Antepartum Predictors of the Development of Type 2 Diabetes in Latino Women 11–26 Months After Pregnancies Complicated by Gestational Diabetes

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In this study, we sought to identify antepartum characteristics that predict the de novo development of diabetes 11–26 months after the index pregnancy in a carefully characterized cohort of women with gestational diabetes mellitus (GDM). Oral and frequently sampled intravenous glucose tolerance tests (OGTTs and FSIGTs), hyperinsulinemic-euglycemic clamps with labeled glucose, and body composition studies were performed on 91 islet cell antibody–negative Latino women with GDM during the third trimester of pregnancy. The women were documented to be diabetes-free within 6 months postpartum. Their diabetes status was ascertained again between 11 and 26 months postpartum. Logistic regression analysis was used to identify independent predictors of the development of diabetes within that interval. Fourteen of the women developed diabetes by World Health Organization criteria 11–26 months after delivery of the index pregnancy. Three antepartum variables were independent predictors of diabetes: the 1-h postchallenge plasma glucose concentration from the 100-g OGTT at which GDM was diagnosed (higher = increased risk; P = 0.003); an index of pancreatic β-cell compensation for insulin resistance, defined as the product of the 30-min incremental plasma insulin:glucose ratio on a 75-g OGTT and the insulin sensitivity index from a hyperinsulinemic-euglycemic clamp (lower = increased risk, P = 0.009); and the basal glucose production rate after an overnight fast (higher = increased risk; P = 0.04). We conclude that postchallenge hyperglycemia, poor pancreatic β-cell compensation for insulin resistance, and elevated endogenous glucose production during pregnancy precede the development of type 2 diabetes in young Latino women by at least 1–2 years. *Diabetes* 48:2430–2436, 1999

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AUC, area under the curve; FFA, free fatty acid; FSIGT, frequently sampled intravenous glucose tolerance test; GDM, gestational diabetes mellitus; ICA, islet cell antibody; OGTT, oral glucose tolerance test; S_G, glucose effectiveness; S_I, insulin sensitivity index.

People with type 2 diabetes generally have three metabolic abnormalities that contribute to their hyperglycemia: insulin resistance, impaired pancreatic β-cell function, and elevated basal glucose production (1–3). The precise order in which these abnormalities develop is not clear. Longitudinal studies of people at risk for type 2 diabetes indicate that insulin resistance is often present long before the development of diabetes (4–6). Poor β-cell function is often reported as a later defect (1,7), although recent prospective studies indicate that poor β-cell function in nondiabetic individuals is predictive of diabetes (5,6,8,9). Cross-sectional studies of glucose production in individuals with a wide range of fasting glycemia levels have yielded conflicting results. Some investigators have reported that elevations in endogenous glucose production occur late in the development of type 2 diabetes, only in association with overt fasting hyperglycemia (10–12). Others have reported direct relationships between fasting glucose and basal glucose production rates in patients with mild type 2 diabetes (13,14). To date, there is very little information from longitudinal studies regarding the timing of elevated glucose production in the development of type 2 diabetes.

We are currently conducting a longitudinal study of Latino women with gestational diabetes mellitus (GDM), a condition that imparts a high risk of diabetes (15–19). The investigation is focused on measures of insulin sensitivity, pancreatic β-cell function, endogenous glucose production, and body composition during pregnancy and at regular intervals thereafter. We found that women in the cohort in the third trimester of pregnancy had markedly reduced insulin secretion, mildly elevated basal glucose production, and mild hepatic and peripheral insulin resistance compared with normal pregnant women (20). We also found that postchallenge hyperglycemia and poor β-cell function in the third trimester predicted the persistence of diabetes within 6 months postpartum (21). In this report, we describe antepartum characteristics that predict the de novo development of type 2 diabetes 11–26 months after delivery in women who did not have diabetes within 6 months postpartum.

