Low concordance between positive antibodies to thyroperoxidase and thyroid ultrasound autoimmune pattern in pregnant women

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Abstract. The diagnostic and prognostic role of thyroid ultrasound (TUS) in pregnant women positive for antibodies to thyroperoxidase (TPOAb) is unclear. The aim of our study was to compare the relation of ultrasound thyroid texture to the thyroid laboratory tests in pregnant women and controls. Using a semi-quantitative assessment we compared TUS in two groups of women with positive TPOAb and/or with thyroid dysfunction (TSH out of 0.06-3.67 mIU/L): 186 women in 1st trimester of pregnancy recruited from universal screening and 67 asymptomatic age-comparable non-pregnant non-postpartum women recruited from screening of general population (controls). Women with previous history of thyroid diseases were excluded. Only 64/131 (48.9 %) of TPOAb-positive pregnant women were TUS-positive (TUS with autoimmune pattern) in comparison with 35/49 (71.4 %) TPOAb-positive controls (p<0.011). Pregnant women had more often TSH >10.0 mIU/L if they were TPOAb-positive/TUS-positive as compared to those TPOAb-positive/TUS-negative (8/64 (12.5 %) vs. 0/67 (0 %), p = 0.009). The prevalence of preterm deliveries among TPOAb-positive women was significantly lower if TPOAb-positivity was not accompanied by TUS-positivity (2/67 (3.0 %) vs. 10/64 (15.6 %) in TPOAb-positive/TUS-positive women, p = 0.028). In conclusion, nearly half of the TPOAb-positive pregnant women did not have an autoimmune pattern in TUS. Normal TUS image in TPOAb-positive pregnant women might be a protective factor for preterm delivery.

Key words: Thyroid texture, Thyroid ultrasound, Antibodies to thyroperoxidase, Pregnancy, Preterm delivery

Questions concerning thyroid diseases in pregnancy and postpartum have been repeatedly discussed in the recent years. The negative impact of thyroid dysfunction on fertility, course of pregnancy and development of offspring has been well described. Therefore, screening for thyroid disorders in pregnancy has been recommended [1-4]. Although several studies suggested that even a positivity to antibodies to thyroperoxidase (TPOAb) with normal thyroid function may increase the risk of fetal loss and preterm delivery [5, 6], the negative impact of positive TPOAb in euthyroid women on the pregnancy remains dubious. Unfortunately, there is a lack of studies concerning the relationship between TPOAb-positivity and autoimmune pattern in thyroid ultrasound (TUS) in pregnancy, and its impact on the course and outcome of pregnancy. The aims of the study were: A) using a semi-quantitative assessment to compare TUS image in two groups of patients: women in 1st trimester of pregnancy positive for TPOAb and/or with thyroid dysfunction (abnormal serum TSH - thyroid stimulating hormone) recruited from universal screening (group A - pregnant) and asymptomatic age-comparable non-pregnant non-postpartum women positive for TPOAb and/or with thyroid dysfunction recruited from screening of gen-
The control group (group B - controls) was recruited from thyroid laboratory screening of general population (group B - controls); B) to determine the impact of changes in thyroid echomorphology in women positive for TPOAb on the course, complications and outcome of pregnancy.

**Patients and Methods**

**Patients and controls**

The study was performed at the Outpatient endocrinological department of the 3rd Department of Medicine of the General University Hospital and 1st Medical Faculty, Charles University in Prague. It was designed as a prospective study. Between years 2005-2009, 5,520 healthy asymptomatic women from iodine sufficient area in the central Czech Republic were screened for TSH and TPOAb in the 9-11th week of pregnancy [7]. All women were advised to be supplemented by 100-150 µg of iodide daily. If TSH and/or TPOAb were out of the reference interval, serum concentrations of FT4 were measured.

