POSTPARTUM THYROIDITIS
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ABSTRACT
Postpartum thyroiditis (PPT) is a syndrome of transient or permanent thyroid dysfunction occurring in the first year after delivery or abortion. It is the most common thyroid disease in the postpartum period with incidence between 5 and 9%. In essence, it is an autoimmune inflammation of the thyroid, caused by changes in humoral and cell-mediated immune response. It has a characteristic biphasic course with an episode of transient thyrotoxicosis followed by transient or permanent hypothyroidism. Of all predisposing factors positive titers of thyroid peroxidase antibodies have the greatest importance. In some of the affected patients the disease course is marked by expressed hormonal disorders causing significant subjective symptoms. This underlines the need for early identification of risk groups aimed at prophylaxis and adequate treatment of thyroid dysfunction in the postpartum period. The frequency of PPT varies between analyses and studies on risk factors do not establish reliable predictive models for progression of the disease. This is due to the different methodology of research and the involvement of a number of genetic and non-genetic factors in different geographic regions. That is why implementation of mass screening programs is now controversial. The discrepancy in the opinions of researchers makes it necessary to have studies of the problem performed in different geographic regions. That is why implementation of mass screening programs is now controversial. The results of these studies can be used to introduce targeted and cost-effective screening for early detection of risk patients and prevention of morbidity and complications of PPT.

Key words: postpartum thyroiditis, hypothyroidism, screening

ПОВОДОВАЯ ПОЛЕЗНОСТЬ
Постпартальный тиреоидит (ППТ) представляет собой синдром переходной или чистой тиреоидной дисфункции, возникающей в первый год после родов или аборта. ППТ самое часто встречаемое тиреоидное заболевание. Его частота в границах 5-9%. Посовейной тяжести эутоиммунного воспаления щитовидной железы, характеризующегося изменениями в гуморальном и клеточно-медированном ответах. Для заболевания характерно бифазное течение с эпизодом переходного тиреотоксикоза, вслед за которым следует переходный или стойкий гипотиреоидизм. Среди предрасполагающих факторов самое большое значение приобретается позитивным титрам тиреопероксидазных антител. У части пораженных пациенток болезнь протекает выраженными гормональными нарушениями, приводящими к значительной субъективной симптоматике. Этот факт определяет необходимость в ранней идентификации рисковых контингентов с целью профилактики и адекватного лечения тиреоидной дисфункции после родов. Частота ППТ варьирует при отдельных анализах, а исследования относительно рисковых факторов не устанавливают надежных прогностических моделей развития заболевания. Это объясняется различной методологией исследований и вмешательством ряда генетических и негенетических факторов в различных географических районах. Из-за этого целесообразность введения массовых скринингных программ представляет дискуссионный вопрос. Необходимы дальнейшие исследования для выявления наиболее целесообразных методов скрининга для раннего обнаружения рисковых пациентов и профилактики болезней, связанных с ППТ.

Ключевые слова: постпартальный тиреоидит, гипотиреоидизм, скрининг
INTRODUCTION

Postpartum thyroiditis (PPT) is a syndrome of transient or permanent thyroid dysfunction occurring in the first year after delivery or abortion. The disease was first described by H. Robertson in 1948. N. Amino et al. made the major contribution to clarifying the pathogenesis and clinical features of this condition in their fundamental studies published in the late 70s and early 80s. In essence postpartum thyroiditis is an autoimmune inflammation of the thyroid gland characterized by destructive changes or stimulating effects on the parenchyma. Typically, it follows a biphasic course, initially with an episode of transient thyrotoxicosis followed by transient hypothyroidism although this is not always the case. In some of the affected women the disease is subclinical and may go unrecognized. The autoimmune pathogenesis of the disease is supported by the presence of circulating thyroid autoantibodies in over 50% of the patients. It is the high incidence of this condition and the risk of developing permanent thyroid dysfunction that justifies the continued efforts of researchers to identify risk patients as early as possible in order to adequately treat and prevent subsequent complications. In recent years, with the advances in bio-technology and the introduction of innovative research methods, new data on the pathogenesis and risk factors for PPT have been accumulated. The increased scientific interest in thyroid diseases, particularly during pregnancy, results in significant expansion of knowledge and the improvement of diagnostic approaches to elucidate thyroid dysfunction during this period. This literature review summarizes the current scientific evidence on the pathogenesis and progression of PPT which helps to modify the diagnostic strategies and recommendations for treatment and monitoring of the disease. Special attention is paid to developments in the clarification of risk factors and the formation of prognostic algorithms for the disease in order to adequately identify risk patients. The need to introduce mass or selective screening programs for pregnant women is still a matter of discussion.