RESEARCH DESIGN AND METHODS

Subjects. Subjects for the present report were selected from a cohort of 150 islet cell antibody (ICA)-negative women participating in a longitudinal study of the pathogenesis of type 2 diabetes after GDM. Selection of the original cohort has

been described in detail (20,21). Briefly, all Latino women referred to Los Angeles County Women's Hospital for management of GDM between August 1993 and March 1995 were asked to participate if they met all of the following criteria: *1*) gestational age between 28 and 34 weeks, *2*) no current or prior insulin therapy, *3*) all fasting serum glucose concentrations <7.2 mmol/l since diagnosis of GDM, *4*) otherwise uncomplicated singleton pregnancy, and *5*) both parents and at least three of four grandparents from Mexico, Guatemala, or El Salvador. All women participated in detailed metabolic testing (below) during the third trimester and were asked to return for glucose tolerance testing within 6 months, then at 15-month intervals after the index pregnancy. Twelve of 122 women who returned within 6 months had persistent diabetes (21) and were excluded from this analysis. Diabetes status of an additional 19 women could not be ascertained between 11 and 26 months postpartum. Data are presented from the 91 women who did not have diabetes within 6 months postpartum (47 had impaired glucose tolerance, 44 had normal tolerance) and whose diabetes status was ascertained between 11 and 26 months (median 15.4 months) after delivery. All subjects gave written, informed consent for participation in the study, which was approved by the Institutional Review Board of the University of Southern California.

Testing protocol. After at least 3 days on a diet that provided ≥150 g of carbohydrate per day, pregnant women came to the General Clinical Research Center after an 8- to 12-h overnight fast on 3 separate days at least 48 h apart.

On one of the three study days, an oral glucose tolerance test ("study OGTT" to distinguish it from the 100-g OGTT used to diagnose GDM) was performed starting between 0700 and 1000. After measurement of height, weight, and triceps and subscapular skinfold thicknesses, patients drank 10 g of D_2O followed 5 min later by 75 g D-glucose. Blood was obtained from an antecubital venous catheter before and 15, 30, 60, 90, 120, and 180 min after the glucose ingestion and placed on ice, and plasma was separated within 20 min and stored at –70°C.

On a second day, a glucose clamp was performed starting between 0600 and 0630. A primed (0.0312 mmol/kg body weight), continuous (2.5×10^{-4} mmol · $min^{-1} \cdot kg^{-1}$) infusion of [6,6-$^2H_2$]D-glucose (tracer) was administered through an antecubital vein for 360 min, using a protocol developed specifically for measurement of glucose turnover in women with GDM (22). A nonprimed infusion of crystalline human insulin (50 mU · $min^{-1} \cdot m^{-2}$ body surface area) was administered during the final 180 min of the tracer infusion. Dextrose containing dideutero-glucose (0.021 mol/l) to minimize changes in plasma tracer enrichment (23) was given at a rate sufficient to maintain arterialized venous plasma glucose at ~4.9 mmol/l during the insulin infusion. Blood for measurement of tracer, hormone, and metabolite concentrations was drawn into ice-cold tubes at –90, –50, –30, and –10 min (basal period) and 160 and 180 min (steady-state period) relative to the start of the insulin infusion. Plasma was separated within 20 min and stored at –70°C.

On a third day, a frequently sampled intravenous glucose tolerance test (FSIGT) was performed starting between 0700 and 1000. Dextrose (300 mg/kg) was injected over 1 min, followed 20 min later by a 5-min infusion of crystalline human insulin (0.03 U/kg). Arterialized venous blood was drawn into iced tubes before (n = 2) and for 240 min after (n = 32) the dextrose injection. Plasma was separated within 20 min and stored at –70°C.

During follow-up, nonpregnant women had a 75-g OGTT after an overnight fast and 3 days on a regular diet. Results were interpreted according to World Health Organization criteria (24).

Laboratory analysis. Glucose was measured by glucose oxidase (Glucose Analyzer II; Beckman, Brea, CA). Insulin was measured by a radioimmunoassay (Novo Pharmaceuticals, Danbury, CT) that measured insulin and proinsulin. C-peptide and glucagon were measured by radioimmunoassay (Linco Research, St. Charles, MO). [6,6-$^2H_2$]Glucose (25) and D_2O plasma enrichment were determined by isotope ratio mass spectrometry. Plasma ICAs were measured in the laboratory of Dr. Jerry Palmer (University of Washington, Seattle, WA) using indirect immunofluorescence with an assay detection limit of 1 JDF unit.

