Impaired Glucose Tolerance of Pregnancy Is a Heterogeneous Metabolic Disorder as Defined by the Glycemic Response to the Oral Glucose Tolerance Test

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OBJECTIVE — Gestational diabetes mellitus (GDM), defined by two abnormal glucose values on a 3-h oral glucose tolerance test (OGTT), is associated with insulin resistance and a low serum concentration of adiponectin. The metabolic implications of impaired glucose tolerance (IGT) of pregnancy (i.e., a single abnormal value on an OGTT), however, are not well established. We sought to evaluate the metabolic phenotype of pregnant women with IGT in relation to the timing of their isolated hyperglycemia.

RESEARCH DESIGN AND METHODS — A cross-sectional study was performed in pregnant women undergoing a 3-h, 100-g OGTT. The OGTT stratified participants into four groups: *1)* GDM ($n = 48$), *2)* 1-h IGT (single elevated value at 1 h) ($n = 15$), *3)* 2-h/3-h IGT (single elevated value at either 2 or 3 h) ($n = 23$), and *4)* normal glucose tolerance (NGT) ($n = 93$). Insulin sensitivity was measured by the validated insulin sensitivity index (IS_{OGTT}) of Matsuda and DeFronzo.

RESULTS — Measures of severity of glycemia (fasting glucose, area under the glucose curve from the OGTT, and glucose challenge test result) were highest in the GDM group, followed by the 1-h IGT, 2-h/3-h IGT, and NGT groups, respectively (each trend $P < 0.0001$). Consistent with this finding, IS_{OGTT} was highest in the NGT group (5.1), followed by the 2-h/3-h IGT (4.6), 1-h IGT (3.8), and GDM (3.2) groups (trend $P < 0.0001$). Furthermore, on multiple linear regression analysis of IS_{OGTT}, both GDM and 1-h IGT were independently associated with reduced insulin sensitivity (whereas 2-h/3-h IGT was not). Mean adjusted adiponectin was highest in the NGT group (15.7 μg/ml), followed by the 2-h/3-h IGT (15.6 μg/ml), 1-h IGT (13.7 μg/ml), and GDM (12.0 μg/ml) groups (trend $P = 0.0024$).

CONCLUSIONS — The metabolic implications of IGT in pregnancy vary in relation to the timing of the abnormal glucose value from the diagnostic OGTT. The metabolic phenotype associated with 1-h IGT resembles that of GDM, whereas the phenotype associated with 2-h/3-h IGT exhibits similarity to that of NGT.

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The oral glucose tolerance test (OGTT) in pregnancy can provide valuable insight into the underlying metabolic phenotype and risk potential of young, otherwise healthy women. Notably, the diagnosis of gestational diabetes mellitus (GDM), based on two abnormal glucose values on a 3-h, 100-g OGTT,

identifies a population of young women at risk of developing type 2 diabetes later in life (1). Indeed, consistent with this risk, the metabolic features of GDM mirror those of type 2 diabetes. These shared characteristics include chronic insulin resistance (i.e., reduced insulin sensitivity), β-cell dysfunction, and low serum concentration of adiponectin, a novel adipocyte-derived protein with putative insulin-sensitizing properties (2–4).

In contrast to GDM, the metabolic implications of impaired glucose tolerance (IGT) in pregnancy, defined by a single abnormal value on a 3-h OGTT, are not well established. Previous studies have suggested that IGT in pregnancy is characterized by an intermediate degree of insulin resistance and a modest decline in serum adiponectin concentration (5,6). These investigations, however, have not accounted for the potential metabolic heterogeneity associated with differences in the timing of the single abnormal glucose value in women with IGT. Indeed, it is conceivable that the metabolic phenotype associated with isolated hyperglycemia at 1 h after glucose ingestion during the OGTT may be distinct from that observed with isolated hyperglycemia at either 2 or 3 h postglucose load. Accordingly, we hypothesized that IGT at 1 h may reflect a more severe metabolic derangement, characterized by insulin resistance and hypoadiponectinemia similar to that in GDM, whereas the metabolic phenotype of IGT at 2 or 3 h may resemble that of normal glucose tolerance (NGT). To test this hypothesis, we sought to compare metabolic features, including blood glucose levels, insulin sensitivity, and adiponectin concentration, in women with GDM, IGT at 1 h, IGT at 2 or 3 h, and NGT, within the context of a cross-sectional study of women undergoing oral glucose tolerance testing in pregnancy.

