Postpartum Metabolic Function in Women Delivering a Macrosomic Infant in the Absence of Gestational Diabetes Mellitus

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OBJECTIVE—Gestational diabetes mellitus (GDM) is associated with fetal macrosomia and maternal postpartum dysglycemia, insulin resistance, and β-cell dysfunction. Indeed, in practice, a prior pregnancy that resulted in a large-for-gestational-age (LGA) delivery is often considered presumptive evidence of GDM, whether or not it was diagnosed at the time. If this clinical assumption is correct, however, we would expect these women to exhibit postpartum metabolic dysfunction. Thus, to test this hypothesis, we assessed metabolic function during and after pregnancy in a cohort of women stratified according to the presence/absence of GDM and LGA delivery, respectively.

RESEARCH DESIGN AND METHODS—A total of 562 women underwent metabolic characterization, including oral glucose tolerance test (OGTT), in late pregnancy and at 3 months' postpartum. The women were stratified into three groups: those with neither GDM nor LGA delivery (nonGDM, $n = 364$), those without GDM but with LGA delivery (nonGDM–LGA, $n = 46$), and those with GDM ($n = 152$).

RESULTS—On logistic regression, GDM predicted postpartum glucose intolerance (OR 4.1 [95% CI 2.5–6.8]; $P < 0.0001$), whereas nonGDM–LGA did not ($P = 0.65$). At 3 months' postpartum, the mean adjusted levels of fasting glucose and area under the glucose curve on the OGTT were significantly higher in the GDM women compared with either nonGDM or nonGDM–LGA (all $P < 0.05$), with no differences between the latter two groups. In a similar manner, mean adjusted insulin sensitivity (Matsuda index) and β-cell function (Insulin Secretion-Sensitivity Index-2) were lower in GDM women compared with either nonGDM or nonGDM–LGA (all $P < 0.05$), again with no differences between the latter two groups.

CONCLUSIONS—Women with nonGDM–LGA do not exhibit postpartum metabolic dysfunction, arguing against the assumption of undiagnosed GDM in these patients.

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Women diagnosed with gestational diabetes mellitus (GDM) have an increased risk of both obstetrical complications during pregnancy (largely due to excessive fetal growth) and the development of prediabetes and type 2 diabetes in the years after delivery (1). Chronic insulin resistance and pancreatic β-cell dysfunction during and after pregnancy play a role in both of these risks (1). Specifically, these women have a chronic β-cell defect such that they are unable to compensate appropriately for the severe insulin resistance of late pregnancy and, thus, develop the gestational hyperglycemia by which GDM is diagnosed. If this maternal hyperglycemia is not treated with glucose-lowering therapy (i.e., diet or insulin), it can lead to fetal hyperglycemia and resultant fetal hyperinsulinemia, the anabolic effects of which will cause macrosomia (2). After the pregnancy, these women have an increased risk of developing prediabetes and type 2 diabetes owing to progressive worsening of their β-cell defect against a background of chronic insulin resistance (1). Thus, clinical hallmarks of GDM include fetal macrosomia and maternal postpartum dysglycemia, insulin resistance, and β-cell dysfunction.

In clinical practice, a previous pregnancy that resulted in the delivery of a large-for-gestational-age (LGA) infant is often considered to be a risk factor for GDM in a subsequent pregnancy (3–5). The rationale is that the previous LGA delivery is considered to be presumptive evidence of GDM complicating that pregnancy, whether or not it was diagnosed at the time. Inherent in this practice is the assumption that GDM was not detected because of either the absence of GDM screening during that pregnancy or its development later in gestation after the time of screening. In this context, we reasoned that if this clinical assumption is correct, then these women should display postpartum metabolic dysfunction, as would be found in women with established GDM. Thus, to test this hypothesis, our objective in this study was to systematically compare and contrast the postpartum metabolic function of women who have delivered an LGA infant in the absence of diagnosed GDM with *1*) women with established GDM (who therefore have metabolic dysfunction) and *2*) women with neither GDM nor LGA delivery (who represent normal control subjects).

