REVIEW ARTICLE

pISSN: 2384-3799 eISSN: 2466-1899
Int J Thyroidol 2020 November 13(2): 85-94
https://doi.org/10.11106/ijt.2020.13.2.85

Recent Issues Related to Thyroid Disease in Pregnancy

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Maternal and fetal complications may occur because of pathologic or immunologic changes during pregnancy. The American Thyroid Association (ATA) suggests an optimal thyroid stimulating hormone (TSH) reference range of 0.50-4.00 mU/L in pregnant women. Based on Korean data, the same range may be applied to Korean pregnant women. According to the ATA guideline, levothyroxine therapy is recommended for thyroid peroxidase antibody (TPOAb)-positive women with a TSH greater than the pregnancy-specific reference range (approximately >4.0 mU/L in Korea) and TPOAb-negative women with a TSH >10.0 mU/L. The presence of TPOAb may be a sign of hypothyroidism due to damage to the thyroid. Because the titer of TPOAb decreases as gestation progresses, its measurement should be performed as early as possible during pregnancy. Although the mechanism is unknown, the association between thyroid autoimmunity and miscarriage/premature delivery is clear. Selenium may reduce the development of postpartum thyroiditis and permanent hypothyroidism; however, routine prescription of selenium is not recommended as it may increase the risk of type 2 diabetes. According to Korean nationwide data, birth defects in antithyroid drug (ATD)-exposed offspring in early pregnancy increased by 1.1 to 2.2% compared with non-exposed offspring. Avoidance of ATD in early pregnancy is the best option, otherwise, it is preferable to switch to propylthiouracil before pregnancy. When methimazole use is unavoidable in early pregnancy, it is recommended to use less than 5 mg per day.

Key Words: Pregnancy, Thyrotropin, Autoantibodies, Antithyroid agents, Malformation

Introduction

Pregnancy causes many changes to the thyroid gland and its function. The production of thyroid hormone during pregnancy increases by 50%. Daily iodine requirement also increases during pregnancy, leading to increase in thyroid volume of 10% and 20-40% in iodine sufficient and deficient areas, respectively. Maternal and fetal complications may occur because of pathologic or immunologic changes during pregnancy. Thyroid autoantibodies have an adverse impact on a pregnant woman (mainly hypothyroidism and miscarriage) and subsequently the fetus. Untreated hyperthyroidism in pregnancy poses risks to both mother and fetus.

In this article, I would like to address the contents presented at the special lecture of the Korean Thyroid Association (KTA) conference held in August 2019.

The Change of Thyroid Function During Pregnancy

1) Increase in TBG concentration results in increase of serum total T4/T3 concentrations

Production of thyroxine binding globulin (TBG) increases from 6-8 weeks of pregnancy due to enhanced hepatic synthesis by increase in estrogen

Received May 21, 2020 / Revised July 17, 2020 / Accepted July 24, 2020
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production. A decrease in TBG degradation due to estrogen-induced sialyation of TBG also contributes to the increase in TBG concentration. Therefore, serum total T4 and total T3 concentrations increase as TBG increases.[1)]

Although measurement of thyroid hormone by liquid chromatography with tandem mass spectrometry is most accurate, its measurement by immunoassay is common in practice. However, immunoassays may vary depending on serum TBG or albumin concentration and iodine intake. The reference range for total T4 during pregnancy should be set 1.5 times higher than the pre-pregnancy range.

2) HCG acts as a TSH agonist in early pregnancy

In early pregnancy, production of human chorionic gonadotropin (hCG) in the placenta increases and its structure is transformed into asialo-hCG to stimulate production of thyroid hormone. It is composed of an α- and a β-subunit; the α-subunit has the same structure as luteinizing hormone (LH), follicle-stimulating hormone (FSH), and TSH, while the β-subunit is a unique structure. hCG acts as a TSH agonist and begins to appear from 3-4 weeks of gestation, increases maximally at 10-12 weeks, then decreases gradually. It plays an important role in development of gestational thyrotoxicosis and hyperemesis gravidarum.[1)]