One hundred eighty-six of those women who were positive in the screening (TSH out of reference interval 0.06-3.67 mIU/L and/or TPOAb >143 kIU/L) but had no previous history of thyroid diseases, were included into the study (group A – pregnant, median age 31 years). Four from 186 positively screened pregnant women were diagnosed with Graves’ hyperthyroidism (suppressed TSH, increased FT4, positive antibodies to TSH-receptor and typical clinical symptomatology and changes in TUS) and treatment with propylthiouracil had been started. Nine had overt hypothyroidism (6 TPOAb-positive and 3 TPOAb-negative), 84 had subclinical hypothyroidism (46 TPOAb-positive and 38 TPOAb-negative), 73 were euthyroid (only TPOAb-positive) and 16 had transient gestational hyperthyroidism. Levothyroxine treatment was started in all women with hypothyroidism and in 44/73 euthyroid women with positive TPOAb (in 137 women during pregnancy and in 4 euthyroid women after delivery). Hypothyroid women became euthyroid within 4 weeks of therapy.

The control group (group B - controls) was recruited from thyroid laboratory screening of general population realized by some general practitioners in the same geographical area (iodine sufficient area in the central Czech Republic). The screening was organized as regular (every 2-4 years) measurements of TSH and TPOAb in adults. If there was a positive result of the screening (TSH out of 0.4-3.67 mIU/L and TPOAb >143 kIU/L), the patient was referred to the Outpatient endocrinological department. The control group (n=67) was selected of the patients with abnormal TSH and/or positive for TPOAb. Inclusion criteria were: women, age-comparable, without previous history of thyroid diseases, asymptomatic, non-pregnant and non-postpartum (at least 2 years after the last pregnancy), no history of treatment for infertility, history of at least one non-complicated delivery at term. To compare with pregnant women only controls with TSH <0.06 mIU/L were included. Therefore the same criteria for pathologic TSH and TPOAb in controls as in pregnancy were used.

In control group 2 women were diagnosed with Graves’ hyperthyroidism and therapy with thyrostatic drugs has been started. Six had overt hypothyroidism (4 TPOAb-positive and 2 TPOAb-negative), 22 had subclinical hypothyroidism (12 TPOAb-positive and 10 TPOAb-negative), 34 were euthyroid (only TPOAb-positive) and 3 had non-thyroidal TSH suppression. Basal characteristic of pregnant women and controls are in Table 1.

### Table 1 Basal characteristic of pregnant women and controls

<table>
<thead>
<tr>
<th></th>
<th>Pregnant</th>
<th>Controls</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median of age</td>
<td>31</td>
<td>32</td>
<td>0.966</td>
</tr>
<tr>
<td>TSH mIU/L</td>
<td>3.67 (1.69-4.91)</td>
<td>2.97 (1.41-5.7)</td>
<td>0.946</td>
</tr>
<tr>
<td>TPOAb kIU/L</td>
<td>723 (95.83.-1990.5)</td>
<td>994 (121.75-2489.25)</td>
<td>0.546</td>
</tr>
</tbody>
</table>

Expressed as median (lower quartile-upper quartile). TSH: serum concentration of thyroid stimulatory hormone, TPOAb: serum concentration of antibodies against thyroperoxidase, Mann-Whitney test.
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Laboratory methods
Serum concentrations of TSH and TPOAb were determined by chemiluminescence method (ADVIA® Centaur™, Bayer, Germany). The determination of reference interval for TSH and cut-off for TPOAb in pregnancy was in detail described in our previous study [7]. The reference interval for TSH was determined with use of selected group of pregnant women with negative TPOAb and without the presence of thyroid diseases in personal history. It was calculated using the log transformation, and then summarized as the geometrical mean (95% CI). The cut-off for TPOAb-positivity was the 90th percentile obtained from selected group of pregnant women with TSH within reference interval and without the presence of thyroid diseases in personal history. Therefore, as “positive” results in the 1st trimester of pregnancy, TSH out of interval 0.06-3.67 mIU/L and/or TPOAb >143 kIU/L were accepted. If TSH and/or TPOAb were out of the reference interval, serum concentrations of FT4 were measured (chemiluminescence method, ADVIA® Centaur™, Bayer, Germany). In women with elevated TSH, who were negative for TPOAb, TgAb were determined (chemiluminescence method, ADVIA® Centaur™, Bayer, Germany).

