Multiple Metabolic Defects During Late Pregnancy in Women at High Risk for Type 2 Diabetes

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Detailed metabolic studies were carried out to compare major regulatory steps in glucose metabolism in vivo between 25 normal pregnant Latino women without and 150 pregnant Latino women with gestational diabetes mellitus (GDM). The two groups were frequency-matched for age, BMI, and gestational age at testing in the third trimester. After an overnight fast, women with GDM had higher fasting plasma glucose (*P* = 0.0001) and immunoreactive insulin (*P* = 0.0003) concentrations and higher glucose production rates (*P* = 0.01) but lower glucose clearance rates (*P* = 0.001) compared with normal pregnant women. During steady-state hyperinsulinemia (~600 pmol/l) and euglycemia (~4.9 mmol/l), women with GDM had lower glucose clearance rates (*P* = 0.0001) but higher glucose production rates (*P* = 0.0001) and plasma free fatty acid (FFA) concentrations (*P* = 0.0002) than the normal women. These intergroup differences persisted when a subgroup of 116 women with GDM who were not diabetic 6 months after pregnancy were used in the analysis. When all subjects were considered, there was a very close correlation between glucose production rates and plasma FFA concentrations throughout the glucose clamps in control (*r* = 0.996) and GDM (*r* = 0.995) groups. Slopes and intercepts of the relationships were nearly identical, suggesting that blunted suppression of FFA concentrations contributed to blunted suppression of glucose production in the GDM group. In addition to these defects in insulin action, women with GDM had a 67% impairment of pancreatic β-cell compensation for insulin resistance compared with normal pregnant women. These results demonstrate that women with GDM have multiple defects in insulin action together with impaired compensation for insulin resistance. Our findings suggest that defects in the regulation of glucose clearance, glucose production, and plasma FFA concentrations, together with defects in pancreatic β-cell function, precede the development of type 2 diabetes in these high-risk women. *Diabetes* 48:848–854, 1999

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Received for publication 6 October 1998 and accepted in revised form 23 December 1998.

FFA, free fatty acid; GDM, gestational diabetes mellitus; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test; S_I, insulin sensitivity index.

Routine clinical assessment of glucose tolerance during pregnancy is used to identify women with gestational diabetes mellitus (GDM). Long-term follow-up of those women indicates that they are at increased risk for diabetes, especially type 2, compared with women who maintain normal glucose tolerance during pregnancy (1–3) and to the general population (4–7). Since a large majority of women with GDM do not have diabetes immediately after the index pregnancy (6,8), GDM has been proposed as a model with which to identify early metabolic defects that precede the development of diabetes in young women. Two approaches have been used in that regard. Longitudinal studies have focused on clinical characteristics and plasma insulin concentrations during pregnancy as possible predictors of diabetes. Those studies have revealed antepartum hyperglycemia, obesity, and low insulin responses to oral glucose to be predictive of the persistence (9) or development (5) of diabetes after pregnancy. Cross-sectional studies have included more detailed measures of antepartum metabolism in small groups of women with and without GDM (10–14). Those studies have consistently revealed impaired pancreatic β-cell function compared with normal pregnant women, but no excess insulin resistance during late pregnancy unless patients have overt fasting hyperglycemia (12).

We are conducting a study that combines these two approaches. Normal women and women with GDM have undergone detailed assessment of pancreatic β-cell function; insulin action on glucose uptake, glucose production, and plasma free fatty acids (FFAs); and body composition during late pregnancy. Women with GDM are being followed prospectively to determine metabolic or morphometric characteristics that predict or attend the development of type 2 diabetes. We have recently reported the antepartum predictors of early postpartum diabetes and impaired glucose tolerance in a subset of the women with GDM who returned for glucose tolerance testing within 6 months after the index pregnancy (15). We now report the results of detailed antepartum metabolic comparisons between the full cohort of women with GDM and women with normal glucose tolerance.

RESEARCH DESIGN AND METHODS

Subjects. Los Angeles County Women's Hospital is a major referral center for women with GDM who are diagnosed in community clinics according to the recommendations of the Third International Workshop Conference on GDM (16). Patients are referred to Women's Hospital if they have any fasting serum glucose concentration 105 mg/dl during pregnancy or if they have a prior history of stillbirth or gestational hypertension. Between August 1993 and March 1995, all Latino women referred to Women's Hospital for GDM were asked to participate in the present study if they *1*) were between 28 and 34 weeks' gestation as assessed by a clin-