RESEARCH DESIGN AND METHODS

—This analysis was conducted in the context of an ongoing observational study of early events in the natural history of type 2 diabetes in which a cohort of women recruited at the time of antepartum screening for GDM is undergoing longitudinal metabolic characterization in pregnancy and the postpartum period. The study protocol has been previously

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described in detail (6,7). In brief, standard obstetrical practice at our institution involves universal screening for GDM in all pregnant women at 24–28 weeks' gestation by 50-g glucose challenge test (GCT), followed by a diagnostic oral glucose tolerance test (OGTT) if the GCT yields an abnormal result. In this study, healthy pregnant women are recruited either prior to or just after their GCT. Regardless of the GCT result, all study participants undergo a 3-h 100-g OGTT to determine their glucose tolerance status in pregnancy. At 3 months' postpartum, participants undergo reassessment by 2-h 75-g OGTT. The study protocol has been approved by the Mount Sinai Hospital Research Ethics Board, and all participants have provided written informed consent. For the current analysis, the study population was restricted to women of Caucasian, Asian, or South Asian ethnicity because these are the three groups for which Canadian-based ethnicity-specific birth weight centiles are available (8,9). The analysis was further restricted to only those women with singleton pregnancies (n = 562) because multiple gestation pregnancy (i.e., twins) can affect fetal growth.

Evaluation of study participants in pregnancy, at delivery, and at 3 months' postpartum

As previously described (6), the antepartum 3-h 100-g OGTT determined glucose tolerance status in pregnancy as follows: *1*) GDM (defined as ≥2 glucose values above the National Diabetes Data Group [NDDG] diagnostic criteria on the OGTT) (10), *2*) gestational impaired glucose tolerance (defined as only 1 glucose value above NDDG thresholds), and *3*) normal glucose tolerance (NGT; no glucose values above NDDG thresholds).

At delivery, data on obstetrical outcome were entered into a database that tracks labor and delivery outcomes at Mount Sinai Hospital. LGA was defined as sex-specific birth weight for gestational age above the 90th percentile of Canadian fetal growth curves for the ethnic group under study (Caucasian, Asian, or South Asian) (8,9). Macrosomia was defined as birth weight ≥4,000 g.

At 3 months' postpartum, participants returned for a 2-h 75-g OGTT, on which glucose tolerance status was defined according to Canadian Diabetes Association guidelines (11). Prediabetes refers to impaired glucose tolerance, impaired fasting glucose, or combined impaired glucose tolerance and impaired fasting glucose (11). Postpartum glucose intolerance collectively refers to prediabetes and diabetes. Interviewer-administered questionnaires were completed and physical examination was performed, including measurement of blood pressure, weight, and waist circumference, as previously described (6).

Laboratory measurements and physiologic indices

All OGTTs were performed in the morning after an overnight fast, with venous blood samples drawn for measurement of glucose and insulin at fasting and at 30, 60, and 120 min (and 180 min in pregnancy) after ingestion of the glucose load. At both baseline and follow-up, glycemia was assessed by glucose tolerance status and by the total area under the glucose curve (AUC_{gluc}) during the OGTT. The primary measure of whole-body insulin sensitivity was the insulin sensitivity index (IS_{OGTT}) of Matsuda and DeFronzo (12). IS_{OGTT} is defined as $10{,}000/\sqrt{[(FPG \cdot FPI) \cdot (G \cdot I)]}$, where FPG is fasting plasma glucose, FPI is fasting plasma insulin, G is mean glucose during the OGTT, and I is mean insulin. Insulin sensitivity (primarily hepatic) was also determined by the inverse of the homeostasis model of assessment of insulin resistance (1/HOMA-IR). HOMA-IR was calculated as (FPG · FPI)/22.5 (13). The primary measure of β-cell function was the Insulin Secretion-Sensitivity Index-2 (ISSI-2), an OGTT-derived measure that is analogous to the disposition index and defined as the product of *1*) insulin secretion measured by the ratio of the area under the insulin curve (AUC_{ins}) to AUC_{gluc} and *2*) insulin sensitivity measured by IS_{OGTT} (14). The insulinogenic index divided by HOMA-IR (insulinogenic index/HOMA-IR) provided a secondary measure of β-cell function (with insulinogenic index defined as the ratio of the incremental change in insulin during the first 30 min of the OGTT to the incremental change in glucose over the same time period) (15).

