High frequency of antithyroid autoantibodies in pregnant women at increased risk of gestational diabetes mellitus

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Abstract

Background: Thyroid autoantibodies (ThyAb) and subclinical hypothyroidism occur more frequently in pregnant women with insulin-dependent diabetes mellitus than in healthy pregnant women. Few studies have investigated the presence of ThyAb in women with gestational diabetes mellitus (GDM), and no significant association between diabetes in pregnancy and thyroid function has been reported.

Objective: To assess the thyroid biochemical profile and estimate the prevalence of ThyAb in a group of pregnant women at increased risk for GDM due to family and personal risk factors, and to investigate the relationship between a positive family history of diabetes or thyroid diseases and the eventual presence of ThyAb during pregnancy.

Methods: Oral glucose tolerance, serum ThyAb and thyroid function were evaluated in 181 pregnant women with increased risk for GDM (study group). Seventeen healthy pregnant women without risk factors for GDM and with a normal glucose tolerance were recruited as controls.

Results: The women who developed GDM showed a mean free thyroxine concentration significantly lower than that observed in the healthy pregnant women and in those with impaired gestational glucose tolerance and normal glucose tolerance. Twenty-nine of the 181 women in the study group (16%) were ThyAb positive. However, the risk of being ThyAb positive during pregnancy was three times greater in the women with positive family history of both diabetes mellitus and thyroid disease than in those with no family history of these conditions.

Conclusions: This study showed that women with increased risk of GDM, mostly those with family history of diabetes mellitus and thyroid disease, also have an increased risk of being ThyAb positive during pregnancy. It also highlighted the importance of evaluating thyroid function in pregnant women with impaired glucose tolerance, in view of their increased risk of subclinical hypothyroidism.

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Introduction

About 10% of women at 16 weeks gestation are positive for thyroid peroxidase antibody (TPOAb), in line with what is found in the general population (1). The presence of TPOAb during pregnancy may be associated with hypothyroidism and it has been reported to be closely related to the increased risk of developing postpartum thyroiditis (PPT) (2). Thyroid autoantibodies (ThyAb) occur more frequently in pregnant women with insulin-dependent diabetes mellitus (IDDM) than in healthy pregnant women (3–5). Moreover, an increased incidence of subclinical hypothyroidism has been reported in pregnant women with IDDM (6). As regards gestational diabetes mellitus (GDM), various non-organ-specific autoantibodies have been found to be associated with the condition (7). However, few studies have investigated the presence of ThyAb in women with GDM, and no significant association between diabetes in pregnancy and thyroid function has been reported (8, 9).

GDM is defined as carbohydrate intolerance of variable severity that begins or is first diagnosed during pregnancy. The prevalence of GDM varies from 0.15 to 12.8% (10–15). This wide range reflects racial or geographical differences in the distribution of genetic or environmental risk factors. Women with GDM are characterized by a relatively diminished insulin secretion, coupled with a pregnancy-induced insulin resistance (16). Glucose tolerance returns to normal after delivery in the majority of women, although several studies have shown that women with previous GDM have a high risk of developing overt diabetes mellitus later in life (17–19). Furthermore, maternal hyperglycemia during pregnancy has been shown to be associated with adverse perinatal and childhood
outcomes (20, 21), and possibly with obesity and diabetes in adult life (22). Screening for GDM is recommended at present in all pregnant women, with the aim of reducing maternal and fetal morbidity during and after pregnancy.

The aims of this study were to assess the thyroid biochemical profile and estimate the prevalence of antithyroid autoantibodies in a group of pregnant women at increased risk of GDM due to family and personal risk factors, and to investigate the relationship between a positive family history of diabetes and/or thyroid diseases and the presence of antithyroid autoantibodies during pregnancy.

**Patients and methods**

Oral glucose tolerance, serum ThyAb and thyroid function were evaluated in 181 pregnant women (mean age at conception 31.2 ± 4.2 years) with increased risk of GDM (study group). These women were considered to be at greater risk of GDM on the basis of a panel of risk factors concerning obstetric, family and personal history in addition to maternal age and clinical problems regarding current pregnancy (Table 1). The pregnant women were outpatients of the Department of Obstetrics and Gynecology of the Tor Vergata University in Rome.

