OBJECTIVE — The purpose of this study was to test the hypothesis that any degree of abnormal glucose homeostasis detected on antepartum screening for gestational diabetes mellitus (GDM) should be associated with an increased risk of postpartum pre-diabetes or diabetes.

RESEARCH DESIGN AND METHODS — In this prospective cohort study, 487 women underwent 1) antepartum GDM screening by a glucose challenge test (GCT) and a diagnostic oral glucose tolerance test (OGTT) and 2) postpartum metabolic characterization by OGTT at 3 months after delivery. Four baseline glucose tolerance groups were defined on the basis of the antepartum GCT/OGTT: 1) GDM (n = 137); 2) gestational impaired glucose tolerance (GIGT) (n = 91); 3) abnormal GCT with normal glucose tolerance on an OGTT (abnormal GCT NGT) (n = 166); and 4) normal GCT with NGT on an OGTT (normal GCT NGT) (n = 93).

RESULTS — The prevalence of postpartum glucose intolerance (pre-diabetes or diabetes) increased across the groups from normal GCT NGT (3.2%) to abnormal GCT NGT (10.2%) to GIGT (16.5%) to GDM (32.8%) (P_trend < 0.0001). On logistic regression analysis, all three categories of abnormal glucose homeostasis in pregnancy independently predicted postpartum glucose intolerance: abnormal GCT NGT odds ratio (OR) 3.6 (95% CI 1.01–12.9), GIGT OR 5.7 (1.6–21.1), and GDM OR 14.3 (4.2–49.1). Furthermore, both in pregnancy and at 3 months postpartum, insulin sensitivity (ISOGTT) and pancreatic β-cell function (insulinogenic index/homeostasis model assessment of insulin resistance) progressively decreased across the groups from normal GCT NGT to abnormal GCT NGT to GIGT to GDM (all P_trend < 0.0001).

CONCLUSIONS — Any degree of abnormal glucose homeostasis in pregnancy independently predicts an increased risk of glucose intolerance postpartum.

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The diagnosis of gestational diabetes mellitus (GDM) identifies a population of young women who have a very high risk of ultimately developing type 2 diabetes in the years after the index pregnancy (1,2). This relationship reflects the fact that both GDM and type 2 diabetes share a similar pathophysiology, characterized by two main metabolic defects: 1) target cell resistance to the activity of insulin (insulin resistance) and 2) insufficient secretion of insulin by the pancreatic β-cells to compensate for this peripheral tissue resistance (β-cell dysfunction) (1,3). Pregnancy is characterized by severe, acquired insulin resistance that has long been thought to provide a short-term challenge to the β-cells, with GDM arising in those women whose β-cells are unable to meet this challenge. It is now understood, however, that the defect in β-cell compensation that characterizes GDM is chronic (not acquired during pregnancy) and therefore may underlie the high risk of type 2 diabetes in women who have a history of previous GDM (1,4).

Although controversy exists regarding the specific protocols to apply, screening for GDM by glucose tolerance testing in pregnancy has become a standard element of obstetrical care (5). With this testing, GDM is diagnosed on the basis of blood glucose levels that exceed specific glycemic thresholds. Affected women identified in this way are then treated with dietary therapy or insulin to reduce glucose levels in pregnancy and improve obstetrical outcome (6). These patients are also advised to undergo testing for type 2 diabetes postpartum (7). It is important to recognize, however, that glucose tolerance testing in pregnancy also identifies many women with glycemic responses that exceed the normal range but that do not meet the thresholds required for the diagnosis of GDM. These women are not typically treated in any way and are not subject to any postpartum surveillance. Indeed, little is known about their postpartum risk of glucose intolerance or diabetes. Given that pregnancy provides a physiologic test of the body’s glucoregulatory capacity, we hypothesized that any abnormality on glucose tolerance testing in pregnancy should reflect a degree of underlying β-cell dysfunction and hence should predict an increased risk of postpartum dysglycemia. In this context, our objective in this study was to systematically evaluate glucose tolerance and metabolic function at 3 months postpartum in a well-characterized cohort of women representing a broad spectrum of glucose homeostasis on GDM screening in pregnancy.

