Gestational Diabetes Identifies Women at Risk for Permanent Type 1 and Type 2 Diabetes in Fertile Age

Predictive role of autoantibodies

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OBJECTIVE — Our aim was to evaluate the predictive value of gestational diabetes mellitus (GDM), diabetes-associated autoantibodies, and other factors for development of clinical diabetes later in life.

RESEARCH DESIGN AND METHODS — In this case-control study the presence of autoantibodies was studied in 435 women with GDM and in healthy matched control subjects. The need for exogenous insulin during GDM was recorded. In the GDM group, the mean follow-up period was 5.7 years and in the control group 6.1 years.

RESULTS — Among the subjects with GDM, 20 (4.6%) developed type 1 diabetes and 23 (5.3%) developed type 2 diabetes, whereas none of the control subjects became diabetic. Two-thirds of those who developed type 1 diabetes tested positive initially for islet cell antibodies (ICAs), whereas 56% of them had autoantibodies to GAD (GADAs) and 38% to the protein tyrosine phosphatase–related IA-2 molecule. Only 2 of the 23 women who presented later with type 2 diabetes tested positive for autoantibodies. According to multivariate analysis, initial age ≤30 years, the need for insulin treatment for GDM, and antibody positivity for ICAs and GADAs were associated with increased risk for clinical type 1 diabetes.

CONCLUSIONS — Pregnancy seems to identify women who are at risk of developing diabetes later in life. About 10% of Finnish women with GDM will develop diabetes over the next 6 years; nearly half of them develop type 1 diabetes and the other half type 2 diabetes. Age ≤30 years, the need for insulin treatment during pregnancy, and positivity for ICAs and GADAs confer a high risk of subsequent progression to type 1 diabetes in women affected by GDM.

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Normal pregnancy induces insulin resistance (1), which may unmask diabetes or reduced insulin secretory capacity. The incidence of gestational diabetes mellitus (GDM) has been reported to be 2–5% during pregnancy (1). The condition is associated with both impaired insulin action and secretion, defects that are also characteristic of type 2 diabetes (2). Women with GDM have a considerable risk of developing type 2 diabetes later in life, but the risk of developing type 1 diabetes is also increased (3–5).

The presence of circulating autoantibodies to various islet cell proteins is one of the most thoroughly characterized immune phenomena associated with type 1 diabetes (6). These autoantibodies are the detectable markers of an ongoing destructive process in the islets and thus provide a potential tool to identify individuals at risk of developing the disease in the future. Diabetes-associated autoantibodies have a high positive predictive value (PPV) for clinical type 1 diabetes among relatives of affected patients. The results of recent studies have implied that the PPV of autoantibodies associated with type 1 diabetes is also high in women with GDM (7). Although the antibody status of women with GDM may vary, depending on the phase of pregnancy and treatment mode for GDM, as well as on the methods used for antibody detection, most investigators have reported an increased frequency and higher levels of such autoantibodies in women with GDM. The reported frequency of GAD antibodies (GADAs) in women with GDM ranges from 0 to 38% (8,9), that of islet cell antibodies (ICAs) from 1 to 38% (5,9,10), that of insulin autoantibodies (IAAs) from 0 to 18% (4,11,12), and that of antibodies to the protein tyrosine phosphatase–related protein 2 molecule (IA-2As) from 0 to 6.2% (7,9).

Although the occurrence of autoantibodies in women with GDM has been analyzed in several surveys, prospective studies including healthy matched control subjects, which would predict morbidity in terms of both type 1 and type 2 diabetes, are lacking. In the present survey we examined the frequency of ICAs, IAAs, GADAs, and IA-2As in women with GDM and in age- and parity-matched healthy control subjects and correlated the presence of the autoantibodies with progression to type 1 or type 2 diabetes. In addition, the predictive value of the need for exogenous insulin during pregnancy for the

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Abbreviations: GADA, GAD antibody; GDM, gestational diabetes mellitus; IA-2A, protein tyrosine phosphatase–related IA-2 molecule antibody; IAA, insulin autoantibody, ICA, islet cell antibody; PPV, positive predictive value.

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

development of later diabetes was evaluated.

