CLINICAL IMPORTANCE OF CERTAIN IMMUNOLOGICAL AND ULTRASOUND THYROID CHARACTERISTICS FOR THE DIAGNOSIS OF POSTPARTUM THYROIDITIS

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Abstract

Introduction: Postpartum thyroiditis (PPT) is an autoimmune disease associated with the presence of thyroid autoantibodies (TAAb) and changes in the morphological characteristics of the thyroid gland.

Aim: To investigate the clinical importance of certain immunological and ultrasound thyroid characteristics for the diagnosis of postpartum thyroiditis.

Patients and methods: 33 women with PPT and a control group of 53 euthyroid postpartum women were included in the study. Serum levels of thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) were measured and ultrasound evaluation of the size and morphology of the thyroid gland was performed during the postpartum period.

Results: 72.7% of the patients with PPT were TAAb+ and in 69.7% of the cases elevated levels of TPOAb were found. In the remaining 27.3% postpartum thyroid dysfunction occurred without immunological abnormalities. The majority of euthyroid women (92.5%) did not have elevated TAAb. Different grades of thyroid hypoechogenicity were established in 91.9% of the patients with PPT, while 24.5% of the women without thyroid dysfunction had abnormal ultrasound findings. The thyroid volume of the women with PPT was significantly greater than that of the control group (p=0.000).

Conclusion: TPOAb are the most significant immunological marker for the diagnosis of thyroid dysfunction during the postpartum period. However, TPOAb+ is not a universal finding among all women with PPT. The ultrasound parameters thyroid volume and hypoechogenicity play an important part in the comprehensive evaluation of patients with hormonal abnormalities during the postpartum period.

Key words: postpartum thyroiditis, thyroid antibodies, TPOAb, thyroid hypoechogenicity

Introduction: Postpartum thyroiditis (PPT) is a syndrome of transient or permanent thyroid dysfunction occurring during the first year after delivery or abortion. It is considered a painless thyroiditis, a part of the spectrum of autoimmune thyroid diseases and is accompanied by destructive or stimulating effects on the thyroid gland. It is characterized by a biphasic course with an episode of transient thyrotoxicosis followed by transient hypothyroidism. Autoimmune pathogenesis of the disease is supported by the presence of circulating thyroid autoantibodies in over 50% of the patients. The clinical, hormonal and immunological abnormalities in women with PPT are accompanied by changes in the morphological characteristics of the thyroid gland. However, in the recommendations of ATA from 2011 it is noted that ultrasonographic examination has little clinical relevance both in assessing the risk of PPT and making the diagnose /17/.

Aim: To investigate the clinical significance of certain immunological and ultrasound characteristics of the thyroid gland for the diagnosis of postpartum thyroiditis.
Patients and methods: 33 patients with PPT (mean age 29.55±0.75 years) and 53 euthyroid postpartum women (mean age 29.87±0.67 years) were included in the study. The general purpose of the study and its design were explained to the patients. The study complied with the recommendations of the Declaration of Helsinki and all participants signed a written informed consent form approved by local Ethic Committee at the Medical University of Plovdiv. All the patients included had no evidence of pre-existing autoimmune thyroid disease. Patients were tested 4.24±1.87 months following delivery. Women who developed postpartum Graves’ disease were excluded from the study. Serum levels of thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) were measured using chemiluminescence immunoassay (Beckman Coulter, Access2). Measurement units and reference ranges are as follows: TSH, 0.34 – 5.60 mIU/l; FT4, 7.86 – 14.40 pmol/l; FT3, 3.60 – 6.00 pmol/l. TPOAb levels were considered positive if above 9 IU/ml (normal range 0 – 9 IU/ml) and TgAb – above 4 IU/ml (normal range 0 – 4 IU/ml). Ultrasound examination was performed by one experienced clinician during the puerperal period using 5-13 MHz linear transducer (Siemens Acuson U300). Thyroid volume was calculated for each lobe individually using Brunn's formula: V (ml) = 0.479 x length x depth x width. Thyroid parenchyma hypoechogenicity was determined by a 4-grade scale compared to the echoic pattern of the prethyroid muscles. The statistical package for the social sciences (SPSS, Inc., Chicago, IL) version 17.0 was used to analyze the collected data. Significant level of p-value was considered less than 0.05.

In 51.5 % (n=17) of the women PPT presented with thyrotoxicosis and 48.5 % (n=16) had evidence of hypothyroidism (tab. 1).