Thyroid ultrasound
An ultrasound examination of the thyroid gland (TUS) was performed by ultrasound equipment (EnVisor by Phillips) with an 8-12 MHz linear probe (model PLF-805ST), allowing a maximum examination depth of 40 mm at a frame rate of 19 Hz. The thyroid volume, texture and presence of nodules were evaluated. To eliminate the inter-individual variability examinations were performed by one experienced physician. The volume of each thyroid lobe was calculated as length (millimeters) x width (millimeters) x depth (millimeters) x 0.479. Ultrasound diagnosis was made on the basis of hypoechogenicity, irregular echo pattern and the presence of nodules. In the present study a model of semi-quantitative evaluation of thyroid texture was applied in order to rend the establishing of diagnosis more objective. Echogenicity was scored as “normal” (uniformly hyperechogenic as compared to the neck muscles), “mildly decreased” (focally of uniformly isoechogenic with the neck muscles) and “strongly decreased” (focally of uniformly hypoechogenic as compared to the neck muscles). Structure was scored as “regular pattern” or “irregular pattern”. Subsequently six categories of the ultrasound diagnosis were determined (Fig. 1): I. Normal thyroid texture (normal echogenicity with regular pattern and without nodules), II. Thyroid nodules (solitary or multiple) without autoimmune pattern, III. Indeterminate thyroid texture (irregular pattern with normal echogenicity), IV. Mild autoimmune pattern (mildly decreased echogenicity with regular pattern), V. Moderate autoimmune pattern (strongly decreased echogenicity with irregular pattern) and VI. Severe autoimmune pattern (strongly decreased echogenicity with irregular pattern).

Statistical analysis
Throughout the text, data are expressed as mean ± standard deviation or median (lower quartile–upper quartile). The Chi-square test, Fisher test, t-test, Mann-Whitney U-test, Kruskal-Wallis test and ANOVA on ranks (Dunn’s method) were used to compare the proportions, means and medians of variables between the groups. All reported p-values are two-sided and p<0.05 was considered as statistically significant. Correlations were tested by Spearman’s correlation coefficient. Statistical software Sigmastat (Jandel Scientific, San Rafael, CA, USA) was used for data analysis.

Results
Thyroid volume
Median of the thyroid volume was 8.5 mL in pregnant women and 8.7 mL in controls (no significant difference). In pregnant women thyroid volume was significantly higher in women with thyroid nodules in comparison with those who had normal TUS (9.85 vs. 8.0, p = 0.016). Thyroid volume correlated negatively with TSH and positively with TPOAb (TSH: \( r = -0.28, p < 0.001, n = 180, \) TPOAb: \( r = 0.155, p = 0.039, n = 179 \)) and also after exclusion of women with Graves’ diseases and transient gestational hyperthyroidism (TSH: \( r = -0.211, p = 0.006, n = 167, \) TPOAb: \( r = 0.234, p = 0.002, n = 166 \)).

