Prepregnancy Weight and Antepartum Insulin Secretion Predict Glucose Tolerance Five Years After Gestational Diabetes Mellitus

BOYD E. METZGER, MD
NAM H. CHO, PHD
SUSAN M. ROSTON, RN
RUTA RADVANY, PHD

OBJECTIVE — To identify phenotypic, genotypic, and metabolic parameters measured at the time of antepartum diagnosis of gestational diabetes mellitus that can indicate the risk of diabetes mellitus at early postpartum (≤6 mo after delivery) and at a 5-yr follow-up.

RESEARCH DESIGN AND METHODS — The recommendations from the National Diabetes Data Group and International Workshop Conferences on Gestational Diabetes Mellitus were used for screening, diagnosing, and subclassifying gestational diabetes mellitus. National Diabetes Data Group criteria were also used for classification of glucose tolerance postpartum. Plasma glucose, insulin, and free fatty acids were measured after an overnight fast. Plasma glucose and insulin were measured 15, 30, 60, 120, and 180 min after the 100-g oral glucose load. Postpartum glucose tolerance was evaluated at 3–6 mo (early), 1 yr, and annually thereafter.

RESULTS — The 5-yr cumulative incidence of diabetes during follow-up after gestational diabetes mellitus was nearly 50%. Among those who had diabetes within 5 yr, a history of diabetes in only the mother was nearly threefold more common than a history of diabetes in only the father (30 vs. 11%, $P < 0.01$). Those who displayed diabetes at early postpartum (≤6 mo) testing had significantly higher antepartum glucose levels at 60, 120, and 180 min compared with those whose early postpartum results were normal. They were also relatively insulinopenic at antepartum testing. Their fasting, acutely stimulated (15 and 30 min), and integrated 3-h response to oral glucose were all significantly lower relative to women who remained normal or had impaired glucose tolerance at early postpartum testing. Women who developed diabetes between 6 mo and 5 yr postpartum were more obese before the index pregnancy, and they had lower fasting, acutely stimulated (15 and 30 min), and integrated (1–3 h) insulin levels compared with women who remained normal or displayed impaired glucose tolerance at 5 yr postpartum. A multiple logistic regression model showed that diabetes present at early postpartum testing was independently associated with higher 2-h glucose and lower basal and total integrated insulin level. Later (≥6 mo–5 yr postpartum) development of diabetes was independently associated with prepregnancy weight and impaired insulin secretion at diagnosis of gestational diabetes mellitus.

CONCLUSIONS — Impaired β-cell function and obesity at diagnosis of GDM were associated with the development of diabetes during a 5-yr, follow-up period. Studies designed to prevent diabetes in this high-risk group should examine strategies to maintain both optimal β-cell function and maximum insulin sensitivity.

From the Department of Medicine, Center for Endocrinology, Metabolism, and Nutrition, Northwestern University Medical School, Chicago; and C.R. Immunology, Loyola University Medical Center, Chicago, Illinois.

Address correspondence and reprint requests to Boyd E. Metzger, MD, Center for Endocrinology, Metabolism and Nutrition, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, IL 60611.

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GDM, gestational diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; NDDG, National Diabetes Data Group; WHO, World Health Organization; FPG, fasting plasma glucose; PIBW, prepregnant percentage of ideal body weight; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance; IRI, immunoreactive insulin; FFA, free fatty acids; HLA, human leukocyte antigen; ANOVA, analysis of variance; CI, confidence interval; RR, relative risk.

More than three decades ago, Wilkerson, O'Sullivan, and Mahan (1–3) initiated studies of glucose intolerance during pregnancy in an effort to identify women at risk for the subsequent development of diabetes. These efforts led to important criteria for the diagnosis of GDM and long-term studies of the population of GDM women identified by these investigators and have clearly confirmed a high risk for the eventual development of diabetes in such subjects. Although they used somewhat different criteria for both the initial diagnosis of GDM and postpartum evaluation, Mestman et al. (4) also reported a high prevalence of glucose intolerance 5 yr after GDM (4). Grant et al. (5) and Henry and Beischer (6) have observed an increased prevalence of diabetes in Australian women in long-term follow-up of GDM diagnosed by criteria defined for their center.