RESEARCH DESIGN AND METHODS

— We studied 435 women who had GDM and a singleton pregnancy and who delivered at Oulu University Hospital, Finland, between 1984 and 1994. All the women included had the diagnosis of GDM for the first time. The control group ($n = 435$) was pair matched for age (±2 years), parity (nulliparous, one to three, and more than three deliveries), and date of delivery, and none of them had a history of GDM, type 1 diabetes, or type 2 diabetes. A 2-h oral glucose tolerance test (75 g) was performed using the following indications: glucosuria, BMI ≥25 kg/m^2, previous delivery of a macrosomic infant (≥4,500 g), or expected macrosomic infant in the current pregnancy. A diagnosis of GDM was made if at least one of the blood glucose concentrations was abnormal. The limits of abnormal capillary blood glucose concentrations used were as follows: fasting ≥4.8 mmol/l, 1 h ≥10 mmol/l, and 2 h ≥8.7 mmol/l, which represent the 97.5 percentile values in Finnish pregnant women and are those recommended by the Finnish Diabetes Association.

The subjects were sent a questionnaire, and they were asked to give informed consent for use of their serum samples and patient history in the study. In the GDM group the mean follow-up period from delivery to the date of completing the questionnaire was 5.7 years (range 1.0–11.6) and in the control group was 6.1 years (1.5–13.1). A venous blood sample had been taken from all women during the first trimester of pregnancy and sent to the National Public Health Institute for rubella screening. The mean age of the women at the time of blood sampling was 31.6 years (17.7–46.5) in the GDM group and 31.3 years (18.8–46.0) in the control group. After the routine analyses, residual sera had been stored at −20°C. A serum sample was available for 395 of the women with GDM (90.8%) and for 388 control women (90.7%). In the questionnaire the subjects were asked whether they had developed diabetes after their index pregnancy and whether they were currently taking medication. The medication was ascertained from the National Central Drug Register maintained by the Finnish Social Insurance Institution. This register has essentially complete population coverage (13). All 435 subjects with GDM were included in the analysis assessing the probability of developing type 1 or type 2 diabetes. Differentiation between type 1 and type 2 diabetes was based on the clinical diagnosis made by the physician in charge of the treatment of the patient. The study protocol was approved by the local ethics committee.

The determination of diabetes-associated autoantibodies (ICAs, IAAs, GADAs, and IA-2As) was described in detail in a previous study by Kulmala et al. (14). The cutoff limit for ICA positivity was 2.5 Juvenile Diabetes Foundation units. The cutoff limits for IAA, GADA, and IA-2A positivity were based on the 99th percentile in nondiabetic Finnish subjects ($n = 105$ for IAAs, 372 for GADAs, and 374 for IA-2As). The limit for IAA positivity was a specific binding of 54 nU/ml, that for GADA was 6.5 relative units, and that for IA-2A was 0.43 relative units. The disease sensitivity and specificity of the assay for ICAs were 100 and 98%, for IAAs were 78 and 100%, for GADAs were 79 and 97%, and for IA-2As were 62 and 97%, respectively. All samples with IAA, GADA, or IA-2A levels between the 97th and 99.5th percentiles were reanalyzed to confirm their status.

Statistical analyses

The Kaplan-Meier method was used to construct life tables for the likelihood of developing diabetes. The follow-up time for each subject was recorded as the time from delivery to the day when the subject completed our questionnaire. CIs were determined by means of the "exact" method.

A logistic regression method was used to identify independent factors that contribute to the development of type 1 diabetes after a pregnancy affected by GDM. The variables selected for the initial analysis were age at the time of the first trimester blood sample, treatment of GDM (insulin or noninsulin), the number of positive autoantibodies (none to three), and positivity for ICAs, IA-2As, and GADAs. Age was treated as a dichotomous variable (≤30 or >30 years). Treatment of GDM was a nominal variable. Only statistically significant variables were included in the final model. The Hosmer-Lemeshow goodness-of-fit statistic (15) was used for assessment of the final model. Logistic regression analysis was performed using the PC version of Professional Statistics, release 11.5.1 (SPSS, Chicago, IL). Differences between groups were tested using Student's t test and the χ^2 test. The chosen level of significance was $P < 0.05$.

RESULTS

— In the GDM group, 4.6% (20 of 435) of the women developed clinical type 1 diabetes and 5.3% (23 of 435) developed clinical type 2 diabetes, whereas none of the control subjects developed diabetes during the follow-up period. There were no differences in the number of previous deliveries between those who developed either type 1 or type 2 diabetes or the rest of the GDM subjects.

