Original Article

Predictors of Postpartum Diabetes in Women With Gestational Diabetes Mellitus

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The aim of this study was to stratify risk for postpartum diabetes in women who have gestational diabetes. Women with gestational diabetes were recruited between 1989 and 1999, and 302 were followed with oral glucose tolerance tests at 9 months and 2, 5, 8, and 11 years postpregnancy. The 8-year postpartum diabetes risk was 52.7% (130 diabetic cases). Risk was increased in women with autoantibodies to GAD and/or insulinoma antigen-2 (adjusted hazard ratio 4.1; $P < 0.0001$), women who required insulin during pregnancy (4.7; $P < 0.0001$), women with BMI >30 kg/m^2 (1.5; $P = 0.04$), and women with more than two prior pregnancies (2.5; $P = 0.02$). Women without these risk factors had a postpartum diabetes risk of 14% by 8 years, and risk rose incrementally to 96% by 8 years in autoantibody-positive women. Parity status, C-reactive protein concentration, a diabetes family history, maternal age, weeks of gestation, and the child's birth weight did not significantly affect risk in multivariate analysis. Prospective diabetes assessment is indicated and intervention should be considered in women with gestational diabetes who are autoantibody positive, require insulin treatment during pregnancy, or are obese. *Diabetes* 55:792–797, 2006

Gestational diabetes mellitus (GDM) complicates ~4% of pregnancies and is defined as glucose intolerance with onset or first diagnosis during pregnancy (1). GDM substantially increases the risk to develop postpartum diabetes and thus identifies a high-risk population for the development of both type 1 and type 2 diabetes. Risk estimates of type 2 diabetes after GDM vary from 17 to 63% within 5–16 years after pregnancy, depending upon the ethnic background of the study population and the detection method for GDM and glucose intolerance (2–4). Like type 2 diabetes, the incidence of postpartum diabetes appears to be increasing (5). Reported risk factors for postpartum diabetes include the detection of islet autoantibodies (6,7), insulin treatment during pregnancy, BMI, and age at delivery (3).

The German GDM study has prospectively followed patients with GDM for up to 11 years for the purpose of estimating diabetes risk and identifying factors that modify risk. Here we report diabetes risk with respect to anthropometric markers such as BMI, insulin requirement during pregnancy, family history of diabetes, the number of previous pregnancies, age at delivery, duration of gestation, or birth weight of child and serological markers such as the presence of islet autoantibodies and serum concentrations of C-reactive protein (CRP) in this cohort.

RESEARCH DESIGN AND METHODS

The German GDM prospective study follows women with GDM from delivery (6,8). Between 1989 and 1999, 302 patients with GDM were recruited from hospitals in Germany and participated in at least one follow-up contact after delivery. GDM was diagnosed following the criteria of the German Diabetes Association using an oral glucose tolerance test (OGTT) with 75-g glucose load. Women were considered to have GDM if two of three capillary blood glucose values exceeded the following limits: >5 mmol/l (fasting) before OGTT, >10.6 mmol/l after 60 min, and >8.9 mmol/l after 120 min. All centers participating in the study were asked to follow the therapeutic guidelines for the treatment of GDM recommended by the Diabetes and Pregnancy Study group of the German Diabetes Association. According to these recommendations, insulin is required if under diet treatment for at least 1 week and capillary blood glucose values exceed the following limits: >5 mmol/l before meals and >7.8 mmol/l 60 min after and >6.7 mmol/l 120 min after meals. Demographic data that included the age at delivery, the numbers of preceding pregnancies, the duration of gestation, the birth weight of the child, diabetes treatment during pregnancy, BMI at the first pregnancy visit (routinely recorded at visit to gynecologist), and whether the patient had a first-degree family history of type 1 or type 2 diabetes were obtained shortly after delivery. Visits that included collection of venous blood, and the completion of a questionnaire on habits and diabetes family history were performed at delivery and at 9 months and 2, 5, 8, and 11 years postpartum. An OGTT was performed at each follow-up visit. The current analysis includes all 302 women who participated in follow-up. The cumulative drop-out rate was 21% by 5 years follow-up. The median follow-up time from delivery to diabetes or last contact was 2.2 years (interquartile range [IQR] 0.9–7.3 years). All patients gave written informed consent to participate in the study. The study was approved by the ethical committee of Bavaria, Germany (Bayerische Landesärztekammer Nr. 95357).