Data analysis. Lean body mass in pregnant women was calculated as total body water/0.76 (26), using the apparent volume of dilution of D_2O as total body water. Percent body fat was calculated as [(total weight – lean weight)/(total weight)] × 100.

Areas under OGTT glucose and insulin curves (AUCs) were calculated by the trapezoid method. Glucose turnover rates during euglycemic clamps were calculated by the Steele equation for non–steady-state conditions, as modified by Finegood et al. (23). FSIGT results were analyzed using the minimal model (MINMOD) program provided by Dr. Richard Bergman (27). The acute insulin response to intravenous glucose was calculated as the incremental area under the insulin curve during the first 10 min of FSIGTs.

Potential predictors of diabetes were compared between groups with and without diabetes by nonpaired t tests or χ^2 analysis. Multivariate logistic regression analysis was performed in three steps to identify independent predictors of diabetes. In model 1, forward stepwise regression was used to select independent predictors with adjusted P values <0.10. All of the variables listed in Tables 1 and 2 were used, plus, from the 75-g study OGTT, the fasting glucose and insulin concentrations, the incremental glucose and insulin AUCs, and the incremental plasma insulin:glucose ratios for the first 60 min. In model 2, plasma glucose concentrations from individual time points of the diagnostic and study OGTTs and insulin concentrations from the study OGTT were added one at a time to model 1. If any addition caused a significant change in the model, combinations of these variables were examined, and the model with the highest overall χ^2 that included variables with $P < 0.10$ was selected. Then all previously rejected variables were reevaluated to see if they changed the model significantly. Finally, in model 3, because β-cell function normally varies reciprocally with insulin resistance (28–30), we evaluated four measures of β-cell compensation for insulin resistance by adding them one at a time to model 2: the product of the FSIGT acute insulin response and either the minimal model insulin sensitivity index (S_I) or the clamp insulin sensitivity index, and the product of the OGTT 30-min insulin:glucose ratio and either minimal model S_I or the clamp sensitivity index. All previously rejected variables were then re-examined to determine whether they changed the model.

Statistical analyses were performed using SAS (SAS Institute, Cary, NC) and Epilog Plus (Epicenter Software, Pasadena, CA). Variables that were not normally distributed were log-transformed before analysis. Arithmetic means (± SD in text and ± SE in the figure) are reported for all variables in units of their original scales. All P values are two-sided.

RESULTS

Fourteen women who did not have diabetes within 6 months postpartum developed diabetes 11–26 months postpartum. These 14 women were similar to the 77 nondiabetic women with regard to many clinical variables (Table 1). Clinical variables that were significantly different between groups were the plasma glucose concentration from the 50-g glucose screening test for GDM, the incremental glucose area on the diagnostic OGTT, and weight gained from the initial postpartum visit to the final follow-up visit. When individual glucose values from the diagnostic OGTT were considered, only the 1-h value was higher in the group that developed diabetes (P = 0.0001).

Plasma glucose concentrations from the study OGTT (Fig. 1) were higher at all time points in the women who developed diabetes, although differences were statistically significant only at 120 and 180 min. Despite their higher glucose concentrations, women who developed diabetes had lower plasma insulin concentrations during the first 90 min after the antepartum glucose ingestion; values were significantly lower at 30, 60, and 90 min. Incremental plasma insulin:glucose ratios were reduced at 15 min (P = 0.02), 30 min (Fig. 1), and 60 min (P = 0.006) in the women who developed diabetes.