A standard 100-g 3-h fasting oral glucose tolerance test (OGTT) was administered late in the second and early in the third trimester (mean gestational age 27.5 ± 4.5 weeks). GDM was diagnosed if two or more of the four threshold plasma glucose values were met or were exceeded, as described previously (23). Impaired glucose gestational tolerance (IGGT) was diagnosed if only one value was met or exceeded (23). Seventeen healthy pregnant women without risk factors for GDM and with a normal glucose tolerance after OGTT were recruited as controls (mean age at conception 28.5 ± 4.8 years; gestational age 24.7 ± 5.0 weeks). The small size of the control group was due to the difficulty of recruiting pregnant women without risk factors for GDM who consented to have the standard OGTT. None of the patients and controls had a personal history of thyroid disease and none was receiving any medication that could influence thyroid function. All the study group and control women were living in Rome or in other urban areas of the Latium region with marginally sufficient iodine intake. All pregnant women taking part in the study gave their written consent to be included.

Thyroid function (free thyroxine (FT₄), free triiodothyronine (FT₃), serum thyroxine binding-globulin (TBG) and thyroid-stimulating hormone (TSH)), serum thyroxine binding-globulin (TBG) and thyroglobulin (Tg) and antithyroglobulin (TgAb) and TPOAb were assessed in the GDM risk group and in the healthy pregnant controls, at the time of the OGTT.

**Postpartum thyroid function assessment**

The thyroid hormone profile was assessed at the 3rd, 6th, 9th and 12th months after parturition. PPT was diagnosed when two or more consecutive FT₄, FT₃ or TSH concentrations were outside the normal reference ranges. Hypothyroidism was defined as increased TSH serum concentrations with or without decreased FT₄ concentrations; thyrotoxicosis was defined as increased serum concentrations of FT₄ or FT₃, or both, with suppressed TSH values.

**In vitro tests**

Plasma glucose concentration was measured by the glucose oxidase method (23). Radioimmunological kits for detection of total T₃ (T₃), total T₄ (T₄), Tg and TSH were purchased from Radim (Pomezia, Italy); serum FT₃, FT₄, TgAb and TPOAb were detected using Brahms RIA kits (Berlin, Germany); serum TBG RIA kits were supplied by Medical System (Genova, Italy).

**Statistical analysis**

The arithmetic mean and standard deviation of thyroid biochemical parameters were calculated. The geometric mean and standard deviation of log values were estimated for the non-normally distributed TSH data. Student’s t-test was used to compare mean values between groups. Differences between proportions were evaluated by χ² test or Fisher’s exact probability test. Test for linear trend (χ² trend) was also performed. Crude risk was estimated by odds ratio (OR) calculation. The 95% confidence interval (CI) was also calculated.

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**Table 1 Risk factors for GDM.**

<table>
<thead>
<tr>
<th>Obstetric history</th>
<th>Family history</th>
<th>Personal history</th>
<th>Current pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity ≥5</td>
<td>Family history of diabetes</td>
<td>Chronic hypertension</td>
<td>Maternal age &gt;35 years</td>
</tr>
<tr>
<td>Previous late abortion</td>
<td>Family history of diabetes</td>
<td>Recurrent infections of genitourinary tract</td>
<td>Pregravidic BMI &gt;25 kg/m²</td>
</tr>
<tr>
<td>Previous preterm delivery</td>
<td>Family history of diabetes</td>
<td></td>
<td>Polihydramnios</td>
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<tr>
<td>Previous macrosomic baby</td>
<td>Family history of diabetes</td>
<td></td>
<td>Excessive weight gain</td>
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<tr>
<td>Previous perinatal death</td>
<td>Family history of diabetes</td>
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<td>Increased fetal biometry</td>
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<td>Previous pregnancy hypertension</td>
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<td>Previous GDM</td>
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<tr>
<td>Previous fetopathy</td>
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<tr>
<td>Previous polyhydramnios</td>
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Table 2 Thyroid parameters observed in the healthy pregnant controls and the study group women classified on the basis of OGTT results. Prevalence of ThyAb is also shown.