Despite the important early findings, the health status of GDM women has received relatively little attention. One contributing factor is that until recent years little standardization of definitions or diagnostic criteria was available. The prevalence of GDM was not well defined because subgroups of pregnant women at highest risk for GDM had been used for the recruitment of cases in some reports; whereas, others are based on universal surveillance of the entire prenatal population. In many early reports, women were not considered to have had GDM unless glucose tolerance was confirmed to be normal by early postpartum testing. The NDDG (7) and three International Workshop Conferences on GDM (8–10) have provided a framework for some standardization. They have recommended that all pregnant women be screened for glucose intolerance by blood glucose testing and that GDM be defined as glucose intolerance of variable severity with onset or first recognition during pregnancy. The definition has applied regardless of whether insulin is used for treatment or the condition per-

sists after pregnancy. Performing reevaluation and classification of glucose tolerance postpartum has been recommended according to the procedures recommended by the NDDG or WHO (7,11). Subsequently, a limited number of reports have been found of postpartum glucose tolerance in women whose GDM was detected and diagnosed by currently recommended procedures (12–18). The populations have been heterogeneous, and most intervals of follow-up have ranged from a few months to two years. In reports from our center, we have stressed the heterogenous nature of GDM with respect to ethnic/racial influences on prevalence, genetic factors, and admixture of subjects at risk for NIDDM, maternal age, and anthropometric characteristics, including the degree of preservation of pancreatic β-cell function (12,13,19). We have suggested that such heterogeneity would contribute to variation in the observed prevalence of diabetes at early postpartum evaluation and in long-term follow-up after the appearance of GDM.

This study presents data from 5 years of longitudinal follow-up of subjects prospectively recruited and serially observed at one center. We have concentrated our efforts on the identification of characteristics present at the time of antepartum diagnosis of GDM, which may be predictive of the long-term risk for diabetes. Preliminary reports of some of the observations have appeared in abstract form (20).

RESEARCH DESIGN AND METHODS

— The systematic approach we have used for screening, diagnosing, and subclassifying GDM by level of FPG has been described previously (21–23). The screening and diagnostic criteria conform to the recommendations of NDDG (7) and the three International Workshop Conferences on GDM sponsored by the American Diabetes Association (8–10) with minor modifications. Subclassification of GDM according to level of fasting glucose was as follows: class A_1: FPG <105 mg/dl; class A_2: FPG 105–129 mg/dl; and class B_1: FPG ≥ 130 mg/dl (8,21). This study concerns glucose tolerance during the 5 yr after delivery of the pregnancy when GDM was diagnosed in 274 subjects (141 class A_1, 94 class A_2, and 39 class B_1). This represented >91% of the subjects who agreed to participate in postpartum follow-up at the time of diagnostic antepartum OGTT. They were prospectively enrolled in our program, and the course of glucose tolerance that has been documented by serial testing is related to metabolic, anthropometric, and genetic characteristics identified at the time of the antepartum diagnosis of GDM. Postpartum tests were performed at 3–6 mo (early), 1 yr, and annually. Test results subsequent to the diagnosis of diabetes are not analyzed in this study.

Phenotypic characteristics, which included weight (expressed as PIBW per Metropolitan Life Insurance Tables) (24), gestational age at diagnosis, maternal age, and parity obtained from medical records when available or from patient recall. For the purpose of our analysis, parity did not include the pregnancy during which GDM was diagnosed.

Metabolic studies

To facilitate comparison with antepartum tests, postpartum OGTTs were performed with 100 g of glucose. Results were considered diagnostic for diabetes when FPG was ≥140 mg/dl (7.8 mM) or when FPG was <140 mg/dl (7.8 mM) but plasma glucose concentrations at 2 h and at least one other intervening sample during the OGTT were ≥200 mg/dl (11.1 mM). IGT was considered present when FPG was <140 mg/dl (7.8mM) and when the plasma glucose value at 2 h was <200 mg/dl (11.1 mM), whereas an intervening plasma glucose value was ≥200mg/dl (11.1 mM). Subjects with plasma glucose values below those designated as IGT are defined as normal. However, it is acknowledged that their mean values might well exceed those of an unselected control population. Thus, we have used the same criteria for classification as those recommended by the NDDG for nonpregnant adults using a 75-g glucose load (7). Measurement of glucose, IRI, and FFA were performed as described previously (25).

