# Each Degree of Glucose Intolerance in Pregnancy Predicts Distinct Trajectories of β-Cell Function, Insulin Sensitivity, and Glycemia in the First 3 Years Postpartum

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## OBJECTIVE

**Glucose intolerance in pregnancy predicts an increased risk of future type 2 diabetes mellitus (T2DM) that is proportional to the severity of antepartum dysglycemia (i.e., highest in women with gestational diabetes mellitus [GDM], followed by those with milder dysglycemia). However, the pathophysiologic changes driving this risk are not known. Thus, we evaluated the longitudinal changes in β-cell function, insulin sensitivity, and glycemia in the first 3 years postpartum after gestational dysglycemia.**

## RESEARCH DESIGN AND METHODS

**A total of 337 women underwent glucose challenge test (GCT) and oral glucose tolerance test (OGTT) in pregnancy, followed by repeat OGTT at 3 months, 1 year, and 3 years postpartum. The antepartum GCT/OGTT identified four gestational glucose tolerance groups: GDM (*n* = 105); gestational impaired glucose tolerance (GIGT; *n* = 60); abnormal GCT, followed by normal glucose tolerance (NGT) on the OGTT (abnormal GCT NGT; *n* = 96); and normal GCT with NGT (*n* = 76).**

## RESULTS

**At each of 3 months, 1 year, and 3 years postpartum, the prevalence of glucose intolerance increased from normal GCT NGT to abnormal GCT NGT to GIGT to GDM (all $P < 0.001$), whereas β-cell function, assessed by the Insulin Secretion-Sensitivity Index-2 (ISSI-2), and insulin sensitivity (Matsuda index), progressively decreased across the groups (all $P < 0.002$). Each group predicted distinct trajectories of ISSI-2, Matsuda index, and fasting and 2-h glucose (all $P < 0.001$). Notably, GDM, GIGT, and abnormal GCT NGT predicted varying rates of declining β-cell function and insulin sensitivity, as well as rising glycemia, compared with normal GCT NGT.**

## CONCLUSIONS

**Each degree of gestational glucose intolerance predicts distinct trajectories of β-cell function, insulin sensitivity, and glycemia in the first 3 years postpartum that drive their differential risk of future T2DM.**


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It is well established that women who are diagnosed with gestational diabetes mellitus (GDM) have an increased risk of developing type 2 diabetes mellitus (T2DM) in the years after the index pregnancy (1–7). Furthermore, it is now recognized that even women with milder degrees of glucose intolerance in pregnancy (i.e., less severe than GDM) have an increased risk of ultimately developing prediabetes and T2DM in the future (6,8–15). These diagnoses of mild gestational dysglycemia can be identified during clinical screening for GDM and include *1*) women with an abnormal antepartum oral glucose tolerance test (OGTT) that does not meet diagnostic criteria for GDM, and *2*) those with a normal OGTT but an abnormal screening glucose challenge test (GCT) (8,9,12,14). Importantly, the risk of postpartum progression to prediabetes/T2DM is proportional to the severity of gestational dysglycemia, being highest in women with GDM and proportionately lower in those with milder abnormalities of antepartum glucose tolerance (8). Thus, the spectrum of abnormal glucose homeostasis in pregnancy identifies a gradient of future diabetic risk in the years thereafter. To date, however, longitudinal study of the pathophysiologic changes that drive this gradient of risk in the early postpartum years has been limited. Therefore, our objective in this study was to elucidate the trajectories of β-cell function, insulin sensitivity, and glycemia during the first 3 years postpartum in a well-characterized cohort of women representing the full spectrum of glucose tolerance in pregnancy.

## RESEARCH DESIGN AND METHODS

### Participants

The study population consisted of women participating in a prospective observational cohort program at our institution in which we are studying the relationship between glucose tolerance status in pregnancy and metabolic function in the years after delivery (9,16,17). In this program, women are first recruited into a pregnancy cohort at the time of antepartum screening for GDM in late second/early third trimester and undergo metabolic characterization at recruitment in pregnancy and again at 3 months and 1 year postpartum. At the latter visit, they are recruited into an ongoing long-term follow-up observational cohort study in which participating women undergo serial metabolic characterization biannually for several years thereafter. The current analysis reports the metabolic trajectories of 337 participants from recruitment in pregnancy to their first assessment in the long-term cohort at 3 years postpartum. The protocols of the pregnancy cohort and the long-term cohort study were approved by the Mount Sinai Hospital Research Ethics Board, and all women provided written informed consent for their participation.

