

# Gestational Diabetes: Antepartum Characteristics That Predict Postpartum Glucose Intolerance and Type 2 Diabetes in Latino Women

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We examined antepartum clinical characteristics along with measures of glucose tolerance, insulin sensitivity, pancreatic  $\beta$ -cell function, and body composition in Latino women with gestational diabetes mellitus (GDM) for their ability to predict type 2 diabetes or impaired glucose tolerance (IGT) within 6 months after delivery. A total of 122 islet cell antibody-negative women underwent oral and intravenous glucose tolerance tests (OGTT; IVGTT), hyperinsulinemic-euglycemic clamps, and measurement of body fat between 29 and 36 weeks' gestation and returned between 1 and 6 months postpartum for a 75-g OGTT. Logistic regression analysis was used to examine the relationship between antepartum variables and glucose tolerance status postpartum. At postpartum testing, 40% of the cohort had normal glucose tolerance, 50% had IGT, and 10% had diabetes by American Diabetes Association criteria. Independent antepartum predictors of postpartum diabetes were the 30-min incremental insulin:glucose ratio during a 75-g OGTT ( $P = 0.0002$ ) and the total area under the diagnostic 100-g glucose tolerance curve ( $P = 0.003$ ). Independent predictors of postpartum IGT were a low first-phase IVGTT insulin response ( $P = 0.0001$ ), a diagnosis of GDM before 22 weeks' gestation ( $P = 0.003$ ), and weight gain between prepregnancy and the postpartum examination ( $P = 0.03$ ). All subjects had low insulin sensitivity during late pregnancy, but neither glucose clamp nor minimal model measures of insulin sensitivity in the 3rd trimester were associated with the risk of IGT or diabetes within 6 months' postpartum. These results highlight the importance of pancreatic  $\beta$ -cell dysfunction, detectable under conditions of marked insulin resistance in late pregnancy, to predict abnormalities of glucose tolerance soon after delivery in pregnancies complicated by GDM. Moreover, the association of postpar-

tum IGT with weight gain and an early gestational age at diagnosis of GDM suggests a role for chronic insulin resistance in mediating hyperglycemia outside the 3rd trimester in women with such a  $\beta$ -cell defect. *Diabetes* 47:1302-1310, 1998

**R**outine glucose tolerance testing for gestational diabetes mellitus (GDM) during pregnancy identifies a group of young women who have glucose tolerance in the upper end of the population distribution at a time when most individuals are insulin resistant from the metabolic changes of pregnancy. Long-term follow-up studies indicate that at least 30-50% of those women will develop diabetes at some time after the index pregnancy (1-5), a cumulative incidence rate that is high compared with the rate in women who maintain normal glucose tolerance (NGT) during pregnancy (1,3,6) and with the prevalence of diabetes in the general population (7). Thus, GDM is an important risk factor for diabetes, especially type 2 (5,8), and may be useful for the development and testing of diabetes prevention strategies.

Knowledge of early metabolic abnormalities that predispose to diabetes may be useful for development of rational prevention strategies. Metabolic abnormalities that have been reported commonly in women with GDM or a history thereof include impaired pancreatic  $\beta$ -cell function during (6,9-13) and after (14-16) pregnancy, insulin resistance after pregnancy (14-17), and obesity (4,14,18,19). Two groups have reported that impaired early insulin responses to oral glucose during pregnancy are predictive of the persistence (4) or development (8) of diabetes after GDM. Until now, there has been no simultaneous assessment of  $\beta$ -cell function, insulin action, and body composition as possible predictors of diabetes. We are currently conducting these assessments longitudinally in a cohort of Latino women with GDM. The present report details the relationship between important regulators of glucose tolerance during the index pregnancy and the presence of impaired glucose tolerance (IGT) or type 2 diabetes within 6 months after delivery.

## RESEARCH DESIGN AND METHODS

**Subjects.** Los Angeles County Women's Hospital provides antepartum care for a large predominantly Latino population in central Los Angeles and serves as a major referral center. Screening for and diagnosis of GDM have been conducted in community-based clinics according to the recommendations of the Third International Workshop-Conference on Gestational Diabetes Mellitus (20).

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ANOVA, analysis of variance; AUC, area under the curve; GCRC, General Clinical Research Center; GDM, gestational diabetes mellitus; ICA, islet cell antibody; IGT, impaired glucose tolerance; IVGTT, intravenous glucose tolerance test; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; OR, odds ratio; RR, relative risk.

Briefly, women who are overweight or who have a prior personal or family history of diabetes are screened for GDM at their initial antepartum visit by measurement of the plasma glucose concentration 1-h after ingestion of 50 g of D-glucose. Women with a value  $\geq 140$  mg/dl undergo a 3-h 100-g oral glucose tolerance test (OGTT) to make or exclude the diagnosis of GDM (20). Women not already diagnosed with GDM between 24 and 28 weeks' gestation have the same screening and diagnostic procedures at that time. Women in the community clinics who are found to have GDM are referred to Women's Hospital for antepartum care if they have any fasting serum glucose concentration  $\geq 5.8$  mmol/l or if they have a prior history of stillbirth. During a 20-month period from August 1993 to March 1995, all Latino women referred to Women's Hospital for antepartum management of GDM were asked to participate in a long-term study of metabolic abnormalities that lead to type 2 diabetes after GDM if they 1) were between 29 and 34 weeks' gestation as assessed by a clinical examination before 12 weeks' gestation or an ultrasound before 20 weeks' gestation, 2) were not on insulin therapy, 3) had all fasting serum glucose concentrations  $< 7.2$  mmol/l since the diagnosis of GDM, and 4) had otherwise uncomplicated singleton pregnancies. Only women whose parents and at least three of four grandparents were from Mexico, Guatemala, or El Salvador were recruited.

Of 223 women who met the inclusion criteria for the study, 153 came for antepartum testing, 150 completed all antepartum testing (described below), and 3 completed an OGTT and body composition studies plus either an intravenous glucose tolerance test (IVGTT) or a glucose clamp. Three of the 153 women had circulating anti-islet cell antibodies (ICAs); they were excluded from the analysis. A total of 122 ICA-negative women returned for an OGTT within 6 months after delivery; their data were analyzed for this report. 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.** At least 3 days after instruction in a diet that provided 30 kcal/kg total body wt (25 kcal/kg for women with a prepregnancy body weight  $> 120\%$  of ideal) as 50% carbohydrate, 20% protein, and 30% fat, subjects came to the General Clinical Research Center (GCRC) on 3 separate days at least 48 h apart and after an 8- to 10-h overnight fast.