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ical examination before 12 weeks or by an ultrasound before 20 weeks; *2*) were not using exogenous insulin at the time of referral; *3*) had all fasting serum glucose concentrations <130 mg/dl since the diagnosis of GDM; and *4*) had otherwise uncomplicated singleton pregnancies. One hundred fifty women met these criteria; 147 completed a full battery of metabolic tests (below) and 3 completed an oral glucose tolerance test (OGTT) plus either a glucose clamp or an intravenous glucose tolerance test (IVGTT). A control group of 25 pregnant women, frequency matched to the GDM group according to age, BMI when not pregnant, and gestational age at testing were selected by contacting women in the obstetrical clinics from which the women with GDM were referred. Women were eligible to be controls if they *1*) had a plasma glucose concentration <130 mg/dl 1 h after a 50-g glucose challenge beyond 24 weeks' gestation; *2*) had no personal or family history of diabetes or glucose intolerance; and *3*) had uncomplicated singleton pregnancies. For both GDM and control groups, only women whose parents and at least three of four grandparents were from Mexico, Guatemala, or El Salvador were recruited. All subjects gave consent for participation in the study, which was approved by the institutional review board of the University of Southern California.

Testing protocol. Women with GDM were instructed to eat a diet that provided 30 kcal/kg current body weight per day (25 kcal/kg for women with a prepregnancy weight >120% of ideal) for at least 3 days before detailed metabolic testing. Normal women were instructed to eat at least three meals per day for 3 days before testing. All subjects came to the General Clinical Research Center for testing on 3 separate days, at least 48 h apart and after 8- to 10-h overnight fasts.

On 1 day, an OGTT was performed starting between 0700 and 1000. Patients rested in bed and drank 75 g D-glucose (Glucose Tolerance Drink; Stephens Scientific, Riverdale, NJ). Blood samples were obtained from an indwelling antecubital venous catheter before and 15, 30, 60, 90, 120, and 180 min after the start of the glucose ingestion. Samples were placed in iced tubes, and plasma was separated within 20 min and stored at –70°C.

On a different day, a glucose clamp was performed starting between 0600 and 0630. A primed (0.035 mmol/kg body wt), continuous ($2.5 \cdot 10^{-4}$ mmol · min^{-1} · 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 pregnant women with GDM (17). A nonprimed infusion of crystalline human insulin (50 mU · min^{-1} · m^{-2} body surface area) was administered during the final 180 min of the tracer infusion. Dextrose (20% wt/vol in water), containing dideutero-glucose (0.021 mmol/ml) to minimize changes in plasma tracer enrichment (18), was given at a rate sufficient to maintain arterialized venous plasma glucose concentrations at ~88 mg/dl during the insulin infusion. Blood samples for measurement of tracer, hormone, and metabolite concentrations were drawn into ice-cold tubes at –90, –50, –30, –10, 30, 60, 90, 120, 160, and 180 min relative to the start of the insulin infusion. Plasma was separated within 20 min and stored at –70°C.

On a 3rd test day, a frequently sampled IVGTT was performed starting between 0700 and 1000. Dextrose (300 mg/kg body wt as 50% solution in water) was injected over 1 min, followed in 20 min by a 5-min infusion of crystalline human insulin (0.03 U/kg body wt). Arterialized venous blood samples were drawn into iced tubes at –15, –5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 26, 28, 30, 33, 36, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 220, and 240 min relative to the start of the dextrose injection. Plasma was separated within 20 min and stored at –70°C.

Laboratory analysis. Plasma glucose was measured by glucose oxidase (Glucose Analyzer II; Beckman, Brea, CA). Plasma insulin was measured by a charcoal precipitation radioimmunoassay (Novo Pharmaceuticals, Danbury, CT) that measures insulin and proinsulin. C-peptide and glucagon were measured in aprotinin-preserved plasma by radioimmunoassay (Linco Research, St. Charles, MO). Plasma FFAs were measured by ^{63}Ni precipitation. [6,6-$^2H_2$]glucose concentrations in infusates and PCA supernatants of plasma were measured by gas chromatography and mass spectrometry after conversion of glucose to its aldonitrile pentaacetate derivative (19). Anti–pancreatic islet cell antibodies (ICAs) in plasma were measured in the laboratory of Dr. J. Palmer by an indirect immunofluorescence assay using human pancreas. The assay has a detection limit of 1 Juvenile Diabetes Foundation International (JDF) unit.

Data analysis. Total areas under OGTT glucose curves 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. (18). IVGTT glucose and insulin data were subjected to minimal model analysis (20) using the MINMOD program provided by Dr. R. Bergman. β-Cell insulin release in response to glucose was assessed two ways: the incremental area under the insulin curve during the first 10 min after the glucose injection (acute insulin response to glucose; AIR_g) and the ratio of the increase above basal in plasma insulin to the increase in plasma glucose 30 min after the OGTT glucose ingestion. The appropriateness of β-cell insulin release in relation to ambient insulin sensitivity was assessed as the product of the minimal model insulin sensitivity index (S_I) and each of the two measures of insulin release, as originally proposed by Bergman and colleagues (21,22).