Measurement of CRP, islet autoantibodies, and HLA typing. Serum was recovered by centrifugation and frozen at −20°C. CRP was measured using a commercial kit (Immundiagnostik, Bensheim, Germany) according to manufacturer's instructions in the serum sample taken 9 months after delivery. CRP was not measured at delivery because partum significantly influences values. Antibodies to GAD and insulinoma antigen-2 (IA-2) were measured in serum collected at delivery by radio binding assays as previously described (9) using [^{35}S] methionine-labeled in vitro–translated recombinant human GAD_{65} and IA-2, respectively. Results were expressed as arbitrary units that were derived from a standard curve. The thresholds for positivity corresponded to the 99th percentile of pregnant control subjects (6). These assays had sensitivities and specificities of 84 and 96% (GAD antibodies) and 66 and 100% (IA-2 antibodies), respectively, in the 2nd Diabetes Autoantibodies Standardization Proficiency Workshop. HLA typing at DRB1 and at DQA1 and DQB1 loci was performed using PCR-amplified DNA and nonradioactive sequence-specific oligonucleotide probes as described previously (8).

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CRP, C-reactive protein; GDM, gestational diabetes mellitus; IA-L, insulinoma antigen-2; IQR, interquartile range; OGTT, oral glucose tolerance test.

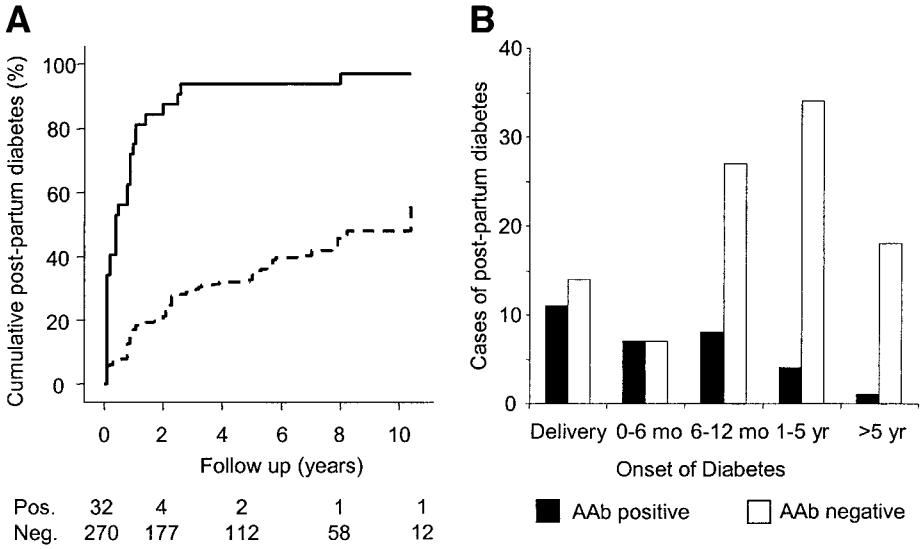

FIG. 1. Progression to diabetes with respect to islet autoantibody status. The life table risk for postpartum diabetes (*A*) is shown for autoantibody-positive (solid line) and autoantibody-negative (broken line) patients with GDM. Numbers below the graph indicate the subjects remaining in follow-up for each group. The number of diabetes cases coming from autoantibody-positive (filled columns) and autoantibody-negative (open columns) at delivery and at time intervals after delivery are indicated in *B*.