Statistical analyses

All analyses were conducted using SAS.9.2 (SAS Institute, Cary, NC). Continuous variables were tested for normality of distribution, and natural log transformations of skewed variables were used, where necessary, in subsequent analyses. The study population was stratified into the following three groups based on glucose tolerance status on the antepartum OGTT and the presence/absence of LGA delivery: *1*) women with neither GDM nor LGA delivery (nonGDM), *2*) women without GDM but with LGA delivery (nonGDM–LGA), and *3*) women with GDM. In both Tables 1 and 2, continuous variables were compared across the groups by analysis of variance, and categorical variables were compared by χ^2 or Fisher exact test. For continuous variables, pairwise comparisons were performed with the Bonferroni method to determine if significant differences existed between any pair of groups. Adjusted mean levels of fasting glucose (Fig. 1*A*), AUC_{gluc} (Fig. 1*B*), IS_{OGTT} (Fig. 1*C*), and ISSI-2 (Fig. 1*D*) were compared between groups by analysis of covariance, after adjustment for age, months' postpartum, ethnicity, family history of diabetes, breastfeeding, and waist circumference. Logistic regression analysis was performed to determine whether GDM and nonGDM–LGA predicted postpartum prediabetes/diabetes, after adjustment for age, months' postpartum, ethnicity, family history of diabetes, breastfeeding, waist circumference, and study group.

RESULTS

Characteristics of study population in pregnancy and at delivery

Table 1 shows the antepartum characteristics and obstetrical outcomes of the nonGDM (n = 364), nonGDM–LGA (n = 46), and GDM (n = 152) groups. The groups differed slightly in weeks' gestation at the time of the antepartum OGTT, which was highest in the nonGDM group (P = 0.0003). They did not differ with respect to age, parity, previous history of GDM, or smoking exposure. There were differences between the groups in established risk factors for GDM, including ethnicity (P = 0.0185), family history of diabetes (P = 0.0022), and prepregnancy BMI (P = 0.0054). In addition, gestational weight gain up to the OGTT differed among the three groups, being lowest in the women with GDM (P = 0.0001).

As would be expected in pregnancy, there were significant overall differences across the three groups with respect to glycemia (GCT, fasting glucose, and AUC_{gluc}), insulin sensitivity (IS_{OGTT} and 1/HOMA-IR), and β-cell function (ISSI-2 and insulinogenic index/HOMA-IR) (all $P < 0.0001$), consistent with the metabolic features of hyperglycemia, insulin resistance, and β-cell dysfunction that characterize GDM. However, it is important to note that these significant differences across the groups were driven primarily by pairwise differences between the GDM and nonGDM groups and between the

Table 1—*Comparison of antepartum characteristics and pregnancy outcome between nonGDM, nonGDM–LGA, and GDM women*