All continuous variables were tested for normality before statistical analyses. Distributions of all insulin values, insulin areas, insulin sensitivity, and ratios of insulin to other variables were positively skewed, so log transformation was applied to those variables. Mean values were compared between groups using nonpaired *t* tests. Linear relationship between variables of interest was assessed using Pearson correlation analysis. Linear regression was used to compare the intercepts and slopes of two straight lines. All reported *P* values were two-sided. Data are mean ± SD in text and tables and mean ± SE in figures.

RESULTS

The 150 pregnant women with GDM were similar to the 25 normal pregnant women with regard to age (30.4 ± 5.6 vs. 29.0 ± 5.7 years; $P = 0.25$), parity (1.9 ± 1.7 vs. 1.5 ± 1.2 pregnancies; $P = 0.29$), prepregnancy BMI (28.8 ± 4.7 vs. 27.6 ± 4.5 kg/m^2; $P = 0.24$), gestational age at metabolic testing (32.8 ± 2.6 vs. 32.3 ± 2.4 weeks; $P = 0.41$), and BMI at testing (32.2 ± 4.9 vs. 31.2 ± 4.5 kg/m^2; $P = 0.32$).

OGTTs revealed significantly higher plasma glucose concentrations in women with GDM at all time points (Fig. 1). Plasma insulin concentrations were lower at –10, 15, and 30 min and higher at 90, 120, and 180 min relative to the glucose ingestion in the women with GDM. The mean of incremental ratios of insulin (expressed in microunits per milliliter) to glucose (expressed in milligrams per deciliter) 30 min after glucose ingestion was reduced by 34% in the women with GDM (1.39 ± 1.32 vs. 2.12 ± 0.87; $P = 0.001$).

During the 90-min basal period before euglycemic clamps (Fig. 2), plasma glucose (97.2 ± 9.0 vs. 84.2 ± 7.6 mg/dl; $P = 0.0001$) and immunoreactive insulin (24.7 ± 14.1 vs. 18.0 ± 7.2 μU/ml; $P = 0.0003$) concentrations were higher in the women with GDM. Their basal C-peptide concentrations were also slightly, but not significantly, higher (2.28 ± 0.53 vs. 2.01 ± 0.82 ng/ml; $P = 0.14$), while their basal glucagon concentrations were lower (37.1 ± 11.6 vs. 53.5 ± 21.4 pg/ml; $P = 0.0001$) than in the controls. Analysis of labeled glucose data during the basal period revealed higher endogenous glucose production (0.50 ± 0.07 vs. 0.47 ± 0.05 mmol · min^{-1} · m^{-2} body surface; $P = 0.01$) (Fig. 3) and lower glucose clearance (96 ± 12 vs. 105 ± 10 ml · min^{-1} · m^{-2}; $P = 0.001$) (Fig. 3) in the GDM group. Across the range of fasting glycemia observed in the control and GDM groups, there was a direct correlation between fasting plasma glucose concentrations and basal glucose production rates ($r = 0.41$, $P < 0.0001$) (Fig. 4) and an inverse correlation between fasting glucose and basal glucose clearance rates ($r = -0.33$, $P < 0.0001$) (Fig. 4). Basal plasma FFA concentrations were higher in the GDM group (446 ± 119 vs. 419 ± 77 μmol/l), but the difference did not achieve statistical significance ($P = 0.16$).

Insulin infusions raised plasma immunoreactive insulin concentrations by an average of 79 ± 19 and 79 ± 16 μU/ml in GDM and control groups, respectively, to steady-state concentrations of 104 ± 24 and 98 ± 15 μU/ml ($P = 0.27$) (Fig. 2). At steady state, glucose clearance rates were lower (162 ± 28 vs. 201 ± 35 ml · min^{-1} · m^{-2}; $P = 0.0001$) (Fig. 3) and glucose production rates were higher (0.16 ± 0.07 vs. 0.10 ± 0.07 mmol · m^{-2} · min^{-1}, $P = 0.0001$) (Fig. 3) in the women with GDM. Steady-state plasma FFA concentrations were also higher in the women with GDM (183 ± 70 vs. 136 ± 47 μmol/l; $P = 0.0002$) (Fig. 5). When considered as changes from baseline, stimulation of glucose clearance (66 ± 27 vs. 96 ± 36 ml · min^{-1} · m^{-2}; $P = 0.0004$) and suppression of glucose production (–0.33 ± 0.07 vs. –0.37 ± 0.08 mmol · min^{-1} · m^{-2}; $P = 0.03$) were significantly blunted in women with GDM, while sup-

