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Diagnosis and Management of Thyroid Disease during Pregnancy and Postpartum: 2023 Revised Korean Thyroid Association Guidelines

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Thyroid hormone plays a critical role in fetal growth and development, and thyroid dysfunction during pregnancy is associated with several adverse outcomes, such as miscarriage and preterm birth. In this review, we introduce and explain three major changes in the revised Korean Thyroid Association (KTA) guidelines for the diagnosis and management of thyroid disease during pregnancy: first, the normal range of thyroid-stimulating hormone (TSH) during pregnancy; second, the treatment of subclinical hypothyroidism; and third, the management of euthyroid pregnant women with positive thyroid autoantibodies. The revised KTA guidelines adopt 4.0 mIU/L as the upper limit of TSH in the first trimester. A TSH level between 4.0 and 10.0 mIU/L, combined with free thyroxine (T4) within the normal range, is defined as subclinical hypothyroidism, and a TSH level over 10 mIU/L is defined as overt hypothyroidism regardless of the free T4 level. Levothyroxine treatment is recommended when the TSH level is higher than 4 mIU/L in subclinical hypothyroidism, regardless of thyroid peroxidase antibody positivity. However, thyroid hormone therapy to prevent miscarriage is not recommended in thyroid autoantibody-positive women with normal thyroid function.

Keywords: Pregnancy; Hypothyroidism; Anti-thyroid autoantibodies

INTRODUCTION

Thyroid disease is common in women, especially during reproductive age. Thyroid-stimulating hormone (TSH), a key hormone regulating thyroid function, is maintained at levels lower than that of non-pregnant women in early pregnancy [1] because it has a structural homology to human chorionic gonadotropin, the levels of which rise in early pregnancy [2].

Since thyroid hormone plays a critical role in fetal growth and development, especially for the brain and nervous system, a sufficient level of thyroid hormone must be maintained during pregnancy [3]. Insufficient thyroid hormone levels may lead to adverse outcomes of pregnancy, such as premature birth, stillbirth, and gestational hypertension [4,5], even in the case of subclinical hypothyroidism [6]. However, excessive thyroid hormone levels may also cause problems, such as premature birth, stillbirth, and preeclampsia [7,8].

Thyroid autoantibodies are detected in patients with Hashi-

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moto's thyroiditis and Graves' disease. Recent studies have reported that thyroid autoantibodies themselves, even without thyroid dysfunction, have a close relationship with pregnancy complications such as miscarriage or preterm delivery [9,10].

Therefore, the proper management of various thyroid diseases during pregnancy is important. In 2014, the Korean Thyroid Association (KTA) published guidelines for the diagnosis and management of thyroid disease during pregnancy and postpartum. In 2022, these guidelines were revised, and the revised KTA guidelines will be published soon.

In this review, we introduce and explain three major changes in the revised guidelines: first, the normal range of TSH during pregnancy; second, the treatment of subclinical hypothyroidism; and third, the management of euthyroid pregnant women with positive thyroid autoantibodies.

NORMAL TSH RANGES IN THE FIRST TRIMESTER OF PREGNANCY

The 2014 KTA guidelines adopted the 2011 American Thyroid Association (ATA) guidelines for the TSH reference range during pregnancy because TSH data measured in Korean pregnant women were not available at that time. According to those guidelines, the normal range of TSH was 0.1 to 2.5 mIU/L in the first trimester, 0.2 to 3.0 mIU/L in the second trimester, and 0.3 to 3.5 mIU/L in the third trimester.