Genetic markers

HLA-A, B, C, and DR typing was performed by the two-stage microcytotoxicity test (26) using 120 and 50 reagents to identify 41 HLA-A, B, C, and DR locus antigens, respectively. Insulin autoantibody measurements were kindly performed by J.S. Soeldner (Sacramento, CA), and the results will be reported in detail separately (B.E. Metzger, J.S. Soeldner, unpublished observations). Cytoplasmic islet cell antibodies were measured at the Scripps Immunology Reference Laboratory (La Jolla, CA). Pedigrees were constructed through a detailed standardized interview. Ascertainment of family history with respect to diabetes was confined to first-degree relatives. Diabetes was considered present among those individuals known to have received treatment with oral hypoglycemic drugs or insulin.

Statistical analysis

A test of normality was applied to all the study variables with a continuous value. Most of the variables were normally distributed in their original form; however, those not normally distributed were log transformed for analysis. The data were analyzed with the SPSS/PC + V4.0 (Chicago, IL) and BMDP/PC (1988 released version, Los Angeles, CA). Dichotomous variables were analyzed by χ^2 test with Yate's correction. Data are presented as means ± SD. The significance of differences among groups was evaluated by ANOVA and post-Hoc (Duncan's) test. $P < 0.05$ (two-tailed) was considered significant. A stepwise multiple logistic regression model (27) was used to evaluate the effects of several potentially confounding variables that have been reported to be associated with diabetes. The specific variables that emerged for

Table 1—*Demographic characteristics and fasting metabolic variables at diagnosis of GDM*

	GDM subgroups			
	A_1	A_2	B_1	*P* values
n	141	94	39	
Age (yr)	31.6 ± 6.2	32.4 ± 5.4	31.2 ± 5.9	NS
PIBW (%)	115.4 ± 24.1	139.0 ± 31.1*	151.6 ± 43.2*	<0.001
Parity (*n*)	1.4 ± 1.6	2.0 ± 1.8†	2.1 ± 2.5	<0.05
Gestational age (wk)	31.9 ± 3.7	28.2 ± 6.2*	22.1 ± 6.6*	<0.001
Glucose (mM)	5.36 ± 0.57	6.38 ± 0.57*	8.13 ± 1.21*	<0.001
IRI (pM)	114.0 ± 79.2	168.0 ± 102.6*	187.8 ± 126.6*	<0.001
FFA (mM)	0.706 ± 0.163	0.760 ± 0.120†	0.710 ± 0.116	0.053

Data are means ± SD. Maternal age is calculated at the time of OGTT; PIBW was ascertained from medical records or if not available, by patient recall; parity is based on obstetrical history before the index pregnancy; and gestational age refers to week of gestation that GDM was diagnosed by OGTT. FPG, IRI, and FFA (in 65% of the subjects) were obtained from basal samples drawn before the diagnostic OGTT. *P* values determined by ANOVA.

*$P < 0.001$ compared with A_1 subclass using Duncan's test.

†$P < 0.05$ compared with A_1 subclass using Duncan's test.

inclusion in the analysis of our data are indicated in the RESULTS. The life-table analysis method was used to estimate the incidence of diabetes (28).

RESULTS— Our GDM population consisted of 65 (23.7%) white, 85 (31.0%) black, 95 (34.7%) Hispanic, and 29 (10.6%) other (Oriental and mixed) subjects. Demographic and metabolic characteristics of the study population are summarized in Table 1. PIBW increased in parallel with the severity of antepartum glucose intolerance ($B_1 > A_2 > A_1$). Maternal age and parity were similar in the three subgroups. GDM was also diagnosed at an earlier stage of pregnancy in the more obese A_2 and B_1 subjects than A_1 subgroup. Some metabolic characteristics at GDM diagnosis are also shown in Table 1. FPG (by definition) and insulin levels were significantly different among the three groups and were also higher in the A_2 and B_1 subgroups (A_2, $P < 0.001$ and B_1, $P < 0.001$ than in the A_1 subgroup). Fasting FFA were higher in the A_2 subgroup ($P < 0.05$ vs. A_1) but not in B_1 subgroup.