RESEARCH DESIGN AND METHODS — The study protocol and laboratory methods have previously been fully described (7,8). The protocol was

Table 1—*Demographic and clinical data by glucose tolerance group*

	GDM	1-h IGT	2-h/3-h IGT	NGT	P†
n	48	15	23	93	
Age (years)	34.0 ± 0.6	33.4 ± 1.2	32.4 ± 0.9	33.2 ± 0.5	0.5061
Weeks' gestation	29.1 ± 0.4	29.9 ± 0.6	29.6 ± 0.5	29.2 ± 0.3	0.6405
Prepregnancy BMI (kg/m^2)	24.7 ± 0.7	23.2 ± 1.2	24.4 ± 1.0	23.9 ± 0.5	0.6290
Weight gain in pregnancy (kg)	11.7 ± 0.7	11.2 ± 1.2	11.2 ± 1.0	11.1 ± 0.5	0.8775
Ethnicity					0.2383
Caucasian (%)	62.5	60.0	78.3	62.4	
Asian (%)	10.4	13.3	13.0	19.4	
South Asian (%)	27.1	26.7	4.4	14.0	
Other (%)	0	0	4.4	4.3	
Family history of diabetes (%)	62.5	60.0	56.5	45.2	0.2195
Previous GDM (%)	18.8	20.0	4.4	4.3	0.0159

*Data are means ±SE or %. †P values represent overall differences across groups as determined by ANOVA for continuous variables and χ^2 for categorical variables.

approved by the Research Ethics Board at Mount Sinai Hospital, and all study participants gave written informed consent. Briefly, participants consisted of 180 healthy pregnant women attending outpatient obstetrics clinics, who had been referred for a 3-h, 100-g OGTT after an abnormal result on a screening 50-g glucose challenge test (GCT) (plasma glucose ≥7.8 mmol/l at 1 h after challenge). Demographic and historical information was obtained by an interviewer-administered questionnaire at the time of the OGTT, as described earlier (7). Venous blood samples for measurement of insulin were drawn at fasting and hourly during the OGTT. 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). The plasma adiponectin concentration was measured at 3 h postglucose [the adiponectin level is not affected by food intake (9)] by radioimmunoassay (Linco Research, St. Charles, MO) with a coefficient of variation of 9.3%.

The OGTT stratified participants into three glucose tolerance groups: *1*) GDM, as defined by the National Diabetes Data Group (NDDG) criteria (requires at least two of the following: fasting glucose >5.8 mmol/l, 1-h postload glucose >10.6 mmol/l, 2-h glucose >9.2 mmol/l, or 3-h glucose >8.1 mmol/l); *2*) IGT, as defined by meeting only one of above criteria; and *3*) NGT, defined as subjects not meeting any of the NDDG criteria (10). It should

be recognized that the NDDG report did not define such an IGT subclassification for pregnancy. In the current analysis, the above definition of IGT has been used to identify subjects with an intermediate degree of glucose intolerance (between NGT and GDM), as evidenced by their single abnormal glucose value.

Of the 39 subjects with IGT, 15 met the 1-h criteria, 10 met the 2-h criteria, 13 met the 3-h criteria, and only 1 person exceeded the fasting threshold. As isolated fasting hyperglycemia is probably metabolically very different (i.e., reflecting significantly impaired suppression of postabsorptive hepatic gluconeogenesis in pregnancy) from postload IGT, the latter individual was excluded from the current analysis (also, this patient may not have been truly fasting). On the other hand, isolated hyperglycemia late in the OGTT at either 2 or 3 h postglucose probably represents similar pathophysiology, distinct from that associated with isolated hyperglycemia early in the OGTT at 1 h. As such, the IGT subjects were stratified into two groups: *1*) 1-h IGT (comprising subjects with isolated hyperglycemia at 1 h) and *2*) 2-h/3-h IGT (comprising subjects with isolated hyperglycemia at either 2 or 3 h postglucose). Thus, in combination with GDM and NGT, there were four study groups in total.