	NonGDM (n = 364)	NonGDM–LGA (n = 46)	GDM (n = 152)	P value
Demographic and clinical features				
Age (years)	34.1 ± 4.3	34.0 ± 4.2	34.3 ± 4.5	0.8772
Weeks' gestation	30 (28–32)	29 (28–30)	29 (28–31)[c]	0.0003
Prepregnancy BMI (kg/m^2)	23.0 (21.1–26.3)	23.5 (21.6–27.4)	24.1 (21.3–28.8)[c]	0.0054
Weight gain in pregnancy up to OGTT (kg)	10.7 (8.0–14.0)	10.9 (8.6–14.7)	10.0 (6.0–13.4)[b,c]	0.0001
Ethnicity (%)				0.0185
Caucasian	83.2	76.1	75.7	
Asian	11.8	23.9	15.1	
South Asian	5.0	0.0	9.2	
Family history of diabetes (%)	52.5	69.6	67.1	0.0022
Parity (%)				0.1628
Nulliparous	56.0	41.3	59.2	
1	33.2	41.3	33.6	
>1	10.7	17.4	7.2	
Previous GDM/macrosomia (%)	4.4	6.5	8.6	0.1691
Smoking exposure (%)				0.7098
Never	68.1	65.2	73.0	
Remote	30.5	32.6	25.0	
Current	1.4	2.2	2.0	
Glucose metabolism				
GCT (mmol/L)	8.0 (6.4–8.7)	8.3 (7.8–9.2)	8.9 (8.2–9.7)[b,c]	<0.0001
Insulin sensitivity				
IS_{OGTT}	5.2 (3.6–7.1)	4.3 (2.6–5.7)	3.2 (2.1–4.9)[b,c]	<0.0001
1/HOMA-IR	0.7 (0.4–1.0)	0.5 (0.3–0.7)	0.5 (0.3–0.8)[c]	<0.0001
β-Cell function				
ISSI-2	797 (650–968)	692 (562–848)[a]	543 (444–629)[b,c]	<0.0001
Insulinogenic index/HOMA-IR	11.7 (8.2–18.1)	10.3 (6.6–14.1)	6.3 (3.4–9.8)[b,c]	<0.0001
Fasting glucose (mmol/L)	4.4 (4.2–4.7)	4.6 (4.3–4.8)[a]	4.7 (4.3–5.2)[c]	<0.0001
AUC_{gluc}	21.5 (19.3–23.5)	22.6 (20.8–24.1)	27.4 (26.4–29.0)[b,c]	<0.0001
Glucose tolerance status (%)				<0.0001
NGT	76.7	65.2	0.0	
GIGT	23.4	34.8	0.0	
GDM	0.0	0.0	100.0	
Obstetrical outcomes				
Length of gestation (weeks)	39 (38–40)	39 (38–40)	38 (37–39)[b,c]	<0.0001
Infant sex (% male/female)	48.4/51.7	52.2/47.8	50.7/49.3	0.8207
Infant birth weight (g)	3,325 (3,080–3,610)	4,208 (3,980–4,420)[a]	3,220 (2,935–3,500)[b,c]	<0.0001

Data for continuous variables are medians followed by interquartile range in parentheses, with the exception of age, which is presented as mean ± SD. Categorical variables are presented as percentages. P values refer to the overall differences across groups as derived from ANOVA for continuous variables (parametric test for normally distributed variables and nonparametric test for skewed variables) and χ^2 test or Fisher exact test for categorical variables. The Bonferroni method was used for pairwise comparisons. GIGT, gestational impaired glucose tolerance. [a]$P < 0.05$ for nonGDM–LGA vs. nonGDM. [b]$P < 0.05$ for nonGDM–LGA vs. GDM. [c]$P < 0.05$ for nonGDM vs. GDM.

GDM and nonGDM–LGA groups. Indeed, the only significant differences between the two nonGDM groups were higher fasting glucose and lower ISSI-2 in the nonGDM–LGA women, albeit in the absence of differences between these two groups in the other measures of glycemia (GCT and AUC_{gluc}) and β-cell function (insulinogenic index/HOMA-IR), respectively.

At delivery, birth weight was highest in the nonGDM–LGA women, reflecting both the group definitions and the effect of glucose-lowering treatment in women with GDM. The groups differed in the length of gestation, which was lowest in the GDM women (overall $P < 0.0001$).

