threefold greater perinatal mortality than those of ATA-negative,^[73] but this conclusion has not been generally accepted.^[20, 75] On the other hand, Negro *et al.*^[75] found an increase in respiratory distress in infants due to their mothers with ATA-positive during pregnancy. In short, these present studies provide suggestive evidence of an association between TAI and adverse newborns outcomes in euthyroid women, which should be considered preliminary and awaits further studies.

TAI and other complications of pregnancy

Some clinical studies have found that postpartum depression (PPD) is related to AITD. However, the mechanism underlying this relationship is unclear.^[76] An established isolated TPOAb-positive mouse model displayed depressive behaviors and a decrease of the concentration of brain-derived neurotrophic factor (BDNF) and 5-HT in the prefrontal cortex without changes in the total T₄ concentration in the prefrontal cortex. So, they hypothesized that the presence of ATA inhibited 5-HT–BDNF interactions and regulated the process of neural remodeling, clinically caused cognition impairment and social misbehavior.^[77] Other hypotheses were proposed that a surge of pro-inflammatory cytokines in autoimmune diseases induces depression.^[78]

Ying's study^[79] has found that TPOAb⁺ euthyroidism in early pregnancy is associated with an increased risk of gestational diabetes mellitus, but meta-analysis did not show this association clearly.^[80] In addition, the most common complications of late pregnancy in AITD patients are abruptio placentae (AP) and PPROM. Compared with TPOAb⁻ pregnancies, the TPOAb⁺ ones suffered from an increased AP risk.^[20] The FaSTER trial^[81] further found TPOAb⁺ women in the first and second trimesters have a higher AP hazard than TPOAb⁻ women. And, a similar but weaker relationship was present for TgAb. However,

ORs for pregnancies with both TPOAb⁺ and TgAb⁺ were much higher (first trimester: 2.10, 95% CI 0.91–4.86; second trimester: 2.73, 95% CI 1.17–6.33).

CONCLUSIONS

The interaction between autoimmune thyroid diseases and complications of fertility and pregnancy is complex. Thyroid autoimmunity and following overt thyroid dysfunction lead to infertility and pregnancy and neonatal complications. Thus, it seems reasonable to screen for TSH concentrations and thyroid antibodies (including TPOAb and TgAb) in infertile women attempting spontaneous or assisted conception. Based on the existing literature, at present, there is insufficient evidence for the beneficial outcomes of antibody titer suppression and hormone supplementation. Considering the possible adverse effects of overtreatment, it is more cautious in particular in patients with ATA-positive and euthyroidism to receive low-dose LT₄ treatment accordingly during conception and pregnancy. In summary, it is now not clearly recommended or opposed whether ATA-positive women with normal thyroid function need levothyroxine during pregnancy, and it is necessary to conduct more investigations to raise our awareness of this issue.

Declarations

Not applicable

Conflicts of Interests

The authors have no conflicts of interest to disclose.

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Authors' Contributions

Li T contributes in study design and critical discussion. Wang JW contributes in manuscript drafting and critical discussion. Li XX contributes in study design and execution. All authors read and approved the final manuscript.

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