ETIOPATHOGENESIS

PPT is an organ-specific polygenic disorder with a different degree of penetration that depends on environmental factors. Development of PPT reflects the state of selective immune tolerance during pregnancy, followed by the immune rebound phenomenon in the postpartum period. The humoral factors that are the most important are the antibodies against the enzyme thyroid peroxidase (TPO Ab) the positive titers in the first trimester determining a relative risk of 40-60% of developing the disease. These antibodies belong to the IgG class and those of IgG1 subclass occur more frequently in hypothyroid patients and cause destruction of the glandular follicles by the mechanism of antibody-dependent cell-mediated cytotoxicity. Antibodies against thyroglobulin (TgAb) are also detected in about 15% of women with PPT, and in 5% of cases they can be the only circulating antibodies. Given that only 50% of the TPO Ab positive women develop clinical symptoms of PPT, it can be assumed that the antibody titer is only a marker for the disease and immunological disorders are mediated by cell-dependent factors. Most often, these are disorders of the balance between lymphocyte subpopulations - Th1, Th2, NK-cells and their regulators T-reg lymphocytes and also complement-related mechanisms where the degree of activation of the complement system correlates with the morphological changes and severity of thyroid dysfunction. Fluctuations in immunological parameters during pregnancy and postpartum period are modulated by altered levels of estradiol, progesterone and cortisol. Besides generalized activation of peripheral circulating lymphocyte populations, during 36th gestational week lower plasma cortisol levels in TPO Ab-positive women are observed. Passage of fetal cells into maternal circulation during the first trimester, a phenomenon known as fetal micro-chimerism might trigger the development of autoimmune diseases in susceptible women as a result of prolonged exposure of the mother’s immune system to foreign (paternal) antigens. Data on the role of fetal micro-chimerism in the pathogenesis of autoimmune thyroid disorders are contradictory. Several studies have shown that with increasing number of pregnancies serum concentrations of TPO Ab also increase, which in turn is associated with a higher risk of development of postpartum thyroiditis. Results of other studies,
however, do not prove a link between the number of pregnancies and the occurrence of autoimmune thyroid diseases.

**RISK FACTORS**

**GENETIC FACTORS**

Genetic factors play a decisive role in the development of autoimmune thyroid diseases. There are a number of genes that predispose to the development of thyroid autoimmunity. Genes of the MHC class I - HLA-A1, -BW62, -CW7 and Class II - DR3, -DR4, -DR5 are of fundamental importance. The latter determine the association of PPT with other manifestations of autoimmune response. For example, Manetti et al. report 5-fold higher frequency of pituitary autoantibodies in women with autoimmune postpartum thyroiditis, compared to healthy controls.\(^7\) Genes outside the MHC class are also involved in violations of the immune response. It has been found that the polymorphism of CTLA-4 (CT60 cytotoxic T lymphocyte antigen-4), and in particular the presence of the G-allele in women with postpartum thyroiditis defines higher titer of TPO Ab and a predisposition to development of hypothyroid disease form.\(^8\)

A study involving over 17000 women shows that with increasing maternal age, the frequency of TPO Ab also increases (4% in women under 20 years, and 10% - over 40 years).\(^6\)

**NON-GENETIC FACTORS**

- Iodine - both iodine excess and iodine deficiency can impair the existing tolerance to thyroid autoantigens, especially in susceptible individuals. After the introduction of iodine prophylaxis a higher incidence of lymphocytic thyroiditis and antithyroid autoantibodies in endemic areas has been observed.
- Smoking affects the immune tolerance to thyroid autoantigens. It has been proven that it is an independent risk factor for the development of PPT (relative risk 3.1).\(^9\)
- Infections - currently the only infectious agent, which based on evidence is associated with autoimmune thyroid pathology, is the hepatitis C virus.\(^10\) Studies conducted in France show an increased incidence of thyroid autoantibodies and overt thyroid dysfunction in patients with chronic hepatitis C who did not undergo interferon treatment compared to healthy controls.
- Radiation - both natural and used in medicine radioactive sources are proven risk factors in the pathogenesis of thyroid diseases. Besides the direct effect of radioactive rays on the thyroid - hypofunction, formation of nodules, and the occurrence of cancer, there is awareness of the stimulating effect on the production of autoantibodies and the development of autoimmune thyroid disease modulated by factors such as sex, age, presence of antibodies, iodine intake with food, etc.\(^9\)
- Medications - a number of drugs induce autoimmune disorders of the thyroid and development of postpartum thyroiditis. The most studied in this respect are lithium, amiodarone, interferon alpha, interleukin 2, and the highly active anti-retroviral therapy, as the risk increases in combination with a positive titer of TPO Ab.