Serum free T4 and free T3 concentrations increase transiently due to the high circulating hCG in the 1st trimester and then gradually decrease to within the normal range in the 2nd and 3rd trimesters. Increase in plasma volume and glomerular filtration rate (GFR) as well as changes in deiodinase activity in the placenta during pregnancy result in decreased free T4 and free T3 concentrations as gestation progresses. Because serum TSH level is suppressed by 20-50% by week 10 due to high circulating hCG, TSH may be misleading in the 1st trimester, and T4 (total or free) will provide a more accurate clinical status. Later in pregnancy, serum TSH levels become reliable and T4 may fall, especially in the 3rd trimester, without indicating hypothyroidism.[1)]

3) Iodine requirement is increased during pregnancy

During pregnancy, GFR increases and reabsorption of iodine in the renal tubules decreases, leading to an increase in iodine loss in the urine. The fetal thyroid begins iodine uptake at 10-12 weeks of pregnancy to produce thyroid hormones. Therefore, the iodine requirement in pregnant women is increased by 50%.[2)] The imbalance between iodine intake and requirement during pregnancy may increase thyroid volume, even in iodine sufficient areas.

In the United States, recommended daily allowances for iodine intake are 150 μg in adults, 250 μg in pregnant women, and 250-290 μg in breastfeeding women.[3,4)] Ingestion of greater than 1100 μg of iodine per day, which is the tolerable upper limit, may cause thyroid dysfunction.[3)] The American Thyroid Association (ATA) recommends that sustained dietary iodine intake exceeding 500 μg/day be avoided during pregnancy due to concerns about the potential for fetal thyroid dysfunction.[5)] However, there is no evidence whether the criteria proposed by the ATA can be applied to iodine excessive areas such as Korea and Japan. In addition, there are no known effects of iodine excess on the fetus during pregnancy. In 2009, Orito et al.[6)] investigated the effects of serum TSH concentration and excessive iodine intake in early pregnancy on the development of fetuses in 514 pregnant women. They reported that 1.9% were miscarried, and the mother's TSH concentration in early pregnancy was independent of neonatal maturity and development up to 1 year of age. Despite the excessive iodine intake, there were no abnormalities in development of the fetuses. However, there was a lack of investigation of the offspring after 1 year in this study.

Median urinary iodine concentration (UIC) is used most frequently to evaluate the iodine status of populations but not individuals.[7,8)] Cho et al.[9)] reported UIC during pregnancy in 344 Korean pregnant women. They found that the median UIC and UIC adjusted by Cr were 427.3 μg/L and 447.9 μg/gCr, respectively. There was no difference in median UIC according to trimester of pregnancy. When all participants were divided by UIC according to World Health Organization

(WHO) criteria, only 13% were in the adequate range (UIC 150–249 μg/L).[10] Two-thirds of participants (65%) showed UIC 250 μg/L or greater (above requirements and excessive). Another 21% had a UIC less than 150 μg/L (insufficient).

Is it Necessary to Perform Thyroid Hormone Tests in All Pregnant Women?

Guidelines on this matter vary among expert groups. In Korea, obstetricians do not perform routine thyroid hormone tests in pregnant women. The KTA recommends the following ambiguous suggestions: 1) There is insufficient evidence to recommend for or against routine TSH screening in early pregnancy; 2) TSH measurement in early pregnancy is performed in high-risk pregnant women, although there is insufficient evidence to recommend for or against the pre-pregnancy TSH test; 3) Routine free T4 measurement during pregnancy is not recommended; and 4) There is insufficient evidence to recommend for or against routine TPOAb screening in early pregnancy.[11] In conclusion, the KTA recommends only serum TSH measurement in early pregnancy and only in high-risk pregnant women. High-risk refers to a history of hyperthyroidism or hypothyroidism; current symptoms/signs of thyroid dysfunction; TPOAb positivity; presence of a goiter; history of head or neck radiation or prior thyroid surgery; age >30 years; type 1 diabetes or other autoimmune disorder; history of pregnancy loss, preterm delivery, or infertility; family history of autoimmune thyroid disease or thyroid dysfunction; morbid obesity (BMI >40 kg/m^2); use of amiodarone or lithium or recent (within 6 weeks) administration of iodinated radiologic contrast; and residing in an area of known moderate to severe iodine insufficiency.

