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Presence of GAD Antibodies During Gestational Diabetes Mellitus Predicts Type 1 Diabetes

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OBJECTIVE — We sought to study the frequency of β-cell–specific autoantibody markers in women with gestational diabetes mellitus (GDM) and to follow these women to estimate the risk of later development of type 1 diabetes.

RESEARCH DESIGN AND METHODS — Of 385 pregnant women with GDM during 1995–2005 in the district of Lund, 24 (6%) women were found positive for at least one of the following: islet cell antibody (ICA), GAD antibody (GADA), or tyrosine phosphatase antibody (IA-2A). The women were followed and autoantibodies reanalyzed. Those who had not developed diabetes did an oral glucose tolerance test. The frequencies of known risk factors for GDM were compared in women with GDM with and without pancreatic autoantibodies.

RESULTS — Among the autoantibody-positive women, 50% had developed type 1 diabetes compared with none among the GDM control subjects ($P = 0.001$), 21% had impaired fasting glucose or impaired glucose tolerance compared with 12.5% among control subjects ($P = 0.3$), and none had developed type 2 diabetes compared with 12.5% among control subjects ($P = 0.1$).

CONCLUSIONS — Autoantibody screening in pregnant women with GDM and follow-up after delivery should be considered for early recognition of type 1 diabetes.

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Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The prevalence may range from 1 to 14% among pregnant women, depending on the population studied (1). In a population-based study in southern Sweden, the prevalence was 1.2% (2), which is comparable with the rest of Sweden. Among 20–50% of women with GDM during previous pregnancies, GDM will recur in subsequent pregnancies (3).

GDM is a heterogeneous disease that can sometimes be managed with dietary treatment alone, while in other cases insulin treatment is required (1). The disease increases the risk of fetal complications such as macrosomia, caesarean delivery (2), and hypoglycemia in the newborn (3). Nonmodifiable risk factors for developing GDM are non-Caucasian ethnicity, older age, positive family history of diabetes (4), and short stature (5). Modifiable risk factors are obesity (4) and a high intake of saturated fat (6).

Women with GDM have an increased risk of developing diabetes later in life (4). Worldwide-reported incidence rates vary from 6 to 62% (7). Most of these women will develop type 2 diabetes, and the frequency of later development of type 2 diabetes has been extensively studied (4). The risk of developing type 1 diabetes is less known. Our own study showed that 7.7% of women with GDM have β-cell–specific autoantibodies present (8). A Danish study found islet cell antibody (ICA) positivity in 2.9% of women with GDM (9). Presumably, these women could be at risk for developing type 1 diabetes, since autoantibodies against pancreatic β-cells can be present many years before the clinical onset of the disease (10). Commercial radioimmunoassay and enzyme-linked immunosorbent assay tests are now available for analyses of GAD antibodies (GADA) (11) and tyrosine phosphatase antibodies (IA-2A) (12) and could easily be done in all patients with GDM.

The purpose of this study was to determine how many women with GDM have β-cell–specific autoantibody markers during pregnancy and to follow these women after delivery to estimate the risk for later development of type 1 diabetes.

RESEARCH DESIGN AND METHODS

— All pregnant woman in the district of Lund are tested with an oral glucose tolerance test (OGTT) consisting of 75 g glucose in solution at the 28th gestational week as a general screening for GDM. Women with a family history of diabetes or those who had GDM during previous pregnancies do the OGTT at the 12th gestational week. Between 1995 and 2005, all women who developed GDM ($n = 385$) were tested for GADA and IA-2A. Those who had GDM before 2004 were also tested for ICA. We found 24 (6%) women with GDM who were positive for at least one of these autoantibodies (only 2 women were not tested for ICA). For each of the 24 women, 2 control subjects ($n = 48$) were selected who had GDM without autoantibodies. The control subjects were matched for year of delivery and age ±5 years.

The 24 autoantibody-positive women and control subjects were compared for family history of diabetes, ethnicity, previous pregnancies with GDM, BMI, need

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Abbreviations: GADA, GAD antibody; GDM, gestational diabetes mellitus; IA-2A, tyrosine phosphatase antibody; ICA, islet cell antibody; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Characteristics for the autoantibody-positive women and GDM control subjects*

