Review Article

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

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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 multi-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
In women with AITD, the TSH level is elevated during pregnancy. A meta-analysis of four studies showed that the baseline TSH concentration of AITD women was higher than that of antibody-negative women. 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.

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). 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 LT$_4$ treatment when trying to conceive normally.

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. In addition, the Monteleone et al. 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. 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.

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. In one of the meta-analysis, 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.


**Pathogenesis of pregnancy loss inAITD 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.\(^{[49]}\) Chen et al.\(^{[48]}\) included a total of 22 clinical analyses onAITD andmiscarriage 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 positiveATA have a superimposed effect on the risk of miscarriage, with normal FT\(_3\) and FT\(_4\) values, whereas an upper normal range ofTSH values in these subjects with RM andAITD.\(^{[43]}\) Therefore, it is believed that LT\(_4\) supplementation treatment cannot only control the level ofTSH 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 inAITD women is that AITD has comorbidities with other autoimmune diseases, such as systemic lupus erythematosus and antiphospholipid antibody syndrome. There is relationship withAITD and non-organ-specific antibodies. InRM women, the value ofCD3\(^+\)/CD4\(^+\) (Th1/Th2 helper cellsexpressing cytokines) inATA-positive individuals is higher than that inATA-negative ones, suggesting that the appearance of ATA may be part of systemic immune dysfunction.\(^{[47]}\) Inwomen with reproductive failure, the number ofCD5\(^+\)/CD20\(^+\) B lymphocytes increases significantly, which are involved in the development of autoimmune diseases.\(^{[48]}\) It was further found that an immune response dominated byTh1 incases of RM and embryo transfer (ET) failure.\(^{[49]}\) It has been confirmedthatINF-\(\gamma\), IL-2, andTNF-\(\alpha\), secreted by Th1 cells, trigger the thrombosis and inflammatory process ofmaternal uterine placental blood vessels and may directly migrate into the uterus through T lymphocytes orNK cells, thus finally cause miscarrage.\(^{[50]}\) 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
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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 LT₄ supplementation has a lower spontaneous abortion than the control group.[53, 54]

However, there are still doubts whether LT₄ 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 ≤ 10 mIU/L with normal FT₃ and FT₄ level) with AITD women also published that LT₄ treatment had no protect effect on live birth (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 LT₄ 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 LT₄ supplementation and intravenous immunoglobulin for ATA-positive female and found out that the delivery outcomes in those with LT₄ 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 LT₄ treatment.[63]

**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.[64] In 1994, Glinoer[65] 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).[66] 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.[67]

**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 μIU/ml. Meanwhile, the impact of LT₄ 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, LT₄ replacement as 0.5 μg/(kg·d) for pregnant women with TSH between 0.5 and 1.5 mIU/L, and 1.0 μg/(kg·d) for those at 1.5–2.5mIU/L, and control group untreated in the first trimester of pregnancy and received LT₄ 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).\textsuperscript{73} 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\textsuperscript{+} more often had intrauterine growth retardation (IUGR) infants than TPOAb\textsuperscript{−} mothers and thus might lead to the climbing incidence of PTD\textsuperscript{73} while the correlation has not been confirmed generally by evidence-based medicine.\textsuperscript{74} Besides, the offspring of ATA-positive mothers had threefold greater perinatal mortality than those of ATA-negative,\textsuperscript{75} but this conclusion has not been generally accepted.\textsuperscript{90, 78} On the other hand, Negro et al.\textsuperscript{79} 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.\textsuperscript{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 T\textsubscript{3} 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.\textsuperscript{77} Other hypotheses were proposed that a surge of pro-inflammatory cytokines in autoimmune diseases induces depression.\textsuperscript{79}

Ying’s study\textsuperscript{78} has found that TPOAb\textsuperscript{+} euthyroidism in early pregnancy is associated with an increased risk of gestational diabetes mellitus, but meta-analysis did not show this association clearly.\textsuperscript{80} In addition, the most common complications of late pregnancy in AITD patients are abruptio placenta (AP) and PPROM. Compared with TPOAb pregnancies, the TPOAb\textsuperscript{+} ones suffered from an increased AP risk.\textsuperscript{20} The FaSTER trial\textsuperscript{81} further found TPOAb\textsuperscript{+} women in the first and second trimesters have a higher AP hazard than TPOAb\textsuperscript{−} women. And, a similar but weaker relationship was present for TgAb. However, ORs for pregnancies with both TPOAb\textsuperscript{+} and TgAb\textsuperscript{+} 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 LT\textsubscript{4} 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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