### Recruitment and Determination of Glucose Tolerance Status in Pregnancy

As previously described (9,16,17), women were first recruited in late second/early third trimester at the time of antepartum screening for GDM. At our institution, women are screened for GDM by a 50-g GCT, followed by referral for diagnostic OGTT if the GCT result is abnormal (plasma glucose ≥7.8 mmol/L at 1 h after ingestion of 50-g glucose load). In the study, all participants undergo a 3-h 100-g OGTT for ascertainment of gestational glucose tolerance status, regardless of the GCT result (i.e., even if the result is normal). Women were recruited before or after the GCT. As previously described (9,17), the recruitment of women after an abnormal GCT served to enrich the study population for those with varying degrees of glucose intolerance. The GCT and 3-h 100-g OGTT in pregnancy enabled stratification of participants into the following four gestational glucose tolerance groups:

1. GDM, as defined by National Diabetes Data Group (NDDG) criteria (18), which require at least two of the following on the OGTT: fasting blood glucose ≥5.8 mmol/L, 1-h glucose ≥10.6 mmol/L, 2-h blood glucose ≥9.2 mmol/L, or 3-h blood glucose ≥ 8.1 mmol/L;
2. Gestational impaired glucose tolerance (GIGT), 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.

Women with GDM received glucose-lowering treatment in pregnancy, consisting of dietary and lifestyle counseling (pertaining to pregnancy and postpartum) with or without antepartum insulin therapy. According to standard clinical practice at our institution, women in the other three glucose tolerance groups did not receive this glucose-lowering therapy. Baseline data regarding medical, obstetrical, and family history were collected by an interviewer-administered questionnaire on the morning of the OGTT (at which time gestational glucose tolerance had not yet been determined).

### Postpartum Assessments at 3 Months, 1 Year, and 3 Years

At 3 months, 1 year, and 3 years postpartum, participants returned to the clinical investigation unit for reassessment, including a 2-h 75-g OGTT on each occasion. Glucose tolerance status was defined on each OGTT according to current Canadian Diabetes Association guidelines (19). Dysglycemia refers to prediabetes (impaired glucose tolerance [IGT], impaired fasting glucose [IFG], or combined IFG and IGT) or diabetes.

At each visit, participants underwent physical examination, including anthropometric assessment and measurement of blood pressure. Data regarding medical, obstetrical, and family history were collected through an interviewer-administered questionnaire. At 1 year and 3 years postpartum, physical activity in the preceding year was assessed with the Baecke questionnaire, an established instrument that has been extensively validated in several populations, including women of childbearing age (20,21). This questionnaire was completed during the OGTT (i.e., before the current glucose tolerance status was known). The Baecke questionnaire measures total physical activity and its three component domains: occupation-associated activity (work index), sport-related physical activity (sport index), and nonsport leisure-time activity (leisure-time index). The work index quantifies exertion related to occupational activities, such as sitting, standing, lifting, and walking, as well as associated effects on the person (e.g., fatigue, perspiration). The sport index characterizes vigorous/sports activity with respect to intensity (using the

updated compendium of physical activities) (22), duration, and frequency. The leisure-time index quantifies exertion associated with nonsport recreational activities (e.g., walking, watching television).

### Laboratory Measurements and Physiologic Indices

All OGTTs were performed in the morning after an overnight fast, with venous blood samples drawn for the measurement of glucose and specific insulin levels at fasting and at 30, 60, and 120 min (and 180 min in pregnancy) after the ingestion of the glucose load. Specific insulin was measured with the Roche Elecsys 1010 immunoassay analyzer and electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval, Quebec, Canada).

Insulin sensitivity was measured on each OGTT with the Matsuda index, an established measure of whole-body insulin sensitivity that has been validated against the euglycemic-hyperinsulinemic clamp (23). β-Cell function was assessed on each OGTT with the Insulin Secretion-Sensitivity Index-2 (ISSI-2), a validated measure of β-cell function that is analogous to the disposition index obtained from the intravenous GTT (IVGTT) (24,25). The ISSI-2 has been directly validated against the disposition index from the IVGTT, with which it exhibits stronger correlation than do other OGTT-derived measures of β-cell function, including the insulinogenic index–based measures and HOMA β-cell (HOMA-B) function, (25) and has been used in clinical trials and observational studies in patients with and without diabetes (17,26–30). ISSI-2 is defined as the product of *1*) insulin secretion measured by the ratio of the area-under-the-insulin curve to the area-under-the-glucose curve and *2*) insulin sensitivity measured by Matsuda index (24,25).

### Statistical Analyses

All analyses were conducted using SAS 9.1 software (SAS Institute, Inc., 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 gestational glucose tolerance groups were assessed at recruitment in pregnancy and at 3 months, 1 year, and 3 years postpartum using the Wilcoxon rank sum test for continuous variables and the $\chi^2$ test or Fisher exact test for categorical variables (Table 1). At each of 3 months, 1 year, and 3 years postpartum, the prevalence of dysglycemia was compared among the gestational glucose tolerance groups by the $\chi^2$ test (Fig. 1). Mixed-models were constructed to evaluate the trajectories of fasting glucose, 2-h glucose, Matsuda index, and ISSI-2 in each group during the postpartum follow-up (from 3 months to 3 years; Table 2). Covariates in these models were model 1: age, ethnicity, family history of diabetes, time-dependent BMI, and months postpartum; model 2: model 1 + duration of breastfeeding in the first year postpartum + total physical activity at 1 year and 3 years; and model 3: model 2 + development of diabetes at 3 months or 1 year (i.e., a diagnosis that might cause subsequent lifestyle changes).