Comparison of thyroid texture in pregnant women and controls
In total, 79/186 (42.5 %) positively screened pregnant women (positive for TPOAb and/or with abnormal TSH) had normal TUS in comparison with 15/67 (22.4...
In positively screened pregnant women (n = 186), 79 (42.5 %) had normal thyroid texture, 7 (3.8 %) had indeterminate thyroid texture, 26 (14 %) had thyroid nodules without autoimmune pattern and 74 (39.8 %) had autoimmune pattern in TUS. In the subgroup of pregnant TPOAb-positive women (n = 131), 46 (35.1 %) had normal thyroid texture, 6 (4.6 %) had indeter-
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Pregnant women (Fig. 3). In severe autoimmune thyroiditis a trend toward higher serum TSH as compared to mild and moderate autoimmune thyroiditis, thyroid nodules and normal thyroid glands was found (Fig. 3). There were no significant differences of serum TSH and FT4 between TUS-positive (with autoimmune pattern) and TUS-negative (without autoimmune pattern) pregnant women, even after exclusion of women with Graves’ disease and transient gestational hyperthyroidism (data not shown). Nevertheless, in the subgroup of pregnant women with elevated TSH (>3.67 mIU/L), 25/51 (49.0 %) TPOAb-positive women had autoimmune pattern in TUS in comparison with 8/41 (19.5 %) TPOAb-negative ones (p = 0.007). Similarly, there was higher percentage of women with TSH >10.0 mIU/L in TPOAb-positive/TUS-positive women in comparison with TPOAb-positive/TUS-negative (8/64 (12.5 %) vs. 0/67 (0 %), p = 0.009). Moreover, in women with TSH >3.67 mIU/L (n = 93), FT4 was lower in TUS-positive as compared to TUS-negative ones (median FT4 11.4±2.43 vs. 13.0 pmol/L, p = 0.017).

Table 2 Thyroid ultrasound texture in TPOAb-positive women

<table>
<thead>
<tr>
<th>TPOAb &gt;143 and/or abnormal TSH</th>
<th>Normal thyroid texture</th>
<th>Autoimmune pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td>Controls</td>
<td>p</td>
</tr>
<tr>
<td>79/186 (42.5 %)</td>
<td>15/67 (22.4 %)</td>
<td>0.007</td>
</tr>
<tr>
<td>74/186 (39.8 %)</td>
<td>41/67 (61.2 %)</td>
<td>0.004</td>
</tr>
<tr>
<td>TPOAb &gt;143 and/or elevated TSH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>76/173 (43.9 %)</td>
<td>12/61 (19.7 %)</td>
<td>0.001</td>
</tr>
<tr>
<td>73/173 (42.2 %)</td>
<td>39/61 (63.9 %)</td>
<td>0.003</td>
</tr>
<tr>
<td>TPOAb &gt;143</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46/131 (35.1 %)</td>
<td>7/49 (14.2 %)</td>
<td>0.011</td>
</tr>
<tr>
<td>64/131 (48.9 %)</td>
<td>35/49 (71.4 %)</td>
<td>0.111</td>
</tr>
<tr>
<td>TPOAb &gt;200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44/128 (34.4 %)</td>
<td>6/47 (12.5 %)</td>
<td>0.009</td>
</tr>
<tr>
<td>64/128 (50 %)</td>
<td>38/47 (80.9 %)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TPOAb &gt;500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29/93 (31.2 %)</td>
<td>2/35 (5.7 %)</td>
<td>0.006</td>
</tr>
<tr>
<td>49/93 (52.7 %)</td>
<td>29/35 (82.9 %)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Normal thyroid texture: normal echogenicity with regular pattern and without nodules.
Autoimmune pattern: mild (mildly decreased echogenicity with regular pattern) or moderate (strongly decreased echogenicity with regular pattern or mildly decreased echogenicity with irregular pattern) or severe (strongly decreased echogenicity with irregular pattern).
Abnormal TSH: thyroid stimulatory hormone more than 3.67 or less than 0.06 mIU/L, elevated TSH: thyroid stimulatory hormone more than 3.67 mIU/L. TPOAb: antibodies against thyroperoxidase (kIU/L). Chi-square test, Fisher test.

