

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

Antoaneta Argatska, Boyan Nonchev

Medical University Plovdiv, Faculty of medicine, Department of Endocrinology

Bld. Vasil Aprilov 15a, 4002, Plovdiv, Bulgaria

e-mail: lakalma@abv.bg

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 diagnosis /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: $V \text{ (ml)} = 0.479 \times \text{length} \times \text{depth} \times \text{width}$. Thyroid parenchyma hypoechoogenicity 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.

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

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).

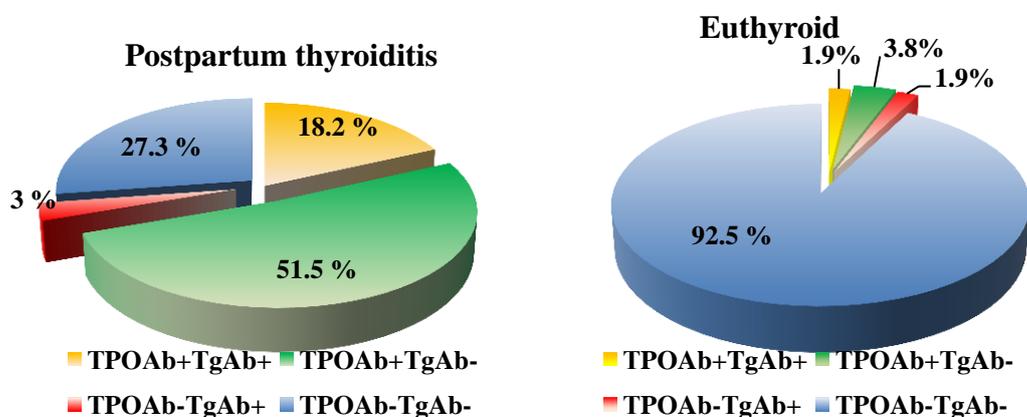


Figure 1. Thyroid autoantibody combinations in patients with PPT and euthyroid postpartum women.

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).

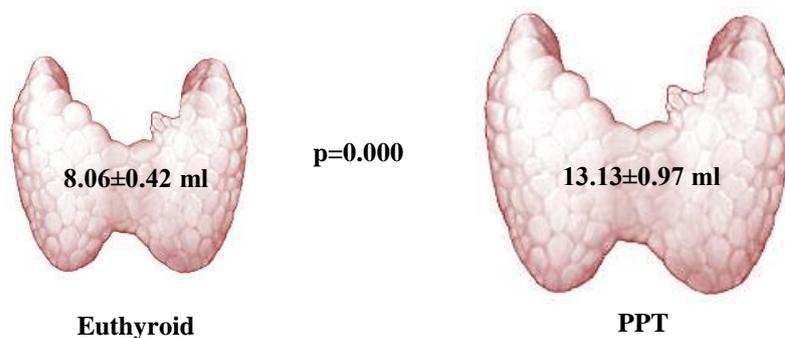


Figure 2. Mean thyroid volume of the women with PPT and the euthyroid postpartum women.

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.

Hypoechogenicity	Euthyroid		PPT		p
	n	%	n	%	
Grade 0	40	75.5	3	9.1	0.000
Grade I	9	17	7	21.2	
Grade II	3	5.7	16	48.5	
Grade III	1	1.9	7	21.2	
Total	53	100.00	33	100.00	

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 TAAb titers had ultrasound changes in the thyroid structure. 27 % ($n=9$) of the women with PPT had no detectable TAAb. In one third of those women neither TAAb 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

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/. Kuijpers et al. observed that in 5 out of 15 women with PPT functional abnormalities developed without TAAb /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 antimicrosomal 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 than that in the euthyroid women. These findings are comparable with those reported by other authors /20/.