Statistical analysis. Diabetes as defined by American Diabetes Association criteria (1) postpartum was the outcome measure. Variables analyzed with respect to diabetes risk were *1*) diabetes treatment during pregnancy, categorized as insulin injections or diet alone; *2*) BMI, categorized as obese (>30 kg/m^2 [10]) or nonobese; *3*) islet autoantibody status, categorized as GAD or IA-2 antibody positive or both GAD and IA-2 antibody negative; *4*) maternal age at delivery, categorized as >35 years or <35 years; *5*) duration of pregnancy, categorized as preterm (<37 weeks as defined by the World Health Organization) or normal term; *6*) first-degree family history of type 1 or type 2 diabetes; *7*) the number of previous pregnancies categorized as none, 1, 2, or >2; *8*) the child's birth weight categorized into tertiles; and 9) serum CRP concentrations 9 months after delivery, categorized as quartiles (<0.8, 0.8–2.5, >2.5–6.5, and >6.5 mg/l).

Time to event methods were used to calculate risks (life table analysis) and to compare outcome (postpartum diabetes) for patients with different covariate status (Cox proportional hazards model). Outcome was compared by univariate analysis, and significant risk factors were entered into a multivariate analysis. Characteristics of autoantibody-positive and -negative patients were compared by Mann-Whitney *U* test or χ^2 test. Correlation between BMI and serum CRP concentration and between BMI and the number of previous pregnancies were assessed by Pearson's correlation coefficient. For all analyses, a two-tailed *P* value <0.05 was considered significant. The SPSS 12.05 was used for statistical analysis.

RESULTS

Postpartum diabetes development. Postpartum diabetes was observed in 130 women (median duration between delivery and diabetes onset: 0.95 years [IQR 0.3–2.5 years]). Twenty-five women remained diabetic after delivery and 105 GDM women intermittently returned to normoglycemia after delivery and developed diabetes thereafter. The 8-year cumulative risk of postpartum diabetes in all GDM women was 52.7% (95% CI 46.3–59.1).

Diabetes risk in autoantibody positive GDM patients. Thirty-two women (10.6%) had antibodies to GAD (n = 28), IA-2 (n = 11), or both (n = 7) at delivery. Thirty-one autoantibody-positive patients developed diabetes by the end of the observation period (Fig. 1). Eleven patients (34%) remained hyperglycemic after delivery, and a further 15 (47%) progressed to diabetes within 1 year. Among the 130 women who developed postpartum diabetes, disease developed significantly faster in autoantibody-positive patients than in autoantibody-negative patients ($P < 0.0001$; Fig. 1*B*). Postpartum diabetes risk in islet autoantibody-positive patients (97% by 8 years [95% CI 90.2–99.9]) was significantly higher than in autoantibody-negative patients (46% by 8 years [40.2–51.0%]; $P < 0.0001$). Islet autoantibody-positive patients had a lower BMI (median 22.9 [21.1–25.7]) than autoantibody-negative patients (26.5 [23.1–30.8]; $P = 0.002$), more frequently required insulin during pregnancy (75 vs. 34%, $P < 0.0001$), and more frequently had either HLA DRB1*03 (DR3) or HLA DRB1*04-DQB1*0302 (DR4-DQ8) haplotypes (77 vs. 39.4%; $P < 0.0001$; Table 1). Islet autoantibody-positive women accounted for 18 (45%) of the 40 women who progressed to diabetes by 6 months postpartum (Fig. 1*B*).

Risk factors for progression to diabetes in autoantibody-negative GDM patients. Postpartum progression to diabetes in islet autoantibody-negative women was significantly influenced by whether insulin treatment was required during pregnancy, by BMI, and by the number of previous pregnancies (Table 2 and Fig. 2). Of 270 islet autoantibody-negative women, 92 (34%) received insulin treatment during pregnancy. Postpartum diabetes risk was 84.5% by 8 years postpartum (95% CI 75.4–93.6) in women who received insulin during pregnancy compared with 23.2% (15.4–31.0) in women who were treated with diet alone ($P < 0.0001$). Postpartum diabetes risk by 8 years was 50.1% (39–61.2) in obese women (n = 80) compared

TABLE 1
Characteristics of islet autoantibody-positive and -negative women with GDM

Variable	Autoantibody positive	Autoantibody negative	Significance (*P*)
n	32	270	
Age at delivery (years)	29.9 (27.5–31.7)	31.4 (28.2–32.8)	0.60
BMI	22.9 (21.1–25.7)	26.5 (23.0–30.8)	0.002
Insulin in pregnancy	24 (75.0)	92 (34.2)	<0.0001
HLA DR3 or DR4-DQ8*	20/26 (77.0)	80/203 (39.4)	<0.0001
8-year diabetes risk†	97 (90–99.9)	46 (40–51)	<0.0001

Data are median (IQR) or *n* (%), unless otherwise indicated. *HLA typing was available on 229 women; †Data are % (95% CI).