In order to determine pregnancy-specific reference ranges of TSH and free thyroxine (T4), it is recommended to select a reference group comprising people who have neither thyroid disease nor thyroid autoantibodies, while taking an adequate amount of iodine [11]. In 2015, Moon et al. [12] published the first study on the reference ranges of TSH and free T4 in Korean pregnant women. They measured serum TSH and free T4 levels in 465 women with no thyroid autoantibodies [12]. However, they did not report their iodine intake. In 2018, Kim et al. [13] reported a study on measurements of TSH, free T4 levels, and urinary iodine concentrations in 417 pregnant women with no thyroid autoantibodies. The results showed that the urinary iodine concentration in pregnant women was higher than the adequate level (397 to 451 μg/day), confirming that Korea was an iodine-sufficient country. Table 1 reports a summary of TSH and free T4 data for each trimester of pregnancy. In these two studies, the upper limit of the TSH reference range exceeded 4.0 mIU/L. However, we did not adopt their results in the revised guidelines because they did not report pregnancy outcomes. The 2017 revised ATA guidelines recommended applying a fixed TSH upper limit of 4.0 mIU/L when population-based data were not available [11]. After the 2017 ATA guidelines were published, a new study was published reporting that adverse pregnancy outcomes, including miscarriage and preterm delivery, did not increase when TSH levels were below 4.0 mIU/L [14]. Furthermore, another study reported that adverse pregnancy outcomes increased in women with TSH levels of 2.5 to 4.0 mIU/L who received levothyroxine (LT4) therapy [15]. Based on the results of these studies, the revised KTA guidelines adopt 4.0 mIU/L as the upper limit of TSH in the first trimester. A TSH level between 4.0 and 10.0 mIU/L, combined with free T4 within the normal range, is defined as subclinical hypothyroidism. A TSH level over 10 mIU/L is defined as overt hypothyroidism regardless of the free T4 level.

Table 1. Trimester-Specific Percentile Values of TSH and Free T4

Variable	2.5th–97.5th percentile	
	Moon et al. (2015) [12]	Kim et al. (2018) [13]
TSH, mIU/L		
First	0.01–4.10	0.03–4.24
Second	0.01–4.26	0.13–4.84
Third	0.15–4.57	0.30–5.57
Free T4, ng/dL		
First	0.83–1.65	0.84–1.43
Second	0.71–1.22	0.68–1.21
Third	0.65–1.13	0.67–1.13

TSH, thyroid-stimulating hormone; T4, thyroxine.

TREATMENT OF SUBCLINICAL HYPOTHYROIDISM DURING PREGNANCY

In the 2014 KTA guidelines, LT4 treatment was recommended for patients with a TSH level >2.5 mIU/L and positive thyroid peroxidase antibody (TPOAb). However, the revised 2017 ATA guidelines suggested complicated criteria for the treatment of subclinical hypothyroidism; they recommended thyroid hormone therapy for pregnant women with positive TPOAb and TSH levels exceeding the upper limit of pregnancy-specific criteria, while thyroid hormone therapy could also be considered for those with positive TPOAb and TSH levels between 2.5 mIU/L and the upper limit of normal, or those with negative TPOAb and TSH levels between the upper limit of normal and 10 mIU/L. The strength of those recommendations, however, was weak due to a lack of evidence [11].

After the 2017 ATA guidelines were released, many papers investigated the effect of LT4 treatment for subclinical hypothyroidism during pregnancy. A retrospective study analyzing the effect of thyroid hormone treatment in 5,405 pregnant women with subclinical hypothyroidism with TSH levels of 2.5 to 10 mIU/L showed that thyroid hormone treatment starting at 28 to 29 weeks decreased the risk of miscarriage by 38%, while increasing the risk of premature birth by 60% [15]. In particular, when the TSH level was 4.1 to 10.0 mIU/L, LT4 treatment reduced the risk of miscarriage by 55%. However, this study did not state whether the patients had thyroid autoantibodies. In another prospective study, Nazarpour et al. [16] randomly divided 131 pregnant women with TPOAb-positive subclinical hypothyroidism (TSH 2.5 to 10 mIU/L) into two groups and compared the results based on thyroid hormone treatment. In the group that received LT4 treatment, the risks of premature birth and neonatal admission were reduced by 70% and 83%, respectively, compared to the group that did not receive LT4 treatment [16]. The effects of LT4 treatment were evident when TSH levels were higher than 4.0 mIU/L, while when TSH levels were below 4 mIU/L, no significant difference was observed according to LT4 therapy. The researchers also compared the effects of thyroid hormone therapy in 366 TPOAb-negative pregnant women divided by various TSH criteria. When the TSH criterion was 2.5 mIU/L or higher, LT4 treatment did not lead to a statistically significant difference in the risk of preterm birth. However, when the TSH criterion was 4.0 mIU/L or higher, thyroid hormone treatment reduced the risk of premature birth by 61% [17]. These results suggest that thyroid hormone therapy could be effective when TSH levels are higher than 4 mIU/L, regardless of TPOAb positivity.