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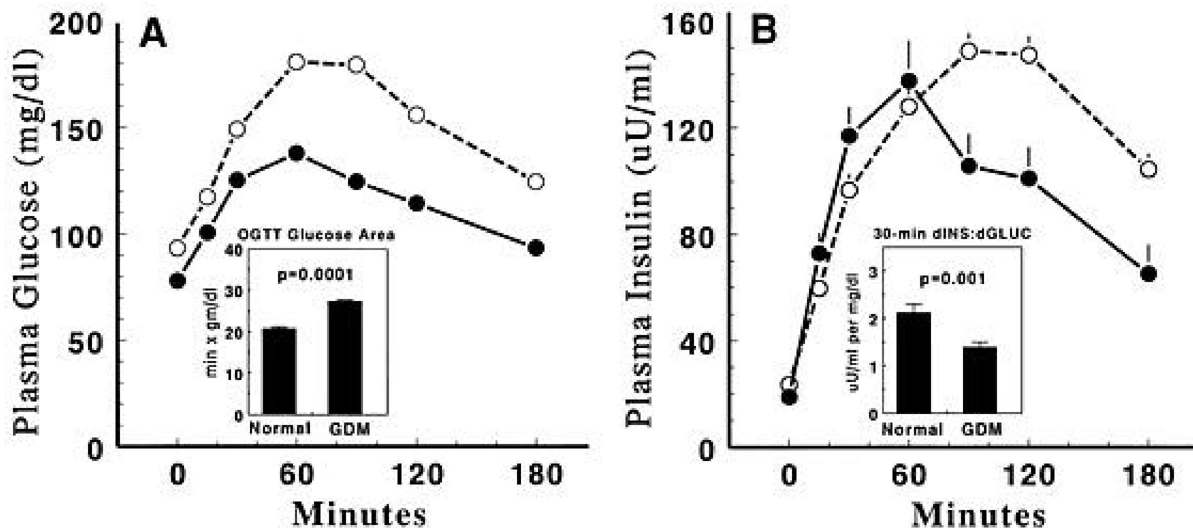

FIG. 1. Plasma glucose (*A*) and insulin (*B*) concentrations in normal pregnant women (●) and women with GDM (○) during 3rd trimester of pregnancy. Insets depict total glucose area (*A*) and incremental plasma insulin-to-glucose ratio at 30 min (*B*) during OGTTs.

pression of plasma FFA concentrations was not significantly different between GDM and control groups (–263 ± 96 vs. –284 ± 79 μmol/l, respectively; $P = 0.34$).

Minimal model analysis of IVGTT data revealed a significantly lower S_I in the women with GDM [0.63 ± 0.47 vs. 1.27 ± 1.16 [$\text{min}^{-1} \cdot (\mu\text{U} \cdot \text{ml}^{-1})^{-1}] \cdot 10^4$; $P = 0.0002$]. Despite this greater degree of insulin resistance, women with GDM had lower acute insulin responses to intravenous glucose (AIR_g: 920 ± 1,024 vs. 1,551 ± 737 $\mu\text{U} \cdot \text{ml}^{-1} \cdot \text{min}$; $P = 0.0001$). The product of S_I and AIR_g was reduced 67% in women with GDM compared with normal pregnant women (519 ± 556 vs. 1,597 ± 837 $\times 10^{-4}$; $P = 0.0001$). The product of S_I and the OGTT 30-min incremental insulin-to-glucose ratio was also reduced 67% in women with GDM (0.77 ± 0.79 vs. 2.30 ± 1.29 $\cdot 10^{-4}\ \text{min}^{-1} \cdot \text{mg}^{-1} \cdot \text{dl}^{-1}$; $P = 0.0001$).

Intergroup comparisons were repeated using all normal pregnant women and a subgroup of 116 women with GDM who were tested within 6 ($n = 110$), 15 ($n = 3$), or 30 ($n = 3$) months after pregnancy and found not to have diabetes. This analysis minimized the probability of including women with undiagnosed diabetes antedating the index pregnancy. The subgroup did not differ significantly from controls regarding age, BMI, parity, or gestational age at testing. The same pattern of differences observed between the entire GDM group and controls was observed between the subgroup and controls for the following parameters: OGTT glucose area; fasting insulin, glucose, and glucagon concentrations; basal and steady-state glucose production and clearance rates during euglycemic clamps; FFA concentrations during hyperinsulinemia; minimal model S_I; and insulin responses to oral and intravenous glucose (Table 1).

Since circulating FFAs have been proposed as important regulators of hepatic glucose production (23–25), we assessed the relationship between plasma FFA concentrations and endogenous glucose production in normal and GDM groups at each time point during euglycemic clamps (Fig. 6). For each group, there was a very strong linear correlation between FFAs and glucose production rates. Moreover, the relationships appeared to fall on the same line in the two groups, since neither the slope nor the intercept differed

