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Course of Autoimmune Thyroiditis During Pregnancy

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Abstract: In recent years, the study of thyroid function during pregnancy, including the level of thyroid antibodies (anti-thyroglobulin antibodies, AT-TG) throughout pregnancy and their impact on pregnancy outcomes, has been the focus of endocrinologists, obstetricians-gynecologists, and pediatricians. In particular, hypothyroidism plays a key role in thyroid dysfunction and affects fetal development. This article examines the changes that may occur during pregnancy in patients with autoimmune thyroiditis.

Keywords: Autoimmune thyroiditis, anti-thyroid peroxidase antibodies (AT-TPO), fetus, hypothyroidism, pregnancy, thyroid gland.

Introduction: Autoimmune thyroiditis is more common among women than men, affecting 5–20% of women of reproductive age. Even if a mother does not have thyroid dysfunction but has anti-thyroid peroxidase antibodies, this can negatively impact pregnancy outcomes, increasing the risk of early miscarriage, preterm birth, intrauterine growth restriction, and fetal neurodevelopmental disorders. The development of these conditions is influenced both by hypothyroidism caused by autoimmune thyroiditis and by the direct effect of anti-thyroid peroxidase antibodies. Hypothyroidism during pregnancy primarily poses a significant risk to fetal development, particularly the central nervous system.

Thyroid Gland and Pregnancy: During physiological pregnancy, significant metabolic changes occur in a woman's body, primarily due to the temporary endocrine organ—the developing placenta. This leads to alterations in the levels of proteins (placental lactogenic hormone, chorionic hormone) and steroid hormones (estriol, estrone, estradiol, progesterone) in the mother's body. The daily production of placental hormones gradually increases and reaches very high levels in the third trimester of pregnancy: approximately 300–400 mg of progesterone, around 200 mg of estradiol, and about 1.5–2 g of placental lactogen.

During pregnancy, under the influence of placental estrogens, the synthesis of thyroxine-binding globulin (TBG) is enhanced, leading to an increase in the levels of T3 and T4 bound to transport proteins in the blood. This process involves the attachment of sialic acids to TBG molecules, which significantly prolongs its half-life and uptake by hepatocytes [8,20]. It has been shown that absolute or relative hyperestrogenemia, which underlies various hyperplastic processes in reproductive organs (such as uterine fibroids, endometrial hyperplasia and polyps, adenomyosis, endometriosis, and fibrocystic mastopathy), is a direct cause of thyroid enlargement. Thyroid gland enlargement during pregnancy [4,24] is primarily attributed to the effects of placental estrogens. The structural similarity between human chorionic gonadotropin (hCG) and thyroid-stimulating hormone (TSH) explains the influence of hCG on thyroid growth and function [6,13,21].

The thyrotropic activity of hCG is approximately 100 times lower than that of TSH. By the end of the first trimester, hCG is responsible for thyroid enlargement and hyperthyroidism in pregnant women [2,18,14]. Increased hCG production leads to transient gestational thyrotoxicosis in 1–2% of pregnant women, often accompanied by hyperemesis gravidarum [15,24].

The causes of thyrotoxicosis during pregnancy may be linked to enhanced expression of the β-subunit of the hCG gene [13] and structural changes in hCG, which prolong its half-life or increase the mass of the syncytiotrophoblast. Other factors contributing to thyroid enlargement include developing iodine deficiency during pregnancy, particularly in the northwestern regions of Uzbekistan. Iodine deficiency occurs due to its transfer to the fetus via the placenta and increased renal iodine clearance as a result of enhanced glomerular filtration [11].

Of course, iodine deficiency is not the only cause of thyroid enlargement during pregnancy, as an average increase in thyroid size by 10–15% is observed even in regions with adequate iodine intake and iodine prophylaxis [21,23].

Thus, thyroid enlargement during pregnancy is associated with placental hormonal function, iodine intake, and urinary iodine levels. Increased metabolism of TBG in the liver leads to elevated total T3 and T4 levels in the blood. Consequently, the levels of free thyroid hormone fractions slightly decrease by the end of pregnancy [9,16]. In iodine-deficient regions, pregnant women often experience hypothyroxinemia, which manifests in a more pronounced form [3,19].

TSH levels in pregnant women typically remain within the physiological range observed in non-pregnant women. The exception is patients with gestational hyperthyroidism, in whom hCG causes TSH levels to drop below 0.2 mIU/L.

Fetal Thyroid Development: The fetal thyroid gland develops from the primitive gut. Its formation begins in the 4th week of pregnancy. By the end of the first trimester, the fetal thyroid is capable of accumulating iodine, synthesizing thyroid hormones, and releasing them into the bloodstream. As pregnancy progresses, total and free T4 levels in fetal blood increase, reaching adult levels by the 36th week. Total and free T3 levels rise to a lesser extent.

By the second trimester, the negative feedback mechanism within the fetal hypothalamic-pituitary-thyroid system is established. At birth, fetal TSH levels are significantly higher than those seen in adults. In the mature maternal placenta, thyroid hormones undergo deiodination and barely reach the fetal circulation. TSH also cannot cross the placental barrier. Thus, the fetal hypothalamic-pituitary-thyroid system functions autonomously, independently of the maternal system.

During the first trimester of fetal development, even before the fetal thyroid gland becomes functional, the fetus remains under the control of maternal thyroid hormones.