## RESULTS

### Comparison of Gestational Glucose Tolerance Groups

A comparison of the 337 women comprising the study population with the 103 women who declined to participate showed no significant differences between the two groups in age, ethnicity, family history of diabetes, glucose tolerance, smoking, and physical activity at 1 year, although the women who declined had slightly lower BMI than the participants (median 23.8 vs 24.7 kg/m$^2$, $P$ = 0.01). Table 1 reports the characteristics of the study population at recruitment in pregnancy and at follow-up at 3 months, 1 year, and 3 years postpartum, stratified into the following four groups based on gestational glucose tolerance status: normal GCT NGT ($n$ = 76), abnormal GCT NGT ($n$ = 96), GIGT ($n$ = 60), and GDM ($n$ = 105). At recruitment, these groups did not differ in age, ethnicity, family history of diabetes, or parity. Prepregnancy BMI was highest in the GDM group ($P$ = 0.04). As expected, insulin sensitivity (Matsuda index) and β-cell function (ISSI-2) in pregnancy both progressively decreased across the four categories of gestational glucose tolerance from normal GCT NGT to abnormal GCT NGT to GIGT to GDM (both $P < 0.001$). Furthermore, these differences in insulin sensitivity and β-cell function persisted at each postpartum visit (3 months, 1 year, and 3 years; all $P \leq 0.002$). Of note, BMI, waist circumference, and physical activity did not differ among the groups at these postpartum assessments (all $P \geq 0.08$).

The persistent postpartum differences in insulin sensitivity and β-cell function were further reflected in the prevalence of dysglycemia (prediabetes or diabetes) in the four groups. Indeed, at each of 3 months, 1 year, and 3 years postpartum, a stepwise increase was found in the prevalence of dysglycemia from the normal GCT NGT group to abnormal GCT NGT to GIGT to GDM (all $P < 0.001$; Fig. 1), with rates of 30–38% in women with GDM. Most of the dysglycemia was prediabetes, with diabetes comprising 10.6% of the dysglycemia at 3 months, 5.4% at 1 year, and 13.0% at 3 years.

### Postpartum Trajectories of Glycemia, Insulin Sensitivity, and β-Cell Function

We next performed mixed-model analyses to determine the predicted postpartum trajectories of fasting glucose, 2-h glucose, Matsuda index, and ISSI-2 in each of the four gestational glucose tolerance groups, after adjustment for age, ethnicity, family history of diabetes, time-dependent BMI, and months since delivery (Fig. 2). As shown in Fig. 2*A*, there was a significant difference among the groups in fasting glucose ($P < 0.001$) that was most apparent at 3 years postpartum but that was otherwise small in its overall magnitude. In contrast, there was a clear difference among the groups in 2-h glucose ($P < 0.001$), with a stepwise increase from normal GCT NGT to abnormal GCT NGT to GIGT to GDM at each postpartum visit (Fig. 2*B*). Furthermore, GDM predicted rising 2-h glucose between 1 and 3 years postpartum, in contrast to the other groups, which showed relative stability of their different degrees of postprandial glycemia between these visits (Fig. 2*B*).

These differences over time in glycemia were mirrored by striking differences between the groups in insulin sensitivity (Matsuda index) and β-cell function (ISSI-2). Indeed, there was a stepwise decrease in the Matsuda index (Fig. 2*C*) and ISSI-2 (Fig. 2*D*) from normal GCT NGT to abnormal GCT NGT to GIGT to GDM (both $P < 0.001$) that was readily apparent at each point in time. Even more revealing were the patterns of change over time in these

**Table 1—Characteristics of the four gestational glucose tolerance groups at recruitment in pregnancy, 3 months postpartum, 1 year postpartum, and 3 years postpartum**