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 GDM screening are undergoing longitudinal metabolic characterization in pregnancy and the postpartum period. Standard obstetrical practice at our institution involves universal screening for GDM in all pregnant women at 24–28 weeks of gestation by a glucose challenge test (GCT), wherein plasma glucose concentration is measured 1 h after ingestion of 50 g of glucose. If the plasma glucose level is ≥7.8 mmol/L, the patient is re-
ferred for a diagnostic oral glucose tolerance test (OGTT).

In the current study, healthy pregnant women attending outpatient obstetrics clinics were recruited in the late second trimester, either before or just after their screening 30-g GCT. Regardless of the GCT result, all participants then underwent a 3-h 100-g OGTT for assessment of glucose tolerance status in pregnancy. At 3 months postpartum, participants returned for reassessment by a 2-h 75-g OGTT. The study protocol was approved by the Mount Sinai Hospital Research Ethics Board, and all participants gave written informed consent. The current analysis was restricted to the first 487 women who had completed both the pregnancy OGTT and the 3-month postpartum OGTT by September 2007, representing 4 years of recruitment.

Baseline evaluation
On the morning of the OGTT in pregnancy, interviewer-administered questionnaires were completed, and anthropometric measurements of height and weight were obtained using a medical scale. In conjunction with the GCT, the OGTT stratified subjects into the following four glucose tolerance groups in pregnancy: 1) GDM, as defined by National Diabetes Data Group (NDDG) criteria (8) (requires at least two of the following on the OGTT: fasting glucose $\geq 5.8$ mmol/l, 1-h blood glucose $\geq 10.6$ mmol/l, 2-h blood glucose $\geq 9.2$ mmol/l, or 3-h blood glucose $\geq 8.1$ mmol/l); 2) gestational impaired glucose tolerance (IGT), as defined by meeting only one of the above NDDG criteria; 3) abnormal GCT with normal glucose tolerance (NGT), as defined by having an abnormal 50-g GCT followed by NGT on the OGTT (defined by meeting none of the NDDG criteria); and 4) normal GCT NGT, as defined by having a normal 50-g GCT followed by NGT on the OGTT.

Postpartum evaluation
Participants returned to the clinical investigation unit for a 2-h 75-g OGTT at 3 months postpartum. Interviewer-administered questionnaires were completed, and a physical examination was performed, including measurement of blood pressure (measured twice 5 min apart by automatic sphygmomanometer [Dinamap Pro 100-400]), weight, and waist circumference.

The 2-h 75-g OGTT characterized postpartum glucose tolerance into one of the following five categories as per current Canadian Diabetes Association clinical practice guidelines (9): 1) diabetes, defined by fasting glucose $\geq 7.0$ mmol/l or 2-h glucose $\geq 11.1$ mmol/l; 2) impaired glucose tolerance (IGT), defined by fasting glucose $< 6.1$ mmol/l and 2-h glucose between 7.8 and 11.0 mmol/l inclusive; 3) impaired fasting glucose (IFG), defined by fasting glucose between 6.1 and 6.9 mmol/l inclusive, with 2-h glucose $< 7.8$ mmol/l; 4) combined IFG/IGT, defined by fasting glucose between 6.1 and 6.9 mmol/l inclusive, and 2-h glucose between 7.8 and 11.0 mmol/l inclusive; and 5) NGT, defined by fasting glucose $< 6.1$ mmol/l and 2-h glucose $< 7.8$ mmol/l.

Pre-diabetes collectively refers to IGT, IFG, and combined IFG/IGT (9). Postpartum glucose intolerance collectively refers to pre-diabetes and diabetes.

Laboratory measurements and physiologic indexes
All OGTTs were performed in the morning after an overnight fast. During all OGTTs, venous blood samples were drawn for measurement of glucose and insulin at fasting and at 30-, 60- and 120-min after ingestion of the glucose load. The 3-h OGTT in pregnancy involved an additional venous blood sample at 180 min. Specific insulin was measured using the Roche Elecsys 1010 immunoassay analyzer and the electrochemiluminescence immunoassay kit. This assay shows 0.05% cross-reactivity to intact human proinsulin and the primary circulating split form (des 31,32).

