

## Evaluation of Thyroid Autoimmunity in Gestational Diabetes Mellitus

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### Abstract

The aim of our study was to determine if there is any association between autoimmune thyroid diseases in patients with gestational diabetes. A total of 180 healthy pregnant women (control) and 45 pregnant women with gestational diabetes mellitus (study group) were enrolled in the study. We could not determine any association between gestational diabetes mellitus and thyroid autoimmunity in pregnant.

**Keywords:** Gestational diabetes mellitus; Thyroid autoimmunity; Antiperoxidase antibody; Antithyroglobulin antibody; Diabetes mellitus; Hashimoto's thyroiditis

### Introduction

Thyroid screening during the first trimester of pregnancy has been an important issue for a couple of years. Some guidelines recommend targeted screening in the first trimester to pregnant women who are at risk for thyroid diseases [1]. But some studies have shown that this would have resulted in missing almost half of the patients at diagnosis if only targeted case-finding had been taken into consideration [2]. About 10-15% of pregnant women have high titers of anti-thyroid peroxidase antibody (TPOAb) which is similar in the normal population [3,4]. For Type 1 Diabetes Mellitus guidelines have recommended thyroid screening in all cases. In addition high titers of TPOAb have been found in pregnant women with gestational diabetes mellitus (GDM) [5]. Some studies have suggested that TPOAb positive pregnant women may have increased GDM risk [6] while other studies could not show this association [7-9]. Several studies found a higher prevalence of thyroid autoimmunity in GDM compared to healthy controls; therefore they suggest that it would be appropriate to extend screening for thyroid diseases to women with GDM [10]. Higher prevalence of thyroid autoimmunity has been found in women who have had previous GDM and has been speculated that gestational hyperglycemia may trigger thyroid autoimmunity [11]. Some studies have shown that instead of the presence of TPOAb, overt hypothyroidism causes an increase in the formation of diabetes mellitus [12].

### Methods

This prospective cross-sectional study was carried out in an University Hospital, Department of Endocrinology and Metabolism, in collaboration with the Department of Obstetrics and Gynaecology. The study was conducted over 1 year from January 2013 to April 2014. A total of 180 healthy pregnant women (control) and 45 pregnant women with gestational diabetes mellitus (study group) were enrolled in the study. The patients attended the outpatient clinic for their first prenatal

visit. Exclusion criteria were patients who had a diagnosis of pregestational diabetes mellitus, history of thyroid disease or a history of a drug that may affect thyroid function and any chronic disease.

At first visit blood was withdrawn for glucose, urea, creatinin, ALT, AST, thyrotropin (TSH), free thyroxine (FT4), free triiodothyronine (FT3), antiperoxidase antibody (TPOAb), antithyroglobulin antibody (TgAb). Height was measured when the patient first attended and weight was measured at every visit. Women diagnosed with GDM were given diet and/or insulin treatment.

Women underwent routine screening for GDM at 24-25 weeks gestation with a 12 hour fasting 75 gr oral glucose tolerance test (OGTT). Blood was withdrawn at 0, 1 and 2 hours. Normal results were <92 mg/dL at baseline, <180 mg/dL at 1 hours, <153 mg/dL at 2 hours. The participants were then divided into two groups. The first group had a normal screening test, the second group had an abnormal glucose tolerance test and were defined as GDM (with 1 abnormal result after the OGTT). National Diabetes Data Group criteria were used to establish the diagnosis [13].

Using a standard data collection sheet, demographic characteristics, past medical history, maternal characteristics (height and weight) were taken in the first visit. Maternal body mass index (BMI) was calculated for every participant.

Serum glucose measurement was analyzed with the hexokinase method on Cobas c501 system (Roche Diagnostics GmbH, Mannheim, Germany). Serum TSH, FT4, FT3, TPOAb, TgAb were measured by Electrochemiluminescence immunoassay method on the Cobas e601 system (Roche Diagnostics GmbH, Mannheim, Germany). The method of measurement was carried out according to the manufacturer instructions. In our laboratory, because we do not have trimester specific TSH ranges we use the following ranges: first trimester, 0.1-2.5 mIU/l; second trimester, 0.2-3.0 mIU/l; third trimester, 0.3-3.0 mIU/l [14].