| | Normal GCT NGT (*n* = 76) | Abnormal GCT NGT (*n* = 96) | GIGT (*n* = 60) | GDM (*n* = 105) | *P* value |
|---|---|---|---|---|---|
| At recruitment in pregnancy | | | | | |
| Age (years) | 34 (32–38) | 34 (32–37) | 34 (32–38) | 35 (33–38) | 0.71 |
| Ethnicity (%) | | | | | 0.40 |
| White | 75.0 | 75.0 | 68.3 | 65.7 | |
| Asian | 6.6 | 9.4 | 11.7 | 17.1 | |
| Other | 18.4 | 15.6 | 20.0 | 17.1 | |
| Family history of T2DM (%) | 40.8 | 52.1 | 55.0 | 59.1 | 0.10 |
| Prepregnancy BMI (kg/m$^2$) | 24.2 (21.5–28.4) | 22.8 (21.0–25.8) | 23.9 (22.2–29.0) | 25.0 (22.1–28.9) | 0.04 |
| Parity (%) | | | | | 0.65 |
| Nulliparous | 56.6 | 53.1 | 48.3 | 50.5 | |
| 1 | 39.5 | 37.5 | 38.3 | 41.0 | |
| >1 | 3.9 | 9.4 | 13.3 | 8.6 | |
| Matsuda index | 5.9 (4.1–7.6) | 5.7 (3.8–7.9) | 3.3 (2.6–5.0) | 3.1 (2.2–4.6) | <0.001 |
| ISSI-2 | 832 (732–993) | 843 (688–1,054) | 617 (535–760) | 522 (426–602) | <0.001 |
| At 3 months postpartum | | | | | |
| Months postpartum | 3 (3–4) | 3 (3–4) | 3 (3–4) | 3 (3–4) | 0.77 |
| BMI (kg/m$^2$) | 25.6 (22.5–29.7) | 25.2 (22.7–28.7) | 26.2 (23.3–30.9) | 26.5 (23.2–29.8) | 0.46 |
| Waist circumference (cm) | 89 (82–99) | 86 (81–92) | 88 (83–94) | 90 (82–97) | 0.11 |
| Breastfeeding (months) | 3 (3–4) | 3 (2–3) | 3 (3–4) | 3 (2–3) | 0.30 |
| Current smoking (%) | 1.3 | 2.2 | 5.3 | 1.9 | 0.54 |
| OGTT | | | | | |
| Fasting glucose (mmol/L) | 4.4 (4.2–4.7) | 4.4 (4.2–4.8) | 4.7 (4.4–4.9) | 4.7 (4.4–5.0) | <0.001 |
| 2-h glucose (mmol/L) | 5.4 (4.7–6.1) | 6.1 (5.2–7.2) | 6.4 (5.2–7.3) | 6.9 (5.7–8.6) | <0.001 |
| Matsuda index | 13.6 (8.7–17.4) | 10.5 (7.6–16.5) | 8.7 (6.0–13.0) | 8.3 (5.9–12.2) | <0.001 |
| ISSI-2 | 826 (670–1,086) | 776 (634–965) | 664 (539–845) | 637 (501–825) | <0.001 |
| At 1 year postpartum | | | | | |
| Months postpartum | 12 (11–13) | 12 (12–13) | 12 (12–13) | 12 (12–13) | 0.22 |
| BMI (kg/m$^2$) | 24.8 (21.5–28.4) | 23.8 (21.8–27.9) | 25.4 (23.0–30.1) | 25.4 (22.5–29.3) | 0.15 |
| Waist circumference (cm) | 85 (77–92) | 83 (76–90) | 86 (80–96) | 87 (80–95) | 0.08 |
| Breastfeeding (months) | 11 (6–12) | 10 (6–12) | 9 (4–12) | 10 (3–12) | 0.36 |
| Current smoking (%) | 2.7 | 3.2 | 8.8 | 2 | 0.20 |
| Total physical activity | 8.1 (7.3–9.3) | 8.6 (7.3–9.3) | 8.3 (7.4–9.0) | 8.3 (7.3–9.1) | 0.99 |
| Sport index | 2.6 (1.8–2.8) | 2.3 (1.5–2.8) | 2.0 (1.8–2.8) | 2.3 (1.8–2.8) | 0.85 |
| Leisure-time index | 3.3 (2.8–3.5) | 3.0 (2.5–3.5) | 3.0 (2.8–3.3) | 3.0 (2.8–3.5) | 0.67 |
| Work index | 3.0 (2.6–3.3) | 3.1 (2.5–3.5) | 3.0 (2.5–3.3) | 3.0 (2.4–3.4) | 0.67 |
| OGTT | | | | | |
| Fasting glucose (mmol/L) | 4.6 (4.4–4.7) | 4.6 (4.4–4.95) | 4.8 (4.6–5.1) | 4.8 (4.5–5.1) | <0.001 |
| 2-h glucose (mmol/L) | 5.3 (4.6–6.0) | 6.0 (4.8–7.15) | 6.1 (5.2–7.3) | 6.8 (5.4–8.4) | <0.001 |
| Matsuda index | 11.1 (6.4–15.5) | 10.0 (5.8–13.8) | 7.5 (4.9–12.5) | 7.6 (4.4–11.0) | 0.002 |
| ISSI-2 | 832 (680–1,060) | 768 (603–1,013) | 690 (490–767) | 629 (487–797) | <0.001 |
| At 3 years postpartum | | | | | |
| Months postpartum | 30 (25–37) | 36 (29–43) | 39 (28–50) | 31 (25–37) | 0.002 |
| BMI (kg/m$^2$) | 24.6 (21.8–29.1) | 24.0 (21.6–28.3) | 24.8 (23.4–30.0) | 25.4 (22.4–30.1) | 0.20 |
| Waist circumference (cm) | 85 (79–97) | 85 (77–92) | 86 (82–96) | 88 (80–97) | 0.13 |
| Current smoking (%) | 4.0 | 2.1 | 15.5 | 2.9 | 0.005 |
| Total physical activity | 8.8 (7.9–9.4) | 8.7 (7.9–9.3) | 9.0 (7.9–9.5) | 8.5 (8.0–9.1) | 0.77 |
| Sport index | 3.0 (2.8–3.5) | 3.0 (2.5–3.3) | 3.0 (2.8–3.3) | 3.0 (2.5–3.3) | 0.55 |
| Leisure-time index | 3.0 (2.5–3.5) | 3.0 (2.5–3.3) | 3.0 (2.5–3.3) | 3.0 (2.8–3.3) | 0.98 |
| Work index | 2.5 (2.2–3.0) | 2.8 (2.3–3.1) | 2.8 (2.4–3.1) | 2.6 (2.3–3.0) | 0.08 |
| OGTT | | | | | |
| Fasting glucose (mmol/L) | 4.6 (4.3–4.8) | 4.5 (4.3–4.8) | 4.8 (4.4–5.2) | 4.9 (4.5–5.2) | <0.001 |
| 2-h glucose (mmol/L) | 5.4 (4.7–6.4) | 5.9 (4.9–7.1) | 6.5 (5.2–7.6) | 6.8 (5.8–8.9) | <0.001 |
| Matsuda index | 10.0 (7.3–12.8) | 8.2 (5.6–12.5) | 7.4 (4.4–10.7) | 6.3 (4.1–9.7) | <0.001 |
| ISSI-2 | 840 (716–1,087) | 820 (629–1,076) | 689 (510–937) | 579 (453–809) | <0.001 |