Characteristics of study population at 3 months' postpartum

At 3 months' postpartum (Table 2), there were differences between the groups in waist circumference and systolic blood pressure ($P = 0.0363$ and $P = 0.0033$, respectively), but not in BMI, diastolic blood pressure, smoking, breastfeeding, and months since delivery. Of note, there were significant overall differences across the groups for all parameters of postpartum glucose homeostasis: IS_{OGTT}, 1/HOMA-IR, ISSI-2, insulinogenic index/HOMA-IR, fasting glucose, and AUC_{gluc} ($P < 0.0001$ for all except 1/HOMA-IR at $P = 0.0052$). As before, however, these overall differences were driven by significant pairwise differences between the GDM women and *1*) the nonGDM group and *2*) the nonGDM–LGA group, respectively. Indeed, there were no significant differences in glycemia, insulin sensitivity, and β-cell function between the two nonGDM groups at 3 months' postpartum.

To further evaluate postpartum metabolic function in women with nonGDM–LGA, we next compared adjusted mean levels of fasting glucose, AUC_{gluc}, IS_{OGTT}, and ISSI-2 between the groups, after adjustment for age, time since delivery, ethnicity, family history of diabetes, breastfeeding, and waist circumference (Fig. 1*A–D*). As shown in Fig. 1*A*, adjusted

Table 2—*Comparison of postpartum metabolic characteristics at 3 months' postpartum between nonGDM, nonGDM–LGA, and GDM women*

	NonGDM (n = 364)	NonGDM–LGA (n = 46)	GDM (n = 152)	P value
Months' postpartum	3.2 (3.0–3.7)	3.4 (3.0–4.0)	3.1 (2.9–3.5)	0.0552
BMI (kg/m^2)	24.7 (22.6–28.3)	25.4 (23.4–29.3)	26.1 (23.1–30.0)	0.2426
Waist circumference (cm)	86.0 (80.0–94.0)	88.8 (83.0–97.2)	88.6 (81.0–98.0)	0.0363
Systolic blood pressure (mmHg)	108 (101–113)	107 (103–114)	111 (103–117)[b]	0.0033
Diastolic blood pressure (mmHg)	64 (60–70)	64 (60–69)	65 (59–71)	0.1264
Current smoking (%)	4.7	2.2	4.0	0.7078
Current breastfeeding (%)	93.7	93.5	95.4	0.7379
Insulin sensitivity				
IS_{OGTT}	11.5 (7.9–16.3)	10.5 (6.1–15.7)	9.1 (6.0–12.7)[b]	<0.0001
1/HOMA-IR	1.3 (0.8–1.8)	1.1 (0.7–1.7)	1.0 (0.6–1.6)[b]	0.0052
β-Cell function				
ISSI-2	985 (820–1,242)	898 (717–1,190)	825 (673–1,014)[a,b]	<0.0001
Insulinogenic index/HOMA-IR	11.2 (7.1–16.9)	10.6 (7.1–17.5)	8.1 (5.3–12.3)[a,b]	<0.0001
Fasting glucose (mmol/L)	4.5 (4.2–4.7)	4.5 (4.3–4.8)	4.7 (4.4–5.0)[b]	<0.0001
AUC_{gluc}	12.5 (10.8–14.1)	12.5 (11.2–14.3)	14.7 (12.9–16.7)[a,b]	<0.0001
Glucose tolerance status (%)				<0.0001
NGT	90.9	84.8	67.8	
Prediabetes/diabetes	9.1	15.2	32.2	

Data for continuous variables are medians followed by interquartile range in parentheses. Categorical variables are presented as percentages. P values refer to the overall differences across groups as derived from ANOVA for continuous variables (parametric test for normally distributed variables and nonparametric test for skewed variables) and χ^2 test or Fisher exact test for categorical variables. The Bonferroni method was used for pairwise comparisons. [a]$P < 0.05$ for nonGDM–LGA vs. GDM. [b]$P < 0.05$ for nonGDM vs. GDM.