Two recent randomized controlled trials (RCTs) investigated the effect of LT4 treatment for pregnant women with subclinical hypothyroidism on childhood neurocognitive outcomes [18,19]. According to a meta-analysis of these two RCTs [20], LT4 treatment for pregnant women with subclinical hypothyroidism had no positive effect on childhood IQ (at the age of 3 or 5). Considering that fetal neurologic development starts early in the first trimester, the timing of LT4 treatment in these studies, starting at 16.6 and 12 weeks of gestational age, may have been too late to evaluate its effect.

In accordance with these results, the revised KTA guidelines recommend LT4 treatment when TPOAb is positive and the TSH level is higher than 4 mIU/L. However, they do not contain a statement about LT4 treatment when the TSH level is between 2.5 and 4 mIU/L. If TPOAb is negative, LT4 treatment can also be considered if the TSH level is higher than 4 mIU/L. The strength of the recommendation was changed from weak to strong.

TREATMENT OF EUTHYROID PREGNANT WOMEN WITH POSITIVE THYROID AUTOANTIBODIES TO PREVENT MISCARRIAGE

TPOAb and thyroglobulin antibody are related to hypothyroidism caused by Hashimoto's thyroiditis, and 5%–14% and 3%–18% of pregnant women are known to be positive for these antibodies, respectively [21]. Thyroid autoantibody positivity, which represents a limited potential to increase thyroid hormone production in accordance with increased demand during pregnancy, results in rising TSH levels during pregnancy [22] and several pregnancy-related complications [23,24].

Spontaneous abortion, which is defined as occurring at less than 20 weeks, is known to occur in 17% to 31% of all pregnancies. A meta-analysis of eight case-control studies showed a relationship between thyroid autoantibodies and miscarriage (pooled odds ratio [OR], 2.55; 95% confidence interval [CI], 1.42 to 4.57), and a meta-analysis of 14 cohort studies also showed a relationship between thyroid autoantibodies and spontaneous abortion (OR, 2.31; 95% CI, 1.90 to 2.82) [10]. However, this study had a limitation since the autoantibody-positive women were older and had higher average TSH levels than autoantibody-negative women. Another meta-analysis showed that thyroid autoantibody-positive women had a significantly higher miscarriage rate than controls (cohort studies [OR, 3.90; 95% CI, 2.48–6.12]; case-control studies [OR, 1.80; 95% CI, 1.25 to 2.60]) [25].

Three RCTs were recently conducted to investigate whether thyroid hormone treatment can reduce miscarriage in thyroid autoantibody-positive women. In the Pregnancy Outcomes Study in Euthyroid Women with Thyroid Autoimmunity After Levothyroxine (POSTAL) study, LT4 treatment did not significantly reduce the risk of miscarriage, and preterm birth. At the same time, it did not increase the live birth rate in TPOAb-positive euthyroid women who became pregnant by *in vitro* fertilization [26]. In the Thyroid AntiBodies and LEvoThyroxine (TABLET) study, LT4 was administered 1 year before fertilization to TPOAb-positive euthyroid women who had experienced one or more miscarriages or had undergone infertility treatment in the UK. In this study, LT4 treatment did not lead to a significant difference in the live birth rate compared to the control group (37.4% in the LT4 group vs. 37.9% in the control group;

Table 2. Large Randomized Controlled Studies of the Effects of LT4 Treatment during Pregnancy in TPOAb-Positive Women with Normal Thyroid Function