There have been reports that 30–55% of subclinical or overt hypothyroidism was undetected by case-finding only in high-risk pregnant women.[12,13] Negro et al.[14] reported that there was no difference in reducing complications between screening and case-finding in the high-risk group, but screening could reduce complications in the low-risk group. Laurberg et al.[15] reported that 200–300 patients with overt hypothyroidism/100,000 population were detected by screenings that were not diagnosed by case-finding only in high-risk groups. Although large-scale prospective studies and consideration for cost-effectiveness are required, it is necessary to positively review the serum TSH measurements in early pregnancy in all pregnant women.

It is Desirable to Set a Country-Specific Range for Serum TSH Concentration During Pregnancy

It is most desirable to set a unique, country-specific range for serum TSH concentration during pregnancy. In 2011, the ATA suggested reference ranges for serum TSH of 0.1–2.5 mU/L in the 1st trimester, 0.2–3.0 mU/L in the 2nd trimester, and 0.3–3.0 mU/L in the 3rd trimester.[16] However, Li et al.[17] screened 4800 pregnant women in the 1st trimester and 2000 non-pregnant women to establish a reference range of serum TSH in Chinese pregnant women. They reported that the median of serum TSH from 4–6 weeks was significantly higher than from 7–12 weeks (2.15 [0.56–5.31] mIU/L vs. 1.47 [0.10–4.34] mIU/L); however, there was no significant difference compared with non-pregnant women (2.07 [0.69–5.64] mIU/L). They also suggested that the reference upper limit of TSH in early pregnancy shifted more upward than previously reported. An upward shift in the reference upper limit of TSH was also supported by studies in other countries.[18-20] In addition, the analysis of serum TSH and free T4 "set-point" in pregnant women showed that reductions in free T4 were observed only when serum TSH was greater than 4.8 mU/L. Therefore, in 2017, the ATA revised the TSH reference range to 0.5–4.0 mU/L in pregnant women if there is no country-specific range.[5] Recently, two studies on TSH reference range during pregnancy in Korea have been published. Moon et al.[19] suggested TSH reference ranges of 0.01–4.10 mU/L in the 1st trimester, 0.01–4.26 mU/L in the 2nd trimester, and 0.15–4.57 mU/L in the 3rd trimester. Kim et al.[20] suggested its ranges of 0.03–4.24 mU/L in the 1st trimester, 0.13–4.84 mU/L in the 2nd trimester, and 0.30–5.57 mU/L in the 3rd trimester.

Effects of Thyroid Autoantibodies on Thyroid Function During Pregnancy

The prevalence of thyroid autoantibodies increases with age.[21] According to NHANES III (1988–1994), the prevalence of thyroid peroxidase antibody (TPOAb) increases to 11.3% in patients' 20s, 14.2% in their 30s, and 18.0% in their 40s, and the prevalence of antithyroglobulin antibody (TgAb) increases to 9.2% in their 20s, 14.5% in their 30s, and 16.4% in their 40s.[21] According to KNHANES VI (2013–2015), the prevalence of TPOAb also increases with age (2.81% in patients' 10s, 4.13% in their 20s, 5.63% in their 30s, 7.94% in their 40s, 11.71% in their 50s, and 10.01% in their 60s).[22] Differences in the prevalence of thyroid autoantibodies between the US and Korea may be due to differences in test kits and positive criteria as well as racial differences. According to NHANES III, the prevalence of TPOAb is higher in whites than in Mexican Americans and blacks (14.3% vs. 10.9% vs. 5.3%).[21]

The thyroid autoantibody titer decreases as gestation progresses.[23] Therefore, TPOAb measurements should be performed as early as possible during pregnancy. Dietary iodine intake may also be associated with the prevalence of thyroid autoantibodies during pregnancy. Shi et al.[24] demonstrated a U-shaped relationship between UIC and thyroid antibody positivity in pregnant women. Interestingly, Cho et al.[9] reported that the prevalence of thyroid autoantibodies in Korean pregnant women did not change or even increased as gestation progressed (TPOAb 3% in the 1st trimester, 3% in the 2nd trimester, and 6% in the 3rd trimester; TgAb 3% in the 1st trimester, 2% in the 2nd trimester, and 2% in the 3rd trimester). Although the Korean results were lower than those of the US reports, it is not currently known why the prevalence of antibodies did not decrease. It is evident that the prevalence of thyroid autoantibodies in Korean pregnant women as well as non-pregnant adults is lower than in Americans.