Some diseases affecting directly or indirectly the immune system show a high risk of PPT. For example, in women with Hashimoto’s thyroiditis on replacement therapy with levothyroxine and preserved thyroid reserves, the frequency of postpartum thyroid dysfunction, is significantly increased. In patients with a history of Graves’ disease the risk is increased to 44%. TPO Ab frequency in patients with type 1 diabetes mellitus, defined in Familial Autoimmune and Diabetes Study, is 26.6%. According to these data the frequency of PPT in women with type 1 diabetes is higher than in the general population and reaches 25%.\(^11\); in women with chronic viral hepatitis - 25%\(^12\); with systemic lupus - 14\%\(^12\). Patients who have restored the euthyroid state after PPT have 70% risk of a new episode of PPT on subsequent pregnancy.\(^13\)

There is some evidence for the development of “postpartum” thyroiditis after abortion between gestational weeks 12 and 16, but the exact frequency of thyroid dysfunction after termination of pregnancy is unclear.\(^14\)

Regarding presently known data on the development of PPT risk factors for the disease are summarized in the Consensus recommendations adopted by the American Thyroid Association.\(^12\) The authors consider appropriate follow-up of thyroid status during pregnancy and in the postpartum period in patients with the following characteristics: aged over 30 yrs; body mass index over 40 kg/m\(^2\); history of thyroid disease or undergone intervention; symptoms of thyroid dysfunction or presence of goiter; positive titer of TPO antibodies; type 1 diabetes or other autoimmune diseases; history of miscarriage or premature birth; history of radiation to the head or neck region; family history of thyroid disease; intake of amiodarone, lithium or recent administration of iodinated contrast media; infertility; residence in an area with moderate or severe iodine deficiency.
CLINICAL PRESENTATION

The classical clinical course of PPT as a rule has two phases - thyrotoxicosis, followed by hypothyroid phase, usually with recovery of the euthyroid state of the gland (32% of cases). The disease may be evidenced only as a transient thyrotoxicosis (19%) or transient hypothyroidism (49%). Hypothyroidism preceded by thyrotoxicosis occurs earlier than if it is an independent manifestation of the disease. Onset of thyrotoxicosis ranges from 1 to 6 months after delivery, usually around the 3rd month, and typically lasts for 1-2 months. It is the result of the release of stored thyroid hormones due to destruction of thyrocytes and has a transitory and self-limiting nature. The clinical symptoms, caused by the hypermetabolic effect of released thyroid hormones, are generally mild, as in approximately 30% of the cases the course is asymptomatic. Most often, the patients report fatigue, palpitations, weight loss, heat intolerance, irritability and anxiety. Psychiatric disorders, fine tremor of the hands, sleep disorders and nervousness are also more common than in euthyroid patients. It is important to differentiate between the thyrotoxic phase of PPT and relapse or onset of Graves’ disease in the postpartum period. From an epidemiological perspective, thyrotoxic phase of PPT occurs 20 times more often than hypothyroid patients. It is important to differentiate between the two diseases can sometimes be difficult, since in some studies up to 25% of women with PPT are positive for antibodies against the thyroid-stimulating hormone receptor.

The hypothyroid phase develops on average 4 to 8 months after the delivery, usually about the 6th month and continues 4-6 months. It is due to the loss of functional thyroid cells as a result of the destructive immune mechanisms. Patients complain of fatigue, weakness, poor concentration, memory loss, constipation, pain in muscles and joints, weight gain. The frequency of depression is higher in the postpartum period in women with overt or subclinical hypothyroidism as well as in euthyroid patients with a positive titer of TPO Ab, as it is understood that the released cytokines (interleukin-1, interleukin-6) in the autoimmune processes affect the central nervous system, in particular behavioral events. Several authors suggest that reduced central serotonergic neurotransmission may be the link between mental illness in the postpartum period and thyroid hypofunction.

