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POSTPARTUM THYROIDITIS

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ABSTRACT

Postpartum thyroiditis is an autoimmune disease of the thyroid gland seen in approximately 8% of women in the postpartum period. Postpartum thyroiditis is a triphasic disease consisting of hyperthyroid, hypothyroid, and euthyroid phases. The pathogenesis of postpartum thyroiditis is not known exactly. However, there are various mechanisms related to pathogenesis. One of these is related to the fetal cell/DNA circulating in the maternal blood to settle in the thyroid gland and the maternal immune system to develop an autoimmune reaction against the thyroid gland in the postpartum period. During pregnancy, fetal cells settle in the thyroid gland and no reaction occurs due to pregnancy-related immunosuppression. Postpartum thyroiditis occurs because immunosuppression disappears in the postpartum period. The method of examining fetal cell/DNA in maternal blood during pregnancy is a non-invasive prenatal test. The non-invasive prenatal testing is a screening test used to detect chromosomal anomalies and some other chromosomal defects. However, there is to our knowledge, not enough studies in the literature directly investigating the relationship between the number of fetal cells/DNA in maternal blood and the development of postpartum thyroiditis. Having reviewed the literature around this topic it can be assumed that there can be a difference in the level of damage in the thyroid gland in the postpartum period, depending on the level of difference in the number of fetal cells in the thyroid gland. In addition, future studies will pave the way for studies on the relationship between autoimmune diseases occurring in the post-pregnancy period and the number of fetal DNA/cells in maternal blood during pregnancy. Therefore, an early diagnosis of pregnancy-related autoimmune diseases will be enabled. ***Keywords:*** Postpartum thyroiditis, pregnancy, hyperthyroidism, hypothyroidism, prenatal diagnosis

INTRODUCTION

Postpartum thyroiditis (PPT) is an autoimmune destructive subacute lymphocytic thyroiditis that develops in a euthyroid woman within 12 months of the postpartum period and has an overall prevalence of 8% (1-3). The prevalence of PPT differs between countries. For example, while its incidence is 1.1% in Thailand, it is 13.3% in Brazil (4). These differences are thought to be related to the postpartum follow-up period and conditions such as iodine intake (4). However, there are high-risk groups for PPT. These risk groups are; type I diabetes patients (prevalence 19.9%), patients with positive family history (20%), and/or previous history of PPT (42.4%) (5). PPT is the most common endocrine disorder associated with pregnancy (3). PPT is accelerated by the rebound effect in the postpartum period after pregnancy-related partial immunosuppression in individuals at risk for autoimmune thyroiditis (6). Signs of PPT are usually not evident in the first six weeks postpartum (3). Therefore, clinicians should be careful about PPT in this period.

Postpartum thyroiditis is triphasic due to changes in hormone levels. Hyperthyroidism is seen first and caused by an excessive and rapid release of thyroid hormone into the blood due to the destruction of thyroid cells. Later, hypothyroidism is observed, which shows that the thyroid gland cannot produce enough hormones due to cell destruction. At the end of 12-18 months after birth, the patient becomes euthyroid again (7). However, 25-30% of women who develop PPT have a risk of developing permanent hypothyroidism within 5-10 years (3, 8). Therefore, women with a history of PPT should be examined at regular intervals. This review was written to draw attention to PPT, which is an important disease since it is the most common pregnancy-related endocrine disorder that occurs in women in the postpartum period, is seen in approximately 8% of pregnancies, and is usually not symptomatic in the first six weeks postpartum.

PATHOGENESIS

Postpartum thyroiditis is a type of thyroiditis with histological features similar to Hashimoto's thyroiditis and lymphocytic infiltration (3). However, it differs from Hashimoto's thyroiditis in that, it does not have the same degree of fibrosis and follicular atrophy as Hashimoto's thyroiditis (9). When women who had PPT were examined, it was revealed that most of the women had autoimmune changes in the thyroid gland before pregnancy, and there was a relationship between PPT and anti-thyroid peroxidase antibodies (TPO-Ab) (3). However, it is not clear that TPO-Ab are the direct causes of PPT. Except for PPT, TPO-Ab are observed in all forms of autoimmune thyroid disease, including Hashimoto's thyroiditis and Graves' disease. The level of TPO-Ab correlates with the severity of lymphocytic infiltration in the thyroid gland and TPO-Ab can induce antibody-dependent cell-mediated cytotoxicity (3, 10).