mean fasting glucose differed across the groups ($P < 0.0001$). Specifically, adjusted fasting glucose was higher in the women with GDM compared with each of the nonGDM groups (both $P < 0.05$) but was not significantly different between the nonGDM and nonGDM–LGA women. Moreover, the very same pattern was observed for AUC_{gluc}, which was again significantly higher in the GDM group but not different between the two nonGDM groups (Fig. 1*B*). This pattern of GDM differing from the nonGDM groups, which themselves were similar to one another, was also apparent with respect to whole-body insulin sensitivity. Indeed, when compared with the GDM women, mean adjusted IS_{OGTT} was significantly higher in the nonGDM and nonGDM–LGA groups, respectively (both $P < 0.05$), but did not differ between these two groups (Fig. 1*C*). In addition, 1/HOMA-IR, which reflects primarily hepatic insulin sensitivity, was not significantly different between the groups ($P = 0.08$). Finally, with respect to β-cell function, mean adjusted ISSI-2 was higher in the nonGDM and nonGDM–LGA women, as compared with GDM (both $P < 0.05$), with no significant difference between the two nonGDM groups (Fig. 1*D*). These findings were mirrored by those for insulinogenic index/HOMA-IR, which was again higher in the nonGDM and nonGDM–LGA women compared with GDM (both $P < 0.05$), with no difference between the nonGDM groups ($P = 0.99$). The findings shown in Fig. 1 were unchanged when these adjusted analyses were repeated with adjustment for BMI rather than waist circumference (Supplementary Fig. 1). In a similar manner, when the adjusted analyses in Fig. 1 were repeated with exclusion of the four women who were using progesterone-only birth control, the findings again remained unchanged (data not shown). It thus emerges that at 3 months' postpartum, the metabolic function of women with nonGDM–LGA is better than that of women with GDM but not different from that of women who had neither GDM nor LGA delivery.

At 3 months' postpartum, there were 76 women with prediabetes and 13 with diabetes. Glucose tolerance status differed across the three groups ($P < 0.0001$), with the GDM group showing the highest prevalence of prediabetes/diabetes (Table 2). To account for the potential influence of covariates on the relationship between study group and postpartum dysglycemia, we performed logistic regression analysis of dependent variable glucose intolerance at 3 months' postpartum (i.e., prediabetes/diabetes). On this analysis, GDM independently predicted postpartum glucose intolerance (odds ratio 4.1 [95% CI 2.5–6.8]; $P < 0.0001$), after adjustment for age, months' postpartum, ethnicity, family history of diabetes, breastfeeding, and waist circumference. In contrast, however, nonGDM–LGA was not a significant predictor of postpartum glucose intolerance (odds ratio 1.7 [0.7–4.1]; $P = 0.65$).

CONCLUSIONS—In this study, we demonstrate that women who deliver an LGA infant in the absence of GDM do not exhibit the postpartum metabolic dysfunction that is characteristic of women with GDM. Specifically, compared with women with established GDM, the nonGDM–LGA group had lower levels of glycemia (fasting glucose and AUC_{gluc}), higher whole-body insulin sensitivity, and better β-cell function at 3 months' postpartum, after adjustment for covariates. Moreover, there were no significant differences in any of these postpartum metabolic parameters between the nonGDM–LGA group and women with neither GDM nor LGA delivery. Altogether, these data argue against the oft-applied clinical assumption that a history of previous LGA delivery is indicative of undiagnosed GDM.

Previous studies show that even in the absence of established GDM in their mothers, macrosomic infants display elevated cord insulin and C-peptide levels