Measures of glycemia and insulin sensitivity

The area under the glucose curve (AUC$_{glucose}$) during the OGTT was calculated using the trapezoidal rule. AUC$_{glucose}$, fasting blood glucose, and the

blood glucose result at 1 h on the 50-g GCT provided continuous measures of the severity of hyperglycemia (and are collectively referred to as measures of glycemia in the text). The index of insulin sensitivity (IS$_{OGTT}$) was determined as originally described by Matsuda and DeFronzo (11). In a validation study in pregnant patients, the IS$_{OGTT}$ showed better correlation with insulin sensitivity derived using the euglycemic-hyperinsulinemic clamp technique than did the homeostasis model assessment of insulin resistance (12).

Statistical analysis

All analyses were conducted using SAS version 8.02 (SAS Institute, Cary, NC). $P < 0.05$ was considered statistically significant. Means ± SEs are presented by study group, with ANOVA used to assess univariate differences among continuous variables and χ^2 analysis used for categorical variables (Table 1). The distributions of IS$_{OGTT}$ and adiponectin were skewed, and thus natural logarithmic transformations of these variables were used in univariate and multivariate analyses, with back-transformed results presented in Figs. 2 and 3. ANCOVA was used to test differences in glycemic parameters (1-h blood glucose result on a 50-g GCT, fasting blood glucose, and AUC$_{glucose}$), IS$_{OGTT}$, and adiponectin in Figs. 1, 2, and 3, respectively. Multiple linear regression analysis of dependent variable logarithmically transformed IS$_{OGTT}$ was used to determine factors that were independently associated with insulin sensitivity. Covariates included in this model were age, weeks' gestation, prepregnancy BMI, weight gain during pregnancy, ethnicity, previous GDM, family history of diabetes, and current glucose intolerance (GDM, 1-h IGT, or 2-h/3-h IGT).