On 1 of the 3 test days, an OGTT was performed to assess plasma insulin and glucose responses. Subjects reported to the GCRC between 0700 and 0900 and were placed in a hospital gown, weighed, measured for height, and placed at bed rest. A single intravenous catheter was placed in an antecubital vein and kept open with physiological saline. At least 30 min later, basal blood samples were obtained, and subjects drank 10 g of D<sub>2</sub>O (Cambridge Isotope Lab, Andover, MA) followed in 5 min by 75 g of D-glucose (Glucose Tolerance Drink; Stephens Scientific, Riverdale, NJ), which was consumed in  $< 5$  min. Additional blood samples were obtained at 15, 30, 60, 90, 120, and 180 min after the start of the glucose ingestion. Blood samples were placed in chilled tubes and kept on ice until centrifugation within 20 min after they were drawn. Plasma was kept at  $-70^{\circ}\text{C}$  until analysis.

On a separate day, a glucose clamp was performed to assess peripheral and hepatic insulin sensitivity. Subjects reported to the GCRC by 0600 and were placed at bed rest. Intravenous catheters were placed in one antecubital vein for infusions and a contralateral dorsal hand vein for blood sampling; the sampling hand was warmed to  $\sim 60^{\circ}\text{C}$  throughout the procedure. A primed ( $0.035$  mmol/kg body wt) continuous ( $2.5 \times 10^{-4}$  mmol  $\cdot$  min $^{-1}$   $\cdot$  kg $^{-1}$ ) infusion of  $6,6$ -<sup>2</sup>H<sub>2</sub> D-glucose ("tracer"; Isotec, Miamisburg, OH) was administered for 360 min. A nonprimed infusion of crystalline human insulin ( $50$  mU  $\cdot$  min $^{-1}$   $\cdot$  m $^{-2}$  body surface area) was administered during the final 180 min of the tracer infusion. Plasma glucose concentrations were measured every 5 min during the insulin infusion (Beckman Glucose Analyzer II; Beckman, Brea, CA). Dextrose (20% wt/vol in water), containing dideutero-glucose ( $0.021$  mmol/cm $^3$ ) to minimize changes in plasma tracer enrichment (21), was given at a rate sufficient to maintain plasma glucose concentrations at  $\sim 4.8$  mmol/l. Blood samples for measurements of substances other than D-glucose were obtained in chilled 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  $-70^{\circ}\text{C}$  before analysis.

On a 3rd test day, an IVGTT was performed to assess pancreatic  $\beta$ -cell function and to obtain measures of insulin- and glucose-dependent glucose utilization. Subjects came to the GCRC by 0700 and were weighed and placed at bed rest. An intravenous catheter was placed in one antecubital vein and a contralateral dorsal hand vein; the hand was heated to  $\sim 60^{\circ}\text{C}$  throughout the test. At least 45 min after catheter placement, 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). Blood samples were obtained 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. Samples were placed in chilled tubes, and plasma was separated within 20 min and stored at  $-70^{\circ}\text{C}$ .

Height was measured with a stadiometer after removal of shoes. Body fat was assessed by measurement of total body water, using plasma D<sub>2</sub>O enrichment before and 180 min after ingestion of 10 g of D<sub>2</sub>O. Hydration constants of 0.76 (22)

and 0.724 (23) were used to calculate fat-free mass from measures of total body water in pregnant and nonpregnant subjects, respectively.

Each woman who completed the detailed antepartum testing was instructed to return at least 6 weeks after delivery for a 75-g OGTT performed identically to the antepartum test.

**Laboratory analysis.** Glucose was measured by glucose oxidase (Beckman Glucose Analyzer II). Insulin was measured by a charcoal precipitation radioimmunoassay (Novo Pharmaceuticals, Danbury, CT) that measures insulin and proinsulin. After conversion of glucose to its aldonitrile penta-acetate derivative (24),  $6,6$ -<sup>2</sup>H<sub>2</sub>-glucose concentrations in infusates and perchloric acid supernatants of plasma were determined by gas chromatography and mass spectroscopy. D<sub>2</sub>O enrichment in a distillate of plasma water was determined by isotope ratio mass spectroscopy after reduction to hydrogen gas by heating at  $550^{\circ}\text{C}$  for 2 h in the presence of elemental zinc (25). Anti-pancreatic ICAs in plasma were measured by an indirect immunofluorescence assay using human pancreas. The assay has a detection limit of 1 Juvenile Diabetes Foundation unit.

**Data analysis.** Total areas under the curves (AUCs) for OGTT glucose and insulin were calculated by the trapezoid method. Glucose turnover rates during euglycemic clamps were calculated using the Steele equations for non-steady-state conditions as modified by Finegood et al. (21). IVGTT glucose and insulin data were subjected to minimal model analysis (26) using the MINMOD program provided by Dr. Richard Bergman. Pancreatic  $\beta$ -cell response to intravenous glucose was expressed as the incremental AUC for insulin during the first 10 min after the glucose injection.

Variables that were tested for associations with postpartum diabetes and postpartum IGT are listed in the APPENDIX and include measures of age, body weight and weight change, glucose tolerance, insulin concentrations and responses to glucose, basal glucose production, peripheral and hepatic insulin sensitivity, and breastfeeding. The distributions of all continuous variables were tested for normality. Gestational age at the diagnosis of GDM was bimodally distributed, so it was dichotomized at the intermodal nadir of 22 weeks for analysis. Distributions of all insulin values and ratios of insulin to other variables were positively skewed, so these variables were log-transformed before statistical analyses. For parameters that were analyzed as continuous variables, mean values were compared among groups of women with NGT, IGT, and diabetic postpartum glucose tolerance by analysis of variance (ANOVA). Fisher's least significant differences test was used for pairwise comparisons between groups when ANOVA revealed significant differences among them. For parameters that were dichotomized for analysis, Fisher's exact test or  $\chi^2$  test was used to compare proportions among the three groups.