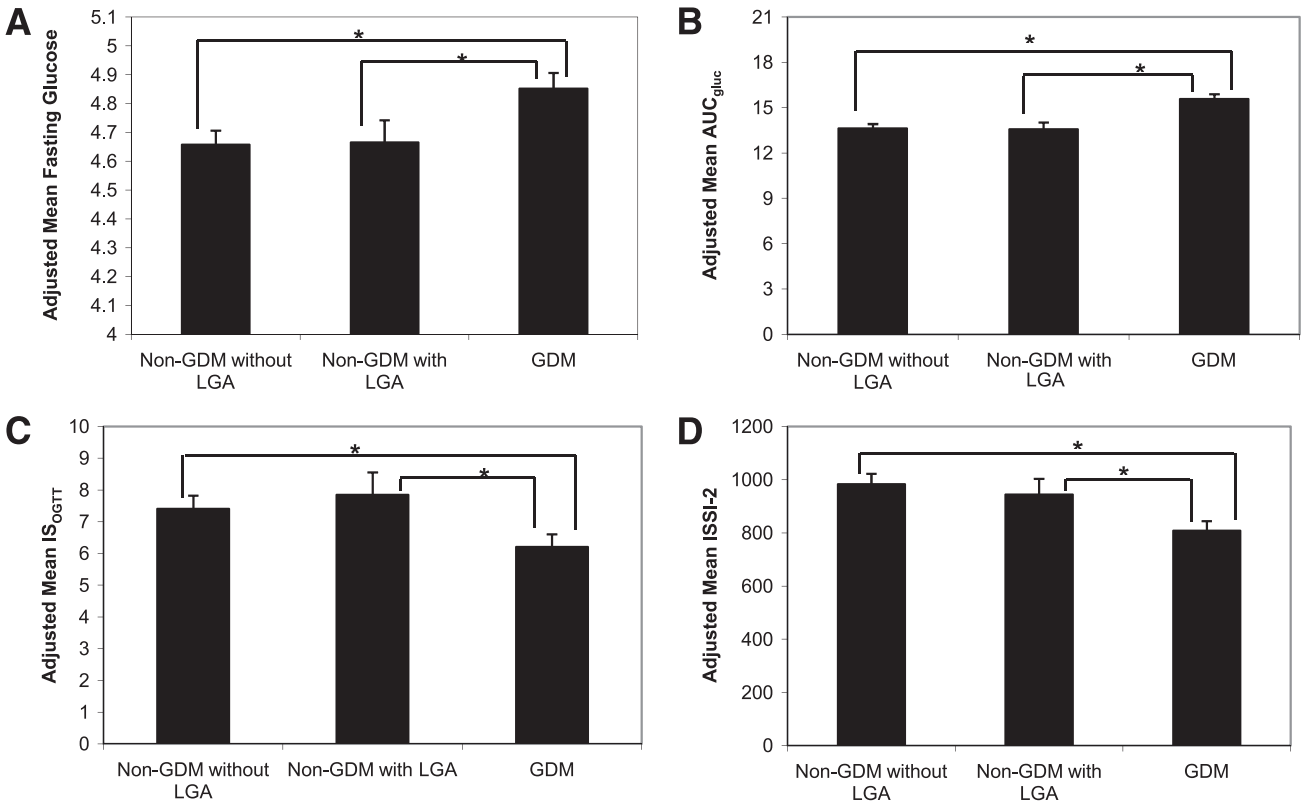

Figure 1—*Adjusted mean levels of fasting glucose* (A)*, AUC_{gluc}* (B)*, IS_{OGTT}* (C)*, and ISSI-2* (D) *by group at 3 months' postpartum, adjusted for age, time since delivery, ethnicity, family history of diabetes, breastfeeding status, and waist circumference. Overall* P *values are* $P < 0.0001$ *for each of* A, B*, and* D*, respectively, and* $P = 0.0006$ *for* C. *$P < 0.05$ *for the indicated pairwise comparison.*

(16,17). These elevated cord levels are indicative of fetal hyperinsulinemia and, hence, support the possibility of undetected maternal glucose intolerance during the pregnancy (16,17). In practice, in the early gestational assessment of a pregnant woman, a reported history of prior delivery of an LGA infant is considered a clinical risk factor for GDM in the current pregnancy (3–5). This is based on the assumption that the previous macrosomia was due to undiagnosed GDM. In this context, it is important to recognize that both GDM and even milder gestational glucose intolerance identify women with chronic defects in β-cell function and insulin resistance, both during and after pregnancy (6,18). As such, it follows that this assumed undiagnosed gestational glucose intolerance in women with a macrosomic infant should predict the presence of postpartum metabolic dysfunction.