Results of early postpartum (within 6 mo of delivery) evaluation of glucose tolerance are shown in Table 2. Of the subjects, 72% participated in early postpartum evaluations. A high prevalence of abnormal results was found in all groups. Some association was present between the severity of glucose intolerance at diagnosis of GDM and diabetes at early postpartum evaluation ($B_1 >$, $A_2 >, A_1$). IGT was also relatively common. Thus, only 65% of the subjects in subclasses A_1 and A_2 and 19% of those in the B_1 group were found to have normal glucose tolerance at early postpartum testing. Subjects in the B_1 group were recognized earlier in pregnancy in addition to the very high prevalence of abnormal outcomes they displayed at early postpartum testing. We have suggested previously that many in this group have unrecognized glucose intolerance before pregnancy (12). Furthermore, they represent only 5% of unselected subjects with GDM (22,23) as opposed to their more frequent appearance in this cohort (many of whom were referred to our center for management). For these several reasons, we have not included the B_1 subgroup in the analysis of follow-up beyond this early postpartum evaluation.

The 5-yr cumulative incidence of diabetes during follow-up of women after the diagnosis of classes A_1 or A_2 GDM is shown in Fig. 1. This is based on the life-table analysis involving all 235 subjects. About 25% were found to have diabetes within 1 yr and 5–6%/yr thereafter. Thus, after 5 yr of follow-up, ~50% of the subjects with A_1 or A_2 GDM had developed diabetes. At the time the diagnosis of diabetes was established by our follow-up tests, ~50% exhibited diagnostically elevated FPG

Table 2—*Early postpartum glucose tolerance in women with GDM*

	Results of glucose tolerance test		
	Normal (*n* [%])	IGT (*n* [%])	Diabetes (*n* [%])
Subgroups			
A_1	64 (68.1)	20 (21.3)	10 (10.6)
A_2	44 (60.3)	12 (16.4)	17 (23.3)
B_1	6 (19.4)	2 (6.5)	23 (74.2)

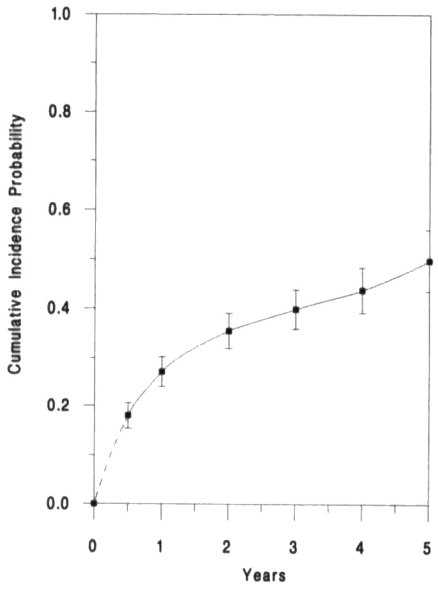

Figure 1—*Cumulative incidence of diabetes mellitus by life-table analysis during 5-yr follow-up after diagnosis of GDM (subclasses A_1 and A_2). Values plotted (■) represent means ± SE for results at 0.5, 1, 2, 3, 4, and 5 yr of follow-up.*

(≥140 mg/dl [7.8 mM]) (7,11). None admitted to symptoms of decompensated diabetes, and only 2% had received treatment with pharmacological agents (oral sulfonylurea). At the last follow-up before their 5-yr postpartum anniversary, on average ~2.5 yr after diagnosis 12.5% were receiving pharmacological treatment (33% insulin, 67% oral sulfonylurea drugs). None displayed typical IDDM clinical characteristics.