TABLE 2
Postpartum diabetes risk in islet autoantibody-negative women with GDM

Variable category	*n*	8-year diabetes risk	Significance (*P*)	HR* (95% CI)	Significance (*P*)
Insulin in pregnancy					
No	178	23.2 (15.4–31.0)			
Yes	92	84.5 (75.3–93.7)	<0.0001	6.2 (4.1–9.6)	<0.0001
BMI					
<30 kg/m^2	187	34.6 (26.2–42.0)			
>30 kg/m^2	80	50.1 (39.0–61.2)	0.003	2.2 (1.5–3.3)	<0.0001
First-degree relatives with diabetes					
No	155	38.1 (28.7–47.5)			
Yes	98	57.3 (45–69.6)	0.10	1.4 (0.9–2.1)	0.10
Age at delivery					
<35 years	207	46.4 (37.9–54.9)			
>35 years	63	53.4 (37.1–69.6)	0.45	1.2 (0.8–1.9)	0.41
Pregnancy duration					
≥37 weeks	249	48.5 (40.6–56.4)			
<37 weeks	21	37.% (12.0–62.0)	0.54	0.8 (0.3–1.7)	0.50
Birth weight of child					
1st tertile	90	45.4 (30.2–60–6)			
2nd tertile	90	40.6 (27.2–54.0)	0.75	0.9 (0.5–1.6)	0.75
3rd tertile	90	50.5 (35.7–66.3)	0.72	1.0 (0.6–1.7)	0.94
Previous pregnancies					
None	125	33.0 (22.5–43.5)			
1	88	53.9 (39.8–68.0)	0.34	1.4 (0.9–2.3)	0.16
2	36	64.8 (39.9–88.7)	0.54	1.6 (0.9–3.0)	0.12
>2	21	75.0 (53.4–96.6)	0.0001	4.2 (2.2–8.3)	0.0001
Serum CRP at 9 months					
1st quartile	36	32.9 (12.5–53.3)			
2nd–4th quartile	111	55.8 (44.4–67.2)	0.04	2.4 (1.2–4.8)	0.02

Data are % (95% CI), unless otherwise indicated. *Unadjusted HR calculated from Cox proportional hazards model.

with 34.6% (26.2–42.0) in nonobese women (P = 0.003). Postpartum diabetes risk increased with each number of previous pregnancies and reached 75% (53.4–96.9) for women with two of more previous pregnancies (P = 0.0001 vs no previous pregnancies).

Of 253 autoantibody-negative GDM women who provided family history data, 98 (38.7%) had a first-degree family history of type 1 and/or type 2 diabetes (29 type 1 diabetes, 74 type 2 diabetes). Postpartum diabetes risk by 8 years was 57.3% (45–69.6) in the 98 autoantibody-negative women who had a first-degree relative with diabetes compared with 38.1% (28.7–47.5) in autoantibody-negative women with no family history (P = 0.10). No significant difference in postpartum diabetes risk was observed between women with a family history of type 1 diabetes and women with a family history of type 2 diabetes (data not shown). Age at delivery, weeks of gestation, and the birth weight of the child were not significant risk factors. No differences were observed in postpartum diabetes risk between autoantibody-negative