Logistic regression analysis was used to examine the relationship between parameters that were quantified during pregnancy and glucose tolerance status postpartum. Two separate analyses were performed: one to find antepartum predictors of postpartum diabetes and one to find predictors of postpartum IGT, both as defined by the American Diabetes Association (27). In the latter analysis, subjects with postpartum diabetes were excluded. In each analysis, univariate methodology was first applied to examine the relationship between individual variables and the development of the outcome of interest (IGT or diabetes). Continuous variables were evaluated in their continuous forms. For purposes of comparing the relative magnitude of the univariate effects across the two different outcomes, relative risks (RRs) based on the continuous variables were computed for units equal to the difference between the medians of the 3rd and 1st tertiles.

Stepwise multivariate logistic regression was used to identify variables that were statistically significant independent predictors of the outcome of interest. The significance level for variable entry and retention in the model was 0.05. All variables were offered to the stepwise regression except the glucose measurements from the individual time points of the 100-g OGTT and the individual glucose and insulin measurements from the 75-g OGTTs, since these were highly correlated with their respective AUCs. Thus, only the fasting levels and AUCs for plasma concentration were offered for glucose and insulin. After the stepwise regression, measurements from the individual time points of the two OGTTs were forced into the final models, one at a time, to determine whether their addition resulted in a statistically significant improvement in the models. Because they did not, only final models from analyses using AUCs are presented. Finally, for purposes of graphic presentation, the risks associated with variables in the final models were estimated by dividing the cohort into tertiles for these variables and then calculating the adjusted RRs of postpartum IGT or diabetes for women in the second and 3rd tertiles compared with women in the first tertile. For these adjusted RRs, two dummy variables representing the second and 3rd tertiles were entered along with continuous values of the adjustment variables.

Statistical analyses were performed using SAS (SAS Institute, Cary, NC) and Epilog Plus (Epicenter Software, Pasadena, CA) computer programs. RRs were estimated as odds ratios (ORs). All reported *P* values are two-sided.

## RESULTS

Compared with the 122 women who returned for postpartum testing, the 28 ICA-negative women who did not return had

TABLE 1  
Clinical characteristics and percent body fat in groups with NGT, IGT, or diabetic glucose tolerance postpartum

	Postpartum status			P value
	NGT	IGT	Diabetes	
<i>n</i>	49	61	12	
Prepregnancy BMI (kg/m <sup>2</sup> )	30.4 ± 5.0*	28.0 ± 4.1*	29.1 ± 4.0	0.02
Antepartum				
Age (years)	30.8 ± 5.2	29.3 ± 5.7	32.3 ± 6.2	0.13
100-g OGTT glucose AUC (mmol/l · min <sup>-1</sup> )	1,645 ± 152*†	1,713 ± 187†‡	1,903 ± 235*†	0.0001
Highest fasting plasma glucose (mmol/l)	5.7 ± 0.6	5.8 ± 0.6	5.9 ± 0.5	0.33
Gestational age at entry (weeks)	33.5 ± 2.6*	32.1 ± 2.4*†	33.8 ± 3.4†	0.009
Weight change from prepregnancy (kg)	7.0 ± 4.4	8.7 ± 4.4*	3.9 ± 5.2*	0.004
Body fat (%)	35.6 ± 6.9	33.2 ± 7.3	34.6 ± 6.7	0.26
Postpartum				
BMI (kg/m <sup>2</sup> )	30.8 ± 4.9	29.4 ± 4.8	29.5 ± 3.5	0.3
Weight change from prepregnancy (kg)	0.6 ± 5.4*	2.7 ± 4.7*†	-0.9 ± 4.5†	0.03
Body fat (%)	36.7 ± 7.1	36.2 ± 6.0	35.4 ± 4.8	0.82
Breastfeeding (% of group)	71*	49*	42	0.03

Data are means ± SD, unless otherwise indicated. P values were determined by ANOVA among three groups. Antepartum age, gestational age at entry, weight change from prepregnancy, and body fat were recorded on the day of the first of three antepartum GCRC visits for detailed metabolic testing. A 100-g OGTT was used to make a diagnosis of GDM. Highest fasting plasma glucose was determined at OGTTs or at clinic visits before metabolic testing. Postpartum data was determined at GCRC visit for 75-g OGTT within 6 months after delivery. \*†‡P < 0.05; values on a line that share the same symbol are significantly different.

a lower mean ± SD BMI (30.5 ± 4.7 vs. 32.6 ± 4.7 kg/m<sup>2</sup>; P = 0.04) and a higher mean glucose AUC on antepartum OGTTs (1,593 ± 236 vs. 1,482 ± 209 mmol/l · min<sup>-1</sup>; P = 0.02) at the time of antepartum metabolic testing. Other variables listed in the APPENDIX did not differ significantly between the two groups. At postpartum testing, 49 (40%) of the cohort had NGT, 61 (50%) had IGT, and 12 (10%) had diabetes. Insulin therapy was administered when two successive antepartum fasting glucose concentrations exceeded 5.8 mmol/l despite diet therapy. Insulin was given during pregnancy, after detailed metabolic testing, to 8.2, 18.7, and 8.3% of the women in the three postpartum diagnostic categories, respectively (P = 0.24).

Comparisons among groups with NGT, IGT, and diabetic glucose tolerance postpartum revealed a small but significant difference in antepartum BMI between groups with NGT and IGT (Table 1). Mean ages at entry into the study did not differ significantly among groups with NGT, IGT, and diabetic glucose tolerance postpartum. AUCs for plasma glucose from the 100-g diagnostic OGTTs increased progressively and significantly in association with worsening postpartum glucose tolerance. By contrast, the highest fasting glucose concentration recorded during pregnancy did not differ significantly among groups. Detailed metabolic testing commenced slightly earlier in the women with IGT than in the other two groups. Women with postpartum diabetes had gained less weight from their stated prepregnancy weight by the time of metabolic testing compared with the other two groups, but there were no significant differences in percent body fat at the time of the detailed antepartum testing. Postpartum BMI and percent body fat also did not differ significantly among groups. However, the greatest weight gain recorded between the two nonpregnant conditions—pregnancy and the postpartum OGTT—was in the women with postpartum IGT (Table 1). Approximately twice as many women in the NGT OGTT group were breastfeeding at the postpartum exam compared with the other two groups.

Slightly more than half of the women in each of the postpartum NGT and IGT groups were first screened for GDM before 20 weeks' gestation (Table 2). Despite this similarity in the frequency of early screening, significantly more women in the postpartum IGT group were diagnosed before 22 weeks' gestation (39 vs. 14%, P = 0.005, Table 2). Only one-fourth of the women in the postpartum diabetes group were first screened before 20 weeks. All of those women were diagnosed with GDM before 22 weeks' gestation.