Serum concentrations of TPOAb did not correlate with FT4 and only poor negative correlation with TSH was found, even after exclusion of women with Graves’ diseases and transient gestational hyperthyroidism (r = -0.177 and -0.160, p = 0.037 and 0.050, respectively). The severity of autoimmune pattern in TUS positively correlated with TPOAb titers in controls but not in pregnant women (Fig. 3). In severe autoimmune thyroiditis a trend toward higher serum TSH as compared to mild and moderate autoimmune thyroiditis, thyroid nodules and normal thyroid glands was found (Fig. 3). There were no significant differences of serum TSH and FT4 between TUS-positive (with autoimmune pattern) and TUS-negative (without autoimmune pattern) pregnant women, even after exclusion of women with Graves’ disease and transient gestational hyperthyroidism (data not shown). Nevertheless, in the subgroup of pregnant women with elevated TSH (>3.67 mIU/L), 25/51 (49.0 %) TPOAb-positive women had autoimmune pattern in TUS in comparison with 8/41 (19.5 %) TPOAb-negative ones (p = 0.007). Similarly, there was higher percentage of women with TSH >10.0 mIU/L in TPOAb-positive/TUS-positive women in comparison with TPOAb-positive/TUS-negative (8/64 (12.5 %) vs. 0/67 (0 %), p = 0.009). Moreover, in women with TSH >3.67 mIU/L (n = 93), FT4 was lower in TUS-positive as compared to TUS-negative ones (median FT4 11.4±2.43 vs. 13.0 pmol/L, p = 0.017).

Relationship of thyroid texture to preterm delivery (PTD) and complications of pregnancy in positively screened pregnant women

In positively screened pregnant women, the frequency of PTD (before 37th week of pregnancy) did not significantly differ either between TPOAb-positive and TPOAb-negative women or between women with low and high TPOAb titers (<500 vs. >500 kIU/L).
Table 3  Thyroid texture (vertically) in pregnant women positive for thyroid laboratory screening with respect to laboratory tests (horizontally)

<table>
<thead>
<tr>
<th></th>
<th>Elevated TSH</th>
<th>Suppressed TSH</th>
<th>TPOAb+ and elevated TSH</th>
<th>TPOAb+ and normal TSH</th>
<th>TPOAb+ regardless of TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>47 (50.5%)</td>
<td>5 (25.0%)</td>
<td>17 (33.3%)</td>
<td>27 (37%)</td>
<td>46 (35.1%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>3 (3.2%)</td>
<td>2 (10%)</td>
<td>2 (3.9%)</td>
<td>2 (2.7%)</td>
<td>6 (4.6%)</td>
</tr>
<tr>
<td>Thyroid nodules</td>
<td>9/93 (9.7%)</td>
<td>9 (45%)</td>
<td>7 (13.7%)</td>
<td>8 (11.0%)</td>
<td>15 (11.5%)</td>
</tr>
<tr>
<td>With AI pattern</td>
<td>34 (36.6%)</td>
<td>4 (20%)</td>
<td>25 (49.0%)</td>
<td>36 (49.3%)</td>
<td>64 (48.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>20</td>
<td>51</td>
<td>73</td>
<td>131</td>
</tr>
</tbody>
</table>

Total: pregnant women positive for thyroid laboratory screening (TSH out of 0.06-3.67 mIU/L and/or TPOAb>143 kIU/L), elevated TSH: thyroid stimulatory hormone more than 3.67 mIU/L, suppressed TSH: thyroid stimulatory hormone less than 0.06 mIU/L, TPOAb+: positive for antibodies against thyroperoxidase (>143 kIU/L), thyroid nodules: thyroid nodules without autoimmune pattern, AI pattern: autoimmune pattern in thyroid ultrasound.

Fig. 3  FT4, TSH and TPOAb with respect to thyroid texture in ultrasound in pregnant women and controls.

Normal (I): normal thyroid texture (normal echogenicity with regular pattern and without nodules), nodules: (II): thyroid nodules (solitary or multiple) without autoimmune pattern, indeterminate (III): indeterminate thyroid texture (irregular pattern with normal echogenicity), mild (IV): mild autoimmune pattern (mildly decreased echogenicity with regular pattern), moderate (V): moderate autoimmune pattern (strongly decreased echogenicity with regular pattern or mildly decreased echogenicity with irregular pattern) and severe (VI): severe autoimmune pattern (strongly decreased echogenicity with irregular pattern).