We examined potential associations between genetic or phenotypic characteristics of the subjects identified at the time of diagnosis of GDM and the propensity to have diabetes at early postpartum testing or during the subsequent follow-up period. The Hispanic subjects exhibited the highest prevalence of diabetes after GDM. At the early postpartum evaluation, the prevalence in Hispanics (24%) was significantly higher ($P < 0.05$) than among blacks (8%). However, racial/ethnic origin was not independently associated with outcome in the multiple logistic analysis (see below). The presence of maternal HLA antigens DR3, DR4, or both DR3 and DR4 (105 cases) was not associated with more frequent or severe glucose intolerance during the 5-yr follow-up than in the 59 cases that were HLA DR3 and DR4 negative. The prevalence of islet cell antibodies was <2% in this cohort of subjects with subclass A_1 or A_2 GDM (0/71 A_1; 2/55 A_2). Insulin autoantibodies were undectable in all 71 subclass A_1 and A_2 subjects examined. Thus, the markers commonly used to identify subjects at risk for IDDM were not of value in predicting the long-range course of glucose tolerance after GDM in this cohort. However, interesting associations were found regarding family history of diabetes. First, in our total cohort a significantly higher frequency of a family history of diabetes was observed in only the mother compared with only the father (51 of 217 [23.5%] vs. 29 of 217 [13.4%]; $P < 0.01$). This confirms the earlier report of Martin et al. (29). The overall prevalence of a history of diabetes among first-degree relatives of women with GDM was not much different in those who developed diabetes (42 of 81 [52%]) compared with those whose glucose tolerance remained normal (37 of 82 [45%]; $P > 0.1$) during 5 yr of follow-up. However, among those who had diabetes within 5 yr, a family history of maternal only diabetes was nearly threefold more common than a paternal only history of diabetes (24 of 81 [30%] vs. 9 of 81 [11%]; $P < 0.01$).

Maternal age and parity (Table 3) were not different among subjects whose glucose tolerance remained normal or was abnormal at early postpartum testing or became abnormal between 6 mo and 5 yr follow-up. Earlier time of gestation at diagnosis of GDM was associated with diabetes during the 5-yr follow-up ($r = -0.14$; $P = 0.04$). However, this did not make an independent contribution in the logistic regression analysis (see below). The patterns differed regarding weight. Those who manifested early postpartum diabetes had significantly lower PIBW than those with normal early postpartum glucose tolerance (Table 3). On the other hand, those who developed diabetes subsequently during the 5-yr follow-up were heavier than those whose glucose tolerance remained normal or impaired (Table 3).

Figure 2 illustrates the antepartum OGTT values for glucose and insulin with the subjects grouped according to their early postpartum classification (Table 3). FPG was nearly identical in the three groups, and plasma glucose did not differ acutely (15 and 30 min) following the oral glucose load. However, the peak response (60 min) was higher in those who displayed diabetes in early postpartum testing, and the hyperglycemia was more prolonged; plasma glucose remained significantly higher at 120 and 180 min. Mean 2-h plasma glucose was 218 mg/dl (12.1 mM) in those with early postpartum diabetes compared with 194 mg/dl (10.8 mM) in those whose early postpartum results were normal. Using a 2-h antepartum OGTT value of ≥200 mg/dl (11.1 mM), the odds ratio for early postpartum diabetes was 2.2 (95% CI = 1.02 − 4.8; $P < 0.05$) compared with those whose 2-h value was <200 mg/dl (11.1 mM). The subjects destined to manifest early postpartum diabetes were relatively insulinopenic throughout (Fig. 2), with antepartum values for fasting, acute response to oral glucose (15 and 30 min) and integrated 3-h response all significantly lower ($P < 0.01$) than in those who remained normal or had IGT at early postpartum testing. The total integrated insulin areas were 160.9 ± 94.9, 135.6 ± 60.6, and 116.0 ± 91.7 ($\times 10^3$) pM · min in normal, IGT, and diabetic subjects.