Study	POSTAL, 2017	TABLET, 2019	T4LIFE, 2022
Country	China	United Kingdom	Netherlands
No. of subjects	600	952	187
Inclusion criteria	TPOAb-positive euthyroid women undergoing IVF excluding women who have experienced more than two spontaneous abortions.	TPOAb-positive euthyroid women who plan to conceive (natural pregnancy, assisted pregnancy) within 12 months, have a history of one or more miscarriages or have undergone infertility treatment.	TPOAb-positive women with normal thyroid function who had experienced two or more recurrent miscarriages.
Mean age	31.3±3.9 years (LT4 group) 31.7±3.8 years (control)	32.5±4.9 years (LT4 group) 32.7±4.9 years (control)	34.9±4.2 years (LT4 group) 33.7±4.7 years (control)
TSH range for normal thyroid function	0.50–4.78 mIU/L	0.44–3.63 mIU/L	Reference value of each institution (0.30–5 mIU/L)
LT4 treatment methods	Initiation of LT4 treatment prior to IVF Starting dose of LT4 2.5 mIU/L≥ TSH: 50 μg/day 2.5 mIU/L< TSH: 25 μg/day (If body weight <50 kg: reduce the starting dose by 50%) TSH target: TSH 0.1–2.5 (1st), 0.2–3.0 (2nd), 0.3–3.0 (3rd)	Administration of 50 μg/day of LT4 from before conception to the end of pregnancy	Administration of LT4 before conception to the end of pregnancy TSH <1.0 mU/L: LT4 0.5 μg/kg TSH 1.0–2.5 mU/L: LT4 0.75 μg/kg TSH >2.5 mU/L: LT4 1.0 μg/kg
Results	Miscarriage: RR=0.97 (95% CI, 0.45–2.10) Live birth rate (≥24 weeks): RR=0.98 (95% CI, 0.78–1.24) Preterm delivery: RR=1.13 (95% CI, 0.65–1.96)	Live birth rate (≥34 weeks): RR=0.97 (95% CI, 0.83–1.14) Miscarriage (<24 weeks): RR=0.95 (95% CI, 0.73–1.23)	Live birth rate (≥24 weeks): RR=1.03 (95% CI, 0.77–1.38) Preterm birth (<34 weeks): RR=1.41 (95% CI, 0.33–6.08)

LT4, levothyroxine; TPOAb, thyroid peroxidase antibody; POSTAL, Pregnancy Outcomes Study in Euthyroid Women with Thyroid Autoimmunity After Levothyroxine; TABLET, Thyroid Antibodies and Levothyroxine; IVF, *in vitro* fertilization; TSH, thyroid-stimulating hormone; RR, relative risk; CI, confidence interval.

relative risk, 0.97; 95% CI, 0.83 to 1.14) [27]. Finally, in the T4LIFE trial, which was conducted among euthyroid TPOAb-positive women with recurrent pregnancy loss, TPOAb-positive euthyroid women who had experienced more than two miscarriages were treated with thyroid hormone before fertilization depending on TSH levels, but there was no significant increase in the rate of live birth (50% in the LT4 group vs. 48% in the placebo group; risk ratio, 1.03; 95% CI, 0.77 to 1.38) [28]. The results of these large randomized controlled studies are summarized in Table 2.

Based on these results, the revised KTA guidelines do not recommend thyroid hormone therapy for thyroid autoantibody-positive women with normal thyroid function for the purpose of preventing miscarriage.

CONCLUSIONS

The revised KTA guidelines define the upper limit of TSH as 4 mIU/L for the first trimester. In addition, based on the results of recent RCTs, the guidelines recommend thyroid hormone therapy for women with subclinical hypothyroidism when the TSH level is higher than 4 mIU/L, regardless of TPOAb positivity. However, LT4 treatment is not recommended for TPOAb-positive women with normal thyroid function for the purpose of preventing miscarriage or premature birth. Nonetheless, there remain uncertain areas in thyroid dysfunction and pregnancy, such as the effect of maternal subclinical hypothyroidism on fetal neurocognitive function. We must obtain high-quality evidence to elucidate these unsolved problems.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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