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ScienceDirect
Metabolism Clinical and Experimental 57 (2008) 522–525
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Is thyroid autoimmunity associated with gestational diabetes mellitus?

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Received 1 June 2007; accepted 12 November 2007

Abstract

Because inflammatory markers have been associated with incident diabetes mellitus, we aimed to evaluate if thyroid peroxidase antibodies (TPOAbs) in early pregnancy are predictive of gestational diabetes mellitus (GDM). Six hundred nineteen pregnant women without former diabetes mellitus were evaluated for TPOAb positivity after booking. A universal GDM screening protocol and the Third Workshop–Conference criteria were used for GDM detection. In addition to bivariate analysis, multivariate logistic regression models were constructed with GDM as the dependent variable and TPOAb positivity as one of the potential predictive ones. The rate of TPOAb positivity was 10%; and that of GDM, 6.9% (6.8% in women without and 8.1% in women with TPOAb positivity, not significant). Thyroid peroxidase antibodies did not enter the multivariate logistic regression model to predict GDM that identified the following independent predictive variables: maternal age (odds ratio [OR] 1.5, 95% confidence interval [CI] 0.57-4.0 for the second tertile; OR 2.84, 95% CI 1.16-6.96 for the third tertile), prior GDM (OR 9.38, 95% CI 3.34-26.39), and diabetes mellitus in first-degree relatives (OR 3.22, 95% CI 1.65-6.27). In conclusion, we have not identified TPOAb positivity in early pregnancy as a predictor of GDM.

1. Introduction

Inflammatory markers have been related to incident diabetes mellitus in middle-aged and elderly subjects [1,2], Pima Indians [3], and pregnant women [4,5]. The underlying mechanism appears to be increased insulin resistance more than decreased insulin secretion [6]. A high prevalence of positivity for thyroid peroxidase antibodies (TPOAbs) has been reported in both women with gestational diabetes mellitus (GDM) [7] and those with polycystic ovary syndrome [8]. The potential link between thyroid autoimmunity and these conditions could be insulin resistance because serum levels of inflammatory cytokines are increased in patients with thyroid autoimmunity [9]. Similarly, patients with subclinical hypothyroidism of autoimmune origin display increased C-reactive protein, which is not modified with thyroid function status [10]. This feature is parallel to the increase in C-reactive protein described for prediabetic subjects with islet cell autoimmunity in some [11] but not all articles [12].

We hypothesized that positivity for TPOAbs is associated with GDM, presumably through increased insulin resistance.

2. Material and methods

2.1. Sample size calculation

The sample size was calculated using Sample Power 1.0 with the following assumptions: (1) rate of TPOAb positivity = 25% in women with GDM [7] and 10% in women without GDM [13], (2) a 10% prevalence of GDM [14], (3) a bilateral *a* error of .05 and a *b* error of .80. The estimated sample size was 600.

2.2. Inclusion criteria

- First analytical assessment at a gestational age less than 20 weeks.

2.3. Exclusion criteria

- Prepregnancy diabetes mellitus.
- Inadequate assessment of TPOAb positivity or glucose tolerance during pregnancy.

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doi:10.1016/j.metabol.2007.11.015

2.4. Subjects

Between May and November 2003, 689 women consecutively booked for pregnancy follow-up in Hospital Sant Joan de Déu de Martorell; and 631 fulfilled inclusion criteria. They were informed about the study and signed a consent form. Twelve women did not complete the GDM screening protocol, so the final analysis was restricted to 619 women.

2.5. GDM screening and diagnosis

A universal screening for GDM with a 50-g oral load was performed at a gestational age of 24 to 26 weeks [15]. Diagnostic criteria of the Third Workshop–Conference on Gestational Diabetes Mellitus were used [16,17].

2.6. Measured variables

In the first blood test performed during pregnancy, TPOAbs and ferritin were measured in the serum remaining from the standard analytical checkup. In each patient, the following variables were registered: (1) anthropometric variables (age, ethnicity, prepregnancy weight and height), (2) additional risk factors for GDM in early pregnancy (family history of DM, prior GDM, smoking, poor obstetric history suggestive of GDM, hemoglobin [18], ferritin [19]), (3) TPOAbs, and (4) glucose tolerance status.