Results of antepartum 75-g OGTTs, which were conducted under carefully controlled conditions in the GCRC, are displayed in Fig. 1. Women who proved to have NGT or IGT postpartum had similar glucose results during the first 90 min of the antepartum test. Glucose levels were slightly, but signifi-

TABLE 2  
Proportions of women screened for GDM before 20 weeks' gestation and diagnosed before 22 weeks' gestation

	Postpartum status			P value
	NGT	IGT	Diabetes	
<i>n</i>	49	61	12	
Screened before 20 weeks' gestation (%)	59	52	25	0.11
Diagnosed before 22 weeks' gestation (%)				
All women	14*	39*	25	0.01
Women screened before 20 weeks	26*†	76*	100†	0.0001

P values were determined by Fisher's exact test. The 20 weeks' gestation is based on a 2-week interval between a positive screening test and performance of a 100-g OGTT. The 22 weeks' gestation is the intermodal nadir in the bimodal distribution of gestational ages at diagnosis of GDM in the cohort. \*†P < 0.03; values on a line that share the same symbol are significantly different.

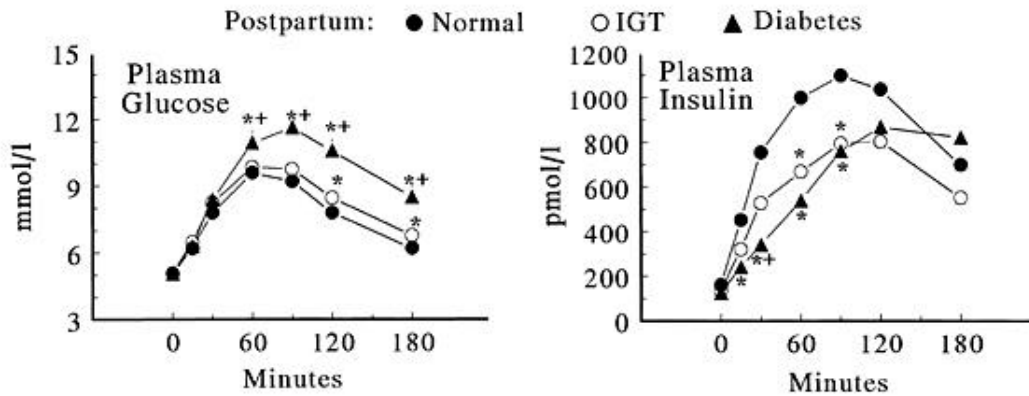


FIG. 1. Plasma glucose and insulin concentrations during 75-g antepartum OGTTs in women with GDM who proved to have NGT, IGT, or diabetic glucose tolerance within 6 months postpartum. Insulin data were log-transformed before statistical comparisons; untransformed means are presented. \* $P < 0.05$  vs. postpartum NGT; + $P < 0.05$  vs. postpartum IGT.

cantly, higher in the postpartum IGT group at 120 and 180 min. Women who proved to have diabetes postpartum had higher postload glucose concentrations than the other two groups from 60 min onward. The total AUC for glucose increased progressively from NGT to IGT to diabetes in the postpartum groups ( $1,408 \pm 205$ ,  $1,493 \pm 176$ , and  $1,728 \pm 183$  mmol/l · min<sup>-1</sup>, respectively;  $P = 0.0001$ ).

Despite similar plasma glucose levels during the first 30 min of the OGTT, there was a progressive decline in insulin responses across the spectrum of postpartum glucose tolerance from normal to diabetic (Fig. 1). Accordingly, incremental plasma insulin:glucose ratios early in the OGTT fell progressively across the spectrum of normal, impaired, and diabetic postpartum glucose tolerance (15-min ratios:  $240 \pm 178$ ,  $150 \pm 68$ , and  $110 \pm 90$  pmol/mmol, respectively,  $P = 0.0001$ ; 30-min ratios:  $221 \pm 214$ ,  $128 \pm 68$ , and  $64 \pm 73$  pmol/mmol, respectively,  $P = 0.0001$ ). Insulin concentrations remained lower in the postpartum IGT group than in the postpartum NGT group throughout the OGTT. Insulin concentrations in the postpartum diabetic group increased during the final 90 min of the OGTT in association with hyperglycemia and were higher than in the other two groups at 180 min.

Basal plasma glucose ( $5.4 \pm 0.5$ ,  $5.4 \pm 0.5$ , and  $5.6 \pm 0.6$  mmol/l;  $P = 0.35$ ) and insulin ( $160 \pm 65$ ,  $138 \pm 44$ , and  $145 \pm 72$  pmol/l;  $P = 0.09$ ) concentrations on the day of glucose clamps were not statistically different among postpartum NGT, IGT, and diabetic groups. Likewise, basal glucose turnover was similar among the groups ( $0.50 \pm 0.07$ ,  $0.49 \pm 0.07$ , and  $0.51 \pm 0.09$  mmol · min<sup>-1</sup> · m<sup>-2</sup> body surface area, respectively;  $P = 0.63$ ). Elevation of plasma insulin levels to  $639 \pm 158$ ,  $580 \pm 131$ , and  $668 \pm 173$  pmol/l in postpartum NGT, IGT, and diabetic groups resulted in similar stimulation of glucose disappearance and suppression of glucose production in the three groups (Fig. 2). By contrast, first-phase insulin responses to an intravenous glucose injection were significantly higher in women who proved to have NGT postpartum than in women who proved to have either IGT or diabetic glucose tolerance (Fig. 3).

Univariate analysis revealed a number of parameters that were associated with either diabetes or IGT within 6 months postpartum (Table 3). For postpartum diabetes, the significant univariate associations were all with antepartum measures of glucose tolerance (higher levels = increased risk) and insulin responses to glucose (lower responses = increased risk). Multivariate analysis revealed two variables that, when tested as continuous variables, were independently associated with the risk of diabetes within 6 months postpartum: the 30-min

incremental plasma insulin:glucose ratio during the antepartum 75-g OGTT (lower = increased risk; adjusted  $P$  value for continuous variable = 0.0002) and the total AUC for antepartum 100-g OGTT glucose (higher = increased risk; adjusted  $P$  value = 0.003). Figure 4, in which RRs are plotted for the second and 3rd tertile compared with the first tertile for each of these independent predictors, reveals that the increased risk of diabetes associated with the 30-min insulin:glucose ratio was limited to the lowest tertile. By contrast, the risk associated with the 100-g OGTT glucose AUC increased progressively from the lowest to the highest tertile. When the multivariate analysis was conducted without the 100-g OGTT, the glucose AUC from the 75-g OGTT was independently associated with the risk of postpartum diabetes. However, the overall goodness of fit of the model was reduced, indicating that the 100-g OGTT, which was conducted before dietary intervention and without insulin measurements, was more strongly predictive of postpartum diabetes.