<table>
<thead>
<tr>
<th></th>
<th>T3</th>
<th>T4</th>
<th>FT3</th>
<th>FT4</th>
<th>TSH†</th>
<th>Tg</th>
<th>TBG</th>
<th>ThyAb+ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range</td>
<td>0.6–2.0 ng/ml</td>
<td>60–120 ng/ml</td>
<td>2.2–5.5 pg/ml</td>
<td>8–18 pg/ml</td>
<td>0.2–4 μIU/ml</td>
<td>0–25 ng/ml</td>
<td>15–32 μg/ml</td>
<td></td>
</tr>
<tr>
<td>Healthy controls</td>
<td>2.6±0.3</td>
<td>134±49</td>
<td>4.1±0.41</td>
<td>7.6±1.5**</td>
<td>1.0±0.5</td>
<td>10±8.4</td>
<td>48±9.0</td>
<td>2 (11.7)</td>
</tr>
<tr>
<td>(n = 17)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>NGT (n = 144)</td>
<td>2.4±0.4</td>
<td>128±37</td>
<td>4.0±0.5</td>
<td>7.4±1.9**</td>
<td>1.3±1.0</td>
<td>12±9.4</td>
<td>48±8.4</td>
<td>24 (16.7)</td>
</tr>
<tr>
<td>IGGT (n = 18)</td>
<td>2.6±0.4</td>
<td>132±72</td>
<td>4.2±0.5</td>
<td>7.2±0.9†</td>
<td>1.2±0.4</td>
<td>9.0±7.9</td>
<td>48±10</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>GDM (n = 19)</td>
<td>2.4±0.5</td>
<td>144±21</td>
<td>4.0±0.6</td>
<td>6.2±1.2</td>
<td>1.3±0.6</td>
<td>15±14</td>
<td>45±11</td>
<td>2 (10.8)</td>
</tr>
</tbody>
</table>

Values are mean ± s.d. or number (%).
† A logarithmic transformation of TSH values was performed to normalize data for analysis.
**P < 0.01 and ††P = 0.01, compared with FT4 in GDM group.

Results

As assessed by the OGTT, 144 pregnant women (79.5%) had normal glucose tolerance (NGT), 18 (9.9%) had IGGT and 19 (10.5%) had GDM. Women with GDM and IGGT received a diet containing 1600 kcal/day. Insulin treatment was started when the 2-h postprandial plasma glucose concentration was greater than 130 mg/dl (23).

A significantly greater mean body mass index (BMI) was found in the women with GDM than in the healthy controls (27.7 ± 6.9 compared with 20.8 ± 1.5 kg/m², P < 0.01).

Table 2 shows the thyroid hormone profile in the healthy pregnant controls (n = 17) and in the study group (n = 181) classified on the basis of the OGTT results. Expected high values of T3, T4 and TBG were within the normal range.

Frequencies of FT4 and TSH serum concentrations in the women of the study group classified on the basis of the OGTT results and in the controls are illustrated in Fig. 1. There was a significant trend towards very low FT4 concentrations in the GDM women compared with those in the healthy pregnant controls (χ²rend = 8.09, P < 0.01). Greater TSH values were also found more frequently when the glucose tolerance was more severely impaired (χ²rend = 3.74, P = 0.05).

Twenty-nine of the 181 women in the study group were ThyAb positive (ThyAb+ve), with a prevalence of 16% (95% CI 11.1 to 22.4). Of these 29 women, five had TgAb, 18 had TPOAb and six had both antibodies. Among the TPOAb+ve women, two developed GDM and three showed IGGT. Furthermore, a significantly greater mean BMI was found in the ThyAb+ve women with low serum FT4 compared with the controls (25.7 ± 5.3 compared with 20.8 ± 1.5 kg/m², P < 0.01). In the control group, two pregnant women (11.7%) were ThyAb positive, both with TgAb and TPOAb; they had TSH and FT4 concentrations within the normal range.

To estimate the possible association of ThyAb in pregnancy and family history of diabetes mellitus, all the 181 patients were grouped on the basis of their family history of diabetes mellitus. A positive history of the condition in first-degree relatives was reported in 61 women (33.7%) (59 reported non-insulin-dependent diabetes mellitus (NIDDM) and two reported IDDM). A significantly greater prevalence of ThyAb was observed in the group of women with familial diabetes mellitus than in those without a family history of diabetes mellitus (24.6% compared with 11.7%, P = 0.04). A greater risk of being ThyAb positive (OR = 2.47; 95% CI 1.03 to 5.96) was also estimated in the group of women with a positive family history of diabetes mellitus. When present, a family history of thyroid disease was also taken into consideration in both the study group and the control women. A positive family history of thyroid disease was present in 45 of the pregnant women of the study group (10 ThyAb positive, 22.2%) and in five of the 17 controls (one ThyAb positive, 20.0%). The pregnant women reported nodules, goiter, or both, in mothers or sisters.