At both baseline and follow-up, glycaemia was assessed by 1) glucose tolerance status, as described above and 2) the total area under the glucose curve ($\text{AUC}_{\text{gluc}}$) during the OGTT, calculated using the trapezoidal rule. Insulin sensitivity was measured using the insulin sensitivity index ($I_{\text{OGTT}}$) of Matsuda and DeFronzo (10,11). B-Cell function was assessed by the insulinogenic index (12) divided by the homeostasis model assessment of insulin resistance (HOMA-IR) (3,13). HOMA-IR was calculated as described by Matthews et al. (14).

Statistical analyses
All analyses were conducted using SAS statistical software (version 9.1; 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. Univariate differences across the four study groups were assessed in pregnancy (Table 1) and at 3 months postpartum (Table 2; Fig. 1) using one-way ANOVA for continuous variables and either a $\chi^2$ test or Fisher’s exact test for categorical variables. Univariate correlations between continuous variables in pregnancy and $\text{AUC}_{\text{gluc}}$ at 3 months postpartum were assessed by Spearman correlation analysis. Multiple linear regression analysis was used to determine which factors in pregnancy were independently associated with logarithmically transformed $\text{AUC}_{\text{gluc}}$ at 3 months postpartum (panel A of the supplemental Table available in an online appendix at http://dx.doi.org/10.2337/dc08-0972). Multivariate logistic regression analysis was performed to determine which pregnancy factors were independently associated with glucose intolerance at 3 months postpartum (panel B of the supplemental Table). The covariates considered in these analyses were those that were either related to postpartum glycaemia on univariate analysis at a significance level of 0.05 or are known/suspected risk factors. The same covariates were tested in both analyses, with the exception of the categorical variable previous GDM, which could not be included in the logistic regression analysis because there were no women in the normal GCT NGT group with a history of previous GDM (i.e., inclusion of this covariate would therefore undermine model stability).

RESULTS
Baseline characteristics of study groups in pregnancy
Table 1 shows the baseline characteristics of the study participants, consisting of 93 women in the normal GCT NGT group, 166 in the abnormal GCT NGT group, 91 in the GIGT group (of whom 19 had a normal GCT), and 137 with GDM (of whom 17 had a normal GCT). As expected, mean $\text{AUC}_{\text{gluc}}$ showed a progressive increase from normal GCT NGT (19.6) to abnormal GCT NGT (21.0) to GIGT (24.3) to GDM (27.7) ($P < 0.0001$). Furthermore, both insulin resistance and B-cell dysfunction followed the same pattern, with $I_{\text{OGTT}}$ (insulin sensitivity) and insulinogenic index/HOMA-IR (B-cell function) both progressively decreasing across these four groups (both $P < 0.0001$).
Having established that the GCT/OGTT identifies four metabolically distinct glucose tolerance groups in pregnancy, we next compared the metabolic characteristics of these groups at 3 months postpartum (Table 2). Importantly, the four groups continued to exhibit marked metabolic differences at 3 months postpartum. Specifically, as in pregnancy, both insulin sensitivity (ISOGTT) and β-cell function (insulinogenic index/HOMA-IR) progressively decreased from the normal GCT NGT group to the abnormal GCT NGT group to the GIGT group to the women with recent GDM (both \( P < 0.0001 \)). Consistent with these differences, glycemia, as measured by AUCgluc on the 3-month postpartum OGTT, increased significantly across these four
groups \( (P < 0.0001) \). Most importantly, these metabolic differences between the groups translated into vastly different rates of glucose intolerance (i.e., pre-diabetes or diabetes) at 3 months postpartum (Fig. 1). Indeed, the prevalence of glucose intolerance rose in a stepwise fashion from 3.2% in the normal GCT NGT group to 10.2% in the abnormal GCT NGT group to 16.5% in the GIGT group to 32.8% in the GDM group (Cochran-Armitage trend \( P = 0.0001 \)). Furthermore, in each group, the bulk of this dysglycemia was IGT (i.e., IGT prevalence rates per group were 2.2% for normal GCT NGT, 10.2% for abnormal GCT NGT, 11.0% for GIGT, and 27.0% for GDM), underscoring the importance of the OGTT for its detection.