On the day of antepartum glucose clamps (Table 2), basal plasma glucose concentrations were significantly higher in the women who developed diabetes. Basal plasma immunoreactive insulin, C-peptide, glucagon, and free fatty acid (FFA) concentrations did not differ significantly between groups. Basal glucose production was higher in the prediabetic group, although the difference was of borderline statistical significance (P = 0.06). Basal glucose clearance rates were nearly identical in the two groups. There was a direct relationship between basal plasma glucose levels and basal glucose production rates in the cohort overall (r = 0.46, P = 0.0001). Insulin infusions raised plasma insulin concentrations by similar amounts (468 ± 60 vs. 456 ± 108 pmol/l, P = 0.61) and to similar levels (Table 2) in women who did and did not develop diabetes, respectively. Steady-state glucose production and clearance rates and plasma FFA concentrations did not differ significantly between groups. Likewise, changes from basal to steady state in glucose production (–0.347 ± 0.086 vs. –0.330 ± 0.066 mmol · $min^{-1} \cdot m^{-2}$, P = 0.40) and clearance (58 ± 27 vs. 66 ± 28 l · $min^{-1} \cdot m^{-2}$, P = 0.32) did not differ significantly between groups. Suppression of plasma FFAs (–214 ± 88 vs. –277 ± 113 μmol/l) tended to be less in the women who developed diabetes (P = 0.06).

TABLE 1
Comparison of clinical characteristics between women who did and women who did not develop type 2 diabetes 11–26 months after pregnancies complicated by GDM

	Diabetes 11–26 months postpartum		
	Yes	No	*P* value
n	14	77	—
Prepregnancy			
BMI (kg/m^2)	29.9 ± 6.4	29.4 ± 4.5	0.76
Antepartum			
Plasma glucose (1-h) at screening (mmol/l)*	10.3 ± 2.9	8.9 ± 1.6	0.01
Gestational age at diagnosis of GDM (weeks)	25.6 ± 7.4	25.9 ± 6.9	0.87
Fasting plasma glucose, diagnostic OGTT (mmol/l)†	6.1 ± 0.6	5.9 ± 0.4	0.17
Incremental glucose area, diagnostic OGTT (min · mol^{-1} · l^{-1})†	0.74 ± 0.20	0.62 ± 0.16	0.02
Age at study entry (years)‡	29.6 ± 5.6	30.3 ± 5.5	0.63
Gestational age at study entry (weeks)‡	33.2 ± 2.4	32.6 ± 2.6	0.45
Weight gain from prepregnancy (kg)‡	9.5 ± 3.7	7.8 ± 4.5	0.21
Systolic blood pressure (mmHg)‡	107 ± 10	107 ± 10	0.92
Diastolic blood pressure (mmHg)‡	63 ± 7	63 ± 7	0.89
Body fat (%)‡	32.7 ± 7.9	34.6 ± 6.7	0.36
Subscapular:triceps skinfold thickness ratio‡	1.36 ± 0.38	1.34 ± 0.26	0.78
At final follow-up visit§			
BMI (kg/m^2)	31.9 ± 4.7	31.3 ± 4.9	0.69
Weight change from initial postpartum weight (kg)‖	4.3 ± 3.0	2.0 ± 5.1	0.04
Breast-feeding (%)	25.0	15.4	0.41

Data are means ± SD. *P* values were determined by nonpaired *t* test or χ^2 analysis. *A 50-g glucose challenge was used to screen for GDM during the index pregnancy. †A 100-g OGTT was used to diagnose GDM. ‡Values at the time of initial 75-g study OGTT performed in the Clinical Research Center. §Values at the time of final OGTT when diabetes status was determined. ‖Calculated as follows: (weight at last follow-up visit) – (weight at initial postpartum visit when diabetes was excluded).

Antepartum FSIGTs (Table 2) revealed a lower acute insulin response to glucose in the women who developed diabetes. Minimal model measures of S_I and glucose effectiveness (S_G) were similar in the two groups. Each of the four measures of β-cell compensation for insulin resistance (products of insulin release during OGTT or FSIGT and insulin sensitivity measured by clamp or FSIGT) was lower in women who developed diabetes than in women who did not (Table 3).

Initial stepwise regression analysis performed by using all variables in Tables 1 and 2 yielded five independent predictors of diabetes (model 1, Table 4) that reflected an association of diabetes at 11–26 months with antepartum glucose intolerance, poor β-cell function, basal glucose overproduction, and clamp insulin resistance. When individual glucose and insulin values from the OGTTs were used (model 2, Table 4), the 1-h glucose value from the diagnostic OGTT replaced the glucose AUC and the FSIGT acute insulin response. The addition of the four measures of β-cell compensation for insulin resistance to model 2 yielded a final predictive model (model 3, Table 4) in which the product of the OGTT 30-min insulin:glucose ratio and the clamp S_I replaced these two individual variables. The 1-h plasma glucose on the diagnostic OGTT and the basal glucose production rate remained significant predictors of diabetes in this model.