Many clinical observations report high incidence of goitre in PPT. This finding, however, is not mandatory and its appearance may be due to the iodine intake. In regions with normal iodine intake no increase of the volume of the gland during pregnancy is observed. Goitre is often related to iodine deficiency, which is a result of the action of growth stimuli in response to the increased hormone demands during pregnancy. In endemic areas, and in women with type 1 diabetes mellitus it is found that the presence of palpable goiter near term significantly increases the likelihood of developing PPT. In a study of F Azizi on 172 patients with subclinical form of PPT, 100% of the women presented with palpable goiter, while almost in half of them the thyroid gland has second degree enlargement.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of PPT is based mostly on clinical suspicion. Women with non-specific clinical or psychological symptoms in the first year after birth should be tested for abnormal thyroid function. Thyrotoxicosis is characterized by a constellation of low levels of thyroid stimulating hormone (TSH) and elevated free fractions of thyroid hormones triiodothyronin (FT3) and thyroxine (FT4). The hypothyroid phase of the disease runs with elevated TSH levels and normal or low levels of FT3 and FT4. High titers of TPO Ab are found in 50% of cases, in about 15% they are in combination with TgAb.

An ultrasound examination of the thyroid gland in most cases reveals diffuse or focal hypoechogeticity due to lymphocytic infiltration and destructive changes. Vascularization of the gland is greatly attenuated. In 14% of women with PPT and TPO Ab the ultrasound image is not typical of subacute autoimmune thyroiditis, while a significant proportion - 39% of TPO Ab positive women without clinical disease have the corresponding ultrasound changes in the gland structure. These findings question the clinical value of ultrasound in the diagnosis and follow-up of the evolution of post-partum thyroid dysfunction.

The destructive nature of the disease is confirmed by increased urinary excretion of iodine both in the thyrotoxic and the hypothyroid phase. Serum thyroglobulin is elevated as an indicator of thyroid destruction. Its levels are not particularly important.
Postpartum Thyroiditis

TREATMENT

Recommendations for treatment of PPT, as summarized in the consensus statements of thyroid associations, do not differ significantly.4,12 The thyrotoxic phase usually occurs with mild clinical symptoms and does not require specific therapy. If there are symptoms of the cardiovascular system such as tachycardia and palpitations, beta-blockers may be used. Propranolol is the drug of choice, which, in addition to its cardiovascular effects, ameliorates the neuropsychiatric disorders as it crosses the blood-brain barrier. The dose is titrated until symptomatic relief is achieved. If there are contraindications for the use of beta-blockers, verapamil is effective in alleviating cardiac symptoms. Antithyroid drugs are not indicated as the condition is inherently a destructive process. The duration of treatment is usually not more than two months and it is continued until the FT4 levels normalize in accordance with the transitional nature of the disorder.

The hypothyroid phase could cause more severe symptoms which deteriorate the quality of life of female patients. Treatment is determined by the severity of hypothyroidism, and the desire of the woman for subsequent pregnancy. In asymptomatic patients with elevated levels of TSH up to 10 mU/L, who do not plan new pregnancy, levothyroxine treatment is not necessary. Recommendation for watchful waiting requires reassessment of hormone values after 4 to 8 weeks and in persistence of elevated TSH levels it is appropriate to initiate a replacement therapy. In women with TSH between 4 and 10 mU/L, who have complaints and wish for a new pregnancy, levothyroxine replacement therapy is started, which is obligatorily indicated in patients with TSH > 10 mU/L, irrespective of the clinical manifestations.4,12 It is recommended that treatment be continued until the end of the first year with subsequent re-evaluation of the condition and needs of thyroid hormones replacement. Avoidance of foods and iodine-rich supplements is advised.