2.7. Laboratory methods

Glucose concentration was measured with a glucose oxidase method in an LX-20 Beckman analyzer (Beckman-Coulter, La Brea, CA). Ferritin concentration was measured with the same equipment using an immunoturbidimetric method (N 10.0-160 *m*g/L). The TPOAbs were measured by a particle enzymoimmunoanalysis in an Axsym analyzer (Abbott Laboratories, Abbott Park, IL) (N <12 UI/mL). The hemoglobin concentration was measured by a Sysmex analyzer (Roche Diagnostics, Mannheim, Germany).

Clinical protocol:

- Oral iron supplementation was initiated when the hemoglobin concentration was lower than 110 g/L.
- When a woman was diagnosed of GDM, she was referred to the monographic GDM clinic. The management protocol included diet, exercise, self-monitoring of capillary blood glucose, clinical follow-up every 1 or 2 weeks, and monthly measurement of hemoglobin A_{1c}. Insulin was prescribed when aimed capillary blood glucose (fasting95 mg/dL, postprandial <135 mg/dL) was not reached. A basal-bolus schema was used.

2.8. Statistical analysis

Qualitative variables were compared using Fisher exact test. The normal distribution of quantitative variables was explored using the Shapiro-Wilk test, and Student *t* test was used for comparison of variables with normal distribution and Mann-Whitney test for those without. Significance was set at a bilateral $P < .05$. A multiple logistic regression analysis with a forward method was used to calculate adjusted odds ratios (ORs) for GDM and the corresponding 95% confidence intervals (CIs). A backward method was also used to explore the OR of variables not entering the model. All potentially predictive variables were fed to the model (diabetes mellitus in first-degree relatives [DMFDR], prior GDM, prior poor obstetric outcome [POO], maternal ethnicity, smoking habit, age, height, prepregnancy weight and body mass index [BMI], multiple pregnancy, as well as ferritin, hemoglobin, and TPOAbs measured before 20 weeks). Variables modeled as categorical (yes/no) were DMFDR, prior GDM, prior POO, ethnicity, smoking habit, multiple pregnancy, and TPOAbs. For the predictors identified, we calculated the population-attributable fraction (AFp) [20]. The *AFp* is defined as the excess number of cases resulting from an exposure divided by the total number of cases in a defined population and is calculated as AFp = proportion of exposed cases × (OR − 1)/OR.

3. Results

In the studied population, the rate of GDM was 6.9% and that of positivity for TPOAbs was 10.0%; additional characteristics are summarized in Table 1. In the bivariate analysis, women with GDM were older than those without and had a higher rate of prior GDM and DM in first-degree relatives; no differences were observed in the rate of TPOAb positivity (11.6% vs 9.9%). In women with and without TPOAb positivity, the corresponding rates of GDM were 8.1% vs 6.8% (not significant).

Age, prior GDM, and DMFDR were also the independent predictors identified in the logistic regression analysis (Table 2). The strongest predictor was prior GDM (OR 9.38) followed by DMFDR (OR 3.22) and age (OR 2.84 for the third tertile and 1.50 for the second). Diabetes mellitus in first-degree relatives and the third tertile for age accounted for the highest AFp because of the higher prevalence of the predictors in the population. Thyroid peroxidase antibodies positivity did not enter the model; in the logistic regression model with a backward method, the OR was 1.52 (95% CI 0.87-2.65).

4. Discussion

We hypothesized that TPOAb positivity was associated with GDM after the evidences linking inflammation and insulin resistance on one side and thyroid autoimmunity and inflammation on the other. According to available information [7], the study was adequately powered to detect a 2.5 increased risk of GDM in women with TPOAb positivity, considering the baseline prevalence of GDM and TPOAb positivity in our population. Our results have not identified an increased rate of GDM in women with positive TPOAbs either in the bivariate (8.1% vs 6.8%) or multivariate analysis. However, the backward logistic regression model

Table 1
Characteristics of the whole pregnant population and women with and without GDM