The two general categories of elevated glucose and poor insulin responses to glucose were also risk factors for postpartum IGT on univariate analysis (Table 3). In addition, diag-

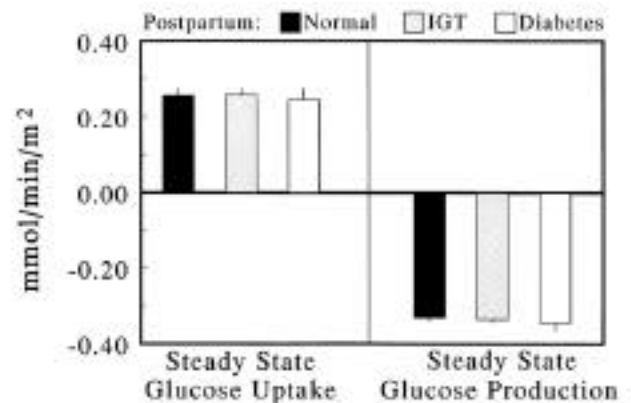


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FIG. 2. Antepartum glucose clamp results from the three groups described in Fig. 1. Peripheral and hepatic insulin sensitivity are expressed as changes in tracer-determined rates of glucose uptake and production, respectively, between the basal period and the final 30 min of 3-h glucose clamps. Final plasma insulin concentrations during clamps were  $642 \pm 132$ ,  $594 \pm 123$ , and  $628 \pm 180$  pmol/l in women with NGT, IGT, and diabetic glucose tolerance postpartum. No significant intergroup differences were detected. Vertical lines on bars are SE.

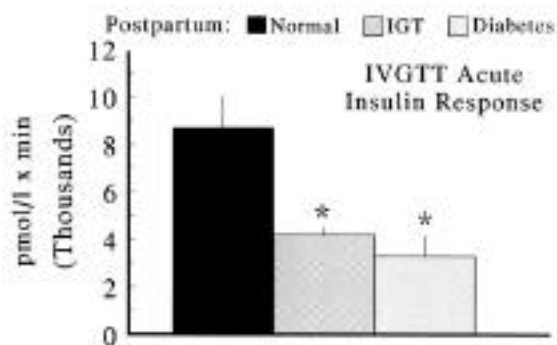


FIG. 3. Incremental insulin AUC during the first 10 min after an intravenous glucose injection during the 3rd trimester of pregnancy in the three study groups. Data were log-transformed before statistical analysis; untransformed data are presented. \**P* 0.01 vs. postpartum NGT. Vertical lines on bars denote SE.

nosis of GDM before 22 weeks' gestation and weight gain from before pregnancy to the postpartum period were univariate risk factors for IGT (Table 3). Multivariate analysis revealed three factors that were independently associated with the risk of postpartum IGT: the first-phase insulin response on the antepartum IVGTT (low = increased risk; *P* = 0.0001), gestational age <22 weeks at diagnosis of GDM (*P* = 0.002), and

weight gain between prepregnancy and the postpartum examination (*P* = 0.03). Plots of the RRs of IGT among tertiles of the cohort for the two continuous variables (Fig. 5) revealed a progressive increase in risk in association with lower first-phase insulin and increasing weight gain. Diagnosis of GDM before 22 weeks' gestation was associated with a 5.8-fold increase in the risk of postpartum IGT compared with later diagnosis of GDM (Fig. 5).

Stepwise logistic regression was also performed using any abnormal glucose metabolism (i.e., postpartum IGT and diabetes combined) as the outcome of interest. Three statistically significant independent predictors emerged: one of the two independent predictors of postpartum diabetes (high glucose AUC on the diagnostic OGTT) and two of the three independent predictors of postpartum IGT (low first-phase insulin response to intravenous glucose and diagnosis of GDM before 22 weeks' gestation).

DISCUSSION

This is the first relatively large-scale examination of glucose tolerance, insulin sensitivity, pancreatic  $\beta$ -cell function, and body composition during pregnancy in relation to the presence or absence of hyperglycemia after pregnancies complicated by GDM. Patients were all Latino, and they were selected to have a >60% probability of developing diabetes within 5 years after their index pregnancies (5). We found several factors that

TABLE 3  
Significant univariate predictors of postpartum diabetes or IGT

	Postpartum diabetes				Postpartum IGT			
	Medians	RR	95% CI	<i>P</i> value	Medians	RR	95% CI	<i>P</i> value
<b>Antepartum</b>								
Plasma glucose (mmol/l)								
GDM screen	7.4, 11.3	5.88	1.80–19.15	0.003	7.4, 10.2	2.10	1.09–4.18	0.03
100-g OGTT AUC	1,537, 1,842	4.70	1.90–11.65	0.0005	1,533, 1,802	1.94	1.00–3.72	0.047
75-g OGTT AUC	1,287, 1,682	11.11	2.88–42.87	0.0008	1,286, 1,639	2.51	1.13–5.58	0.02
Plasma insulin (pmol/l)								
15-min 75-g OGTT	194, 462	0.30	0.11–0.85	0.02	215, 469	0.59	0.33–1.05	0.07
30-min 75-g OGTT	284, 817	0.16	0.05–0.49	0.002	317, 829	0.52	0.27–1.02	0.06
60-min 75-g OGTT	382, 1,170	0.29	0.10–0.85	0.02	411, 1,173	0.32	0.14–0.76	0.01
90-min 75-g OGTT	452, 1,286	0.51	0.18–1.43	0.20	486, 1,319	0.42	0.20–0.89	0.02
IVGTT AIR <sub>g</sub>	2,117, 8,670	0.24	0.08–0.67	0.007	2,502, 9,329	0.12	0.04–0.33	0.0001
Insulin:glucose ratio (pmol/l per mmol/l)								
15-min 75-g OGTT incremental	80, 244	0.27	0.11–0.68	0.006	88, 251	0.30	0.14–0.65	0.002
30-min 75-g OGTT incremental	56, 226	0.07	0.02–0.26	0.0001	76, 231	0.34	0.16–0.71	0.004
60-min 75-g OGTT incremental	61, 207	0.39	0.17–0.89	0.03	72, 210	0.52	0.27–0.99	0.047
Gestational age at diagnosis of GDM (<22 weeks)	—	0.85	0.22–3.34	0.82	—	3.89	1.5–10.07	0.005
<b>Postpartum</b>								
Weight change from prepregnancy weight (kg)	–4.5, 6.4	0.28	0.06–1.36	0.11	–4.2, 6.6	2.48	1.03–6.00	0.04