RESULTS — Study participants were stratified into the following four groups based on the number and timing of elevated glucose results during the OGTT: *1*) GDM (i.e., two elevated glucose values) ($n = 48$); *2*) 1-h IGT (single elevated value at 1 h) ($n = 15$); *3*) 2-h/3-h IGT (single elevated value at either 2 or 3 h) ($n = 23$); and *4*) NGT (no elevated glucose values) ($n = 93$). As shown in Table 1, there were no significant differences among these groups with respect to age, weeks' gestation, prepregnancy BMI, weight gain in pregnancy, ethnicity, and family history of diabetes. A history of GDM in a previous pregnancy, however, was much more
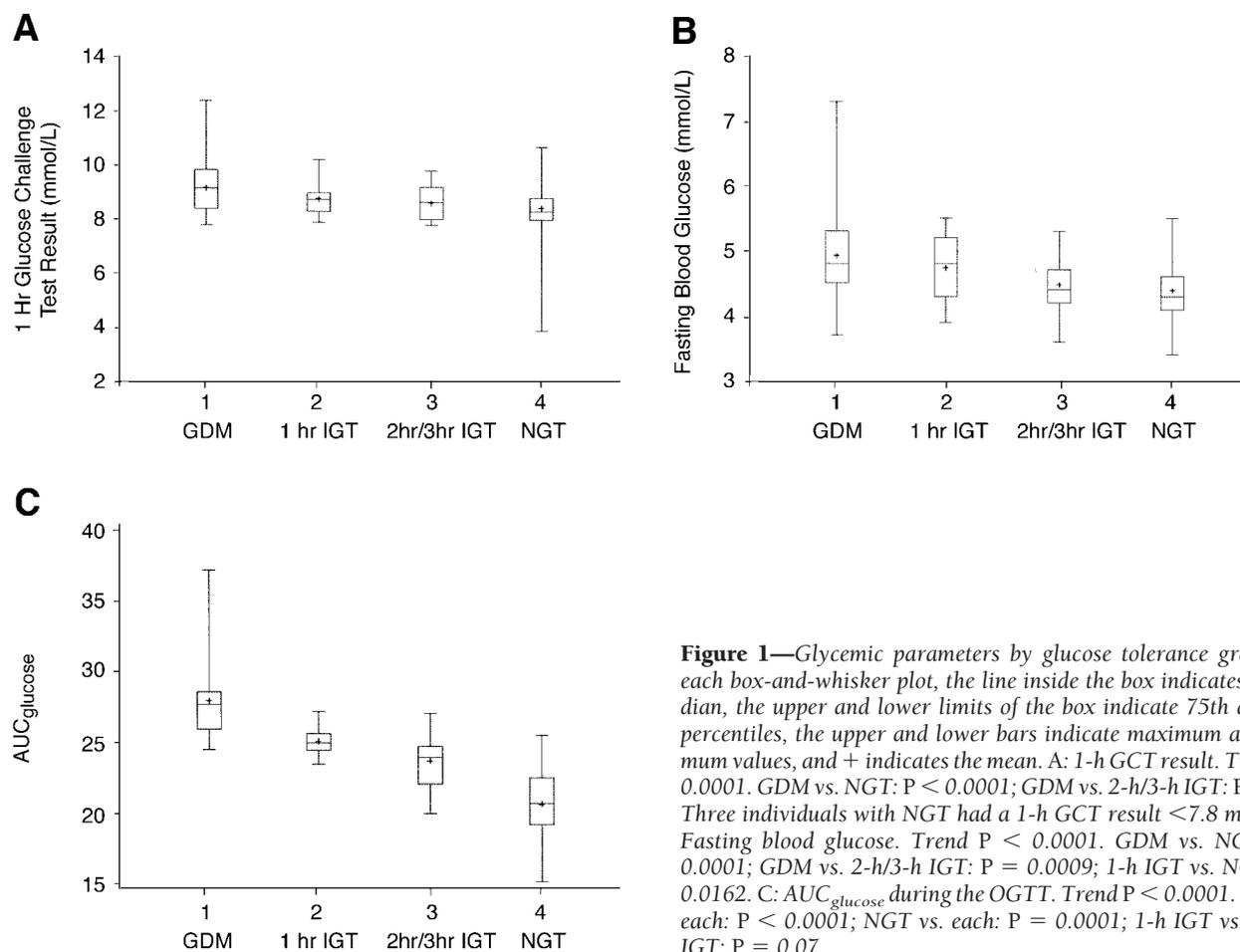
A

B

C

Figure 1—*Glycemic parameters by glucose tolerance group. For each box-and-whisker plot, the line inside the box indicates the median, the upper and lower limits of the box indicate 75th and 25th percentiles, the upper and lower bars indicate maximum and minimum values, and + indicates the mean. A: 1-h GCT result. Trend* P < *0.0001. GDM vs. NGT:* P < *0.0001; GDM vs. 2-h/3-h IGT:* P = *0.01. Three individuals with NGT had a 1-h GCT result <7.8 mmol/l. B: Fasting blood glucose. Trend* P < *0.0001. GDM vs. NGT:* P < *0.0001; GDM vs. 2-h/3-h IGT:* P = *0.0009; 1-h IGT vs. NGT:* P = *0.0162. C: AUC_{glucose} during the OGTT. Trend* P < *0.0001. GDM vs. each:* P < *0.0001; NGT vs. each:* P = *0.0001; 1-h IGT vs. 2-h/3-h IGT:* P = *0.07.*

prevalent in the GDM group (18.8% prevalence within group) and 1-h IGT group (20% prevalence) than in the 2-h/3-h IGT group (4.4%) and the NGT group (4.3%) (overall $P = 0.0159$).

Similar to the findings regarding previous GDM, evaluation of glycemic parameters (1-h blood glucose result on a 50-g GCT, fasting blood glucose, and $AUC_{glucose}$ from the OGTT) also suggested a pattern wherein 1-h IGT bore similarity to GDM and 2-h/3-h IGT resembled NGT (Fig. 1). The 1-h GCT result was highest in the GDM group (9.2 mmol), followed in turn by 1-h IGT (8.8 mmol/l), 2-h/3-h IGT (8.6 mmol/l), and NGT (8.4 mmol/l) groups, respectively (trend $P < 0.0001$) (Fig. 1*A*). Similarly, both fasting blood glucose (Fig. 1*B*) and $AUC_{glucose}$ (Fig. 1*C*) exhibited the same pattern (GDM > 1-h IGT > 2-h/3-h IGT > NGT) (both trend $P < 0.0001$). Furthermore, adjustment for previous GDM did not significantly change any of these relationships (data not shown).