Table 1. Mean hormonal values of the patients according to the postpartum thyroid function.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PPT Thyrotoxicosis</th>
<th>PPT Hypothyroidism</th>
<th>Euthyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mIU/l)</td>
<td>0.04±0.01</td>
<td>52.07±17.79</td>
<td>1.98±0.79</td>
</tr>
<tr>
<td>FT4 (pmol/l)</td>
<td>26.35±3.30</td>
<td>6.63±0.76</td>
<td>10.72±1.37</td>
</tr>
<tr>
<td>FT3 (pmol/l)</td>
<td>9.93±1.63</td>
<td>3.93±0.22</td>
<td>4.83±0.53</td>
</tr>
</tbody>
</table>

Results: Measurement of TPOAb and TgAb is commonly used in clinical practice for the diagnosis of autoimmune thyroid disorders. In the group with PPT TPOAb were prevalent - 69.7% (n=23). Positive TgAb titers were present in 21.2 % (n=7) of the women with PPT, and in 3% (n=1) of the women were the only antibody. In 27.3 % (n=9) of the women postpartum thyroid dysfunction occurred with negative titers of thyroid antibodies (fig. 1).
The majority of the euthyroid postpartum women (92.5 %) had no laboratory evidence of immunological disorders, and only in 4 cases (7.5 %) were established positive titers of thyroid autoantibodies (fig. 1). The difference in the distribution of thyroid autoantibody combinations between the two groups of women studied was statistically significant \( \chi^2 = 40.541, p = 0.000 \).

The mean thyroid volume of the women with PPT was 13.13±0.97 ml and was greater with 62.9 % than the volume of the euthyroid women (8.06±0.42 ml). The difference was statistically significant (Mann-Whitney U-test, p=0.000) (fig. 2).

Figure 2. Mean thyroid volume of the women with PPT and the euthyroid postpartum women.

Structural changes of the thyroid gland were more common in the women with PPT compared to the euthyroid group (90.9 % vs 24.6 %, p=0.000). In the euthyroid women the ultrasound abnormalities consisted of predominantly mild degree of hypoechogenicity. Thyroid hypoechogenicity was more prominent in the patients with thyroid dysfunction and almost half of the women had grade 2 hypoechogenicity on US examination (tab. 2).

Table 2. Grades of thyroid hypoechogenicity in the euthyroid women and patients with PPT.

<table>
<thead>
<tr>
<th>Hypoechogenicity</th>
<th>Euthyroid</th>
<th>PPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>Grade I</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Grade II</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Grade III</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>33</td>
</tr>
</tbody>
</table>

The difference between the severity of thyroid structural abnormalities in the women who developed PPT and the control group was statistically significant \( \chi^2 = 43.165, p=0.000 \).

All patients with PPT and positive TAAab titers had ultrasound changes in the thyroid structure. 27 % (n=9) of the women with PPT had no detectable TAAab. In one third of those women neither TAAab nor US changes were present, while in the other cases various degree of thyroid hypoechogenicity was observed.

The value of TPOAb and US hypoechogenicity as a diagnostic tool was calculated. TPOAb+ showed specificity of 94.34 % and sensitivity of 69.70 %. Presence of US hypoechogenicity had specificity of 75.47 % and sensitivity of 90.91 % in diagnosing postpartum thyroid dysfunction.

Discussion: PPT is usually characterised by positive titers of thyroid autoantibodies. TPOAb are found in over 50 % of the cases, in 15 % together with TgAb /10/. TgAb are present less frequently - in about 15 % of the cases, and in less than 5% are sole thyroid autoantibody /10/. In women with
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Elevated levels of both types of autoantibodies, typically the concentrations of TPOAb are higher /5/. In a small percentage of women, however, PPT develops without circulating thyroid antibodies, which questions the immune pathogenesis of thyroid dysfunction /7/. Kuipjens et al. observed that in 5 out of 15 women with PPT functional abnormalities developed without TAAAb /9/. The authors also found that in those patients there were no abnormalities in cell-mediated immunity apart from the pregnancy-related changes. Despite the small number of cases, researchers have proposed the existence of two forms of PPT: TPOAb+ or autoimmune form seen in two thirds of the studied women (classic model of PPT) and TPOAb- or non-autoimmune form in one third of patients. Development PPT in TPOAb- women has been described in other studies and in some analyzes the frequency of these cases reaches 44-55% /2,6,18,19/. The reasons for these results are diverse - use of insensitive laboratory methods, especially in older studies, determining antithyrocyte antibodies /12/, presence of only TgAb, prevalence of cell-mediated immune mechanisms, time of sampling, specific characteristics of the population studied.