Age

Women who developed type 1 diabetes were significantly younger (mean 27.2 years [range 17.7–40.2]) at the time of blood sampling than those who developed type 2 diabetes (34.0 years [20.5–42.4]; $P < 0.001$) and those who did not develop diabetes (31.8 years [18.0–46.5]; $P < 0.0005$). The mean type 1 diabetes–free period was shorter (2.9 years [0–7.1]) than the type 2 diabetes–free period (4.7 years [0–8.5]; $P = 0.011$). Life-table analysis (Fig. 1*A*) showed that the mean type 1 diabetes–free survival time was shorter in women ≤30 years at the time of blood sampling than in women >30 years (log-rank $P = 0.0015$).

Insulin treatment for GDM

During pregnancy, 35.6% (155 of 435) of the women with GDM were treated with insulin. Eighteen of the 20 women with GDM (90%) who developed type 1 diabetes and 18 of those 23 subjects (78.3%) who developed type 2 diabetes were receiving insulin therapy. Insulin treatment for GDM had a PPV of 13% and a sensitivity of 90% for subsequent type 1 diabetes. Life-table analysis (Fig. 1*B*) showed that the mean type 1 diabetes–free period was shorter in women who needed insulin for GDM than in women who did not receive insulin for GDM (log-rank $P < 0.0001$).

Autoantibodies

At least one antibody reactivity was detected in 16.7% (66 of 395) of the women in the GDM group and in 2.8% (11 of 388) of women in the control group (difference 13.9% [95% CI 9.8–17.9%]). Among the women with GDM who were treated with insulin during pregnancy, 16.1% (22 of 137) tested positive for reactivity to at least one autoantibody,