DISCUSSION

By studying high-risk Latino women who were proven not to have diabetes within 6 months after pregnancies complicated by GDM, we identified metabolic defects that were present during pregnancy and at least 1–2 years before the onset of type 2 diabetes. In keeping with prior reports from cohorts that were characterized in less detail, we found that the degree of hyperglycemia (8,9,19,31–35) and the severity of pancreatic β-cell dysfunction (8,9) during late pregnancy were independently predictive of diabetes after GDM. Those characteristics were also predictive of the persistence of diabetes within 6 months after pregnancy in the cohort from which women in the present analysis were derived (21). However, unlike prior studies in women with GDM or other high-risk groups, we found that basal glucose production in late pregnancy was elevated in women who were destined to develop diabetes 11–26 months later, and more importantly, that glucose overproduction was an independent predictor of diabetes. This novel finding and our prior observation (20) that glucose production is elevated in pregnant women with GDM compared with normal pregnant women indicate that endogenous glucose overproduction is present before the onset of type 2 diabetes in young, high-risk Latino women. The abnormality is likely to reflect dysregulation of gluconeogenesis (36,37) and could represent either hepatic or renal glucose overproduction after the 10–12 h overnight fast employed in this study (38).

Our conclusions from this prospective study differ from some cross-sectional studies (11–13) that have suggested elevated basal glucose production occurs relatively late in the course of type 2 diabetes. It is important to note that the method used to measure basal glucose production in this study was developed specifically for women with GDM over the range of fasting glycemia encountered in this cohort. The bolus:infusion ratio and basal blood sampling schedule were based on kinetic analysis of data from 12-h tracer infusions in five pregnant Latino women with GDM, as published previously (22). This approach allowed us to detect basal glucose

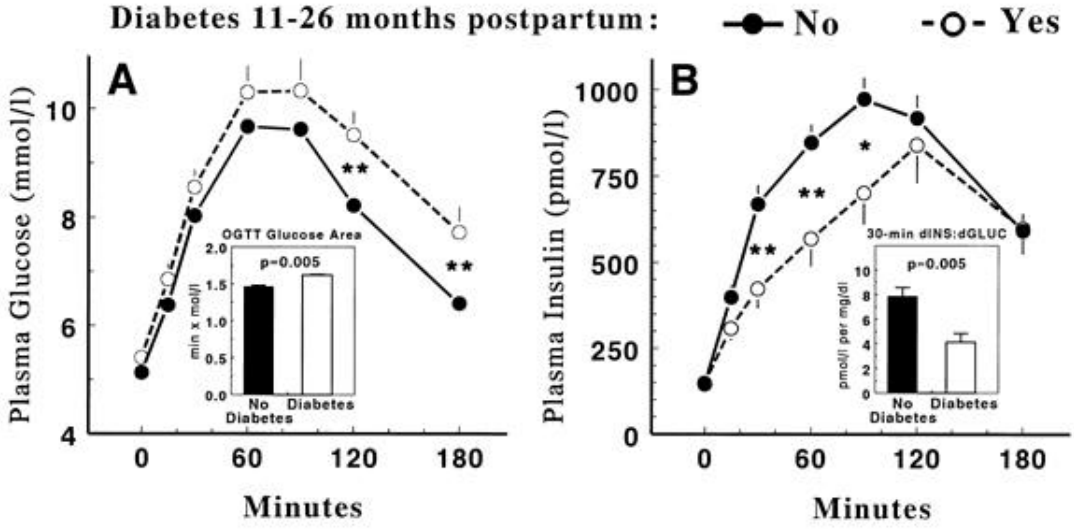

FIG. 1. Plasma glucose (*A*) and insulin (*B*) concentrations during the third trimester of pregnancy in women with GDM who did or did not develop diabetes 11–26 months after the index pregnancy. Inserts depict total glucose area (*A*) and incremental plasma insulin:glucose ratio at 30 min (*B*) during OGTTs. **P* ≤ 0.05, ***P* ≤ 0.02 between groups. Diabetes 11–26 months postpartum: ●, no; ○, yes.