In TPOAb-positive euthyroid women, serum TSH level increased as gestation progressed, with approximately 20% of women having a supranormal TSH value at delivery.[25,26] Medici et al.[27] reported that serum TSH level was significantly higher and free T4 level was significantly lower in TPOAb-positive pregnant women than in TPOAb-negative pregnant women. They also reported significantly higher prevalences of subclinical and overt hypothyroidism in TPOAb-positive pregnant women than in TPOAb-negative pregnant women (subclinical hypothyroidism 20.1% vs. 2.4%, overt hypothyroidism 3.3% vs. 0.1%). Therefore, TPOAb positivity was associated with higher maternal TSH level, lower free T4 level, and 8- and 26-fold higher risks of subclinical and overt hypothyroidism, respectively. Therefore, euthyroid pregnant women who are positive for TPOAb or TgAb should have serum TSH concentration measured at pregnancy confirmation and every 4 weeks through mid-pregnancy.[5]

The presence of thyroid autoantibodies may be a sign of thyroid dysfunction due to damage to the thyroid; this suggests a high likelihood of failure to supply thyroid hormone, which increases in demand during pregnancy.[28] Autoimmune thyroid disease occurs due to an absence of adequate T-cell tolerance. In the initial stage, genetic and environmental factors cause thyrocyte damage and exposure of various thyroid antigens. Antigen-presenting cells (APCs) recognize these antigens and infiltrate the thyroid gland. After processing the antigen, the thyroidal APCs migrate to lymphoid tissue where they activate T cells. CD4+ T cells mediate B-cell activation and thyroid antibody induction. T cells also release cytokines and have a direct cytotoxic effect on the thyroid gland. Cytotoxic T cells, B cells, macrophages, cytokines, and thyroid antibodies infiltrate the thyroid gland and induce apoptosis and destruction of the thyrocyte.[28]

Serum TSH Cut-off Values for Thyroid Hormone Therapy during Pregnancy

Administration of levothyroxine (L-T4) depends on the positivity of TPOAb and serum TSH concentration measured at early pregnancy. In the 2011 ATA guidelines, the upper reference limits for serum TSH concentration during pregnancy were 2.5 mU/L in the 1st trimester and 3.0 mU/L in the 2nd and 3rd trimesters.[16] Since then, many studies have shown that the TSH

upper limit can be set differently by iodine status, TSH assay, body mass index, geography, ethnicity, and TPOAb positivity. According to the 2017 ATA guidelines, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range during pregnancy.[5] Reference ranges should be defined in healthy TPOAb-negative pregnant women with optimal iodine intake and without thyroid illness. If the pregnancy-specific upper limit of serum TSH is not available in a particular country, 4.0 mU/L may be used.

According to the 2017 ATA guidelines, L-T4 therapy is recommended for TPOAb-positive women with serum TSH concentration greater than the pregnancy-specific reference range (approximately >4.0 mU/L in Korea) and TPOAb-negative women with serum TSH >10.0 mU/L. L-T4 therapy may be considered for TPOAb-positive women with serum TSH >2.5 mU/L and TPOAb-negative women with serum TSH concentration greater than the pregnancy-specific reference range (approximately >4.0 mU/L in Korea).[5] For reference, the upper limit of serum TSH for Korean pregnant women is as follows: TSH 4.10-4.24 mU/L in the 1st trimester, 4.26-4.84 mU/L in the 2nd trimester, and 4.57-5.57 mU/L in the 3rd trimester.[19,20] However, prescribing L-T4 in early pregnancy requires a conservative approach. I recommended starting at a serum TSH concentration of 2.5 mU/L or higher. This recommendation is supported by Liu et al.,[29] in which the frequency of miscarriage increased in TPOAb-positive women with serum TSH >2.5 mU/L. In addition, in most cases, TPOAb measurement is not performed or is performed too late, so there is a high possibility of false-negatives.