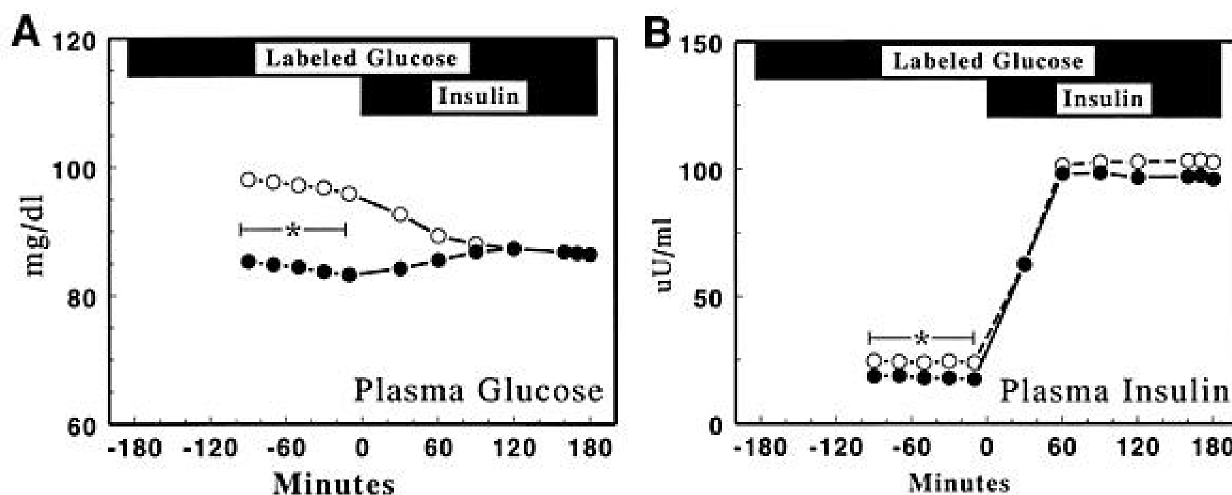

FIG. 2. Plasma glucose (*A*) and insulin (*B*) concentrations in normal pregnant women (●) and women with GDM (○) during euglycemic clamp studies. A primed infusion of [6,6-$^2H_2$]-labeled glucose was given from –180 to 180 min according to a protocol developed specifically for use in pregnant women with GDM (19). A nonprimed infusion of human insulin was given from 0 to 180 min. *$P < 0.01$ between groups.

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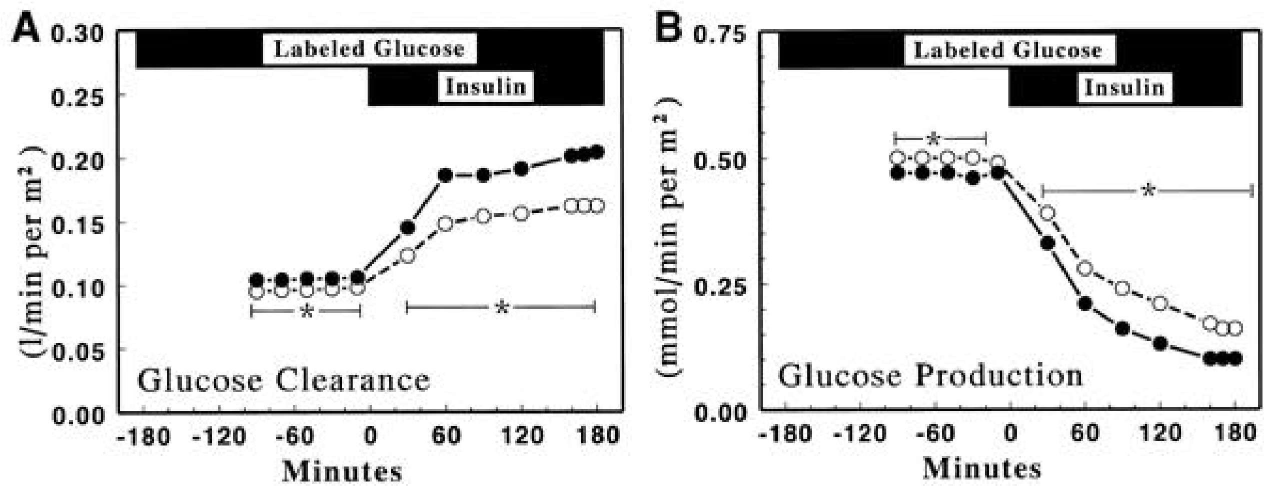

FIG. 3. Plasma glucose clearance (*A*) and endogenous glucose production (*B*) in normal pregnant women (●) and women with GDM (○) during hyperinsulinemic clamp studies. *$P < 0.02$ between groups.

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significantly between the relationships ($P > 0.6$). Analogous plots for glucose clearance versus FFAs also revealed a linear relationship in each group (Fig. 6), but the groups fell on lines with different slopes ($P = 0.005$) and intercepts ($P = 0.0001$).