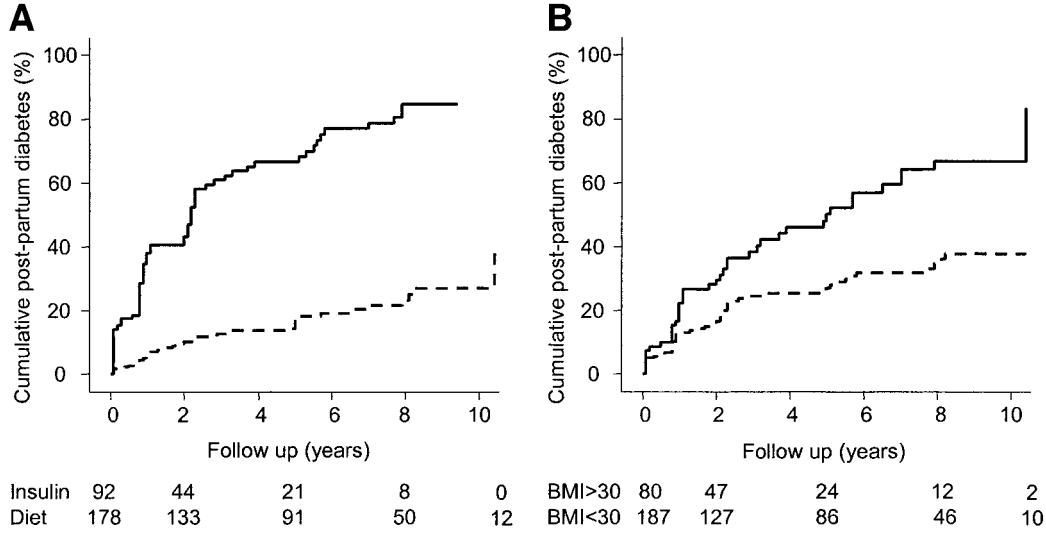

FIG. 2. Postpartum diabetes risk in antibody-negative patients. Risk is shown for treatment during pregnancy (*A*) categorized as insulin treated (solid line) and treated with diet alone (broken line) and for BMI (*B*) categorized as >30 (solid line) and <30 (broken line). Numbers below the graph indicate the subjects remaining in follow-up for each group.

TABLE 3
Multivariate analysis of risk in women with GDM

Variable category	Adjusted HR (95% CI)*	Significance (*P*)
Autoantibody positive	4.1 (2.6–6.7)	<0.0001
Insulin in pregnancy	4.7 (3.2–7.1)	<0.0001
BMI >30 kg/m^2	1.5 (1.0–2.2)	0.04
Previous pregnancies		
None	reference	
1–2	1.2 (0.8–1.7)	0.45
>2	2.5 (1.1–5.3)	0.02
Serum CRP at 9 months		
>0.8 mg/l	1.2 (0.7–2.2)	0.47

*HRs were also adjusted for age as a continuous variable.

women with or without HLA DR3 or DR4-DQ8 (data not shown).

Serum CRP concentrations have been indicated as a predictive marker of diabetes (11,12). We therefore examined whether they could discriminate diabetes risk in women who had GDM. Serum CRP concentrations were measured in the 9-month visit samples from 147 of the autoantibody-negative women who were still nondiabetic and participated in further follow-up visits. CRP concentrations were higher in women who developed postpartum diabetes (median 3.4 mg/l [IQR 1.3–8.5]) than women who remained nondiabetic postpartum (2.4 mg/l [0.7–5.0]; $P = 0.01$). Women with CRP levels in the highest three quartiles (>0.8 mg/l) had a higher risk of developing postpartum diabetes than women with CRP levels in the lowest quartile (hazard ratio [HR] 2.4 [95% CI 1.2–2.4]; $P = 0.02$), and postpartum diabetes risk was incremental with increasing CRP concentration (data not shown). CRP concentrations correlated significantly with BMI ($r = 0.43$; $P < 0.001$), however, and were not a significant predictor of diabetes in a multivariate analysis (Table 3).