Women with Graves’ disease and transient gestational hyperthyroidism (“gestational thyrotoxicosis”) were excluded. AIT: autoimmune thyroiditis, FT4: median serum concentrations of free thyroxine (pmol/L), TSH: median serum concentrations of thyroid stimulatory hormone (mIU/L), TPOAb: median serum concentrations of antibodies against thyroperoxidase (kIU/L), the differences of TPOAb between severe autoimmune pattern and other types of thyroid texture were significant in both pregnant and control women, the severity of autoimmune pattern positively correlated with TPOAb titers in controls but not in pregnant women (p <0.05, ANOVA on ranks, Dunn’s method).
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and elevated and not elevated TSH (>3.67 vs. <3.67 mIU/L). There were no significant differences in serum concentrations of TSH, FT4, TPOAb and thyroid volume between women with PTD and delivery at term. The rate of PTD among TPOAb-positive women was 8.4 %. TPOAb-positive women without autoimmune pattern in TUS had significantly lower prevalence of PTD as compared to those TPOAb-positive women with autoimmune pattern in TUS (TPOAb-positive/TUS-negative: 2/67 (3.0 %) vs. TPOAb-positive/TUS-positive: 10/64 (15.6 %), p = 0.028), regardless of the treatment with levothyroxine (Fig. 4). The prevalence of PTD did not differ between women who were and who were not treated with levothyroxine before and during pregnancy. Regardless of TPOAb positivity, the birth weight and the prevalence of birth loss and several complications of pregnancy (preeclampsia, arterial hypertension, gestational diabetes etc.) did not statistically differ between women with and without autoimmune pattern in TUS (data not shown).

Discussion

Not only hypothyroidism but even a presence of positive TPOAb in euthyroid women increased in several studies risk of fetal loss and preterm delivery [5, 6]. However, whether the TPOAb positivity is in some pregnant women only a laboratory phenomenon or it is always accompanied by morphological changes in TUS remains unclear.

Studies concerning TUS in pregnancy are scarce, mostly aimed at the assessment of thyroid volume. According to several studies thyroid volume increased during pregnancy both in iodine-sufficient [8] and iodine-deficient areas [9]. In our study conducted in an iodine sufficient area, thyroid glands of positively screened pregnant women were rather small (median of volume 8.5 mL) and thyroid volume did not significantly differ from controls. The median volume was lower than in age-comparable non-selected non-pregnant Czech women in the study of Dvorakova et al. (median 11.8 mL in group of women aged 31-35 years) [10]. However it is difficult to explain, thyroid volume correlated negatively with TSH and positively with TPOAb. Nevertheless, statistical significances were very low. Therefore, is possible that the correlations were only casual.

Several studies concerning the correlation of thyroid texture with TPOAb-positivity and/or thyroid function in common (non-pregnant) population were published.

Fig. 4 Prevalence of preterm delivery in women positive for thyroid antibodies and autoimmune ultrasound pattern – comparison with other studies. Panel A: our study group, panel B: other studies, TPOAb+: positive for antibodies against thyroperoxidase, TPOAb+/TUS+: with autoimmune pattern in thyroid ultrasound, TUS+: positive for antibodies against thyroperoxidase and against thyroglobulin, Chi-square test.
In patients with Hashimoto’s thyroiditis, high graded hypoechogenicity was associated with large goiters, increased TSH levels and increased TPOAb titers [11]. Fifteen percent of subjects with normal thyroid ultrasound had elevated serum TSH and 10.4 % were TPOAb-positive [12]. Twenty percent of unselected subjects had hypoechogenic and 13.7 % had irregular pattern in TUS [13]. Unselected subjects without overt thyroid diseases with autoimmune pattern in TUS had significantly higher TSH and increased risk of having of positive TPOAb in comparison with controls with normal TUS [14]. According to Dvorakova et al. [15] decreased thyroid echogenicity can be an early indicator of serious thyropathies before laboratory dysfunction and clinical symptoms appear. In the study of Raber et al. there was 85-96 % positive predictive value for TPOA-positive patients and 91 % negative predictive value for TPOAb-negative subjects [16]. Hypoechogenicity in TUS in postpartum thyroiditis had a prognostic significance for development of thyroid dysfunction [17].