Continuous data are shown as median (interquartile range) and categorical data as proportions. The *P* values refer to overall differences across the groups by Wilcoxon rank sum test for continuous variables and by $\chi^2$ test or Fisher exact test for categorical variables.

measures. Indeed, although each gestational glucose tolerance group showed the same pattern of decreasing insulin sensitivity from 3 months to 1 year to 3 years postpartum, they each did so along a distinct track (or different level) of insulin sensitivity (Fig. 2*C*). Furthermore, although each of the four groups exhibited a different level of β-cell

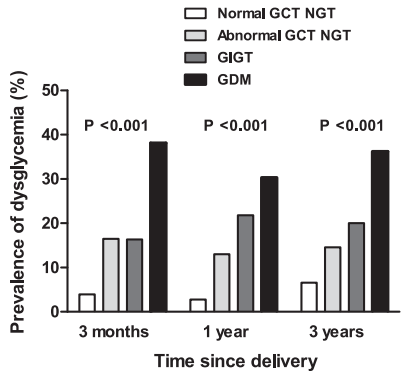


**Figure 1**—Prevalence of dysglycemia (prediabetes or diabetes) over time within each of the four gestational glucose tolerance groups. The *P* values refer to overall comparison across the groups at the indicated time point.

function, women with recent GDM had a pattern of declining β-cell function over time, unlike the other three groups, which did not show this deterioration (Fig. 2*D*). Thus, although gestational glucose tolerance predicts distinct degrees of postpartum metabolic function (glycemia, insulin sensitivity, β-cell function), it is noteworthy that GDM is specifically characterized by worsening of postprandial glycemia and β-cell function during the first 3 years after delivery, after adjustment for diabetes risk factors. In addition, these findings were unchanged with adjustment for waist circumference (as a time-dependent variable) in place of BMI (data not shown).

### Rates of Change of Glycemia, Insulin Sensitivity, and β-Cell Function

In a series of mixed-model analyses, we next compared the rates of change in fasting glucose, 2-h glucose, Matsuda index, and ISSI-2 among the gestational glucose tolerance groups during the duration of follow-up (Table 2). Compared with the normal GCT NGT group (reference), the GIGT and GDM groups both showed a modest but significantly higher rate of increase in fasting glucose over time (Table 2*A*). For 2-h glucose, all three gestational glucose intolerance groups exhibited higher rates of increase than the reference group, which progressively rose from abnormal GCT NGT to GIGT to GDM in all models (Table 2*B*). Similarly, these groups showed an analogous pattern of greater deterioration of insulin sensitivity in all models evaluating their rates of change in Matsuda index (Table 2*C*). Most importantly, compared with the reference group, GIGT and GDM both exhibited significantly greater worsening of β-cell function over time in all models (Table 2*D*). In sensitivity analyses, the findings in Table 2 were largely unchanged for each outcome upon further adjustment of model 3 for *1*) having a subsequent pregnancy during follow-up (as did 54 women) or *2*) mode of contraception (data not shown).