The associations between antepartum glucose tolerance at diagnosis of GDM and the development of diabetes later during the 5-yr follow-up are shown in Fig. 3. Subjects are grouped, as in Table 3, and those with diabetes at early postpartum testing are excluded. In

Table 3—*Antepartum phenotypic characteristics of GDM women*

	Classification of glucose tolerance			
	Normal	IGT	Diabetic	*P* value
Early postpartum				
n	108	32	37	NS
Age (yr)	31.7 ± 6.0	32.0 ± 5.6	33.0 ± 4.9	NS
PIBW (%)	129.4 ± 32.2	123.6 ± 30.2	119.7 ± 19.5*	NS
Parity (*n*)	1.5 ± 1.6	1.5 ± 1.2	1.7 ± 1.9	NS
After 5-yr follow-up*				
n	91	33	48	
Age (yr)	31.4 ± 5.8	31.7 ± 6.7	32.3 ± 6.6	NS
PIBW (%)	124.4 ± 33.6	119.3 ± 25.7	135.4 ± 26.3†	0.06
Parity (*n*)	1.6 ± 1.7	1.3 ± 1.5	2.1 ± 1.9	NS

Data are means ± SD. *P* values determined by ANOVA. Maternal age, PIBW are as defined in Table 1. These antepartum variables are described for subjects followed beyond the early postpartum study through 5 yr postpartum. Their classification is based on the last study performed 5 yr postpartum.
*Diabetic subjects at early postpartum evaluation were excluded from the analysis of outcome at 5 yr.
†$P < 0.05$ compared to normal glucose tolerance group using Duncan's test.

contrast to the early postpartum results, the degree of hyperglycemia at diagnosis of GDM showed no relationship to late development of diabetes (i.e., ≥6 mo-5 yr postpartum). However, as with the early postpartum findings, those at risk for later development of diabetes had lower fasting, acutely stimulated (15 and 30 min), and chronically stimulated (1-h, 2-h, 3-h, and integrated) insulin than those who remained normal or displayed IGT at 5 yr.

As indicated in Table 3, those who developed diabetes during long-term follow-up were more obese before the index pregnancy. We also examined the relationship between changing weight and glucose tolerance during follow-up. Weight was relatively stable over the 5-yr observation period in all groups. The change in PIBW between early postpartum testing and the time of diagnosis of IGT or diabetes did not differ from the weight change in those who remained normal (2.4 ± 6.0 vs. 0.72 ± 6.2%, $P > 0.1$).

To identify which antepartum demographic, phenotypic, and metabolic variables related with glucose tolerance status at ≤6 mo and 5 yr postpartum testing, we performed multiple logistic

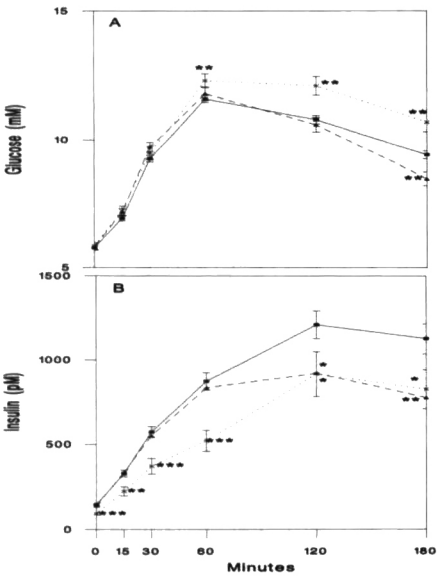

Figure 2—*Antepartum GTTs in GDM subjects (subclasses A_1 and A_2) grouped according to their early postpartum classification. Indicated are plasma glucose (A) and plasma insulin concentrations (B). Values are antepartum OGTT results in subjects who were classified as normal (■——■), IGT (▲----▲), and diabetic (– – –×– – –) at early postpartum evaluation. Values plotted represent means ± SE. *, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$ compared with the normal early postpartum glucose tolerance group by Duncan's test.*