**Determinants of postpartum glucose intolerance**

Having identified high rates of postpartum glucose intolerance within each category of abnormal antepartum glucose homeostasis, we next sought to identify the antepartum factors that predict dysglycemia at 3 months postpartum. On Spearman univariate correlation analysis, the pregnancy factors that were most strongly associated with postpartum AUC\(_{\text{gluc}}\) were measures of glycemia, including AUC\(_{\text{gluc}}\) in pregnancy \( (r = 0.43, P < 0.0001) \), GCT result \( (r = 0.36, P < 0.0001) \), and fasting glucose \( (r = 0.26, P < 0.0001) \). Other significant correlates of postpartum AUC\(_{\text{gluc}}\) were prepregnancy BMI \( (r = 0.17, P = 0.002) \) and age \( (r = 0.13, P = 0.0043) \).

On multiple linear regression analysis (panel A of the supplemental Table), all three categories of abnormal glucose homeostasis in pregnancy were independently associated with dependent variable log AUC\(_{\text{gluc}}\) at 3 months postpartum (GDM \( t = 8.00, P < 0.0001 \); GIGT \( t = 5.43, P < 0.0001 \); abnormal GCT NGT \( t = 3.03, P = 0.0026 \)). Other significant covariates were age \( (t = 3.00, P = 0.0028) \), nonwhite ethnicity (Asian \( t = 2.77, P = 0.0059 \); other ethnicity \( t = 2.22, P = 0.027 \)), prepregnancy BMI \( (t = 2.47, P = 0.0141 \) ), and previous GDM \( (t = 2.37, P = 0.0181 \) ).

Finally, logistic regression analysis (panel B of the supplemental Table) was performed to identify the pregnancy factors that independently predict glucose intolerance at 3 months postpartum. As expected, GDM was an independent predictor (odds ratio [OR] 14.3, 95% CI 4.2–49.1). Importantly, however, both of the other two categories of abnormal glucose homeostasis in pregnancy were also significant independent predictors of postpartum glucose intolerance with OR 5.7 (1.6–21.1) for GIGT and 3.6 (1.01–12.9) for abnormal GCT NGT.

**CONCLUSIONS** — In this report, we demonstrate that standard antepartum screening for GDM identifies four metabolically distinct glucose tolerance groups in pregnancy whose differences in insulin sensitivity, B-cell function, and glucose handling persist at 3 months postpartum. Indeed, the prevalence of postpartum glucose intolerance progressively increases across these four groups. Most importantly, any degree of abnormal glucose homeostasis in pregnancy (i.e., not just GDM) independently predicts glucose intolerance at 3 months postpartum. Thus, antepartum GDM screening provides an opportunity to obtain insight into a woman’s future risk of pre-diabetes and type 2 diabetes.

Women with GDM, who have chronic insulin resistance and a chronic defect in their insulin secretion-sensitivity relationship, are identified on the basis of hyperglycemia on glucose tolerance testing in pregnancy. The current data demonstrate that standard GDM screening can actually identify four distinct groups with differences in insulin sensitivity, B-cell function, and glycemia in pregnancy. Specifically, compared with normal GCT NGT, GDM and GIGT were associated with lower insulin sensitivity, poorer B-cell function, and greater glycemia. In addition, abnormal GCT NGT was associated with greater glycemia (AUC\(_{\text{gluc}}\)) than normal GCT NGT, although significant differences in insulin sensitivity and B-cell function were not detected with the measures used in this study.

The significance of this readily achievable identification of these four groups (through standard clinical care with GCT and OGTT) becomes apparent when one considers that the metabolic differences between these groups persist into the postpartum period. Importantly, the current data demonstrate that even mild glucose intolerance in pregnancy portends an increased risk of glucose intolerance postpartum. In particular, women with GIGT are clearly distinct from those with normal GCT NGT, on the basis of lower insulin sensitivity, poorer B-cell function, and greater glycemia. Furthermore, as in pregnancy, the abnormal GCT NGT group exhibited greater glycemia (AUC\(_{\text{gluc}}\)) than the normal GCT NGT group, with no detectable dissimilarity in B-cell function, suggestive of a persistent difference in glucoregulation between these groups (the pathophysiological basis of which remains unclear). Indeed, the abnormal GCT NGT and GIGT groups exhibited surprisingly high rates of pre-diabetes/diabetes at 3 months postpartum (10.2 and 16.5%, respectively). This relationship has escaped clinical attention to date because it is driven largely by the high prevalence of IGT in these groups. As such, in the absence of systematic evaluation of postpartum glucose intolerance by OGTT, as in this study, the high rates of pre-diabetes would not be detected.