By the end of the third trimester, placental permeability to maternal thyroid hormones slightly increases. Thyroid hormones are essential for the normal growth and development of the fetus, the differentiation of its organs and tissues—primarily the morphological and functional development of the central nervous system—the regulation of metabolic processes, and the formation of adaptive responses. This importance is explained by the fact that, unlike T3 and T4, thyroid hormones barely cross the blood-brain barrier.

The levels of total and free thyroxine (T4), triiodothyronine (T3), thyroid-stimulating hormone (TSH), and thyrotropin-releasing hormone (TRH) gradually increase from the 17th–20th week to the 34th–37th week of pregnancy as gestation progresses. The established direct correlation between thyroxine and TSH levels at these stages of development indicates that the negative feedback mechanism within the fetal hypothalamic-pituitary-thyroid system is not yet fully developed.

However, there is reliable evidence supporting the existence of a functional negative feedback mechanism between the thyroid gland and the pituitary gland during the antenatal period. This is confirmed by the increased thyroid volume and TSH levels in fetuses and newborns with primary hypothyroidism, as well as the reduction of these parameters following the administration of thyroxine into the amniotic cavity.

Autoimmune thyroiditis (AIT) is a chronic autoimmune disease of the thyroid gland and is one of the most common causes of primary hypothyroidism. It occurs 5 to 10 times more frequently in women than in men. Anti-thyroid autoantibodies, one of the hallmarks of the disease, are found in 5–26% of women of reproductive age. According to a study by Wigghem, the annual risk of developing hypothyroidism in women with high levels of anti-thyroid peroxidase (TPO) antibodies is 2.1%. Anti-thyroid antibodies are detected in 13–20% of pregnant women.

The frequent occurrence of AIT in certain family members, as well as the presence of specific HLA system antigens (HLA-DR3 and HLA-DR5), suggests a genetic predisposition to the disease. These antigens are also associated with an increased susceptibility to other systemic and organ-specific autoimmune diseases, such as rheumatism, rheumatoid arthritis, systemic lupus erythematosus, Graves' disease, type 1 diabetes, autoimmune adrenal insufficiency, autoimmune oophoritis, diffuse alopecia, and others. The onset of AIT is often preceded by infectious diseases, excessive sun exposure, or an excessive intake of iodine.

AIT can develop either with thyroid gland enlargement (Hashimoto's goiter) or without an increase in gland volume (atrophic thyroiditis). In both cases, histological examination reveals lymphoid and plasmacytic infiltration in thyroid tissue, destruction of the follicular apparatus, and fibrosis.

In the 1950s, thyroid autoantigens (thyroglobulin and the microsomal antigen—thyroid peroxidase) were identified, and the first experimental model of autoimmune thyroiditis was developed by immunizing rabbits with homologous thyroid extracts. Under the influence of T-helper cells, B-lymphocytes transform into plasma cells and produce autoantibodies against thyroglobulin and thyroid peroxidase. Anti-thyroid autoantibodies interact with T-killer cells in the follicular epithelium. Additionally, TPO autoantibodies bind to the C1/C3 fraction of the complement system, forming cytotoxic pathogenic immune complexes that act on thyrocytes.

Intensive destruction of thyroid epithelial cells can lead to a significant increase in T3 and T4 levels in the blood and a decrease in TSH levels, resulting in destructive thyrotoxicosis. As the volume of functioning thyroid tissue decreases, a temporary or permanent decline in thyroid function occurs, leading to transient or permanent hypothyroidism.

In 5.9% of women, remission of autoimmune thyroiditis (AIT) by the end of pregnancy is followed by an exacerbation in the postpartum period, known as postpartum thyroiditis. This condition develops in one-third of women who had detectable thyroid peroxidase (TPO) autoantibodies in their blood at the beginning of pregnancy. The disease may initially present with signs of thyrotoxicosis due to the destruction of thyroid parenchyma (occurring 2–4 months after childbirth), followed by a phase of transient hypothyroidism (6–8 months postpartum). In 19.2% of women with significant primary hypothyroidism, the first symptoms of the disease appear 1–2 years after childbirth.

Clinical manifestations of AIT without changes in thyroid function are rare. In the hypertrophic form of the disease, patients may experience an increase in neck volume and complain of pressure in the anterior neck region. On palpation, the thyroid gland appears enlarged and firm. If the goiter reaches a significant size, it may compress adjacent organs. In the focal form of thyroiditis, localized thyroid induration may be perceived as a nodular goiter, sometimes requiring fine-needle aspiration biopsy (FNAB) to differentiate it from thyroid tumors. A characteristic ultrasound sign of the disease is a diffuse decrease in thyroid tissue echogenicity.

The diagnosis of AIT is based on a combination of findings: in some cases, a "wooden" gland density on palpation, a distinct echographic thyroid structure, and elevated levels of anti-thyroid autoantibodies in the blood. The functional state of the thyroid gland depends on the amount of preserved parenchyma and the intensity of destructive processes.

There are reports suggesting that AIT may be associated with infertility, particularly in women with external genital endometriosis or polycystic ovary syndrome (PCOS). Some studies indicate that most women with hyperplastic processes in the reproductive system show decreased thyroid function, and in rare cases, thyroid enlargement.

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