Variables appear in table if univariate analysis yielded *P* < 0.05 for either postpartum diabetes or IGT. Insulin variables were log-transformed before calculation of RRs, CIs, and *P* values. Postpartum diabetes analysis was based on all subjects (*n* = 122); postpartum diabetes as outcome variable. Postpartum IGT analysis was based on subjects without postpartum diabetes (*n* = 110); postpartum IGT as outcome variable. Medians were of first and third tertiles. RR, calculated as OR per difference between medians of third and first tertiles except for gestational age at diagnosis of GDM, in which case ORs were calculated as <22 vs. 22 weeks. A 100-g OGTT was used to diagnose GDM. The 75-g OGTT was conducted at the GCRC. AUC denotes area under OGTT glucose curves in millimoles per liter x minute; glucose values at individual times of 100-g and 75-g OGTT were also associated with postpartum IGT and diabetes. Acute insulin response to intravenous glucose (AIR<sub>g</sub>) was calculated as incremental AUC for plasma insulin during first 10 min after glucose injection. The 75-g OGTT incremental was calculated as (insulin at stated time – basal insulin)/(glucose at stated time – basal glucose).

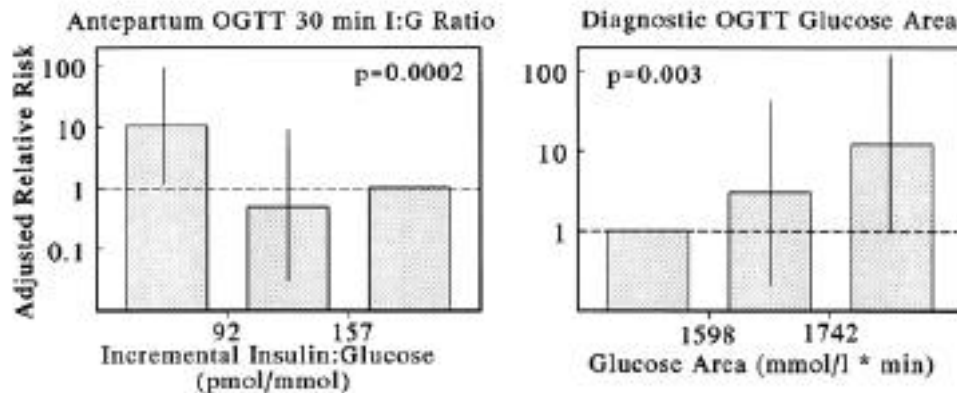


FIG. 4. Two independent predictors of postpartum diabetes. For each predictor, the adjusted RR for diabetes is depicted for each of the two highest risk tertiles relative to the lowest risk tertile. Vertical lines on bars are 95% CIs. Tertile breaks appear on the x-axis. Dashed line is RR of 1.0. *P* values listed on the panels were calculated using continuous variables.

were related to glucose tolerance within 6 months after those pregnancies. Two antepartum variables were predictive of type 2 diabetes: reduced early insulin responses and elevated glucose concentrations during antepartum OGTTs. These two associations are in agreement with the findings of Metzger et al. (4) in a cohort of white, black, Hispanic, and Asian women. The association of postpartum diabetes with poor antepartum insulin responses was independent of antepartum glucose levels, highlighting the importance of a  $\beta$ -cell defect in the pathogenesis of diabetes soon after GDM. The association of diabetes with antepartum hyperglycemia could reflect either the presence of undiagnosed diabetes before pregnancy (28) or very rapid and marked deterioration of maternal glycemia in a subset of women whose hyperglycemia persisted postpartum. Our study design, which did not include measures of glucose tolerance before pregnancy, does not allow us to distinguish between those two scenarios. However, it is important to note that both reduced early insulin responses and postchallenge hyperglycemia were documented only 2–8 months before the detection of type 2 diabetes. Thus, we can only conclude from the present analysis that these abnormalities are present relatively late in the pathogenesis of type 2 diabetes. Longer follow-up will be required to determine whether they are also early risk factors for diabetes that develops much later after the index pregnancy.

IGT soon after GDM portends an 80% risk of developing diabetes within 5 years in Latinas (5). Thus, the three antepartum variables that were linked to postpartum IGT in this

cohort are likely to represent relatively early defects in the pathogenesis of type 2 diabetes. The strongest predictor of postpartum IGT was a poor  $\beta$ -cell response to intravenous glucose during the 3rd trimester. This finding highlights the importance of  $\beta$ -cell dysfunction as an early abnormality in patients predisposed to type 2 diabetes. The importance of such a defect may be underestimated unless insulin secretion is considered in light of ambient insulin sensitivity, as proposed by Bergman (29) and demonstrated by Lillioja et al. (30) in prospective studies of Pima Indians and by Ryan et al. (16) in cross-sectional studies of women with prior GDM. The conduct of IVGTTs in late pregnancy in the present study allowed us to assess  $\beta$ -cell function under conditions of marked insulin resistance. Under those conditions, women destined to have IGT postpartum manifested a mean reduction of 52% in their first-phase  $\beta$ -cell response to intravenous glucose compared with women with NGT postpartum (Fig. 3). The  $\beta$ -cell defect was particularly impressive in view of the similarities in fasting glucose concentrations and oral glucose tolerance that were observed in the two groups during late pregnancy (Fig. 1). In fact, antepartum plasma glucose concentrations were not independently predictive of postpartum IGT, further highlighting the importance of pancreatic  $\beta$ -cell dysfunction in women who are at very high risk for developing type 2 diabetes within 5 years.