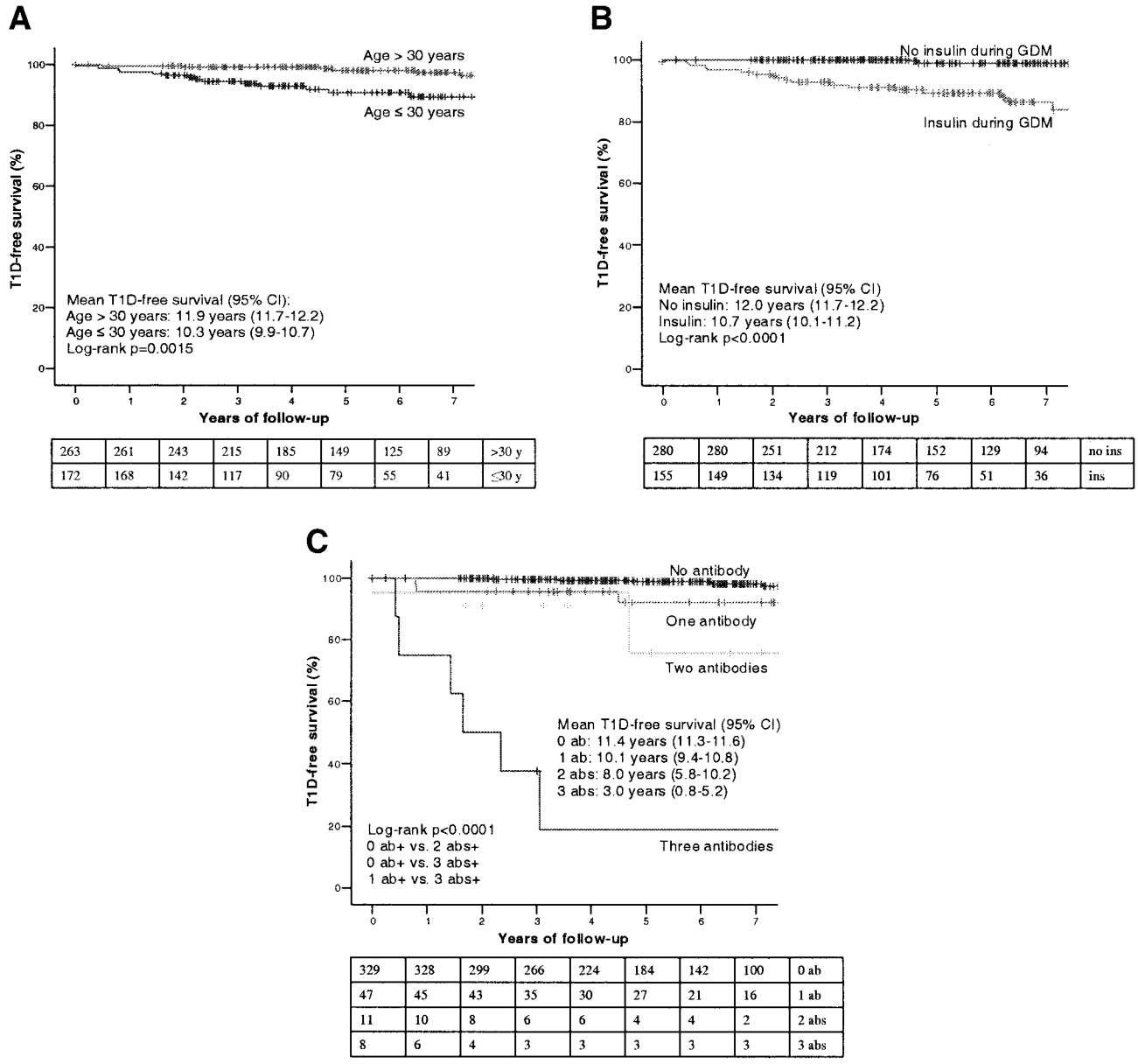

Figure 1—*Probability of remaining nondiabetic among 435 women with GDM in relation to age during pregnancy* (A)*, insulin use for GDM* (B)*, and number of positive autoantibodies (abs)* (C)*. T1D, type 1 diabetes.*

whereas the corresponding proportion was 16.9% (43 of 255) among those who were not treated with insulin. None of the untreated 212 women who were antibody negative developed type 1 diabetes, whereas 5 of them (2.4%) developed type 2 diabetes during the follow-up period.

Sera for antibody analyses were available from 16 of the 20 subjects who developed type 1 diabetes and from all 23 who developed type 2 diabetes. Of the type 1 diabetic patients, 68.8% (11 of 16) had antibodies, whereas only 8.7% (2 of 23) of the type 2 diabetic subjects were antibody positive (difference 60.1% [95% CI 34.6–85.5%]). The type 1 diabetic patients who were antibody negative during pregnancy (5 of 11) developed type 1 diabetes later than those who were antibody positive (1 of 16) (type 1 diabetes–free period [mean ± SD] 2.0 ± 0.9 vs. 1.6 ± 0.5 years, respectively; $P = 0.008$).

The prevalences of the various autoantibodies in the GDM and the control groups are presented in Table 1. For ICAs, 10 of 16 (62.5%) women who developed type 1 diabetes were ICA positive. The PPV and sensitivity of ICA for type 1 dia-

Table 1—*Prevalences of antibodies in the GDM and control groups*

Autoantibody	GDM group	Control group	Difference (%)
ICA	48/385 (12.5)	1/388 (0.3)	12.2 (8.9–15.5)
GADA	23/393 (5.9)	8/388 (2.1)	3.8 (1.1–6.5)
IA-2A	18/385 (4.7)	3/387 (0.8)	3.9 (1.6–6.2)
IAA	4/382 (1)	2/388 (0.5)	0.5 (−0.7 to 1.8)

Data are *n* (%) or difference (95% CI).

betes were 21 and 63%, respectively. For GADAs, 9 of 16 (56.3%) women who developed type 1 diabetes were GADA positive. The PPV and sensitivity of GADAs for type 1 diabetes were 39 and 56%, respectively. For IA-2As, 6 of 16 (37.5%) women who developed type 1 diabetes tested positive for IA-2As. The PPV and sensitivity of IA-2As for type 1 diabetes were 33 and 38%, respectively. All of the IA-2A–positive women who developed either type 1 or type 2 diabetes tested positive for ICAs as well. For IAAs, none of IAA-positive women developed type 1 or type 2 diabetes during the follow-up period. Thus, both the predictive value and sensitivity of IAA for type 1 diabetes were 0. Life-table analysis showed a statistically longer type 1 diabetes–free period in ICA-, GADA-, and IA-2A–negative women compared with antibody-positive women (log-rank $P < 0.0001$).