	Whole population	Women without GDM	Women with GDM	*P*
N	619	576 (93.1%)	43 (6.9%)	
Age (y)	29.4 ± 4.9	29.6 ± 4.8	32.6 ± 5.2	<.001
Ethnicity (%)				NS
White	76.9	76.7	79.1	
Hispanic	10.7	10.6	11.6	
Other	12.5	12.7	9.3	
Smoking habit (%)	34.0	34.3	30.2	NS
DMFDR (%)	28.0	25.7	58.1	<.001
Multiple pregnancy (%)	1.3	1.0	4.7	NS
Prior POO (%)	12.5	11.8	20.9	NS
Prior GDM (%)	3.1	1.7	20.9	<.001
GA at 1st evaluation	14 (6-19)	14 (6-19)	14 (10-16)	NS
GA at glucose tolerance assessment	27 (14-34)	27 (14-34)	28 (14-32)	NS
Weight (kg)	61 (40-123)	60 (40-123)	63 (40-123)	NS
Height (cm)	161 (145-182)	161 (145-182)	160 (150-175)	NS
BMI (kg/m^2)	23.14 (16-44.6)	23.14 (16-44.6)	24.2 (17.8-44.6)	NS
Ferritin (μg/L)	27.8 (0.5-393)	27.8 (0.5-393)	24.5 (6.8-89.9)	NS
Hemoglobin (g/dL)	12.3 (8.9-15)	12.3 (8.9-15)	12.7 (10.8-14.6)	NS
TPOAbs (%)	10	9.9	11.6	NS

GA indicates gestational age; NS, nonsignificant.

to predict GDM provided a nonsignificant 1.52 OR for TPOAb positivity; to test the possibility that this 50% increase is real, another study with a different (and clearly higher) sample would be required.

We have identified prior GDM, DMFDR, and age as independent predictors of GDM. All these factors had already been reported as independent predictors of GDM [21-24]. The ORs described in this article for prior GDM [22,24], DMFDR [24], and maternal age [21,22,24] are within the published range. We also provide the corresponding AFp for these predictors. Understandably, the highest ones correspond to predictors that display a high prevalence in the population (third tertile of age and DMFDR); but we want to draw attention to the fact that prior GDM accounts for 18.67% of the GDM cases, which is not negligible. This is due to the high OR associated to this predictor and to the relatively high rate of prior GDM among women diagnosed of GDM in current pregnancy. All the other potentially predictive variables were not included in the model; and we want to highlight that BMI, ethnicity, ferritin, and multiple pregnancy were among them. We attribute the nonidentification of ferritin and multiple pregnancy to an insufficient power of this study to identify predictors of low prevalence and/or that are weak. The nonidentification of ethnicity and BMI seems more surprising. The lack of association of GDM with non-white ethnicity is not unexpected taking into account the high prevalence of GDM in the Spanish population nonattributable to women with multiracial ethnicity [17]. The nonidentification of BMI seems even more striking, but overweight and obese women are those already identified as having prior GDM or DMFDR. In a multiple regression model where DMFDR and prior GDM were not considered, BMI reached borderline significance (data not shown).

The lack of association between thyroid autoimmunity and GDM herein reported is difficult to reconcile with the articles of Hornnes et al [25] and Fernández Soto et al [26], which would favor the departing hypothesis. Hornnes et al studied women with thyroid autoimmunity with and without postpartum thyroiditis and a control group. The 3 groups displayed similar glucose tolerance after delivery; but women with thyroid antibodies and later postpartum thyroiditis had reduced glucose tolerance and a trend toward higher fasting insulin in late pregnancy nonattributable to islet cell autoimmunity [25]. In pregnant women with type 1 diabetes mellitus, Fernández-Soto et al reported that those positive for TPOAbs displayed a higher glycohemoglobin and insulin requirements in the second and third trimesters, which would favor either a higher insulin resistance and/or deficiency in this group [26].

Table 2
Multivariate logistic regression model for the prediction of GDM (forward method)

Predictive variable	Outcome variable: GDM		
	OR	95% CI	AFp (%)
Age			
1st tertile	1		
2nd tertile	1.5	0.57-4.0	9.3
3rd tertile	2.84	1.16-6.96	36.15
Prior GDM	9.38	3.34-26.39	18.67
DMFDR	3.22	1.65-6.27	40.06
ROC curve	Area		
	0.738	0.649-0.828	

ROC indicates receiver operating characteristic.

In conclusion, we have not identified TPOAb positivity in early pregnancy as a predictor of GDM.

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