Evaluation of insulin sensitivity, using the validated IS_{OGTT}, supported the observed glycemic trends across the four

study groups. Indeed, IS_{OGTT} was highest in the NGT group (5.1), followed in turn by the 2-h/3-h IGT (4.6), 1-h IGT (3.8), and GDM (3.2) groups, respectively (trend $P < 0.0001$) (Fig. 2). In addition, insulin sensitivity was *1*) significantly higher in the NGT group than in the 1-h IGT group (pairwise $P = 0.0225$) and *2*) significantly higher in the 2-h/3-h IGT group than in the GDM group (pairwise $P = 0.0016$). To further evaluate independent associations between these glucose tolerance groups and insulin sensitivity, we performed multiple linear regression analysis of the dependent variable IS_{OGTT}. A model fully adjusted for age, weeks' gestation, prepregnancy BMI, weight gain during pregnancy, ethnicity, previous GDM, family history of diabetes, and current glucose intolerance (GDM, 1-h IGT, and 2-h/3-h IGT) reconciled 32.9% of the variance in IS_{OGTT}. Importantly, both GDM ($t = -5.80$, $P < 0.0001$) and 1-h IGT ($t = -2.66$, $P = 0.0087$) emerged as negative independent correlates of IS_{OGTT}, indicating that both groups were associated with reduced insulin sensitivity (i.e., increased

insulin resistance). On the other hand, 2-h/3-h IGT was not significantly associated with insulin sensitivity. Other independent correlates of IS_{OGTT} in this analysis were prepregnancy BMI ($t = -4.94$, $P < 0.0001$), weight gain in pregnancy ($t = -2.45$, $P = 0.0154$), Asian ethnicity ($t = -2.64$, $P = 0.0090$), and South Asian heritage ($t = -2.16$, $P = 0.0326$).

Given these differences in insulin sensitivity among the four study groups, serum adiponectin emerged as a factor of particular interest. Adiponectin levels were highest in the NGT (15.7 μg/ml) and 2-h/3-h IGT (15.7 μg/ml) groups, followed in turn by the 1-h IGT (13.7 μg/ml) and GDM (11.8 μg/ml) groups, respectively (trend $P = 0.0009$) (Fig. 3*A*). Indeed, adiponectin concentration was significantly higher in the 2-h/3-h IGT group than in the GDM group (pairwise $P = 0.0058$). Furthermore, these relationships were essentially unchanged by adjustment for potential covariates including age, weeks' gestation, prepregnancy BMI, weight gain in pregnancy,
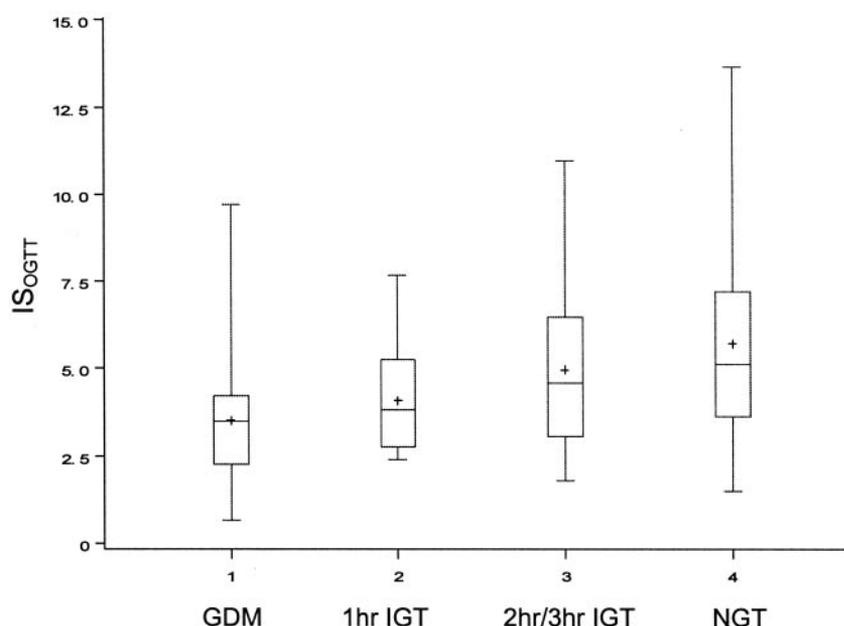
Figure 2—*IS$_{OGTT}$ by glucose tolerance group. For the box-and-whisker plot, the line inside the box indicates the median, the upper and lower limits of the box indicate 75th and 25th percentiles, the upper and lower bars indicate maximum and minimum values, and + indicates the mean. Trend* P < 0.0001. GDM vs. NGT: P < 0.0001; GDM vs. 2-h/3-h IGT: P = 0.0016; 1-h IGT vs. NGT: P = 0.0225.