None of the women with GDM or the control subjects were positive for all four antibodies. Eight of the women with GDM and none of the control subjects were positive for three antibodies (ICAs, GADAs, and IA-2As). All eight of the women with GDM required insulin therapy during pregnancy; six of them developed type 1 diabetes and one developed type 2 diabetes. Eleven of the women with GDM and one of the control subjects were positive for two antibodies. During the follow-up period, 18.2% (2 of 11) of those with GDM developed type 1 diabetes and 1 developed type 2 diabetes. The highest PPV was 75%, with the combination of ICAs, GADAs, and IA-2As, whereas the highest sensitivity (50%) was achieved using the combination of ICAs and GADAs. Life-table analysis (Fig. 1*C*) showed that the mean type 1 diabetes–free period shortened as the number of positive antibodies increased. The type 1 diabetes–free period was significantly shorter in women with two or three positive antibody reactivities when compared with antibody-negative subjects (log-rank $P < 0.0001$).

Logistic regression analysis

The data fitted logistic regression analysis well, as indicated by the Hosmer-Lemeshow goodness-of-fit test ($P = 0.539$ in model 1, 0.691 in model 2, and 0.576 in model 3). The first logistic regression model revealed that independent factors associated with progression to type 1 diabetes after GDM were age ≤30 years at the time of blood sampling, exogenous insulin for GDM, and at least one positive autoantibody reactivity (Table 2). In this model the odds ratio (OR) increased as the number of positive antibodies increased. In the second model, the individual types of antibody were included in the analysis to evaluate which of them were independent factors. In this model both ICAs and GADAs were significant predictors, whereas IA-2As were not. In the third model IA-2As were excluded, and the significant independent factors were age ≤30 years, insulin for GDM, and ICA and GADA positivity.

Table 2—*Results of three logistic regression models to analyze independent factors for type 1 diabetes after pregnancy in women with GDM*

Variable	OR (95% CI)	*P* value
Model 1		
Age ≤30 years*	5.033 (1.224–20.689)	0.025
Insulin for GDM†	10.836 (2.069–56.752)	0.005
No. of positive antibodies‡		
1	5.646 (1.120–28.453)	0.036
2	7.013 (1.001–49.115)	0.050
3	66.427 (9.209–479.177)	<0.0005
Model 2		
Age ≤30 years*	3.854 (0.982–15.128)	0.053
Insulin for GDM†	20.955 (3.069–143.093)	0.002
ICA positivity‡	10.320 (1.916–55.582)	0.007
GADA positivity‡	7.631 (1.245–46.788)	0.028
IA-2A positivity‡	0.462 (0.047–4.572)	0.509
Model 3		
Age ≤30 years*	3.932 (1.008–15.336)	0.049
Insulin for GDM†	16.331 (2.977–89.573)	0.001
ICA positivity‡	9.460 (2.154–41.545)	0.003
GADA positivity‡	4.745 (1.066–21.119)	0.041

*Age at the time of blood sample during pregnancy; OR against women >30 years. †OR against women without insulin for GDM. ‡OR against women negative for antibodies.

CONCLUSIONS — In this large age- and parity-matched case-control study we focused on evaluating risk factors predictive of development of diabetes after a pregnancy affected by GDM. During a mean of 6 years of follow-up, 10% of the women with GDM developed diabetes. The manifestation of GDM had an extremely high sensitivity in detecting subjects who later developed diabetes because all the women in the control group remained nondiabetic. Accordingly, pregnancy seems to identify women who have reduced insulin secretory capacity or who have insulin resistance and are at risk of developing diabetes later in life. A similar dramatic difference in the risk of progression to diabetes among women with and without past GDM has been observed earlier in smaller series (16,17). These present results demonstrate that subjects at high risk for permanent diabetes can be identified.

The risk among women with GDM of subsequent progression to type 1 and type 2 diabetes was about 5% for both types of diabetes in our Finnish population; earlier investigators reported type 1 diabetes incidence rates ranging from 1.7 to 7% (7,16,18). In 1997, the overall risk of type 1 diabetes in Finnish women aged 15–44 years was 6.8 of 1,000 (19), which suggests that the prevalence of type 1 diabetes after GDM is significantly increased. The incidence of type 2 diabetes here was low when compared with earlier reports after longer follow-up periods, the incidence being 14% in the Danish population (17), 50% in the U.S. (20), and up to 70% in Navajo women with previous GDM (21). One reason for the difference may be that we had no oral glucose tolerance test data during follow-up and the diagnosis of type 2 diabetes was based on questionnaire information and on the use of oral antihyperglycemic medication. In addition, other factors that may explain the discrepant results are the diagnostic criteria for type 2 diabetes, ethnicity of the study population, weight gain after pregnancy, subsequent pregnancies, age, and family history of diabetes (17,21).