Apart from TPO-Ab, various factors such as maternal immune modulators and environmental factors also play a role in the pathogenesis of PPT. It has been shown that the CD4/CD8 ratio and the number of activated T cells are higher in women with PPT than in healthy women (11). However, when TPO-Ab-positive women with PPT were compared with TPO-Ab-positive euthyroid women, it was shown that plasma cortisol levels at the 36th week of pregnancy was lower and gamma interferon levels were higher in

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TPO-Ab-positive women with PPT (3). This situation reveals that the risk of developing PPT is higher in the group with less immunosuppression during pregnancy than TPO-Ab-positive women (11).

The appearance of fetal cells in the maternal circulation is called fetal microchimerism (12). Fetal cells begin to appear in the maternal circulation one week after the onset of pregnancy (12). Studies have shown the presence of fetal cells in the thyroid gland in women with autoimmune thyroid disorders (12, 13). Fetal cells, which pass into maternal blood during pregnancy, migrate to the thyroid gland and then settle in the thyroid gland. Intrathyroidal fetal cells survive due to immunosuppression during pregnancy. In the postpartum period, the immunosuppressed state disappears, and the maternal immune system is activated against fetal intrathyroidal cells (12). As a result, thyroid gland destruction and PPT occur. This theory is another theory about the development of PPT.

There are also various studies on the role of environmental factors such as smoking in the pathogenesis of PPT. A positive relationship was found in the meta-analysis by Vestergaard (14).

SIGNS AND SYMPTOMS

Postpartum thyroiditis is a triphasic disease, including hyperthyroidism, hypothyroidism, and euthyroidism. Therefore, the symptoms in patients differ according to the period of the disease. Findings in PPT usually do not appear in the first six weeks (3). Later, due to the destruction of the thyroid gland, symptoms appear in the first 1-4 months of the postpartum period. Hyperthyroidism symptoms occur in the first month of the postpartum period and last about 1-2 months (15, 16). During this period, patients may experience irritability, palpitations, anxiety, unexplained weight loss, tremor, insomnia, and heat intolerance (16). However, the findings of hyperthyroidism in PPT are usually mild (3). For this reason, it may not be noticed or may be misinterpreted by the patients depending on post-pregnancy changes. After the postpartum period of thyrotoxicosis, hypothyroidism occurs. The hypothyroid period occurs between the third and the ninth months of the postpartum period and lasts for four to six months (3, 16). During this period, the patient may experience low energy, forgetfulness, lack of concentration, cold intolerance, memory problems, constipation, weight gain, and dry skin, or the patient may be asymptomatic (16). The relationship between PPT and depression has not been demonstrated (17). However, since the findings are more pronounced in the hypothyroid period, most PPT patients consult a clinician during the hypothyroid phase. Most patients become euthyroid approximately 12 months after giving birth (16).

DIAGNOSIS

Laboratory Tests

Since PPT is a triphasic disease, the findings in laboratory tests change according to the stages of the disease. In the thyrotoxicosis phase, which is the first phase of the disease, thyroid-stimulating hormone (TSH) is suppressed, and thyroxine (T4) levels are high. In the hypothyroid phase, T4 and triiodothyronine (T3) levels are observed to be low. In the third phase, the euthyroid phase, T3 and T4 levels are within the normal range. In addition, most patients are TPO-Ab-positive (17, 18). However, thyroglobulin antibody can also be observed as positive (17).

Imaging Findings

Radioactive iodine uptake is low in the thyrotoxic phase of PPT (18). When the thyrotoxic phase is over, radioactive iodine uptake in the hypothyroid phase is found to be normal or high (18). On the ultrasonography (USG) of PPT, heterogeneous hypoechogenic thyroid tissue is often observed (19). In the study of Shahbazian et al. (19), thyroid volume was found to be 77% higher in the initial period of PPT compared to the control group. However, after remission of the disease, the mean thyroid volume was found to be reduced by 25% (19). USG is recommended as an adjunct to laboratory tests in PPT (18, 19).