Association of Miscarriage with Thyroid Autoimmunity

Miscarriage is defined as pregnancy failure before 24 weeks of gestation. Approximately 10 to 15% of all pregnancies end in early spontaneous miscarriage before 10 weeks of pregnancy. Chromosomal abnormalities, advanced maternal and paternal age, underweight or overweight, smoking, and high alcohol consumption are known to be associated with increased chance of miscarriage. It may also occur due to antiphospholipid syndrome, uterine abnormalities, endocrine abnormalities, and use of various drugs.[28]

Many studies have shown that the frequency of miscarriage in pregnant women with thyroid autoantibodies is significantly higher than in pregnant women without thyroid autoantibodies. Stagnaro-Green et al.[30] reported that thyroid autoantibody-positive pregnant women miscarried at a rate of 17%, compared with 8.4% for autoantibody-negative pregnant women. Thangaratinam et al.[31] performed a meta-analysis of 31 studies (19 cohort and 12 case-control) involving 12,126 pregnant women to assess the association between thyroid autoantibodies and miscarriage. Of the 31 studies, 28 showed a significant positive association between thyroid autoantibodies and miscarriage. van den Boogaard et al.[32] also reported in a meta-analysis that presence of thyroid antibodies was associated with an increased risk of miscarriage and recurrent miscarriage compared with absence of thyroid antibodies. Since thyroid autoantibodies were measured after 10 weeks of pregnancy in most studies, it is likely that the risk of miscarriage caused by autoantibodies was underestimated.

Liu et al.[29] investigated the miscarriage frequency in pregnant women according to the presence of thyroid autoantibodies and serum TSH levels. They reported that the presence of autoantibodies increased the risk of miscarriage by 2.7 to 9.6 times irrespective of the serum TSH levels, and TSH level above 5.2 mU/L increased the risk of miscarriage by 3.4 to 9.6 times regardless of the presence of autoantibodies. They emphasized that the risk of miscarriage also increased 5-fold when autoantibodies were accompanied with a TSH within the range of 2.5-5.2 mU/L.

Several studies have presented other possible explanations for the relationship between thyroid autoantibodies and miscarriage.[28] First, autoimmune thyroid disease is often accompanied by other autoimmune diseases (SLE, antiphospholipid antibody syndrome, etc.) that have high frequency of miscarriage.[33,34] Second, the presence of thyroid autoantibodies is an expression of generalized immune abnormalities, which inevitably increases the frequency of miscarriage.[34-36]

Third, the TSH receptor-blocking antibody blocks the LHCG receptor and suppresses the production of estrogen/progesterone necessary for maintenance of pregnancy.[37]

Is Thyroid Hormone Therapy Reasonable in TPOAb-Positive Pregnant Women to Reduce Miscarriage?

Negro et al.[26] reported that L-T4 treatment in TPOAb-positive pregnant women significantly decreased the chance of miscarriage and premature delivery compared with TPOAb-positive pregnant women without treatment (miscarriage, 3.5% vs. 13.8%; premature delivery, 7% vs. 22.4%). The miscarriage and premature delivery rates of TPOAb-positive pregnant women taking L-T4 were similar to those of TPOAb-negative pregnant women who did not take L-T4 (miscarriage, 3.5% vs. 2.4%; premature delivery, 7% vs. 8.2%). In 2012, Lepoutre et al.[38] reported the same results. The miscarriage rate was significantly higher in the non-treated TPOAb-positive pregnant women compared with the treated women (16% vs. 0%). However, it is not conclusive that L-T4 treatment lowers the risk of miscarriage in pregnant women with thyroid autoantibodies, because of other different results.[39] L-T4 treatment in pregnant women with high serum TSH level is helpful, but the effect is still unclear in those with serum TSH <2.5 mU/L. L-T4 treatment is best to start at 25 to 50 μg per day.[5] Recently, two large-scale prospective studies have been conducted to confirm the usefulness of L-T4 treatment in TPOAb-positive pregnant women. One is the TABLET (**T**hyroid **A**nti**B**odies and **LE**vo**T**hyroxine) trial in UK.[39] This study conducted a double-blind, placebo-controlled trial to investigate whether L-T4 treatment (50 μg per day) would increase live-birth rates among euthyroid women who had TPOAb and a history of miscarriage or infertility. This study concluded that use of L-T4 in TPOAb-positive euthyroid women did not result in a higher rate of live births than placebo (37.4% vs. 37.9%). There were no significant differences in other pregnancy outcomes, including pregnancy loss or preterm birth, or in neonatal outcomes. Another study, the T4-LIFE study in the Netherlands, aims to determine the effect of L-T4 administration on live birth rate in euthyroid TPOAb-positive women with recurrent miscarriage.[40] This is a multicenter, placebo-controlled, randomized trial and is ongoing. The primary outcome is live birth, defined as the birth of a living fetus beyond 24 weeks of gestation. Secondary outcomes are ongoing pregnancy at 12 weeks, miscarriage, preterm birth, (serious) adverse events, time to pregnancy, and survival at 28 days of neonatal life.