An association between abnormal glucose tolerance postpartum and an early gestational age at diagnosis of GDM has been reported by several groups, including our own, in less

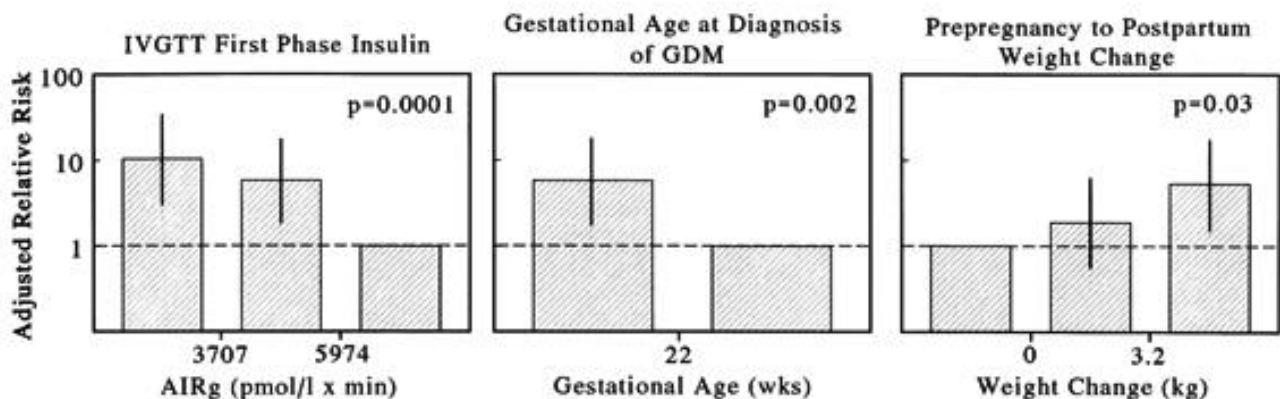


FIG. 5. Three independent predictors of postpartum IGT. Format for data presentation matches Fig. 4, except that gestational age at diagnosis was analyzed as a dichotomous variable as described in text.

detailed studies of women with GDM (5,6,31,32). One potential explanation for this association is that some well-known risk factors for glucose intolerance in nonpregnant individuals (e.g., obesity) also serve as indications for screening pregnant women for GDM before the standard interval of 24–28 weeks' gestation (20). If that explanation were responsible for the association between an early diagnosis of GDM and postpartum IGT in this cohort, we would have found more screening tests early in pregnancy in the group with postpartum IGT than in the postpartum NGT group. We did not. In fact, a slightly higher fraction of the postpartum NGT women were screened before 20 weeks (Table 2). However, a much larger proportion of the postpartum IGT group was found to have GDM after early screening. Thus, it appears that the women with postpartum IGT were more hyperglycemic early in pregnancy due to some factor that was either not measured or not accounted for in the statistical analysis. Chronic insulin resistance could be that factor. Several groups (14–16) have reported insulin resistance in nonpregnant women with a history of GDM compared with women who maintained NGT during pregnancy. Catalano et al. (12) have also reported abnormally low insulin sensitivity in women with GDM during the 2nd trimester, before the metabolic changes of late pregnancy make all women very insulin-resistant. Those observations indicate that two types of insulin resistance are present in women with GDM: the normal insulin resistance of late pregnancy and more chronic insulin resistance, as seen in other groups at risk for type 2 diabetes (33–35). Women with the chronic form of insulin resistance will become hyperglycemic earlier in pregnancy than women with similar  $\beta$ -cell dysfunction whose only insulin resistance is acquired late in gestation. The chronic insulin resistance will also persist after pregnancy, contributing to glucose intolerance in women with limited  $\beta$ -cell reserve. Therefore, we speculate that chronic insulin resistance contributed to the development of glucose intolerance both early in pregnancy and after delivery in the postpartum IGT group. We also predict that such insulin resistance will increase the risk of future diabetes, a prediction that we are currently testing prospectively.

The lack of association between an early gestational age at diagnosis and postpartum diabetes most likely was related to the fact that women with postpartum diabetes were screened relatively late compared with the other two groups; only 25% were screened before 20 weeks' gestation. When screened at that early interval, they were uniformly diagnosed with GDM before 22 weeks' gestation, indicating that at least the subset who were screened before 20 weeks were hyperglycemic at that early time. Whether the late screening in the other postpartum diabetic women reflects limited participation in antepartum care, a lack of high-risk clinical profile (e.g., less weight gain than the other groups), or some other factor cannot be ascertained from the present study.

The 3rd association with postpartum IGT was the amount of weight gained from prepregnancy to the postpartum examination. Among the three study groups, women with postpartum IGT started with the lowest BMI before pregnancy, gained the most weight during pregnancy, and manifested the greatest increase in weight relative to prepregnancy when tested <6 months postpartum. The last of these three observations reflects the maternal component of weight gain that persisted after delivery, and

the multivariate analysis revealed such weight gain to be independently associated with the risk of postpartum IGT. In fact, every 10 pounds of maternal weight gained from prepregnancy increased the risk of having postpartum IGT by a factor of 1.63. Differences in body fat did not account for the impact of weight gain on the risk of diabetes in the multivariate analysis, although fat distribution, which was not assessed in this study, might have played a role. Because postpartum IGT carries a very high risk for type 2 diabetes within 5 years (5), it follows that maternal weight that is gained during pregnancy but not lost postpartum places women at increased long-term risk for diabetes. No such relationship was found for women with diabetes immediately postpartum; they actually lost weight on average from their prepregnancy weights. We can only speculate that their antepartum hyperglycemia was already sufficiently severe to override any impact of weight changes on the immediate postpartum risk of diabetes. Our findings regarding postpartum IGT are complementary to reports from other groups indicating that maternal BMI preceding pregnancy (4,19) is a risk factor for diabetes in the years after detection of GDM and our own observation that weight gain after the index pregnancy increases the subsequent risk of diabetes (36). Clearly, obesity is an important risk factor for diabetes in women with a history of GDM. The mechanisms that mediate this risk remain speculative, and serial measurements of insulin sensitivity after pregnancy will be required to determine whether insulin resistance mediates the effect of weight gain on the risk of diabetes.