Type 1 diabetes results from destruction of the pancreatic β-cells, leading gradually to absolute insulin deficiency.

Most often the reason is immune-mediated destruction (22). Type 2 diabetes is characterized by disorders of insulin action and secretion, either of which may be a predominant feature (22). Type 2 diabetes is usually diagnosed in patients older than those with type 1 diabetes (22). In the present study these characteristics of type 1 and type 2 diabetes were already evident in the women with GDM at the time of pregnancy. Those who developed type 1 diabetes were younger, and 69% had autoantibodies, reflecting immune-mediated destruction of the pancreatic β-cells and insulin deficiency, resulting in GDM. Only two women with the subsequent diagnosis of type 2 diabetes tested positive for autoantibodies in the sample taken years before the diagnosis. These women most likely had late-onset autoimmune diabetes, which comprises 10–15% of all initial diagnosis of type 2 diabetes among Caucasians (23,24). Accordingly, about 90% of the women in whom type 2 diabetes was diagnosed had "true" type 2 diabetes, indicating that insulin resistance rather than destruction of the pancreatic β-cells was the reason for their impaired glucose tolerance during pregnancy. The frequency of insulin use for GDM was, however, similar among those who presented with type 1 diabetes and those with the diagnosis of type 2 diabetes.

According to our results, the independent factors contributing to the development of type 1 diabetes after GDM were age ≤30 years, insulin use for GDM, and the number of positive autoantibodies. Women with GDM who were ≤30 years of age seem to have an increased risk of postpartum type 1 diabetes than older women. Moreover, as expected, type 1 diabetes developed sooner than type 2 diabetes after delivery, which is logical because the incidence of type 1 diabetes peaks among children and adolescents (22). In addition, the use of insulin for GDM, which reflects the severity of the disease, was an independent factor increasing the risk of development of postpartum type 1 diabetes. Fuchtenbusch et al. in 1997 (7) have also reported that insulin use for GDM is associated with an increased risk of postpartum type 1 diabetes. In the present study, one-third of all the women with GDM required insulin treatment because dietary counseling and diet were not sufficiently effective to achieve normoglycemia. The sensitivity of insulin use was 90% for subsequent development of type 1 diabetes. On the other hand, women with GDM who did not require insulin and were negative for antibodies had a very low risk of developing diabetes later because none of them developed type 1 diabetes and only 2.4% developed type 2 diabetes during the follow-up period.

The presence of several autoantibody reactivities has been shown to increase the risk of development of type 1 diabetes (7,14,25). We found that even one positive antibody was a significant predictor to increase the risk of postpartum type 1 diabetes. The type 1 diabetes–free period shortened as the number of positive antibodies increased, probably reflecting the severity of pancreatic β-cell destruction. All women who tested positive for three antibody reactivities required insulin for their GDM, and 75% of them developed type 1 diabetes during the follow-up period.

None of the women who developed type 1 diabetes tested positive for IAA. The lack of insulin antibodies is explained by the fact that the serum sample was obtained by the end of the first trimester well before the initiation of any exogenous insulin therapy. IA-2As did not represent an independent risk factor for the development of type 1 diabetes, whereas both ICAs and GADAs did. None of the women with type 1 diabetes would have been missed if IA-2As had not been analyzed. This finding is in accordance with data reported by Fuchtenbusch et al. (7), who also showed that positivity for both GADAs and ICAs, but not for IA-2As, contributes independently to the risk of type 1 diabetes postpartum. The possible contribution of parity to the risk of development of type 1 diabetes was evaluated, but in contrast to the data reported by Fuchtenbusch et al. (7), it did not turn out to be a significant risk factor.

In summary, pregnancy appears to very efficiently identify those subjects who have impaired glucose tolerance and are subsequently at risk of developing postpartum diabetes. The risk of developing type 1 diabetes after GDM is increased if the woman is ≤30 years of age during pregnancy, needs insulin therapy for GDM, and tests positive for ICAs and/or GADAs. In these patients, careful follow-up after pregnancy is indicated, in particular because early diagnosis of type 1 diabetes has been reported to be associated with preserved endogenous insulin secretion and decreased frequency of microvascular complications (26).

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