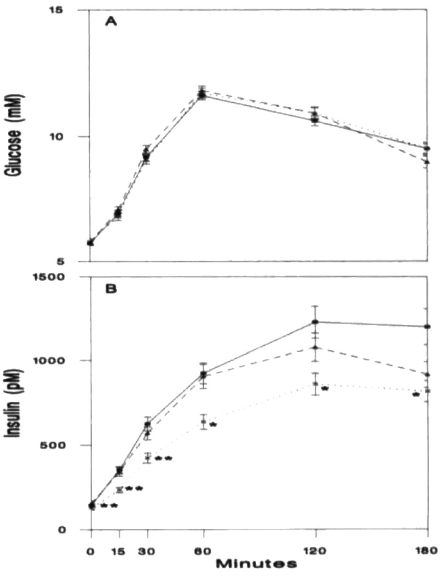

Figure 3—*Antepartum GTTs in GDM subjects (subclasses A_1 and A_2) grouped according to their classification at 5-yr follow-up (diabetes subjects at early postpartum evaluation are excluded). Indicated are plasma glucose (A) and plasma insulin (B) concentrations. Values are antepartum OGTT results in subjects who were classified as normal (■——■), IGT (▲----▲), and diabetic (– – –×– – –) at 5-yr follow-up. Values plotted represent means ± SE. *, $P < 0.05$; and **, $P < 0.01$ compared with the normal glucose tolerance group at 5-yr follow-up by Duncan's test.*

Table 4—*Stepwise multiple logistic regression model for postpartum diabetes*

Variable	Coefficient	SE	P value
Glucose tolerance status early			
2-h glucose	0.028	0.008	<0.001
Basal IRI	−3.95	0.998	<0.0001
Stimulated IRI	−1.25	0.699	0.07
Glucose tolerance status at 5 yr			
PIBW ≥120	1.04	0.43	<0.001
Parity	0.193	0.114	0.09
Integrated IRI	-6.2×10^{-5}	2.03×10^{-5}	<0.01

The process used for the selection of the variables to be included in the model is described in the text. Those represented in the analysis of association with glucose tolerance status at 5 years are ethnicity, maternal age, family history of diabetes, parity, obesity (PIBW ≥120), basal glucose, basal insulin, 2-h glucose, 3-h total integrated insulin, and 30-min stimulated insulin secretion from the antepartum diagnostic OGTT. The table lists those variables that remained in the model indicating independent association with 5-yr postpartum development of diabetes mellitus. Subjects with diabetes at early postpartum evaluation were excluded from the analysis of association with outcome at 5 yr.

regression analyses (Table 4). Inclusion variables for the multivariate analysis, however, were preselected because some of the study variables (demographic, phenotypic, and metabolic) were highly intercorrelated (e.g., insulin and glucose values at various times during the OGTT). The preselection was made by using Pearson correlation method. The representative variables among highly intercorrelated indexes (e.g., insulin and glucose) were selected on the basis of the degree of correlation with the dependent variable (glucose tolerance status). As shown in Table 4, hyperglycemia (2-h glucose) and impaired overall insulin secretion (basal IRI) are each strongly associated with the risk of early postpartum diabetes. In addition, impaired acute insulin response (stimulated IRI) remained in the model with a marginal association ($P = 0.07$), suggesting that this characteristic of β-cell function is in some degree also associated with early development of diabetes. The antepartum variables that are related to the development of diabetes subsequent to early postpartum testing are indicated in Table 4. Maternal obesity and impaired insulin secretion (as reflected in total integrated insulin response over 3 h) were found to contribute to the risk of developing diabetes during the later interval of follow-up in those not diabetic at early testing. Maternal weight and parity are highly inter-related but we cannot fully exclude a small independent effect of parity.

CONCLUSIONS— This study is based on prospective, longitudinal follow-up of GDM women in whom the antepartum screening, diagnostic procedures and criteria, and postpartum follow-up testing followed the recommendations of the three workshop conferences on GDM (8–10) with minor modifications. To facilitate comparison with antepartum tests, postpartum OGTTs were performed with 100 g of glucose. In normal subjects, peak plasma glucose concentrations and their return toward baseline over 2 h are very similar with 75- and 100-g oral glucose loads (30); whereas, postchallenge insulin secretion increases substantially in proportion to the glucose load. We have confirmed these findings in a group of 22 nonpregnant women of childbearing age (data not shown). By contrast, subjects with abnormal glucose tolerance may have more hyperglycemia as a function of glucose dose. Thus, the relative proportion of cases designated as IGT may have been higher and that of diabetes somewhat lower if a 75-g oral glucose load had been administered postpartum. However, the glucose load used to evaluate oral glucose tolerance should not affect the identification of other factors that influence glucose tolerance.