Finally, to elucidate the clinical implication of these distinct trajectories, we evaluated how the postpartum metabolic effect of weight gain of 1 kg may vary depending on gestational glucose tolerance status. Indeed, for two women with identical age, ethnicity, family history, height, weight, and duration of follow-up, a 1-kg increase in weight during the 3-year postpartum follow-up would have very different effects, depending on their gestational glucose tolerance. Specifically, in a woman with normal GCT NGT, this 1-kg increase in postpartum weight would lead to a 0.15% decline in ISSI-2, a 2.05% decline in Matsuda index, a 0.07% increase in fasting glucose, and a 0.11% increase in 2-h glucose. In contrast, if the woman instead had GDM, this same 1-kg weight gain would lead to an eightfold greater decline in ISSI-2 (1.21% vs. 0.15%), an almost identical fall in the Matsuda index (2.08% vs. 2.05%), a threefold greater increase in fasting glucose (0.21% vs. 0.07%), and a fivefold greater increase in 2-h glucose (0.59% vs. 0.11%).

## CONCLUSIONS

In this study, we demonstrate a stepwise increase in the prevalence of dysglycemia at each of 3 months, 1 year, and 3 years postpartum, as gestational glucose tolerance worsens from normal (normal GCT NGT) to mildly abnormal (abnormal GCT NGT) to moderately abnormal (GIGT) to GDM. At each postpartum time point,

**Table 2—Mixed models showing the rate of change in fasting glucose (*A*), 2-h glucose (*B*), Matsuda index (*C*), and ISSI-2 (*D*) in each of the four gestational glucose tolerance groups over the duration of follow-up, adjusted for model 1, model 2, and model 3**

| | Normal GCT NGT (reference) | | Abnormal GCT NGT | | GIGT | | GDM | |
|---|---|---|---|---|---|---|---|---|
| | Estimate | *P* value | Estimate | *P* value | Estimate | *P* value | Estimate | *P* value |
| *A*: Fasting glucose | | | | | | | | |
| Model 1[a] | — | — | 0.0014 | 0.90 | 0.0470 | **<0.001** | 0.0470 | **<0.001** |
| Model 2[b] | — | — | 0.0005 | 0.96 | 0.0500 | **<0.001** | 0.0440 | **<0.001** |
| Model 3[c] | — | — | −0.0040 | 0.78 | 0.0040 | **0.003** | 0.0370 | **0.006** |
| *B*: 2-h glucose | | | | | | | | |
| Model 1 | — | — | 0.1020 | **0.001** | 0.1380 | **<0.001** | 0.2310 | **<0.001** |
| Model 2 | — | — | 0.1100 | **0.002** | 0.1370 | **<0.001** | 0.2320 | **<0.001** |
| Model 3 | — | — | 0.0570 | **0.04** | 0.0740 | **0.02** | 0.1270 | **<0.001** |
| *C*: Matsuda index | | | | | | | | |
| Model 1 | — | — | −0.1670 | **0.007** | −0.1830 | **0.009** | −0.2960 | **<0.001** |
| Model 2 | — | — | −0.1790 | **0.007** | −0.1750 | **0.02** | −0.3100 | **<0.001** |
| Model 3 | — | — | −0.1530 | **0.02** | −0.1420 | **0.05** | −0.2590 | **<0.001** |
| *D:* ISSI-2 | | | | | | | | |
| Model 1 | — | — | −0.0700 | 0.14 | −0.2320 | **<0.001** | −0.2960 | **<0.001** |
| Model 2 | — | — | −0.0670 | 0.22 | −0.2180 | **<0.001** | −0.2840 | **<0.001** |
| Model 3 | — | — | −0.0040 | 0.94 | −0.1390 | **0.02** | −0.1640 | **<0.001** |

Boldface indicates $P < 0.05$. [a]Model 1: age + ethnicity + family history of diabetes + time-dependent BMI + months postpartum. [b]Model 2: model 1 + duration of breastfeeding + physical activity at 1 year and 3 years. [c]Model 3: model 2 + development of diabetes at either 3 months or 1 year.