DISCUSSION

The present study is the first relatively large-scale, detailed investigation of glucose metabolism in pregnant women with gestational diabetes. The women were all Latino and, based on their antepartum OGTT characteristics, were projected to have a 65% risk of developing type 2 diabetes within 5 years (6). When studied during late pregnancy, they manifested several defects in insulin action compared with pregnant women with normal glucose tolerance. First, they had 6% higher glucose production and 9% lower glucose clearance after an overnight fast compared with normal pregnant women, despite higher fasting glucose and immunoreactive insulin concentrations, similar C-peptide concentrations, and lower glucagon concentrations. Glucose production and clearance were correlated with fasting glucose concentrations, suggesting that both parameters contributed to the mild elevations of fasting glucose in women with GDM. Second, women with GDM had less suppression of glucose production and less stimulation of glucose clearance compared with the normal women in response to similar elevations of plasma insulin within the physiologic range. These findings provide unequivocal evidence for resistance to insulin's effect on glucose utilization and production that is above and beyond the physiologic insulin resistance of late pregnancy. Third, there was a tendency for circulating FFA concentrations to be higher in women with GDM, although intergroup differences were significant only during physiologic hyperinsulinemia. This finding suggests resistance to insulin's effect on lipolysis as well; studies of fatty acid turnover will be required to test the validity of this suggestion. All of the defects in women with GDM were present in a subgroup proven not to have diabetes after pregnancy (Table 1), indicating that our findings cannot be explained by the inclusion of women with undiagnosed type 2 diabetes in the cohort.

In the face of exaggerated insulin resistance, women with GDM had reduced pancreatic β-cell function during late pregnancy compared with normal pregnant women. This reduction was estimated to be in the range of 34–41% based on simple comparisons of first-phase insulin responses to intravenous glucose and early insulin responses to oral glucose between normal pregnant and GDM groups. The magnitude of the β-cell defect was likely underestimated by these

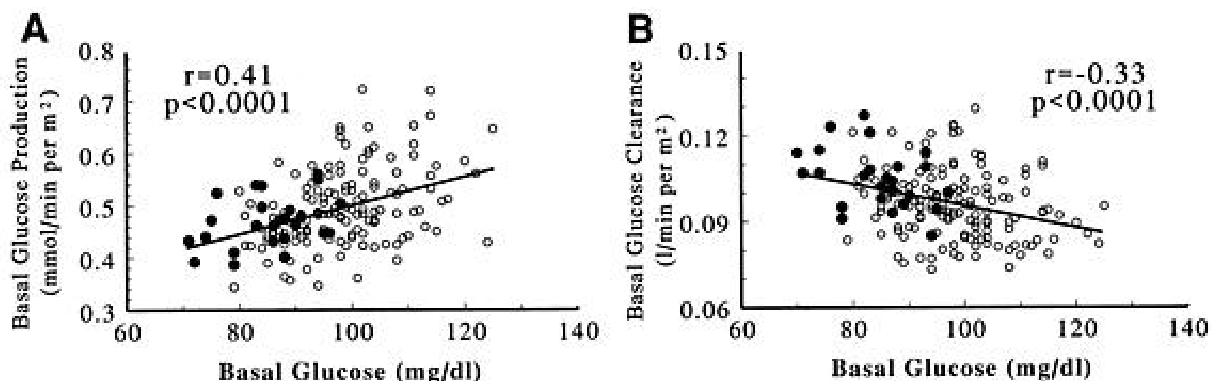

FIG. 4. Relationships between basal plasma glucose concentrations on day of euglycemic clamps and basal glucose production (*A*) or plasma glucose clearance (*B*) in normal pregnant women (●) and women with GDM (○). Lines depict linear regression for all subjects combined.

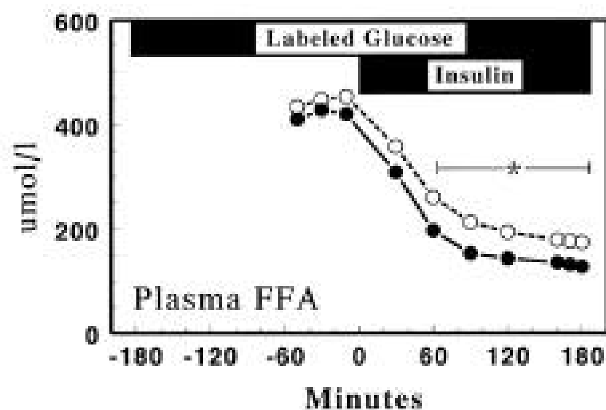

FIG. 5. Plasma FFA concentrations during euglycemic clamps in normal pregnant women (●) and women with GDM (○). *P = 0.0002 between groups.

simple comparisons, however, since the women with GDM were more insulin resistant than the normal pregnant women. When insulin responses were considered relative to ambient insulin sensitivity, the β-cell defect in our high-risk patients with GDM was 67%, approximately twice the magnitude suggested by comparisons of the insulin responses alone. Thus, our patients had a profound defect in β-cell function at a time when their fasting plasma glucose concentrations were, on average, <100 mg/dl. This defect was found to be predictive of the presence of diabetes within 6 months after pregnancy in the subset of women with GDM who returned for OGTTs at that time (15).