production that was elevated an average of 7.9% in prediabetic women. This increase was approximately the same magnitude as their increase in fasting glucose on the day of clamps (7.2%), when the duration of fasting was carefully controlled in all subjects. Because the duration of fasting alters glucose concentrations in late pregnancy (39,40), the basal data from the clamps provided the most reliable measures of fasting glycemia for comparison among women in the cohort. Analysis of those data revealed a direct correlation between basal glucose concentrations and basal glucose production rates despite the relatively narrow range of fasting glycemia in the cohort (4.4–6.9 mmol/l). These findings, combined with the

TABLE 2
Comparison of glucose clamp and FSIGT results between women who did and women who did not develop type 2 diabetes 11–26 months after pregnancies complicated by GDM

	Diabetes 11–26 months postpartum		
	Yes	No	*P* value
n	14	77	
Hyperinsulinemic-euglycemic clamp			
Basal			
Plasma glucose (mmol/l)	5.8 ± 0.7	5.4 ± 0.4	0.008
Plasma insulin (pmol/l)	165.6 ± 61.2	150.6 ± 105	0.21
Plasma C-peptide (ng/ml)	2.37 ± 0.39	2.27 ± 0.50	0.48
Plasma glucagon (pg/ml)	38.4 ± 6.0	35.5 ± 9.6	0.32
Plasma FFAs (μmol/l)	417 ± 119	453 ± 119	0.31
Glucose production (mmol · min^{-1} · m^{-2})	0.534 ± 0.077	0.495 ± 0.070	0.06
Glucose clearance (ml · min^{-1} · m^{-2})	98 ± 12	97 ± 12	0.74
Steady state			
Plasma glucose (mmol/l)	4.9 ± 0.2	4.8 ± 0.1	0.40
Plasma insulin (pmol/l)	636 ± 132	606 ± 156	0.40
FFAs (μmol/l)	202 ± 98	174 ± 70	0.21
Glucose production (mmol · min^{-1} · m^{-2})	0.187 ± 0.098	0.165 ± 0.065	0.43
Glucose clearance (ml · min^{-1} · m^{-2})	156 ± 30	163 ± 30	0.42
S_I (mmol · min^{-1} · m^{-2} per μU/ml × 10^3)	7.13 ± 3.42	8.04 ± 2.71	0.20
FSIGT			
Acute insulin response (mmol · l^{-1} · min^{-1})*	3,030 ± 2,502	6,702 ± 7,752	0.0002
Minimal model S_I (min^{-1} per μU/ml × 10^4)†	0.51 ± 0.46	0.62 ± 0.45	0.29
Minimal model S_G (min^{-1} × 10^2)‡	1.92 ± 0.45	2.01 ± 0.44	0.49

Data are means ± SD. *P* values were determined by nonpaired *t* test. Basal values are the means of data collected during the last 90 min of the 3-h basal tracer infusion period. Steady-state values are the means of data collected during the final 30 min of the 3-h euglycemic insulin infusion period. Clamp S_I was calculated as follows: (steady-state glucose infusion rate)/(steady-state plasma insulin – basal plasma insulin). *Incremental plasma insulin area during the first 10 min after glucose injection. †The change in glucose fractional disappearance rate due to increase in plasma insulin above basal. ‡The glucose fractional disappearance rate at basal plasma insulin.