The early postpartum results in this larger cohort confirm and extend our earlier findings (12,13). Thus, a substantial portion of each subclass of GDM displayed early postpartum diabetes. The figure was nearly 75% in those with diagnostic elevations of FPG at discovery of GDM (Class B_1), and they were not considered in the overall 5-yr analysis or in the multiple logistic regression analyses. The 235 subjects in the A_1 and A_2 subclass were heterogeneous with respect to racial/ethnic mix, maternal age, obesity, family history of diabetes, and gestational age at diagnosis. In initial univariate analyses, some of these characteristics were associated with diabetes at early postpartum testing (e.g., higher prevalence in Hispanic subjects, those with a family history of diabetes in only the mother, and early gestational age at diagnosis). Severity of antepartum glucose intolerance and impaired islet function (basal, acute, and integrated insulin secretion) were also associated with early postpartum glucose intolerance; obesity was not. However, when the logistic regression model was applied, only the severity of antepartum glucose intolerance (as represented by the 2-h plasma glucose concentration in the diagnostic OGTT) and impaired β-cell function (basal IRI and 30 min IRI concentration in the diagnostic OGTT) emerged as independent factors related to the presence of early postpartum diabetes. Thus, some of the other heterogeneous characteristics we (12,13,19) and others (15–18) have observed in GDM at risk for early postpartum glucose intolerance are likely mediated by one or the other of these independent associations.

Two characteristics were also associated with the risk of developing diabetes during the extended follow-up (up

to 5 years) after the early postpartum evaluation. These were obesity (expressed as PIBW before the index pregnancy) and once again, impaired insulin secretion during the antepartum OGTT (represented in the logistic regression as integrated insulin response). We are not certain why the factors that contribute independently to the risk of diabetes after GDM differ at early postpartum testing and subsequently. However, we suggest that those with the most severe glucose intolerance and relative insulin deficiency need no additional factors to show glucose intolerance postpartum. Indeed, it is tempting to speculate that some of them may have had glucose intolerance antedating the pregnancy (12,13,31). The importance of obesity was recognized in O'Sullivan's early reports (3,32,33) and by others in more recent reports (5,6,17,34). This association is reminiscent of the close relationship between obesity and NIDDM in the population at large.

The relative contribution of primary defects in insulin action vis-à-vis primary defects in β-cell function to the pathogenesis of NIDDM is controversial (35). We have reported previously that 66–75% of women with GDM, when confronted with the insulin resistance of late gestation, exhibit impaired acute β-cell function relative to that of normal pregnant control subjects (a majority also have reduced total insulin responses to glycemic challenge) (36,37). Others have observed defects in β-cell function and insulin resistance in some women with normal glucose tolerance after GDM (38–40). The data from this study and our earlier reports (12,20) suggest that impaired β-cell function at diagnosis of GDM is an important indicator of postpartum diabetes at both early and late follow-up. Damm et al. (41) also reported recently that relative insulinopenia during OGTT in late pregnancy is an independent predicitive factor for diabetes 2–11 yr after GDM in Danish women. Together, these observations strongly suggest that limitation in β-cell function may appear early in the natural history of evolving glucose intolerance in women who have had GDM and in such cases is not simply a late manifestation of sustained hyperglycemia.

Our findings may carry other implications regarding the development of NIDDM in women with prior GDM. The women in our cohort showed little weight change during the follow-up period after GDM. Thus, an effort to limit or reverse the obesity-dependent risk for developing diabetes would have to entail achieving and presumably maintaining weight reduction, not simply preventing further weight gain. The presence of both major risk factors, insulin resistance (represented by obesity) and impaired β-cell function (GDM subjects with integrated insulin response in the lowest tertile), conveyed a particularly high risk for later diabetes development (RR 8.0). These relationships suggest that studies attempting to prevent diabetes development in this high-risk group should examine strategies that will maintain both optimal β-cell function and maximal insulin sensitivity.

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