The finding of elevated basal glucose production in women with GDM was surprising, given prior reports (26–28) of a lack of elevation of basal glucose production in patients with fasting glycemia in the range observed in our patients (81–125 mg/dl). However, Osei (29) reported elevated basal glucose production in nondiabetic relatives of patients with type 2 diabetes, suggesting that elevated glucose production can occur in the absence of overt fasting hyperglycemia. The mechanism underlying the increased production was not tested directly in this study. However, we found a very strong correlation between circulating FFA concentrations and glucose production rates during euglycemic insulin infusions in women with GDM and in normal pregnant women. Moreover, the relationships were identical in shape, suggesting that the elevations in FFA concentrations contributed in an important way to the elevated glucose production during clamps in women with GDM. This observation is consistent with more direct studies in dogs (23) and humans (24,25) that revealed elevations or reductions in glucose production rates in response to manipulations that, respectively, raised or lowered circulating FFA concentrations. Viewed in the context of those prior studies, our results suggest that the observed resistance to insulin's effect on glucose production in women with GDM was actually mediated by resistance at the level of the fat cell rather than at the level of the liver or kidneys.

Our findings must be interpreted in light of previous work on glucose regulation in women with GDM or a history thereof. Catalano et al. (30) have conducted the most detailed metabolic testing of women with GDM before the present study. In a small number of lean women, they found no evidence for excess peripheral or hepatic insulin resistance in GDM during late pregnancy. They did report a reduction in insulin-mediated glucose uptake during early pregnancy and prior to conception, leading to the speculation that women with GDM may have underlying insulin resistance that is masked by the insulin resistance of late pregnancy. Indeed, Ward et al. (31,32) and Ryan et al. (33) have reported insulin

TABLE 1
Antepartum comparisons between women with GDM who did not have diabetes after pregnancy and normal women

Parameter	GDM	Control	P value
n	116	25	—
OGTT			
Plasma glucose area (min · g · dl^{-1})	26.5 ± 3.5	20.7 ± 2.0	0.0001
30-min incremental insulin:glucose	1.54 ± 1.42	2.12 ± 0.87	0.0001
Basal glucose clamp			
Plasma glucose (mg/dl)	97.2 ± 9.0	84.6 ± 7.2	0.0001
Plasma insulin (μU/ml)	25.6 ± 15.3	18.0 ± 7.2	0.002
Plasma C-peptide (ng/ml)	2.30 ± 0.49	2.01 ± 0.82	0.11
Plasma glucagon (pg/ml)	36.3 ± 10.8	53.5 ± 21.4	0.0002
Plasma FFA (μmol/l)	444 ± 116	419 ± 77	0.21
Glucose production (mmol · min^{-1} · m^{-2})	0.50 ± 0.07	0.47 ± 0.05	0.03
Glucose clearance (ml · min^{-1} · m^{-2})	96 ± 12	105 ± 10	0.0009
Steady-state glucose clamp			
Glucose production (mmol · min^{-1} · m^{-2})	0.17 ± 0.07	0.10 ± 0.07	0.0001
Glucose clearance (ml · min^{-1} · m^{-2})	161 ± 28	201 ± 35	0.0001
Plasma FFAs (μmol/l)	182 ± 71	136 ± 47	0.0004
IVGTT			
S_I [min^{-1} · (μU · ml^{-1})$^{-1}$] × 10^{-4}	0.64 ± 0.50	1.27 ± 1.16	0.0009
Acute insulin response (μU · ml^{-1} · min)	1,018 ± 1,114	1,551 ± 737	0.0001

Data are means ± SD. Nondiabetic glucose tolerance tests were obtained within 6 months after pregnancy in all normal women and within 6 (n = 110), 15 (n = 6), or 30 (n = 3) months after the index pregnancy in women with GDM. P values were determined by nonpaired t test. Data for basal glucose clamp were obtained during the last 90 min of 180-min basal tracer infusion before insulin infusion; those for steady-state glucose clamp were obtained during the last 30 min of insulin infusion.

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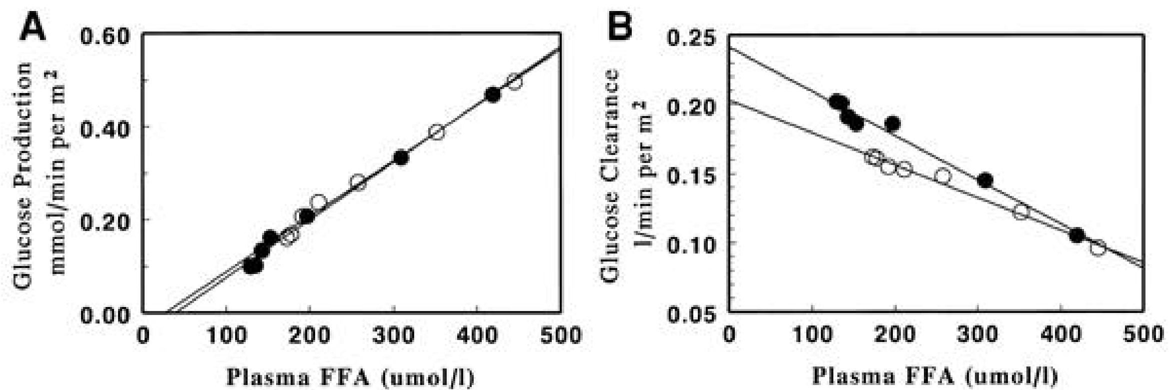