FOLLOW UP

Thyroid dysfunction in the postpartum period is usually transient and the majority of women recover the euthyroid state by the end of the first year after delivery.18 However, even after the hypothyroid phase is over, changes may be noticed in the ultrasound image of the gland and in radioiodine uptake. These changes reflect an underlying chronic autoimmune thyroiditis, which is the reason for the persistence of the hypothyroid phase of PPT and development of lasting hypothyroidism during long-term follow-up. In some analyses, the incidence of permanent thyroid dysfunction after PPT is greater. Azizì et al. found that over 50% of patients with subclinical hypothyroidism during PPT develop persistent, mostly subclinical hormone deficiency after discontinuation of treatment with levothyroxine.17

The risk of permanent hypothyroidism in women with a history of PPT requires monitoring of thyroid function at least once a year. In TPO Ab positive women who did not have post-partum thyroid dysfunction, the incidence of hypothyroidism during 7-year follow-up is 5%. Factors associated with a higher risk for the development of a lasting hypothyroidism are the severity of the initial hypothyroid phase of PPT and development of lasting hypothyroidism during PPT develop persistent, mostly subclinical hormone deficiency after discontinuation of treatment with levothyroxine.17

PREVENTION

Analyses evaluating the relationship of TPO Ab with morbidity associated with pregnancy and the postpartum period and potential benefits of early intervention in women with positive titers are scarce and do not give clear advice on designing a universal method for prevention. Two randomized placebo-controlled studies evaluate the effect of the application of iodine and levothyroxine during pregnancy.
to prevent PPT in TPO Ab positive women. None of the applied interventions reduced the incidence of PPT; iodine intake even enhanced thyroid dysfunction. Therefore, these preventive strategies are considered inefficient and are not recommended. In another randomized placebo-controlled study, R Negro et al. found that administration of selenium in pregnant women significantly reduced positive postpartum TPO Ab titers and the risk of developing PPT. Since this is the only research and there are no other studies to confirm these positive results, the intake of selenium cannot yet be introduced for prevention of PPTD.

SCREENING

The high frequency of thyroid dysfunction in the postpartum period and related complications raise the question of the need for early screening to identify patients at risk. At present, there are no reliable prognostic indicators whose predictive value meets the requirements for the design of a screening strategy. The American Association of Clinical Endocrinologists recommends screening for thyroid dysfunction of all women planning pregnancy and/or in the first trimester of pregnancy. In the recommendations issued by the American Thyroid Association there is the opinion for evaluation of thyroid function during pregnancy only in risk patients, which is in line with the analysis of the Endocrine Society. However, Vaidya et al. showed in a study that screening only risk patients would miss a third of women with prominent or subclinical hypothyroidism which questions the clinical value of selective screening.

The majority of researchers believe that TPO Abs are the most important indicator which increases the risk of postpartum thyroid dysfunction. Their importance is mainly determined by the high frequency of positive titers in early pregnancy, easily accessible and standardized laboratory techniques for measuring them and their proven role as a risk factor for permanent hypothyroidism and PPTD. Their prognostic significance, however, varies between analyses. Ambiguous assessment of sensitivity, specificity and positive predictive value of markers are linked to differences in survey methodology, time period for sampling and some characteristics of the study population which independently increase the risk of PPTD (iodine intake, genetic predisposition, age, parity, presence of type 1 diabetes, family history of thyroid pathology). Development of PPT in TPO Ab negative patients calls into question the prognostic value of this indicator as a universal screening marker.

Currently the most common prognostic model for determining the risk of PPT is associated with the evaluation of TPO Ab titers in combination with clinical and history data suggestive of impaired thyroid function. In a follow-up of 98 pregnant women Mamede da Costa et al. report 10.2% risk of developing PPTD within the first year after delivery. Data analysis found that the sensitivity, specificity and positive predictive value (PPV) of TPO Ab for the prediction of PPTD were respectively 60.0%, 95.5% and 60%. PPV of the indicator increased from 60 to 82.4%, when combined with the risk factors of family history and the presence of goiter.

CONCLUSIONS

PPT is the most common thyroid disease in the postpartum period. In part of the affected patients it proceeds with marked abnormalities in thyroid hormone balance, causing significant subjective symptoms. This underlines the need for early identification of risk patients for prophylaxis and adequate treatment of thyroid dysfunction in the postpartum period. Some analysis show significant variations in the frequency of PPT, and studies on risk factors do not establish reliable predictive models for disease progression. This is due to the different methodology of research and the involvement of a number of genetic and non-genetic factors in different geographic regions. Therefore, the relevance of introducing mass screening program is a matter of discussion. Various researchers’ opinions motivate the study of the problem in each center and defining prognostic risk characteristics specific to the region and the population covered. Data from these studies can be used to introduce targeted and cost-effective screening for early detection of risk patients and prevention of morbidity and complications of PPT.

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Folia Medica 2014; 56(3): 145-151
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