TABLE 3
Comparison of measures of β-cell compensation for insulin resistance between groups that did and did not develop diabetes 11–26 months after pregnancies complicated by GDM

Compensation index			Diabetes 11–26 months postpartum		
Insulin sensitivity	×	β-Cell function	Yes	No	*P* value
n			14	77	
Clamp S_I	×	OGTT 30-min incremental insulin:glucose*	5.3 ± 3.4	12.9 ± 10.2	0.0004
Minimal model S_I	×	OGTT 30-min incremental insulin:glucose	0.42 ± 0.038	0.88 ± 0.65	0.005
Clamp S_I	×	FSIGT first-phase insulin	3,463 ± 3,441	8,630 ± 10,062	0.0001
Minimal model S_I	×	FSIGT first-phase insulin	286 ± 353	560 ± 386	0.001

Data are means ± SD. The compensation index is the product of insulin sensitivity × insulin secretion, as described by Bergman (28). *P* values were determined by nonpaired *t* test. See Table 2 for an explanation of clamp S_I, minimal model S_I, and FSIGT first-phase insulin. *Calculated from the 75-g study OGTT as follows: (30-min plasma insulin – basal plasma insulin)/(30-min plasma glucose – basal plasma glucose) × 10^3.

marked similarity of basal plasma glucose clearance among women who did and did not develop diabetes, indicate that elevated basal glucose production contributed to the mildly elevated fasting glucose levels in the prediabetic group. Gerich (13) and Fery (14) made analogous observations in people with mild type 2 diabetes. Our findings expand those prior observations by demonstrating that elevated glucose production actually preceded the development of type 2 diabetes. Thus, we conclude that dysregulation of glucose production is an early defect in the pathogenesis of type 2 diabetes. This concept is supported by the report of Osei (41) that elevated glucose production is present in nondiabetic relatives of people with type 2 diabetes.

The mechanisms responsible for elevated basal glucose production in prediabetic women are not clear from this study. The women had basal insulin and C-peptide concentrations similar to those of women who did not develop diabetes. Thus, elevated glucose production in the former group was not due to poor pancreatic β-cell function, in contrast to the postprandial glucose overproduction reported by Mitrakou et al. (42) in nonpregnant people with impaired glucose tolerance. Rather, the prediabetic women in the present study appeared to have resistance to insulin's effects on glucose production under basal conditions. The resistance was not explained by intergroup differences in basal glucagon or circulating FFA concentrations (43–45). In fact, basal FFA concentrations were not correlated with basal glucose production rates in the cohort (r = –0.08, P = 0.44). Primary genetic differences in hepatic or renal glucoregulation, differences in circulating gluconeogenic substrate supplies (e.g., fatty acid flux), and differences in neurohormonal regulation of glucose production remain possible but untested explanations.

In contrast to basal glucose production, suppression of glucose production during antepartum clamps was not signi-

TABLE 4
Independent predictors of diabetes 11–26 months after pregnancies complicated by GDM

	P value	Unadjusted RR (95% CI)*	Adjusted RR (95% CI)†
Model 1 (χ^2 = 27.24)			
Incremental glucose area, diagnostic OGTT	0.009	7.7 (1.5–38.6)	15.0 (1.1–207.9)
FSIGT acute insulin response	0.02	0.08 (0.009–0.7)	0.08 (0.005–1.0)
OGTT 30-min incremental insulin:glucose	0.03	0.09 (0.01–0.8)	0.10 (0.005–2.2)
Basal glucose production rate	0.05	3.4 (0.6–18.1)	7.0 (0.8–63.1)
Clamp S_I	0.06	0.4 (0.1–1.7)	0.15 (0.02–1.2)
Model 2 (χ^2 = 30.09)			
1-h plasma glucose, diagnostic OGTT	0.004	13.8 (1.6–116.3)	22.0 (1.5–328.5)
OGTT 30-min incremental insulin:glucose	0.01	0.09 (0.01–0.8)	0.08 (0.005–1.1)
Basal glucose production rate	0.04	3.4 (0.6–18.1)	6.8 (0.70–65.5)
Clamp S_I	0.06	0.4 (0.1–1.7)	0.18 (0.03–1.2)
Model 3 (χ^2 = 29.32)			
1-h plasma glucose, diagnostic OGTT	0.003	13.8 (1.6–116.3)	15.2 (1.4–166.3)
β-Cell compensation index	0.009	0.06 (0.007–0.5)	0.09 (0.009–0.9)
Basal glucose production rate	0.04	3.4 (0.6–18.1)	5.3 (0.63–44.4)