Unfortunately, there is lack of information on thyroid morphology in pregnancy. Our study is the first concerning the relationship between thyroid texture and laboratory parameters in pregnancy. Pregnant women were screened for serum TSH and TPOAb and if the screening was positive, serum FT4 was measured. Women were not universally screened for antibodies to thyroglobulin (TgAb). The reasons were economical aspects and also, according to our experiences, lower specificity of the TgAb-tests used in our area as compared to TPOAb-tests. However, TgAb were determined in women with elevated TSH who were negative for TPOAb. TgAb were positive in 6/41 of these cases. Due to this small size data with TgAb were not analyzed.

In our study, 42.5 % of pregnant women with positive TPOAb and/or abnormal TSH (“screening positive”) in the 1st trimester had normal TUS. It was significantly more than 22.4 % in controls. Women with positive screening and normal TUS included all of the 16 women with transient gestational hyperthyroidism, 46 TPOAb-positive women, 16 TPOAb-negative women with elevated TSH and surprisingly one patient with Graves’ diseases. Similarly, 43.9 % of women with positive TPOAb and/or elevated TSH (>3.67 mIU/L) had normal TUS in comparison with 19.7 % in controls. Vice versa, only 48.9 % of TPOAb-positive women had autoimmune pattern in TUS in comparison with 19.7 % in TPOAb-positive controls. Therefore, regardless of the TPOAb titers, only 49-53 % TPOAb-positive pregnant women had autoimmune pattern in TUS in comparison with 71-83 % in TPOAb-positive controls. It is much less than was referred by Shahbazian et al. [18] in the case of postpartum thyroiditis (117/119 (98.5 %)). In the “screening positive” women (abnormal TSH and/or positive TPOAb) the differences in prevalence of autoimmune pattern in TUS between pregnant women and controls could be partly explained by presence of women with transient gestational hyperthyroidism among pregnant women. However, the differences were even more significant in subgroups of women with positive TPOAb and elevated TSH (Table 2). Therefore, presence of transient gestational hyperthyroidism in part of pregnant women and/or the same lower limit for TSH in pregnant and control women would be probably not the explanation. Similarly, the differences can not be caused by different rate of indeterminate ultrasound texture, because it was comparable in pregnant women (4.2 %) and controls (5.9 %).

In fact, there are two ways to explain the low prevalence of ultrasound autoimmune pattern in TPOAb-positive pregnant women: a low sensitivity of TUS or a low specificity of TPOAb-posivity. However, several previous studies have shown a good sensitivity of TUS for the diagnosis of early stages of Hashimoto’s thyroiditis and subclinical hypothyroidism in non-pregnant subjects [14, 15, 16, 18]. Similarly, the specificity of TPOAb in common population is high and was nearly 100 % for histological findings of Hashimoto’s thyroiditis [19, 20]. Consistently, we found relatively good concordance between TPOAb-positivity and ultrasound autoimmune pattern in controls (71-83 % according to several titers). Moreover, in contrast to pregnant women, there was positive correlation between TPOAb titers and severity of ultrasound autoimmune pattern in controls (Fig. 3). Therefore, it seems that in significant part of positively screened pregnant women TPOAb-positivity may be only a laboratory phenomenon without morphological changes of thyroid texture. We can speculate that there may be lower specificity of TPOAb just in pregnancy as compared to common population. The reason could be for example some non-specific activating of immunity in the 1st trimester of pregnancy.
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presence of fetal antigens. However, if it was the reason, the prevalence of TPOAb-positivity among pregnant women should be relatively high. It was 12.2 % in our study - similar as was observed in common non-pregnant age-comparable female population (11-12 %) [21]. On the contrary, it should be noted that we used pregnancy-specific cut-off for TPOAb-positivity (143 kIU/L as the 90th percentile). If we used the cut-off recommended by manufacturer (60 kIU/L) (as were used in studies with common population), the prevalence of TPOAb-positivity could be raised nearly two times (22.1 %) [7]. Unfortunately, the limitation of our study is that we could not establish the prevalence of TPOAb positivity in control group, because only the data of “screening positive” subjects, who were referred to endocrinological outpatients department, were available. Similarly, the prevalence of TPOAb-positivity among young non-pregnant women without history of thyroid diseases is not available in Czech Republic. Therefore, the reasonable explanation of low concordance of TPOAb-positivity and autoimmune ultrasound pattern in pregnancy may be that in part of the women TPOAb-positivity indicates early stages of autoimmune thyroiditis with negative ultrasound for now and partly it may be a laboratory phenomenon with unknown significance. Only well controlled and prospective follow-up studies could resolve this question.