The identification of pre-diabetes is important because up to 70% of affected
individuals may eventually develop type 2 diabetes (15). Thus, the high rates of pre-diabetes in the three categories of abnormal antepartum glucose homeostasis suggest that the young women in these groups have an increased risk of future type 2 diabetes. Although this risk is well established for women with GDM (2,16–19), there has been limited study of this issue in women with lesser degrees of glucose intolerance in pregnancy. Recently, Vamberegue et al. (20) reported that GIGT was independently associated with glucose intolerance at 6.75 years postpartum, with an adjusted OR of 4.57 (95% CI 1.47–14.22), which was similar to that reported herein. Furthermore, based on administrative data, Carr et al. (21) recently reported that women with a history of GIGT have an increased risk of developing diabetes. Importantly, the current study extends these findings by 1) careful stratification of subjects into four glucose tolerance groups in pregnancy (with GCT and OGTT in all subjects), 2) use of a prospective study design with ascertainment of postpartum glucose tolerance status by OGTT in all subjects, 3) the demonstration of significant differences in insulin sensitivity and β-cell function between the groups, and 4) the demonstration that even abnormal GCT NGT (i.e., a milder abnormality than GIGT) independently predicts postpartum glucose intolerance.

The significance of our study rests in its illustration of the concept that the spectrum of abnormal glucose homeostasis in pregnancy identifies a continuum of risk for postpartum glucose intolerance and that this spectrum extends to levels of antepartum dysglycemia far less severe than GDM. Interestingly, our demonstration that, compared with their truly normal peers with normal GCT NGT, women with GIGT and even those with abnormal GCT NGT have metabolic perturbations that translate into an increased risk of postpartum glucose intolerance is consistent with an emerging body of literature indicating that these two groups (like women with GDM) have an enhanced risk of adverse obstetrical outcomes (22–27). These obstetrical data have posed the question as to whether glucose-lowering treatment in pregnancy, as prescribed for GDM, should be instituted for these groups of women. In the same way, the current data raise the possibility that postpartum follow-up for diabetes surveillance (as is currently recommended after GDM) should be considered for women with GIGT and possibly those with abnormal GCT NGT. The importance of this question is underscored by the fact that the population in question is young women of child-bearing age, in whom early detection and/or prevention of diabetes could have enormous public health implications. Further long-term follow-up will be needed, with a particular emphasis on the cost-benefit implications of any postpartum screening strategies under consideration.

A limitation of the current study is that the CIs surrounding the adjusted ORs in the logistic regression analysis of postpartum glucose intolerance are relatively wide, probably reflecting limitations in power. Nevertheless, our findings are supported by the complete consistency of the associations between each abnormal glucose tolerance group in pregnancy and 1) postpartum glycosuria (both glucose intolerance and AUCgluc), 2) insulin resistance, and 3) β-cell dysfunction. Furthermore, although the other independent determinants of postpartum AUCgluc did not persist as significant predictors of the categorical outcome of postpartum glucose intolerance, it should be noted that the three abnormal glucose tolerance groups in pregnancy were the only significant independent predictors of both the continuous and the categorical measure of postpartum glycosuria (supplemental Table). A second limitation is that this analysis was performed in the first 487 women who returned for their study visit at 3 months postpartum, representing nearly 70% retention of the originally recruited cohort. Although we cannot fully exclude the possibility that loss-to-follow-up may have biased the study groups in some way, it is encouraging that the women who did not return were similar to the participants who did return with respect to demographic and clinical features, including ethnicity, family history of diabetes, and BMI at 3 months (determined from weight reported on telephone questionnaire follow-up with nonrepeaters). Furthermore, the retention of a large number of subjects within each of the four baseline glucose tolerance groups also supports the relevance of this analysis.

In summary, standard antepartum screening for GDM identifies four metabolically distinct glucose tolerance groups in pregnancy, whose differences in insulin sensitivity, β-cell function, and glucose tolerance persist at 3 months postpartum. Importantly, any degree of abnormal glucose homeostasis in pregnancy (i.e., not just GDM) independently predicts glucose intolerance at 3 months postpartum. Thus, clinical screening for GDM, as currently practiced, provides an opportunity to obtain insight into a woman’s future risk of pre-diabetes and type 2 diabetes, information that may have implications for diabetes surveillance and prevention.

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