The reference range for free thyroxine was: 0.93-1.7 ng/dL, and for free triiodothyronine 2.0-4.4 pg/mL. Positivity for Anti TPO and Anti Tg antibodies was considered when levels were >100 IU/mL and >115 IU/mL respectively. Women with TSH level >2.5 mIU/l and decreased

FT4 concentration and TSH  $\geq 10.0$  mIU/l irrespective of FT4 levels were both defined as overt hypothyroidism. Women with TSH levels between 2.5-10 mIU/l with a normal FT4 level were defined as subclinical hypothyroidism. Subclinical hyperthyroidism was defined as a decreased TSH ( $<0.2$  mIU/l) and normal FT4 levels and clinical hyperthyroidism was defined when TSH was decreased and FT4 levels or FT3 levels were elevated [15].

### Statistical Analyses

The statistical analysis of the data was carried out using SPSS software (version 11.5.SPSS Inc.). Whether the distributions of variables were normally distributed or not was determined by Kolmogorov Smirnov test. Continuous and discrete variables were expressed as mean  $\pm$  SD values and median (minimum-maximum). Categorical variables were expressed as number of cases (n) or (%). The mean differences among groups were compared by using Student's t test and Mann Whitney U test. Categorical variables were tested with Fisher's test. A P value of  $< 0.05$  was taken as statistically significant.

### Results

A total of 230 pregnant women were enrolled in the study. The mean  $\pm$  SD age of the women with GDM was  $31.0 \pm 3.9$  years and that of non GDM women was  $29.5 \pm 4.6$  years. The mean  $\pm$  SD of BMI in the GDM and non GDM group was  $24.7 \pm 4.6$  kg/m<sup>2</sup> and  $23.2 \pm 4.5$  kg/m<sup>2</sup> respectively (p=0.01).

When the whole group was studied, 180 (78%) pregnant women were euthyroid, 15 (6.5%) had subclinical hypothyroidism, 7(3%) had subclinical hyperthyroidism, 4(1.1%) had hyperthyroidism, 1 (0.4%) had overt hypothyroidism, 9(3.9%) had low FT3 (1.3%) had low levels of freeT3 and freeT4, and 11 (4.8%) had isolated hypothyroxinemia. The thyroid hormone profiles between groups are shown in Table 1.

State	GDM + (n=45)	GDM – (n=185)	p value
TSH§( mIU/l)	1.6 (0.0-5.9)	1.5 (0.0-8.0)	0.9
FT4§( ng/dL)	1.1 (0.8-3.0)	1.1 (0.5-2.7)	0.8
FT3§( pg/mL)	3.0 (1.0-5.8)	3.0 (0.9-5.4)	0.8
TgAb $\infty$ (IU/ml)			0.1
Positive		18 (9.7%)	
Negative	1 (2.2%)	167 (90.3%)	
TPOAb $\infty$ (IU/ml)	44 (97.8%)		1.0
Positive	3 (6.7%)	16 (8.6%)	
Negative	42 (93.3%)	169 (91.4%)	
Both TPOAb/TgAb positive $\infty$	-	7 (3.8%)	0.3
Both TPOAb/TgAb negative $\infty$	41 (91.9%)	158 (85.4%)	0.3

**Table 1:** Thyroid hormone and thyroid autoimmunity in patients with and without GDM n= number of patients; §, number is given as median (min-max);  $\infty$ , n (%); GDM: Gestational Diabetes Mellitus; FT3: Free Triiodotronin; FT4: Free Thyroxine; Tpoab: Antiperoxidase

Antibody; Tgab: Antithyroglobulin Antibody; p value  $< 0.05$  was statistically significant.