In our study, TPOAb titers did not significantly correlate with thyroid function, even after exclusion of women with Graves’ diseases and transient gestational hyperthyroidism from the analysis. However, we found a trend to higher serum TSH in severe autoimmune thyroiditis (according to the ultrasound pattern) as compared to the other ultrasound diagnoses (Fig. 3). Moreover, 12.5 % of TPOAb-positive pregnant women with positive TUS had an elevated TSH (>10.0 mIU/L), as compared to none women with negative TUS (p = 0.009). Similarly, in women with elevated TSH (>3.67 mIU/L), FT4 was lower in TUS-positive as compared to TUS-negative ones. Therefore, we observed a tendency to impaired thyroid function in pregnant women if TPOAb-positivity was accompanied by positive TUS, regardless of TPOAb titers.

The relationship between thyroid dysfunction, thyroid autoimmunity and the risk of preterm delivery (PTD) and complications of pregnancy has been well described [5, 6]. The rate of PTD varied from 4 to 26.8 % in TPOAb-positive women and 3.8-2 % in TPOAb-negative controls [22, 23, 24, 25]. The causality of this association is unknown. Negro et al. [25] documented a significant decrease in PTD in euthyroid TPOAb-positive women after the treatment with levothyroxine. This suggests that a potential etiology of the PTD maybe subtle hypothyroidism [26]. Another etiology to be explored maybe the impact of placental thyroid hormone receptor expression, which has been documented to be increased in fetuses with intrauterine growth retardation [27]. In our study, the prevalence of PTD in TPOAb-positive women was comparable with the previous studies (8.4 %). However, TPOAb-positive women without autoimmune pattern in TUS had significantly lower prevalence of PTD as compared to those TPOAb-positive with autoimmune pattern in TUS (3.1 vs. 15.2 %) (Fig. 4). Therefore, normal TUS image in TPOAb-positive pregnant women might be a protective factor for PTD. The analysis of thyroid laboratory parameters per se (without TUS) did not show any relationship to the frequency of preterm deliveries and other complications of pregnancy. However, the negative results may be skewed by the fact that the analysis was performed only in positively screened women. Nevertheless, some other previous studies also didn’t find any link between TPOAb titers and obstetric complications [23, 28].

In conclusion, our study has shown that unlike the general female population, nearly a half of the TPOAb-positive pregnant women do not have an autoimmune pattern in thyroid ultrasound. However, if it is a result of low diagnostic sensitivity of ultrasound in early stages of autoimmune thyroiditis or a consequence of lower specificity of TPOAb in pregnancy as compared with common population remains unclear and should be a subject of future research. The frequency of hypothyroidism and preterm deliveries was in our study rather related to the presence of autoimmune pattern in TUS than to the TPOAb titers per se. Normal TUS image in TPOAb-positive pregnant women might be a protective factor for preterm delivery. Therefore, TUS may be helpful to identify the TPOAb-positive women with higher risk of hypothyroidism and/or preterm delivery.

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References