Hypoechoogenicity 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 lymphoplasmatic infiltration. The typical US image of the thyroid in women with PPT is characterized by diffuse or multifocal hypoechoogenicity due to lymphocytic infiltration and destructive changes /1/. It has been found that the grade of hypoechoogenicity 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 hypoechoogenicity whereas only 3 % of the control group had structural abnormalities /1/. Shahbazian et al. established thyroid hypoechoogenicity 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:

1. Adams H, Jones MC, Othman S et al. The sonographic appearances in postpartum thyroiditis. *Clin Radiol* 1992 May;45(5):311–5.
2. Amino N, Tada H, Hidaka Y. Postpartum autoimmune thyroid syndrome: a model of aggravation of autoimmune disease. *Thyroid*. 1999 Jul;9(7):705-13.
3. Antonangeli L, Maccherini D, Cavaliere R et al. Comparison of two different doses of iodide in the prevention of gestational goiter in marginal iodine deficiency: a longitudinal study. *Eur J Endocrinol* 2002 Jul;147(1):29–34.
4. Barca MF, Knobel M, Tomimori E et al. Prevalence and characteristics of postpartum thyroid dysfunction in São Paulo, Brazil. *Clin Endocrinol (Oxf)*. 2000 Jul;53(1):21-31.
5. Beever K, Bradbury J, Phillips D et al. Highly sensitive assays of autoantibodies to thyroglobulin and to thyroid peroxidase. *Clin Chem* 1989 35:1949–54.
6. Filippi U, Brizzolara R, Venuti D et al. Prevalence of post-partum thyroiditis in Liguria (Italy): an observational study. *J Endocrinol Invest* 2008 Dec;31(12):1063-8.
7. Fukayama H, Nasu M, Murakami S et al. Examination of antithyroid effects of smoking products in cultured thyroid follicles: only thiocyanate is a potent antithyroid agent. *Acta Endocrinol (Copenh)* 1992;127:520–5.
8. Jaén Díaz JI, López De Castro F, Cordero García B et al. Incidence of postpartum thyroiditis and study of possible associated factors. *Med Clin (Barc)*. 2009 Apr 25;132(15):569-73.
9. Kuijpers JL, De Haan-Meulman M, Vader HL et al. Cell-mediated immunity and postpartum thyroid dysfunction: a possibility for prediction of disease? *J Clin Endocrinol Metab* 1998 Jun;83(6):1959-66.
10. Lazarus JH, Premawardhana LDKE. Postpartum Thyroiditis. From: Weetman AP. *Contemporary Endocrinology: Autoimmune Diseases in Endocrinology*. Totowa, New Jersey: Humana Press; 2008:177-92.

- 11.Lervang HH, Pryds O, Kristensen HP. Thyroid Dysfunction after Delivery: Incidence and Clinical Course. *Acta Medica Scandinavica* 1987;222(4):369–74.
- 12.Nikolai
- 13.Parkes AB, Adams H, Othman S, Hall R, John R, Lazarus JH. The role of complement in the pathogenesis of postpartum thyroiditis: ultrasound echogenicity and the degree of complement induced thyroid damage. *Thyroid* 1996;6:177–82.
- 14.Pedersen OM, Aardal NP, Larssen TB et al. The value of ultrasonography in predicting autoimmune thyroid disease. *Thyroid* 2000 Mar;10(3):251-9.
- 15.Premawardhana LDKE, Parkes AB, John R et al. Thyroid peroxidase antibodies in early pregnancy: utility for prediction of postpartum thyroiditis and implications for screening. *Thyroid* 2004 Aug;14(8):610-5.
- 16.Rasmussen NG, Hornnes PJ, Høier-Madsen M et al. Thyroid size and function in healthy pregnant women with thyroid autoantibodies. Relation to development of postpartum thyroiditis. *Acta Endocrinol (Copenh)*. 1990 Oct;123(4):395-401.
- 17.Stagnaro-Green A, Abalovich M, Alexander E et al. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. *Thyroid* 2011 Oct;21(10):1081-125.
- 18.Stagnaro-Green A, Schwarz A, Gismondi R et al. High rate of persistent hypothyroidism in a large-scale prospective study of postpartum thyroiditis in Southern Italy. *J Clin Endocrinol Metab* 2011 Mar;83(6):652-7.
- 19.Shahbazian HB, Sarvghadi F, Azizi F. Prevalence and characteristics of postpartum thyroid dysfunction in Tehran. *Eur J Endocrinol*. 2001 Oct;145(4):397-401.
- 20.Shahbazian HB, Sarvghadi F, Azizi F. Ultrasound characteristics and follow-up in postpartum thyroiditis. *J Endocrinol Invest* 2005 Jul;28(7):410-2.