Combination of risk factors for prediction of postpartum diabetes. By multivariate analysis (Table 3), a significant contribution to postpartum diabetes risk in GDM women was observed for autoantibody positivity (adjusted HR 4.1 [95% CI 2.6–6.7]; $P < 0.0001$), insulin requirement during pregnancy (4.7 [3.2–7.1]; $P < 0.0001$), BMI >30 (1.5 [1.0–2.3]; $P = 0.04$), and more than two previous pregnancies (adjusted HR vs. no previous pregnancies 2.5 [1.1–5.1]; $P = 0.02$). Women were stratified on the basis of autoantibody positivity, insulin treatment, and BMI (there were too few cases to further stratify on the number of pregnancies). Of 293 GDM women for whom complete data were obtained, 124 (42.5%) were islet autoantibody negative, were treated with diet alone during pregnancy, and had a BMI <30 kg/m^2 and therefore had none of the selected risk factors. Only 15 (12%) cases of postpartum diabetes occurred in these women. Risk for postpartum diabetes in these 124 women was 14.2% by 8 years (95% CI 6.2–22.2). Diabetes risk in the remaining 169 women was incremental depending upon which of the risk factors they had (Fig. 3). Diabetes risk was highest in women who had islet autoantibodies, followed by autoantibody-negative women who were treated with insulin during pregnancy ($n = 92$; 8 years' risk 84.5% [95% CI 75.3–93.7]; $P < 0.0001$ vs. antibody-positive women), followed by islet autoantibody-negative, diet alone–treated women who had a BMI >30 kg/m^2 ($n = 45$; 8 years' risk 51% [31.8–70.2]; $P < 0.0001$ vs. autoantibody-negative insulin-treated women; $P = 0.001$ vs. women with none of the risk factors). BMI did not influence risk in islet autoantibody-negative GDM women who were treated with insulin during pregnancy (8 years' risk 87.6% [72.6–99.9] in obese women vs. 81% [64.3–96.7] in nonobese women, $P = 0.67$; data not shown).

DISCUSSION

Postpartum diabetes is relatively common in women who develop GDM during pregnancy. Here it is demonstrated that the risk for postpartum diabetes can be discretely

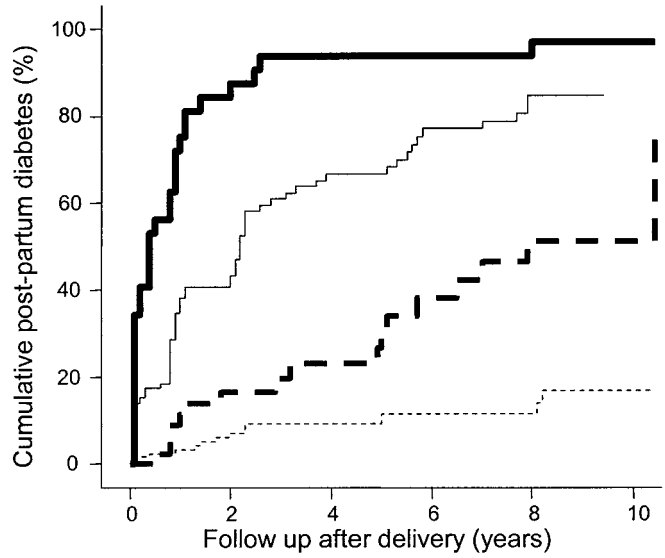

FIG. 3. Combining risk factors for classification of postpartum diabetes risk. Life table analysis of patients with GDM categorized as autoantibody positive (thick solid line); autoantibody negative, and insulin treated during pregnancy (thin solid line); autoantibody negative, diet treated during pregnancy, and having a BMI >30 (thick broken line); and autoantibody negative, diet treated, and BMI <30 (thin broken line).

categorized during pregnancy. Risk was highest, and almost 100% within a few years postdelivery, in islet autoantibody-positive GDM women, followed by islet autoantibody-negative GDM women who required insulin therapy to manage diabetes during pregnancy, and obese islet autoantibody-negative GDM women who did not require insulin therapy during pregnancy. Risk was lowest in nonobese, islet autoantibody-negative GDM women who did not require insulin reaching 14% by 8 years postdelivery.