Of the 45 patients with GDM 33 (73.3%) were euthyroid, 4(8.9%) had subclinical hypothyroidism, 1(2.2%) had subclinical hyperthyroidism, 1(2.2%) had hyperthyroidism, 5 (11.1%) had low FT3, 1(2.2%) had both low FT4 and FT3. Of the non GDM pregnant women, 147(79.5%) were euthyroid, 11(5.9%) had subclinical hypothyroidism, 6(3.2%) had subclinical hyperthyroidism, 11(5.9%) had isolated hypothyroxinemia, 1(0.5%) had hypothyroidism, 3 (1.6%) had hyperthyroidism, 4(2.2%) had low FT3, and 2(2.2%) had both low FT4 and FT3. There was no statistically significant difference between the thyroid hormone tests between the GDM and non GDM pregnant women.

Averall, 16.5% of the patients had anti thyroid antibodies (either TPOAb or TgAb, or both ). Nineteen (8.2%) of the pregnant women had the presence of TPOAb and 19(8.2%) had the presence of TgAb. Seven (3%) had the presence of both TPOAb and TgAb.

Of the pregnant women with GDM, 4(8.8%) were thyroid autoantibody positive. Of these women 3(6.7%) had TPOAb and 1(2.2%) had TgAb positivity. Of the healthy pregnant women, 34(18.4%) were thyroid autoantibody positive. Of these women 16 (8.6%) had TPOAb and 18 (9.7%) had TgAb positivity. There was no significant difference between TPOAb (p=1.0) and TgAb antibodies (p=0.13) between the GDM and non GDM pregnant women (Table 1).

Among the TPOAb + pregnant women (n=19), three patients developed GDM. Among the TgAb + patients (n=19), one patient developed GDM. The presence of TPOAb did not increase the risk of GDM (OR=0.75, 95%CI: 0.210-2.710, p=1.0).

The BMI was  $23.7 \pm 4.9$  kg/m<sup>2</sup> and  $23.5 \pm 4.5$  kg/m<sup>2</sup> in the TPOAb+ and TPOAb- pregnantwomen, respectively (p=0.8). We couldn't find any association between TPOAb positivity and GDM. The BMI was  $22.4 \pm 2.6$  kg/m<sup>2</sup> and  $23.6 \pm 4.75$  kg/m<sup>2</sup> in the TPOAb+ and TPOAb- pregnant women, respectively (p=0.3).

### Discussion

In our study, we could not determine any association between pregnant women GDM with and thyroid autoimmunity. In our study 8.2% of the pregnant women were TPOAb positive. Montaner et al. who found a 10% positivity for TPOAb [7]. They speculated that GDM would be the cause of thyroid autoimmunity. However, they found no difference in the prevalence of thyroid antibodies between GDM and non GDM pregnant women.

Agarwal et al. studied 80 GDM and 221 non GDM pregnant women but could not find an association between GDM and the presence of TPOAb [8]. There were no differences between any thyroid function tests between the two groups. Pregnant women with positive TPOAb had a higher mean TSH than TPOAb negative pregnant women. In addition, Kumru et al. found no association between thyroid dysfunction and anti-TPO positivity with GDM [16].

On the other hand Olivieri et al. studied 181 pregnant women and found that women with increased risk of GDM had an increased risk of being TPOAb positive during pregnancy (Olivieri A). Thyroid autoantibodies were positive in 16% of the pregnant women [6]. Presence of TPOAb was 9.9% and TgAb was 2.7%.

Karakosta et al. studied 1170 pregnant women and demonstrated that the combination of high TSH and positive thyroid antibodies in

the first trimester was associated with an increased risk for GDM [17]. TPOAb positivity was not associated with increased risk for GDM.

Nakova et al. found a high prevalence of hypothyroxinemia in GDM pregnant women and higher TPOAb titres in pregnant women with Type 1 diabetes mellitus [18]. Sharifi et al. and Chang et al., also found an association between Type 1 diabetes mellitus and TPOAb positivity [19,20].

Screening for thyroid autoimmunity should be performed for all pregnancies with Type 1 Diabetes Mellitus. Data is not sufficient to recommend screening for thyroid autoimmune disease in GDM pregnancies. More studies in this field with larger study size should be performed.

## Conclusion

In this study, GDM patients were not different from non GDM pregnant women in respect with thyroid autoimmunity and thyroid function tests. Further studies should be evaluated to see if there is a causal relationship.

The authors declare that there is no conflict of interest regarding the publication of this paper.

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