In order to evaluate a possible combined effect of positive family history of thyroid disease and diabetes mellitus in the pregnant women, the distribution of ThyAb prevalence in the pregnant women in the study group classified on the basis of their family history of diabetes mellitus or thyroid disease was investigated (Fig. 2). Only those women who gave full information (respondent women, n = 169) were considered for this analysis. Four groups were identified: group A included 89 pregnant women without familial diabetes mellitus and thyroid disease; group B comprised 22 women with a positive family history of thyroid disease; group C were 35 women with a positive family history of diabetes mellitus; group D included 23 women with a positive family history of both diabetes mellitus and thyroid disease. A ThyAb prevalence of 13% was observed in group A, 9% in group B, 20% in group C, and 35% in group D. The prevalence of ThyAb observed in this group was significantly greater (P < 0.01) than that observed in the group of

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pregnant women without a family history of diabetes mellitus and thyroid disease (group A). In addition, the risk of the presence of ThyAb during pregnancy in these groups was estimated by calculation of OR values. OR = 1 was established in group A as the reference value, OR = 0.6 (95% CI 0.09 to 3.43) was found in group B, OR = 1.6 (95% CI 0.51 to 4.97) in group C, and OR = 3.4 (95% CI 1.06 to 5.5) in group D.

**Postpartum thyroid function assessment**

At the time of the study, a complete postpartum follow-up was obtained in 20 of the 29 patients who were ThyAb positive during pregnancy. Nine of the 20 patients (45%) developed PPT: four showed hypothyroidism during the follow-up and five exhibited a thyrotoxic phase followed by a hypothyroid phase. All
nine of these women with PPT had normal glucose tolerance during pregnancy, and four of the nine were still hypothyroid at the end of follow-up and then started L-thyroxine therapy.

Discussion

Carbohydrate intolerance is the most common metabolic complication of pregnancy. At present several risk factors have been recognized to identify pregnant women at increased risk of GDM in their current pregnancy (18). The screening for GDM in women with significant risk factors permits a prompt instigation of a diet, insulin treatment, or both, when necessary, and the reduction of maternal and fetal morbidity during and after pregnancy (23–26).

Generally, during pregnancy maternal thyroid function remains normal. However, variations in serum T₃, T₄ and TBG observed in pregnancy largely reflect associated changes in sex steroid production. In fact, under the influence of estrogens, the production rate of TBG is increased and its peripheral degradation rate is decreased because of its high sialic acid content. This causes increased concentrations of serum TBG and a high binding capacity of the protein for T₄ and T₃ (27, 28). Small changes are observed in FT₄ serum concentrations during pregnancy. Generally, these increase slightly during the first trimester and then decrease. These changes resemble those of ‘non-thyroidal illness’ and may contribute to the saving of energy during pregnancy (29). In this study, a significantly lower FT₄ mean value was observed in the women with GDM than in either the other women in the study group or the healthy pregnant controls. Moreover, the increased risk of subclinical hypothyroidism in the women with GDM was also indicated by the distribution of the serum FT₄ and TSH concentrations found in the women of the study group classified on the basis of the OGTT results (Fig. 1). The FT₄ concentrations were more frequently lower than the lower limit of normal when the glucose tolerance was more severely impaired. In addition, the distribution of TSH concentration was shifted towards greater TSH values in the women who developed GDM compared with that in the remainder of the study group and the controls. These results are consistent with a previous study in which pregnant rats with streptozotocin-induced diabetes mellitus are used as a model of maternal diabetes (30). In that study, the effects of different degrees of diabetes mellitus on maternal and fetal circulating thyroid hormones were investigated. It was reported that impaired maternal thyroid hormone status was related to the degree of the metabolic imbalance. Moreover, T₄ and T₃ concentrations in the fetal brain were found to be lower than normal, and the expected increase in the fetal brain type II 5’ deiodinase activity (31, 32) was not observed. The low cerebral T₃ improved only with adequate insulin treatment of the dams. In humans before 12 weeks gestation, when the fetal thyroid gland becomes active, the mother is the unique source of thyroid hormones. During the middle and last trimesters, thyroid hormones are supplied by both the mother and the fetus, but mostly by the mother (33). All this highlights the importance of adequate maternal thyroid secretion. Recently, an increased risk for impaired cognitive development has been reported, not only in children of women with undetected or inadequately treated thyroid deficiency during pregnancy (34), but also in children of pregnant women with increased titers of TPOAb and normal thyroid function (35).