Independent predictors were identified by logistic regression analyses, as described in RESEARCH DESIGN AND METHODS. Model 1 stepwise regression used variables listed in Tables 1 and 2. Model 2 evaluated the impact of individual OGTT glucose and insulin values on model 1. Model 3 evaluated the impact of four measures of pancreatic β-cell compensation for insulin resistance (products of insulin sensitivity and insulin secretion from OGTT, FSIGT, and glucose clamp) on model 2. *Highest versus lowest tertile of variable based on univariate analysis. †Highest versus lowest tertile for each variable, adjusted for other variables in model. *P* values are based on analysis of continuous variables, adjusted for other variable in the model. See Table 2 for an explanation of clamp S_I and β-cell compensation index.

ficantly different between groups that did and did not develop diabetes. Because plasma insulin concentrations achieved during clamps were in the high physiologic range, we cannot exclude the possibility of hepatic resistance to lower but suprabasal insulin concentrations.

As has been reported previously (8,9,21), we observed that poor insulin responses to glucose during the third trimester were predictive of diabetes after pregnancies complicated by GDM. Responses to both oral and intravenous glucose were associated with diabetes (model 1), although only the response to oral glucose was independently predictive of diabetes when the 1-h glucose value from the antepartum diagnostic OGTT entered the model (model 2). The consistent finding that β-cell dysfunction during pregnancy is an independent predictor of diabetes after GDM highlights the importance of a pancreatic β-cell defect early in the pathogenesis of type 2 diabetes (5,6). Our findings also shed some light on the nature of the β-cell defect. When measures of insulin sensitivity and secretion were analyzed separately (models 1 and 2), poor β-cell function was a clear risk factor for diabetes, and insulin resistance measured by the clamp was important as well. When products of insulin sensitivity and secretion were included as measures of β-cell compensation for insulin resistance (model 3), a low β-cell compensation index replaced the separate measures of insulin secretion and sensitivity as an independent predictor of diabetes. This finding highlights the importance of assessing β-cell function in relation to ambient insulin sensitivity (28). Moreover, in light of previous reports that insulin-resistant conditions such as weight gain (8,46) and additional pregnancies (46,47) increase the risk of diabetes after GDM, our findings support the concept that GDM identifies women with a pancreatic β-cell defect that is characterized by maladaptation to insulin resistance.

The strongest single predictor of diabetes in all models was postchallenge hyperglycemia, a consistent finding in other studies of diabetes after GDM (8,9,19,21,31–35). It is not surprising that glucose intolerance during pregnancy predicted diabetes 1–2 years later, since the diagnosis of diabetes after pregnancy was based on OGTT 2-h glucose values in 9 of the 14 diabetic women. It was somewhat surprising that none of the major determinants of glucose tolerance (β-cell function, peripheral and hepatic insulin sensitivity, glucose effectiveness) proved to be superior to the 1-h glucose concentration at the diagnostic OGTT in predicting diabetes. This observation suggests that other factors or a combination of determinants of glucose tolerance were operative in the prediabetic members of our cohort. For example, nutritional factors operative at the time of diagnosis of GDM may have contributed to high 1-h glucose values in women who then improved their eating habits during pregnancy but reverted to their prediagnosis habits after delivery. Alternatively, the precision of glucose measurements may have been greater than that of the other measures, providing a stronger statistical association with diabetes despite important pathophysiologic impact of the more mechanistic factors. Whatever the explanation, the strong association between glucose tolerance at diagnosis of GDM and the risk of diabetes 11–26 months after delivery has important clinical implications, since plasma glucose concentrations during OGTTs are readily available to care providers.

In summary, we identified postchallenge hyperglycemia, poor β-cell compensation for insulin resistance, and elevated basal glucose production during pregnancy as independent predictors of type 2 diabetes between 11 and 26 months after delivery in women with GDM. Our findings indicate that a defect in the regulation of endogenous glucose production precedes the development of diabetes in very-high-risk young women, although we did not test whether this defect was specific to pregnancy or persisted after delivery. Our observations provide a rationale for targeting glucose overproduction, along with insulin resistance that may contribute to β-cell dysfunction (46–48), when developing strategies for prevention of diabetes after GDM.

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