This study presents one of the longest prospective follow-ups of diabetes after gestational diabetes in a cohort that includes diet- and insulin-treated patients characterized for islet autoantibodies. Previous studies reported that women with GDM have a 17–63% risk to develop postpartum diabetes within 5–16 years (2). Variation has been attributed to ethnicity and methods used for screening. Our prospective study in a European Caucasian population observed a 53% cumulative 8-year risk to progress to diabetes, a risk that is >10-fold that of the German adult female population, estimated to be 4 per 1,000 person-years (13).

Islet autoantibodies were found in a relatively small proportion of GDM women, consistent with previous studies that found islet autoantibodies in 5–18% of patients (5–7). Despite the low prevalence, diabetes risk in the antibody-positive fraction was very high and diabetes development was relatively rapid, such that almost 50% of cases of postpartum diabetes that occurred within 6 months of delivery were from autoantibody-positive women. Typical of autoimmune diabetes, the autoantibody-positive women had a normal BMI and an increased prevalence of HLA DR3 or DR4-DQ8 haplotypes, and the majority required insulin to treat their diabetes during pregnancy.

Although autoantibody-negative GDM patients had a substantially lower risk for developing postpartum diabetes than autoantibody-positive patients, they were the major source of postpartum diabetes cases, especially those that occurred ≥1 years after delivery. Many of these patients had features typical of pre-diabetes (14). Previous studies found that insulin treatment during the index pregnancy was an important risk factor (3,15), and some but not all studies found that BMI influenced the risk of postpartum diabetes (5,15). Both were strong, independent risk factors for postpartum diabetes in islet autoantibody-negative GDM women in our study. Insulin requirement, present in one-third of islet autoantibody-negative patients, was a dominant risk factor. Surprisingly, BMI did not further influence risk in GDM patients who received insulin during pregnancy. BMI did influence risk in GDM women who were treated with diet alone during pregnancy. A high number of previous pregnancies was also a risk factor. Preterm delivery and age at delivery were described to be risk factors in some studies (3) but had no significant influence on postdelivery type 2 diabetes development in our cohort. Remarkably, around one-third of the women with GDM had a first-degree relative with either type 1 or type 2 diabetes. Postpartum diabetes risk, however, was not significantly increased in GDM women with a diabetes family history. It is likely that family history of type 2 diabetes was underestimated due to a relatively young age of the parents of the mothers with GDM and that this may bias findings with respect to diabetes outcome relative to diabetes family history.

There has been substantial interest in the role of inflammation in the pathogenesis of diabetes (16–18) and of inflammatory markers such as CRP for predicting diabetes (11,12,19–22). CRP was described by some studies (11,12) to be a BMI-independent risk factor, while in other studies the association of CRP and diabetes was significantly attenuated by adjustment for BMI (22). In our study, serum CRP concentrations measured 9 months after delivery were associated with the risk of postpartum diabetes. CRP concentration was correlated with subject BMI, however, and did not contribute to risk above that already conferred by BMI in a multivariate analysis. Measurement of serum CRP concentrations, therefore, does not appear to provide additional benefit in estimating diabetes risk in women who had GDM. The discrepancy between our study and the findings of Pradham (11), in which CRP concentrations were independent predictors of diabetes in healthy middle-aged women may reflect the fact that the women in our study had a higher a priori risk for diabetes and were younger than in the study of Pradham.

Of particular benefit to treatment and prevention of diabetes was the finding that postpartum diabetes risk in women with GDM could be discretely categorized on the basis of relatively simple criteria. Islet antibody positivity, insulin requirement, or obesity during pregnancy identified 115 (88%) of 130 cases of postpartum diabetes. Islet autoantibody measurement appears well justified in cohorts of GDM patients, at least in patients who are not obese and who require insulin therapy. All GDM women who require insulin during pregnancy or who are obese are also at high risk for postpartum diabetes and are likely to benefit from postpartum monitoring. In light of effective prevention of type 2 diabetes through lifestyle intervention (23–30), similar intervention is likely to be effective in this subgroup of GDM women. Consistent with this, the possibility of preventing diabetes in women with previous GDM though pharmacological intervention has been investigated in the TRoglitazone In the Prevention Of Diabetes study (31), in which troglitazone and later pioglitazone were used in treatment arms.

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