Non-Invasive Prenatal Test (NIPT)

In most countries, USG and maternal serum screening markers are used in the first and/or second trimester to detect chromosomal anomalies and other congenital anomalies. There is a 2-7% false-positive risk in these screening tests (20). Invasive diagnostic tools such as chorionic villus sampling (CVS) and amniocentesis are used when positivity is detected in these screening tests. CVS is typically done between the 11th to 14th weeks, while amniocentesis is performed after the 15th week of gestation (20). The risk of miscarriage due to these tests is approximately 1-2 ‰ depending on the procedure (21, 22). This situation reveals the importance of developing new tests for diagnosis and screening. One of the tests developed for this purpose is the non-invasive prenatal test (NIPT). NIPT relies on the presence of circulating free DNA (cfDNA) in maternal blood. The presence of fetal cfDNA in maternal blood was first shown in 1997 (23). NIPT is a screening test used to examine the fetal cfDNA in the maternal blood and to detect fetal chromosomal aneuploidies such as trisomy 13 (Patau syndrome), trisomy 18 (Edwards' syndrome), trisomy 21 (Down syndrome) (23). The false-positive rate of NIPT (1-3%) is lower than pregnancy screening tests and there is no risk of miscarriage (20). NIPT was developed to avoid direct contact with the fetus/placenta and not to compromise the health of the fetus (24). NIPT is based on examining fetal DNA in a blood sample taken from the mother during pregnancy (24). Fetal DNA can be analyzed from the 9th week of gestation (25). Fetal DNA samples can be obtained from maternal plasma and serum samples greater than 10 μL (23, 24).

The fetal fraction in maternal blood is important in NIPT. Fetal fraction is the ratio of fetal cfDNA to total cfDNA in maternal blood. Fetal cfDNA originates from placental trophoblasts. Therefore, NIPT can be considered as a test that examines fetal DNA samples that have passed into maternal blood (24, 26). Fetal fraction should be at least 4% in NIPT tests to be considered successful (23, 25, 27). However, studies that investigated the first 10-14 days of pregnancy found that fetal fraction increased by more than 10% in first weeks of gestation (fetal fraction may be affected depending on factors such as the weight of the mother, singleton, or multiple pregnancies.) (23). NIPT is a very important test in early diagnosis and its sensitivity and specificity is greater than 99% in the detection of common chromosomal anomalies such as trisomy 13, trisomy 18, trisomy 21 (28).

TREATMENT

Treatment of PPT requires extra attention as women breastfeed their infants. If symptoms are mild during the first phase of PPT, hyperthyroidism (thyrotoxicosis), treatment is usually not needed. However, if symptoms are severe, beta-blockers can be used to control symptoms (18). After the patient has entered the hypothyroid phase, if necessary, L-Thyroxine (L-T4) can be used for symptomatic treatment. If L-T4 is not started, TSH levels should be checked every 1-2 months until the 12th postpartum month (29). The use of L-T4 up to 12 months postpartum is still under discussion (18). The

use of L-T4 in patients should be evaluated according to the risk of developing permanent hypothyroidism (29). When the patient enters the euthyroid phase, the patient should be followed up. In case of permanent hypothyroidism, patients should use L-T4 regularly and TSH levels should be monitored at regular periods (29).

CONCLUSION

Postpartum thyroiditis is an autoimmune, triphasic (hyperthyroid phase, hypothyroid phase, and euthyroid phase) disease observed in 8% of pregnant women (1-3). Various factors are involved in the pathogenesis of PPT. These factors are; TPO-Ab, fetal microchimerism, and smoking. However, there are no studies on the number of fetal cfDNA in maternal blood and the risk of developing PPT. Having reviewed the literature around this topic it can be assumed that there can be a difference in the level of damage in the thyroid gland in the postpartum period, depending on the number of fetal cells in the thyroid gland. In addition, future studies will pave the way for studies on the relationship between the emergence of autoimmune diseases in the post-pregnancy period and fetal cfDNA level in maternal blood during pregnancy. Therefore, an early diagnosis of pregnancy-related autoimmune diseases will be enabled.

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