In the studied group 10 (27.3 %) of the cases of PPT had negative titers of TPOAb. The frequency is similar to that reported in earlier studies and relatively higher compared to contemporary data. In a study of Premawardhana et al., however, thyroid disorders in the postpartum period did not develop in TPOAb- women /15/. The results are comparable with those of Shahbazian et al. /19/ who established TPOAb in 61.5 % of the cases with PPT as well as in 19 % of the euthyroid postpartum women. TgAb were found in 58 % of the patients with hormonal abnormalities and in 7 % among the control group.

Changes in the thyroid volume determined by ultrasound examination have been widely discussed in the context of the problem. In several studies the development of PPT was associated with the presence of goiter /11/. Rasmussen et al. indicate that the thyroid volume do not differ between patients with and without postpartum thyroid dysfunction and thus can not be used as a diagnostic feature /16/. Barca et al. do not establish differences in thyroid volume among patients with PPT in relation to thyroid antibodies levels and the extent of structural changes in the thyroid parenchyma /4/. In a prospective study by Diaz et al. the average volume of the thyroid gland on the third postpartum month in patients with PPT was not statistically different from the control group (11.51±4.86 vs 12.29±3.45 ml, p=0.455) /8/.

The data on the relationship between the thyroid volume and thyroid function in women with PPT have shown inconsistent results, so that thyroid volume has been regarded as an additional factor for the diagnosis of PPT. Our results show significant differences in the thyroid volume between the patients according to the thyroid function. In the women who developed PPT the thyroid volume was significantly higher that that in the euthyroid women. These findings are comparable with those reported by other authors /20/.

Hypoechogenicity is a characteristic ultrasound feature of the thyroid parenchyma in patients with autoimmune thyroid diseases. The frequency of this finding varies from 19 % to 95 % /14/. Echogenicity of the thyroid parenchyma depends on the follicle amount, form and size as well as on the amount of connective tissue strands, the acoustic properties of the colloid, the type of blood supply, the presence of lymphoplastic infiltration. The typical US image of the thyroid in women with PPT is characterized by diffuse or multifocal hypoechogenicity due to lymphocytic infiltration and destructive changes /1/. It has been found that the grade of hypoechogenicity correlates with the degree of lymphocytic infiltration and hormonal abnormalities in women with PPT /13/.

In a study of Adams et al. 86 % of the women with PPT showed varying degrees of thyroid hypoechogenicity whereas only 3 % of the control group had structural abnormalities /1/. Shahbazian et al. established thyroid hypoechogenicity in 96 % of the PPT cases compared to 7 % among the control group (p<0.001) /19/, and in a subsequent study the incidence of ultrasound
changes in women with postpartum thyroid dysfunction reached 98.5% /20/.

US findings are not invariably consistent with the hormonal and immunological parameters of thyroid function. Some authors state that in 14% of women with PPT who are TPOAb+ thyroid hypoechogenicity was not observed. On the contrary, US changes were found in 39% of the women with positive TPOAb titers but without evidence of thyroid dysfunction /1/. Parkes et al. described several cases of severe structural abnormalities in the thyroid gland not linked with thyroid dysfunction /13/. Other authors concluded that the development of PPT may not be a consequence of the lymphocytic thyroiditis in the postpartum period and suggested that there might be other factors leading to progression of thyroid dysfunction /3/.

Our results indicate that thyroid hypoechogenicity is a characteristic feature of PPT, as observed in over 90% of the cases. The frequency of this finding is significantly higher in women with thyroid dysfunction than euthyroid postpartum women. For the majority of patients with PPT (60%) is common moderate hypoechogenicity and the incidence of mild and severe hypoechogenicity are approximately equal (18.9% and 16.5% respectively). Thyroid hypoechogenicity in the postpartum period is established in some women without functional thyroid disorders but is usually mild and transient.

**Conclusion:** TPOAb are the most significant immunological marker for the diagnosis of PPT, but in a considerable number of cases no abnormal immunological parameters are detected. Ultrasonographic examination of the thyroid gland is an important part of the comprehensive evaluation of women with PPT, and in some cases morphological changes may be the only manifestation of thyroid disorders during the postpartum period.

**References:**

12. Nikolai