	Antibody-positive women with GDM	Antibody-negative women with GDM	*P*
n	24	48	
Age (years)*	29.5 (27.0–34.0)	30.0 (27.0–34.0)	NS
BMI (kg/m^2)†	24.5 (22.4–28.4)	25.4 (21.9–30.1)	NS
Heredity‡	15 (62.5)	22 (45.8)	NS
Ethnicity			
Scandinavian	21 (87.5)	37 (77.1)	NS
Non-Scandinavian	3 (12.5)	11 (22.9)	NS
OGTT value during pregnancy§	10.0 (9.4–12.0)	9.5 (9.1–10.4)	NS
GDM during previous pregnancy	8 of 19 (42.1)	9 of 42 (45.2)	NS
Insulin during the pregnancy	14 (58.3)	18 (37.5)	NS
Birth weight of the child (g)	3,430 (3,170–3,770)	3,710 (3,330–4,080)	NS
Caesarean delivery	5 (28.8)	8 (16.7)	NS

Data are median (interquartile range) or *n* (%). *Age of mother at time of pregnancy, when the autoantibodies were discovered. †Values are from the first trimester. ‡Family history of type 1 or type 2 diabetes among first- or second-degree relatives. §During pregnancy week 12 or 28.

for insulin therapy during pregnancy, plasma glucose level at the OGTT, birth weight of the child, and number of caesarean deliveries. At follow-up, the frequency of women with diabetes and impaired glucose tolerance (IGT) after GDM was also studied.

The time of follow-up for the autoantibody-positive women varied between 6 months and 10 years after the pregnancy with GDM (median 7 years). Women with autoantibodies who had developed diabetes were asked to reanalyze the autoantibodies GADA and IA-2A. Those who had not developed diabetes were asked to both reanalyze GADA and IA-2A and to do a new OGTT. The classification of diabetes was based on the guidelines given by the American Diabetes Association (1). The study was approved by the ethical committee in Lund, Sweden.

The women who had not developed diabetes did a 75-g 2-h OGTT. The test was done in the morning after an overnight fast of at least 8 h. The glucose values were measured in capillary plasma both at fasting and after 2 h. The World Health Organization criteria for impaired fasting glucose (IFG) (6.1–6.9 mmol/l), IGT (8.6–12.2 mmol/l), and diabetes (fasting >6.9 and 2-h >12.2 mmol/l) were used (13).

GADA were analyzed in a radioimmunoprecipitation assay using in vitro translated human GAD65 labeled with ^{35}S-methionine (11). Levels were expressed as an index calculated in relation to a positive and negative standard. Indexes <0.08 (97.5th percentile) were considered negative. The sensitivity was 70% and specificity 100% when tested in the Diabetes Antibody Standardization Program (14).

IA-2As were also analyzed in a radioimmunoprecipitation assay (12). An index <0.05 (97.5th percentile) was considered negative. The sensitivity was 50% and the specificity 100% when tested in the Diabetes Antibody Standardization Program (14). The thresholds for positivity in the GADA and IA-2A assays were based on analyses of 833 control subject without diabetes.

ICAs were analyzed by immunofluorescence. Human pancreas of blood type O was used as antigen (15). The samples were diluted until negative, and the highest positive titer was then converted to JDF-U (Juvenile Diabetes Foundation units) according to a standard curve for this method. The detection limit was 6 JDF-U, which was considered positive. This method had a sensitivity of 100% and a specificity of 88% when tested in the International Diabetes Workshop (16). This method was replaced by the IA-2A test in 2004.

Table 2—*Development of diabetes among the autoantibody-positive and -negative women*

	Antibody positive	Antibody negative	*P*
n	24	48	
Type 1 diabetes	12 (50.0)	0	0.001
Type 2 diabetes	0	6 (12.5)	NS
IFG/IGT	5 (20.8)	5 (10.4)	NS

Data are *n* (%).

Statistics

The results are shown as median (interquartile range) because the values are not normally distributed. Mann-Whitney *U* test was used for comparisons of levels. The frequencies are shown as *n* (%). For comparisons of frequencies, the χ^2 test was used and Fischer's exact test when working with low numbers. A *P* value <0.05 was considered significant. SPSS, version 11.0, for Mac was used for the analysis.

RESULTS — Among the 24 women with autoantibodies during GDM, 95.8% (23 of 24) were positive for GADA and 29.2% (7 of 24) were positive for IA-2A. Only 22 of 24 women had been tested for ICA, and among these, 59.1% (13 of 22) were found positive. Positivity for two autoantibodies was found in 54.2% (13 of 24) of the 24 women, and 27.3% (6 of 22) were found positive for all three autoantibodies (only 22 women had been tested for all three).

Women with autoantibodies during GDM were compared with women who also had GDM but without autoantibodies in respect to age, BMI, heredity for diabetes, non-Scandinavian ethnicity, glucose value at first OGTT, insulin treatment during pregnancy, birth weight of child, and mode of delivery. None of these variables differed significantly between the two groups of women (Table 1).