The associations between thyroid autoimmunity and miscarriage/premature delivery are clear, although its mechanism is unknown. However, uncertainty remains about the association of thyroid autoimmunity with other obstetric complications.[28]

The Role of Selenium on Prevention of Postpartum Thyroiditis

Thyroid autoimmunity improves during pregnancy but worsens after delivery. Postpartum thyroiditis occurs between 6 and 12 weeks postpartum and mostly recovers within 1 year. It occurs again in 50 to 70% of postpartum women with previous history after the second pregnancy. It occurs 5.7 times more frequently in TPOAb-positive women, and permanent hypothyroidism occurs in 12 to 30%. Serum TSH measurement should be performed at 3 and 6 months and annually after delivery in postpartum women with TPOAb, history of postpartum thyroiditis, or type 1 diabetes.[41]

Selenium is an essential trace mineral and a component of selenoproteins, which are involved in the production of thyroid hormones and in regulating the immune response. Selenium decreases thyroid inflammatory activity in patients with autoimmune thyroiditis. Negro et al.[42] conducted a prospective, randomized, placebo-controlled study to examine whether selenium supplementation during and after pregnancy influenced thyroid autoimmunity. They divided 151 TPOAb-positive pregnant women into two groups: 77 TPOAb-positive women received selenomethionine 200 μg/day (group 1) and 74 TPOAb-positive women received placebo (group 2) during pregnancy and postpartum. They reported that postpartum

thyroiditis and permanent hypothyroidism were significantly lower in group 1 compared with group 2 (postpartum thyroiditis, 28.6% vs. 48.6%; permanent hypothyroidism, 11.7% vs. 20.3%). However, Mao et al.[43] reported that low-dose selenium supplementation (60 μg/day) in pregnant women with mild-to-moderate deficiency had no effect on decreasing TPOAb concentration or the prevalence of TPOAb positivity during pregnancy. Stranges et al.[44] investigated the effect of long-term selenium supplementation (200 μg/day) on the incidence of type 2 diabetes. They reported that type 2 diabetes developed in 12.6 selenium recipients/1000 person-years compared to 8.4 placebo recipients/1000 person-years during an average follow-up of 7.7 years (HR 1.55 [95% CI: 1.03 to 2.33]). They concluded that long-term selenium supplementation may increase risk for type 2 diabetes.

Selenium may reduce the development of postpartum thyroiditis and permanent hypothyroidism. However, routine long-term prescription of selenium is not recommended as it may increase the risk of type 2 diabetes. Short-term selenium prescriptions during and after pregnancy are worth considering for high-risk women. In the future, large-scale research should be conducted on this subject.

Relationship between Birth Defects and Antithyroid Drugs in Early Pregnancy

Antithyroid drugs (ATD) are the treatment mainstay of hyperthyroidism during pregnancy, but potential teratogenic effects have been reported. All ATDs, including propylthiouracil (PTU), methimazole (MMI) and carbimazole (CMZ), are equally effective in controlling hyperthyroidism during pregnancy. However, they cross the placenta and may cause problems, particularly during first-trimester organogenesis. In 2009, the concern of a rare but fatal PTU-induced hepatotoxicity was raised.[45,46] The U.S. Food and Drug Administration (FDA) and the ATA recommended PTU use only in the 1st trimester, to be switched to MMI by the 2nd trimester.[5,47] However, this recommendation has potential side effects from both drugs.