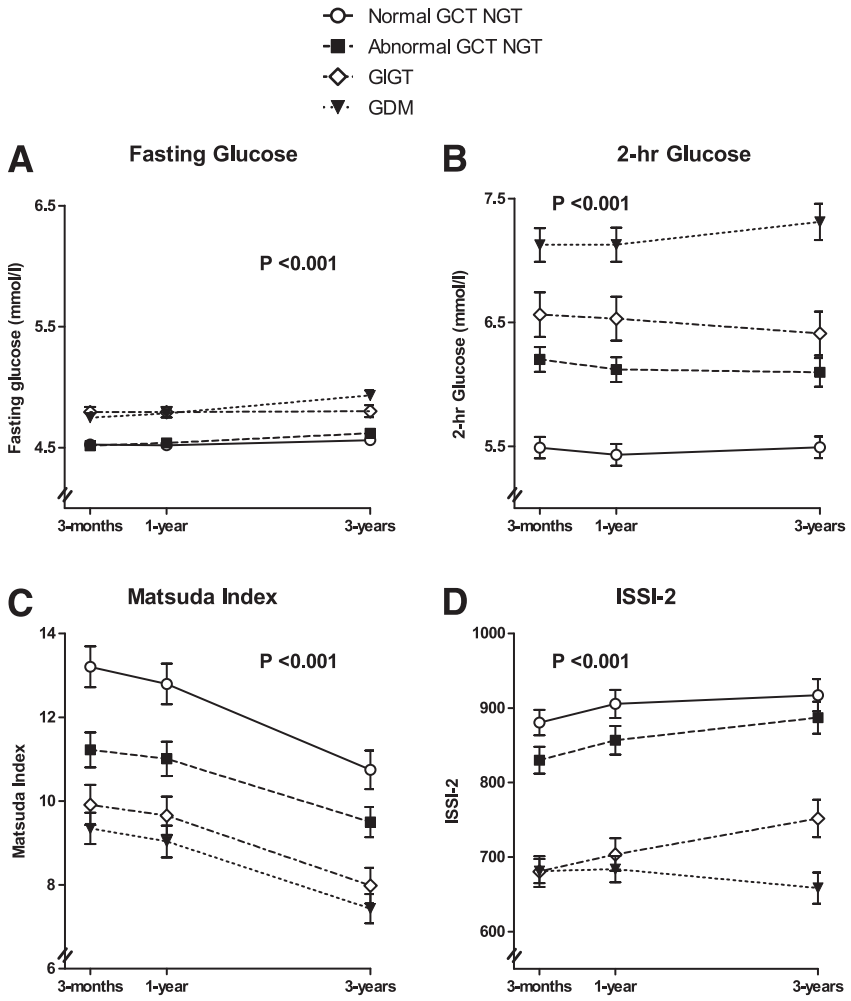


**Figure 2**—Predicted trajectories of fasting glucose (*A*), 2-h glucose (*B*), Matsuda index (*C*), and ISSI-2 (*D*) by gestational glucose tolerance group, after adjustment for age, ethnicity, family history of diabetes, time-dependent BMI, and months postpartum. The *P* values refer to the comparison among groups of their average values across all time points. Range bars show the SEM.

there was an analogous gradient of β-cell dysfunction, insulin resistance, and increasing glycemia across these four groups. Most importantly, each degree of gestational glucose intolerance independently predicted distinct trajectories of β-cell function, insulin sensitivity, and glycemia during the first 3 years postpartum. It thus emerges that the spectrum of glucose intolerance in pregnancy may enable anticipation of the course of metabolic function in the first 3 years after delivery.

A series of previous studies have demonstrated that each degree of dysglycemia in pregnancy predicts a proportionately increased future risk of T2DM in the years thereafter, with GDM representing the most extreme element on both of these related continua (8–14). The presumed physiologic basis for this relationship is that women who develop gestational dysglycemia have a chronic β-cell defect that *1*) yields insufficient compensation for the severe insulin resistance of late pregnancy (resulting in their diagnostic antepartum hyperglycemia) and *2*) underlies their predisposition to the subsequent development of T2DM (17). Indeed, previous studies have confirmed that women with each degree of gestational dysglycemia (GDM, GIGT, and abnormal GCT NGT) have chronic β-cell dysfunction that is detectable both during pregnancy and on cross-sectional evaluation after delivery (9,17,31–33). To date, however, there have been few longitudinal studies of the changes over time in β-cell function, insulin sensitivity, and glycemia in these groups.

Limiting features of the few longitudinal studies comprising this literature have included the assessment of only women with GDM (without comparators), restriction to a single ethnic group, and modest duration of follow-up or number of assessments. Specifically, long-term studies in a cohort of 72 Mexican American women with GDM showed that β-cell function declined over time in this patient population, although these analyses did not have a comparison with a control group with normal gestational glucose tolerance (34–36). In a recent study of 235 Mexican American women evaluated on two occasions in the first 5 years after pregnancy, Xiang et al. (37) reported that the 93 women with previous GDM had faster deterioration of β-cell compensation and insulin sensitivity than the 142 women without a history of GDM (some of whom were siblings or cousins of the women with GDM). Lastly, we previously demonstrated postpartum deterioration of β-cell function after glucose intolerance in pregnancy but with only two measurements, at 3 and 12 months after delivery, such that a reliable estimation of longer-term metabolic trajectories was not possible (17,29).

In this context, the current study was designed to address these limitations through specific elements of the study design. First, this cohort is large (*n* = 337) and consists of a multiethnic population (71% of which was white). Second, this study population underwent prospective ascertainment of glucose tolerance in pregnancy, yielding a cohort that spans the full spectrum of gestational glucose tolerance and enabling comparative assessment of truly normal controls (normal GCT NGT), women with intermediate degrees of gestational dysglycemia, and those with GDM. Third, this cohort underwent systematic metabolic characterization three different times after pregnancy, thereby making it possible to apply mixed-model analysis and elucidate the trajectories of metabolic features during the first 3 years postpartum.