Follow-up

At follow-up, four times as many women among those who were autoantibody positive had developed diabetes (50%) compared with the GDM control subjects (12.5%). All of the GDM control subjects who had developed diabetes had developed type 2 diabetes, while those among the autoantibody-positive GDM women had developed type 1 diabetes. Twice as many women among those who were autoantibody positive had a disturbed glucose metabolism but not manifest diabetes (Table 2).

Of the women who had developed type 1 diabetes, 100% (12 of 12) had GADA during pregnancy. Among the women with autoantibodies who developed diabetes, 41.7% (5 of 12) developed diabetes within 6 months after delivery, 50% (6 of 12) within 1 year, and 83.3% (10 of 12) within 4 years. The other two women who developed type 1 diabetes later were diagnosed 5 and 8 years after having GDM with autoantibodies.

Among the 12 women with known type 1 diabetes, 6 chose to participate in the follow-up and reanalyze GADA and IA-2A. GADA persisted in 83.3% (5 of 6) and IA-2A in 33.5% (2 of 6) of these women. Of the 12 women who were not diagnosed with diabetes, 11 were willing to do a new OGTT and reanalyze GADA and IA-2A. GADA persisted in 81.8% (9 of 11) and IA-2A in 18.2% (2 of 11), and 45.5% (5 of 11) of these women had disturbed glucose metabolism (IGT was found in 27.3% [3 of 11] and IFG in 18.2% [2 of 11]).

CONCLUSIONS — Among women with GDM during pregnancy, ~6% have β-cell–specific autoantibodies that are characteristic of type 1 diabetes. The purpose of this study was to follow up these women to estimate the risk for later development of type 1 diabetes. We found that 50% of these women had developed type 1 diabetes, and an additional 21% had IGT or IFG after a follow-up time that varied from 6 months to 10 years. One-half of the patients (50%) were diagnosed with diabetes within 1 year after delivery and 83% within 4 years.

All of the women who had developed type 1 diabetes during follow-up were previously positive for GADA. Of those women who had not developed diabetes, GADA persisted in 82% and IA-2A in 18%, which might indicate a continuously ongoing autoimmune process. Since the follow-up time varied, it is likely that an additional number of women will develop type 1 diabetes in the future.

Previous studies have shown that pancreatic autoantibodies during GDM are predictive for the development of type 1 diabetes (9,17). In a Danish study, ICA could be demonstrated during GDM, and 75% of these women developed type 1 diabetes later in life, with a sensitivity of 50% and specificity of 99% (9). When all three autoantibodies (GADA, IA-2A, and ICA) were tested during GDM in a study in Germany, 29% of the women positive for at least one antibody had developed type 1 diabetes within 2 years postpartum (17). In our study, none of the control subjects, consisting of women with GDM without autoantibodies, had developed type 1 diabetes. On the other hand, 12.5% had developed type 2 diabetes. The fact that none of the control subjects had developed type 1 diabetes strengthens the theory that autoantibodies during pregnancy strongly influence the course of and might be a substantial risk for type 1 diabetes.

When comparing certain known risk factors for the development of GDM, we could observe a tendency to lower frequency of family history of diabetes and higher presence of ethnicity outside Scandinavia in the control group compared with the autoantibody-positive women, although the difference did not reach significance. In the control group, there was a tendency toward higher BMI, while plasma glucose level in the OGGT and frequency in number who needed insulin therapy were higher in the group with autoantibodies, though still without significant differences. One reason for this could be the limited number of patients. Other studies have shown that pregnant women with higher BMI have an increased risk of delivering children who are large for gestational age (18,19). On the other hand, strict metabolic control in women with GDM showed no significant influence on the birth weight of the child (19). In this study, all women had GDM, and we could not detect any difference between the birth weight of the children in respect to the presence of autoantibodies. Previous studies have also shown that there is a higher frequency of caesarian delivery among women with GDM compared with healthy women (2). The frequency of caesarean delivery in this study was equally high in both groups.

The autoimmune process that leads to the development of type 1 diabetes probably begins several years before the disease. The increased insulin resistance during pregnancy leads to an increased demand on the remaining and affected β-cells. A pregnancy could therefore uncover an early stage of type 1 diabetes and be interpreted as just GDM.

In conclusion, this study has shown that having β-cell–specific autoantibodies during GDM increases the risk of developing type 1 diabetes later in life. The commercial kits for GAD antibodies that are used today are cheap, and the antibody analysis is simple and could therefore be applied on all GDM patients. Autoantibody screening in pregnant women with GDM and follow-up after delivery should therefore be considered for early recognition of type 1 diabetes.

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