A Danish nationwide study was conducted to determine the degree to which the use of ATD in early pregnancy is associated with an increased prevalence of birth defects.[48] Andersen et al.[48] reported that all ATDs were significantly associated with birth defects (PTU 8.0%, MMI/CMZ 9.1%, both 10.1%, no ATD 5.4%, non-exposed 5.7%). Both were associated with urinary system malformation and PTU with malformations in the face and neck region. Omphalocele, omphalomesenteric duct anomalies, and MMI embryopathy (aplasia cutis, choanal/esophageal atresia) were common in MMI/CMZ-exposed children.

Subsequently, a Korean nationwide study was conducted to examine the association between maternal prescriptions for ATD during the 1st trimester and congenital malformations in 2,885,000 pregnant women using the Korean National Health Insurance database.[49] Seo et al.[49] reported that the prevalence of malformations in ATD-exposed offspring was significantly higher than in those of women who were not prescribed ATDs during pregnancy (PTU 7.04%, MMI 8.13%, both 7.98%, no ATD 5.94%). Use of PTU in early pregnancy lowers the incidence of birth defects by 1.1% compared with use of MMI, but it is lowered by only 0.15% when MMI is changed to PTU in early pregnancy. PTU was associated with musculoskeletal and urogenital malformations and MMI with malformations of nervous, circulatory, and digestive systems and MMI embryopathy. Interestingly, malformations began to develop even at low doses of PTU from the beginning of use, and there was no difference in the frequency of malformation even when the period of use or the dosage increased. On the other hand, with use of MMI, a small number of malformations began to develop at a low dose, but the risk of malformation abruptly increased from a period of use of 1.5 months or more or a cumulative dose of 495 mg or more compared with a low dose (1 to 126 mg). They concluded that not using ATD in early pregnancy was best, followed by switching to PTU before pregnancy. When use of MMI is unavoidable in early pregnancy, it is recommended to use less than 5 mg per day.

Summary

1. Increase in TBG concentration during pregnancy results in increase of serum total T4/T3 concentrations. Therefore, the reference range for total T4 during pregnancy should be set 1.5 times higher than the pre-pregnancy range.

2. Because serum TSH level is suppressed by 20-50% by week 10 due to high circulating hCG, TSH may be misleading, and T4 (total or free) will provide a more accurate clinical status in the 1st trimester.

3. Iodine requirement in pregnant women is increased by 50%, leading to increase in thyroid volume of 10% and 20-40% in iodine sufficient and deficient areas, respectively.

4. The Korean Thyroid Association recommends only serum TSH measurement in early pregnancy of high-risk pregnant women. However, there have been reports that 30-55% of subclinical or overt hypothyroidism was undetected by case-finding only in high-risk pregnant women.

5. It is most desirable to set a unique, country-specific range for serum TSH concentration during pregnancy. The American Thyroid Association (ATA) recommended the TSH reference range to 0.5-4.0 mU/L in pregnant women, and it is consistent with the Korean situation.

6. Thyroid autoantibody has an adverse impact on a pregnant woman, mainly hypothyroidism and miscarriage. Because its titer decreases as gestation progresses, its measurements should be performed as early as possible during pregnancy.

7. According to the 2017 ATA guidelines, thyroid hormone (L-T4) therapy is recommended for TPOAb-positive women with serum TSH >4.0 mU/L and TPOAb-negative women with serum TSH >10.0 mU/L. It may be considered for TPOAb-positive women with serum TSH >2.5 mU/L and TPOAb-negative women with serum TSH >4.0 mU/L. However, considering the frequency of miscarriage increased in TPOAb-positive women with serum TSH >2.5 mU/L and TPOAb measurement is not performed or is performed too late, so there is a high possibility of false-negatives, it is worth considering that L-T4 therapy starts at a serum TSH of 2.5 mU/L or higher.

8. L-T4 therapy is not recommended in TPOAb-positive pregnant women to reduce miscarriage.

9. Selenium may reduce the development of postpartum thyroiditis and permanent hypothyroidism. However, routine long-term prescription of selenium is not recommended as it may increase the risk of type 2 diabetes.

10. Not using anti-thyroid drug in early pregnancy is best, followed by switching to PTU before pregnancy. When use of methimazole is unavoidable in early pregnancy, it is recommended to use less than 5 mg per day.

Conflicts of Interest

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

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