None of the measures of hepatic or peripheral insulin sensitivity obtained during the 3rd trimester was associated with the risk of IGT or diabetes within 6 months postpartum. This lack of association may be due at least in part to the fact that physiological changes of late pregnancy lead to marked insulin resistance in virtually all women. Thus, any underlying differences in chronic insulin sensitivity among postpartum groups may have been obscured by the physiological changes of late pregnancy. In addition, the number of patients in our cohort who had diabetes within 6 months after pregnancy was small, limiting our power to detect predictors of diabetes. Nonetheless, we were able to detect significant associations between poor  $\beta$ -cell function and postchallenge hyperglycemia during pregnancy and the risk of postpartum diabetes, and we found no relationship between antepartum insulin sensitivity and postpartum IGT, despite the much larger number of women with that condition. Therefore, we conclude that the degree of insulin resistance in the 3rd trimester was not an important predictor of abnormal glucose tolerance within 6 months after GDM. Rather, it appears that the universal insulin resistance of pregnancy plays an important role in bringing to clinical attention women with limited  $\beta$ -cell reserve who are, thereby, at risk for diabetes or IGT after delivery.

The incidence rate of diabetes soon after pregnancy in this study was similar to the rate we observed in a much larger cohort of predominantly Latino women with recent GDM (5). By contrast, the incidence of IGT was nearly twice as high, a finding that was very likely the result of our study design. Patients were selected not at random, but after having at least one fasting glucose concentration  $\geq 5.8$  mmol/l during pregnancy. This selection criterion was designed to provide a relatively high rate of diabetes for long-term studies of

diabetes after GDM. Thus, the rates of diabetes and IGT reported herein cannot be extrapolated to Latino women with GDM in general. However, the women did have a broad range of fasting glycemia and other variables, making the comparisons of risk across the cohort useful in identifying characteristics that are potentially important in the pathogenesis of type 2 diabetes.

In summary, in an analysis that focused on measures of antepartum  $\beta$ -cell function, insulin sensitivity, and body composition in women with GDM, we found that antepartum hyperglycemia and poor insulin responses to oral glucose were independent risk factors for diabetes within 6 months after delivery. Poor insulin responses to intravenous glucose, an early gestational age at diagnosis of GDM, and weight gain between prepregnancy and postpartum periods were independent risk factors for postpartum IGT, a condition that is associated with a very high 5-year diabetes risk. These findings highlight the importance of  $\beta$ -cell dysfunction in determining the risk of diabetes after GDM. They also are consistent with the concept that chronic insulin resistance persisting after pregnancy will increase that risk. Studies of the pathogenesis and prevention of type 2 diabetes after GDM should focus on the relationship between  $\beta$ -cell function and insulin action in women whose hyperglycemia is initially identified under conditions of insulin resistance in late pregnancy.

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#### APPENDIX: DEFINITION OF VARIABLES TESTED FOR AN ASSOCIATION WITH IGT OR DIABETES WITHIN 6 MONTHS AFTER GDM

##### Prepregnancy variables

**Body weight (kg).** Stated or measured weight from patient's clinical record

**BMI ( $\text{kg}/\text{m}^2$ ).** Calculated from measured height at first antepartum visit and prepregnancy weight from clinical record

##### Antepartum variables

**Age (years).** At time of first of three GCRC visits

**Gestational age (weeks).** Using menstrual dates and clinical exam before 12 weeks' gestation or ultrasound exam before 20 weeks' gestation

- At screening for GDM: date of first 1-h glucose screening test for GDM
- At diagnosis of GDM: date of first 3-h OGTT that met National Diabetes Data Group criteria for GDM

**Diagnostic OGTT variables.** From 100-g 3-h OGTT at which GDM was diagnosed

- 0-, 1-, 2-, and 3-h plasma glucose concentrations

(mmol/l)

- Total AUC for glucose, by trapezoid method

**Study OGTT variables.** From 75-g 3-h OGTT conducted in GCRC

- 0-, 1-, 2-, and 3-h plasma glucose concentrations (mmol/l)
- 0-, 1-, 2-, and 3-h plasma insulin concentrations (pmol/l)
- Total AUC for glucose and insulin, by trapezoid method
- Ratios of increment in insulin above basal to increment in glucose above basal at 15 and 30 min after the glucose ingestion

**Glucose clamp variables ( $\text{mmol} \cdot \text{min}^{-1} \cdot \text{m}^2$  body surface area).**

- Basal endogenous glucose production: calculated from Steele equation using mean of five plasma glucose and  $6,6\text{-}^2\text{H}_2$  glucose enrichment values ( $-90$ ,  $-70$ ,  $-50$ ,  $-30$ , and  $-10$  min)
- Peripheral insulin sensitivity: increment above basal in glucose disappearance rate, calculated by Steele equation using data from 160 to 180 min of clamp
- Hepatic insulin sensitivity: decrement below basal in endogenous glucose production rate, calculated by Steele equation using data from 160 to 180 min of clamp

**IVGTT variables.**

- First-phase insulin response ( $\text{pmol}/\text{l} \cdot \text{min}^{-1}$ ): incremental AUC for plasma insulin during first 10 min after the start of a 1-min glucose injection, calculated by trapezoid method
- $S_I$  ( $\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1} \times 10^4$ ): increase in fractional glucose disappearance attributed to an increase in plasma insulin above basal, calculated by minimal model analysis (26)
- $S_G$  ( $\text{min}^{-1}$ ): fractional glucose disappearance rate at basal insulin, calculated by minimal model analysis (26)

**Body composition variables.**

- Weight change from prepregnancy (kg): calculated from measured weight at first visit for detailed metabolic testing and recorded prepregnancy weight in patient's clinical record
- BMI ( $\text{kg}/\text{m}^2$ ): calculated from measured height and weight at first of three GCRC visits for detailed metabolic testing
- Body fat (%): calculated as  $[\text{total weight} - \text{lean weight}]/\text{total weight}$ ; measured at 75-g antepartum OGTT. Lean mass was calculated as  $\text{TBW}/0.76$  (22), where TBW = total body water, determined as apparent volume of dilution of 10 g of  $\text{D}_2\text{O}$

##### Postpartum variables

**BMI ( $\text{kg}/\text{m}^2$ ).** Calculated from measured height and weight at postpartum OGTT

**Weight change from prepregnancy (kg).** Calculated from measured weight at postpartum OGTT and recorded prepregnancy weight in patient's clinical record

**Body fat (%).** Calculated as for antepartum percent fat, except that lean mass was calculated as  $\text{TBW}/0.724$  (23) and body weight was the weight recorded at the postpartum OGTT visit

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