FIG. 6. Relationship between plasma FFA concentrations and endogenous glucose production rates (*A*) and glucose clearance rates (*B*) during euglycemic clamps in normal pregnant women (●) and women with GDM (○). Each symbol represents the group mean at one of the designated time points during the clamp (basal, 30, 60, 90, 120, 160, and 180 min relative to start of the insulin infusion). Lines depict linear regression within each group. Neither slopes nor intercepts of the two lines in *A* differed significantly ($P > 0.6$). Slopes ($P = 0.005$) and intercepts ($P = 0.0001$) of the two lines in *B* were significantly different.

resistance in nonpregnant women with a history of GDM compared with nonpregnant women with no such history, supporting the existence of chronic insulin resistance in women who develop GDM. In only one other study (12) have women with GDM been reported to have excess insulin resistance compared with normal pregnant women during late pregnancy. The interpretation of those results is complicated by the fact that a majority of the five patients studied had overt fasting hyperglycemia, making it impossible to distinguish between secondary causes (e.g., glucotoxicity) and primary causes of insulin resistance. In none of the previous reports has there been any projection of the true risk of diabetes in the study cohort. The present report indicates that women with GDM and a high risk of diabetes within 5 years already have insulin resistance that is above the insulin resistance of late normal pregnancy. That finding suggests mechanisms for underlying and perhaps chronic insulin resistance in women with GDM that are additive to mechanisms underlying the normal insulin resistance of pregnancy. In keeping with that concept, Garvey et al. (34) found that women with GDM have a defect in insulin-mediated translocation of GLUT4 in adipocytes that does not occur in normal pregnant women.

Defects in β-cell function have been reported in women who develop GDM by a number of investigators who have studied pregnant (3,5,9,12–14,30) and nonpregnant (31–33,35) patients. In part, the ability to detect such defects is enhanced by pregnancy, which narrows the range of insulin sensitivity in all women through the induction of marked insulin resistance. Under those conditions, interindividual differences in the capacity of β-cells to compensate for insulin resistance may be magnified, and women with low β-cell capacity may develop mild hyperglycemia that characterizes GDM. Our findings in a large cohort of patients not only confirm a prominent β-cell defect compared with normal pregnant women, they also highlight the need to assess β-cell function in light of ambient insulin sensitivity (22). Failure to do so would have resulted in a nearly twofold underestimation of the magnitude of the β-cell defect in our patients with GDM.

In summary, we have conducted the first relatively large-scale investigation of factors regulating glucose metabolism during late pregnancy in women with GDM and a high risk of type 2 diabetes within 5 years. Those women manifested clear resistance to insulin's effects on glucose clearance and production, along with a tendency for resistance to the effects on suppression of FFA concentrations, compared with normal pregnant women. Resistance to insulin's effects on glucose production were tightly correlated with resistance to suppression of lipolysis, suggesting that insulin resistance in fat cells may contribute to hepatic insulin resistance even in the absence of overt fasting hyperglycemia. Women with GDM also had a 67% reduction in pancreatic β-cell compensation for insulin resistance compared with normal pregnant women. Our findings indicate that women with GDM have multiple metabolic defects that may contribute to their relatively mild hyperglycemia during pregnancy. Short-term follow-up of the cohort has already revealed that poor β-cell function and postchallenge hyperglycemia predict the persistence of diabetes after delivery (15). Long-term follow-up will determine which, if any, of the metabolic defects identified during pregnancy predict the de novo development of type 2 diabetes in later life.

ACKNOWLEDGMENTS

This work was supported by *1*) grant R01-DK-46374 and P30-DK 17047 from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH); *2*) grants M01-RR-43 and M01-RR-425 from the General Clinical Research Center Branch of the National Center for Research Resources, NIH; and *3*) the Medical Research Service of the Department of Veterans Affairs.

We thank Dr. Richard Bergman for his input during preparation of the manuscript; Isabel Nader, Norma Chavez, and Maria Victor for their help in recruiting patients; Susie Nakao and the nurses of the General Clinical Research Center for their help in conducting the metabolic studies; Justo Diaz, Mike Salce, and Lilit Zeberians for their technical assistance; and Dr. Jerry Palmer for measurement of plasma islet cell antibody titers.

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