To date, however, there has been limited study of this question. In a study of 122 women evaluated at 48 hours' postpartum, Bukulmez and Durukan (19) found that nonGDM women with macrosomic infants had higher glucose levels than women with neither GDM nor infant macrosomia. In contrast, at 2 years' postpartum, Moses et al. (20) compared the fasting metabolic profile of 18 women with LGA infants against that of 18 women with appropriate-for-gestational-age infants, carefully matched for maternal age, BMI, parity, and 2-h glucose level on the antepartum OGTT. It should be noted that they found no differences in fasting glucose, A1C, insulin, or lipids between these two groups. These studies thus offer conflicting findings.

In attempting to resolve this conflict, the current study is supported by three key strengths in its design. First, this study is prospective, such that all participants were systematically assessed by an OGTT both in late pregnancy and at 3 months' postpartum, thereby enabling ascertainment of glucose tolerance status both during and after pregnancy. Second, insulin sensitivity and β-cell function were evaluated on these OGTTs, thereby obtaining insight on the pathophysiologic hallmarks of GDM. Lastly, in comparison with the prior studies, the current study has a much larger sample size consisting of 562 women, stratified into positive control subjects (women with established GDM) and negative control subjects (women with neither GDM nor LGA delivery). In the context of this study design, we demonstrate that the postpartum metabolic profile of women delivering an LGA infant in the absence of GDM is similar to that of their peers with neither GDM nor LGA delivery and very different from that of women with established GDM.

Although not specifically addressed by the current study, it is likely that the clinical assumption that an LGA infant reflects undiagnosed maternal glucose intolerance may have been more appropriate in the past, when the prevalence of overweight/obesity was lower. When the Pedersen hypothesis (i.e., that maternal hyperglycemia causes macrosomia through fetal hyperglycemia and hyperinsulinemia) (21) was first forwarded in 1952, women were generally leaner than nowadays. At that time, maternal hyperglycemia was the primary determinant of fetal overgrowth (2,21,22). In the setting of the current obesity epidemic, however, Catalano and Hauguel-De Mouzon (2) have suggested that maternal adiposity, rather than glycemia, is likely now the predominant factor contributing to excessive fetal

growth, a concept supported by recent analyses (23,24). Indeed, our findings also support this position, for we were unable to demonstrate postpartum defects in carbohydrate metabolism in nonGDM–LGA women. Furthermore, it follows from these data that the practice of interpreting a previous LGA delivery as presumptive evidence of undiagnosed GDM may no longer be appropriate in the modern setting.

Our study is limited by the use of surrogate indices of insulin sensitivity and β-cell function. However, direct measures such as clamp studies would be difficult to implement in a study of this size (N = 562) because of their cost, invasiveness, and time requirement (particularly for new mothers). Moreover, we have used two established and validated measures for both insulin sensitivity and β-cell function, with generally consistent results observed in each case (12–15). A second limitation is the possibility of misclassification, in that some women in the nonGDM groups could have developed GDM later in the pregnancy (i.e., after the OGTT) and, hence, were not appropriately classified as belonging to the GDM group. However, this misclassification would have biased against the current results. As such, this possibility only strengthens the current conclusions.

In summary, nonGDM women with an LGA infant do not display the postpartum metabolic dysfunction of women with established GDM, specifically dysglycemia, insulin resistance, and β-cell dysfunction. Furthermore, these women are not metabolically distinct from their peers with neither GDM nor LGA delivery. Thus, an LGA delivery in the absence of GDM is not necessarily indicative of undiagnosed gestational glucose intolerance but, rather, may be due to the influence of other factors, such as obesity. These data suggest that the long-standing clinical assumption that delivery of an LGA infant reflects undiagnosed maternal hyperglycemia may no longer be appropriate in modern practice.

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