As regards the presence of ThyAb, our results showed that pregnant women with increased risk for GDM (study group) have a prevalence of ThyAb that is greater (16%) than that observed in the general population of women (10%) within the first trimester.
of pregnancy (36). This finding becomes more significant when it is noted that the pregnant women were tested for ThyAb at the time of the OGTT – late in the second or early in the third trimester. It is well known that circulating concentrations of thyroid antibodies decrease during pregnancy, both in patients with autoimmune thyroid disease and in women without previously known thyroid diseases but who are found to be positive at screening for ThyAb (37). Furthermore, not only the incidence but also the titer of ThyAb have been reported to be greater in the first than in the third trimester of gestation (38). As regards thyroid function and the presence of ThyAb, a significantly greater BMI mean value was found in the ThyAb-positive women with low FT₄ serum concentrations than in the controls. This finding may afford a clue as to a thyroid hypofunction actually present in these women.

One of the most frequent risk factors for GDM is a positive family history of diabetes mellitus. In this study such a family history was present in 33.7% of the study group women. Results showed that the women with a positive family history of diabetes mellitus were twice as likely to be ThyAb positive during pregnancy (OR = 2.47) as those without such a history. Nevertheless, to evaluate a possible combined effect of positive family history of thyroid disease and diabetes mellitus in the pregnant women, we studied the distribution of ThyAb in the pregnant women classified on the basis of their family history of diabetes mellitus, thyroid disease, or both (Fig. 2). Our results showed that women with a positive family history of diabetes mellitus and thyroid disease (group C) had a significantly greater risk of being ThyAb positive during pregnancy (OR = 3.4) than those with no family history of diabetes mellitus and thyroid disease (group A). These findings suggest that a combined familial background of diabetes mellitus and thyroid disease provides a high risk for the occurrence of an anti-thyroid autoimmune response.

An increased prevalence of antithyroid autoantibodies has been reported in the first-degree relatives of patients with IDDM (39, 40) and a background of familial immune hyperactivity has been suggested to explain this association. No similar studies have been made in first-degree relatives of patients with NIDDM, because a non-autoimmune etiology is generally reported. Nevertheless autoimmune pathogenesis has been described in some patients with NIDDM (41, 42). These individuals are believed to have a slowly evolving form of IDDM, defined as ‘latent autoimmune diabetes in adults’ (LADA) (43, 44). In this study, the presence of LADA patients among the first-degree relatives of the pregnant women can not be excluded, so that the high frequency of ThyAb in the women of the study group might be explained by a common immunological dysregulation. However, despite the high prevalence of ThyAb in the 181 women at risk of GDM, no increased ThyAb frequency (10.5%) was found in the subgroup of pregnant women developing GDM. These results confirm the finding of Lapolla et al. (9) of a low prevalence of ThyAb in a group of patients with GDM who were tested for several organ-specific autoantibodies during the third trimester of pregnancy. Our findings suggest that it is not impaired glucose tolerance itself but rather a family history of diabetes mellitus that represents a risk factor for the presence of ThyAb in pregnancy.

At present, the usefulness of routine screening for ThyAb and thyroid function during pregnancy is controversial (1, 32, 33, 35, 45, 46). A screening program should be at least introduced in ‘at risk’ groups of pregnant women. The present study showed that women with increased risk of GDM, mostly those with family history of diabetes mellitus and thyroid disease, also have an increased risk of being ThyAb positive during pregnancy. Moreover, attention was drawn to the importance of evaluating thyroid function in pregnant women with impaired glucose tolerance, in view of their increased risk of subclinical hypothyroidism.

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