These trajectories are particularly informative and offer insight into the differential diabetic risk of these groups. First, it is apparent that the spectrum of gestational glucose tolerance translates to analogous gradients of β-cell function, insulin sensitivity, and glycemia at each of 3 months, 1 year, and 3 years postpartum.

Second, each strata of gestational dysglycemia predicts varying rates of declining β-cell function and insulin sensitivity, and rising glycemia, compared with women with completely normal glucose homeostasis in pregnancy, independent of clinical risk factors for diabetes (Table 2). However, these changes take place along distinct tracks (Fig. 2), the patterns of which are revealing. Indeed, besides the poorest metabolic profile at each point in time, GDM predicts a pattern of declining β-cell function and rising 2-h glucose in the first 3 years postpartum that is unlike that of the other groups. In contrast, GIGT and abnormal GCT NGT predict consistently poorer metabolic function (β-cell function, insulin sensitivity, glycemia) than that of women with normal gestational glucose tolerance (normal GCT NGT) but with comparable patterns of change over the 3 years. In other words, the trajectories suggest that GDM is a chronic metabolic disorder that is specifically characterized by deterioration of β-cell function and rising postprandial glycemia in the early postpartum years that drives the high risk of progression to T2DM in affected women. In contrast, GIGT and abnormal GCT NGT are also chronic metabolic disorders but are characterized by far more gradual deterioration that will likely require a longer period of time for clinical manifestation of their intermediate diabetic risk. It is also of interest that insulin sensitivity declined in all four gestational glucose tolerance groups (including normal GCT NGT) during the first 3 years postpartum (Fig. 2*C*), raising the question of whether pregnancy has an adverse long-term effect on insulin resistance. However, at present, whether this decline in insulin sensitivity continues in subsequent years is not known.

These insights hold potential clinical implications. First, these data suggest that careful analysis of the glycemic response to the stress test of pregnancy offers an opportunity to anticipate the longitudinal course of metabolic function during the first 3 years after delivery in all pregnant women (not just those with GDM).

Second, the effect of a modifiable factor, such as postpartum weight gain, may differ markedly depending on the gestational glucose tolerance group, as illustrated earlier by the example of women with GDM experiencing a far greater adverse effect on metabolism than those with normal gestational glucose homeostasis; this concept is consistent with a previous report that demonstrated a more pronounced effect of prepregnancy overweight on future T2DM in women with GDM than in their peers (38).

Third, an understanding of these trajectories can potentially inform strategies that are targeted to an individual woman's likely course of metabolic function. Specifically, their differing patterns of change over time suggest that the gestational glucose tolerance groups likely warrant different clinical surveillance strategies for optimal early detection of progression to dysglycemia. For example, although GDM will require the most intense clinical surveillance, GIGT and abnormal GCT NGT may dictate an intermediate approach in this regard, in contrast to the truly low-risk patient population with normal GCT NGT. Similarly, clinical advice regarding the likely metabolic effect of weight gain may be tailored according to gestational glucose tolerance status.

A limitation of this study is that β-cell function and insulin sensitivity were assessed with OGTT-based surrogate indices rather than with clamp studies. However, their time-consuming and invasive nature would have made clamp studies difficult to complete on three occasions during 3 years in 337 new mothers. The serial assessments of the current protocol were essential for elucidating the patterns of change over time described in this report. Moreover, the ISSI-2 and Matsuda index are validated measures that have been widely used in previous studies (17,23–30), and the serial OGTTs on which they were determined made it possible to also assess glucose tolerance status.

Another possible limitation is that the testing protocol and diagnostic criteria for GDM in this study may not be the same as those used at other institutions, which can affect the generalizability of our findings. However, the application of different glycemic thresholds for diagnosing GDM would not obscure our key demonstration that the entire spectrum of gestational glucose intolerance is associated with analogous gradients in the longitudinal changes over time in β-cell function, insulin sensitivity, and glycemia.

Finally, changes in dietary patterns were not assessed in this study and could have affected the outcomes. However, because major dietary modification generally translates into changes in weight, the inclusion of time-dependent BMI in all of the models likely mitigated the effect of this potential confounder.

In conclusion, each degree of gestational dysglycemia predicts varying rates of declining β-cell function and insulin sensitivity in the first 3 years postpartum compared with women with completely normal glucose homeostasis in pregnancy. These differential changes likely underlie the gradient of future diabetic risk associated with the spectrum of antepartum dysglycemia. Most importantly, each element of the latter spectrum predicts distinct trajectories of β-cell function, insulin sensitivity, and glycemia, an understanding of which may enable the tailoring of clinical strategies for mitigating the manifestation of diabetic risk in young women.

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