ethnicity, previous GDM, and family history of diabetes (Fig. 3*B*).

CONCLUSIONS — In this report, we demonstrate that IGT in pregnancy is a heterogeneous disorder, insofar as its metabolic implications vary in relation to the timing of the abnormal glucose value from a diagnostic OGTT. Indeed, IGT at 1 h is independently associated with greater hyperglycemia, higher insulin resistance, and lower adiponectin concentration than IGT at 2 or 3 h. Furthermore, the metabolic phenotype associated with IGT at 1 h resembles that of GDM, whereas IGT at 2 or 3 h exhibits similarity to NGT. Thus, the clinical relevance of IGT in pregnancy may depend upon the timing of the isolated hyperglycemia upon which the diagnosis is based.

The diagnosis of GDM typically leads to blood glucose monitoring, dietary counseling, and insulin therapy as needed, in an effort to maintain euglycemia and reduce the risk of adverse maternal-fetal outcomes, including fetal macrosomia and birth injury (1,13). IGT in pregnancy, on the other hand, typically does not prompt a specific intervention. However, a growing body of evidence suggests that intervention in IGT may be warranted. Observational data from the Toronto Tri-Hospital Gestational Diabetes Project indicated that increasing car-

bohydrate intolerance in women without GDM is associated with a graded increase in adverse maternal-fetal outcomes (14). Furthermore, IGT has been linked with increased rates of macrosomia, premature rupture of membranes, prematurity, breech presentation, and cesarian section (15–18). Importantly, subjects with IGT in these studies have not been stratified on the basis of the timing of hyperglycemia during an OGTT. Because of its metabolic similarity to GDM in the current report, it would be of interest to determine whether IGT at 1 h is more strongly associated with adverse pregnancy outcomes than IGT at 2 or 3 h. The current findings suggest that this possibility warrants investigation.

Unlike pregnancy outcome, the metabolic characteristics of IGT in pregnancy have not been studied extensively. In a study of 110 pregnant women undergoing a 3-h 100-g OGTT, Ergin et al. (5) found that insulin resistance was significantly higher in IGT than in NGT. Similarly, within the current dataset, we have previously observed an intermediate degree of insulin sensitivity in IGT, between that of NGT (highest sensitivity) and GDM (lowest sensitivity) (6). The present analysis extends these observations by stratifying subjects with IGT based on the timing of hyperglycemia. Importantly, this approach reveals that IGT at 1 h is

independently associated with reduced insulin sensitivity, unlike IGT at 2 or 3 h. Furthermore, this result is consistent with earlier work showing that the likelihood of fetal hyperinsulinemia is increased when the 1-h glucose result exceeds 8.9 mmol/l (on a 75-g OGTT), leading to the suggestion that the 1-h value may provide the most appropriate diagnosis of abnormal glucose tolerance in pregnancy (19–21).

In the current analysis, women with 2-h/3-h IGT exhibited mean adiponectin concentrations similar to those of subjects with NGT and significantly higher than those of women with GDM. Given the insulin-sensitizing effects of adiponectin, high circulating levels of this protein may contribute to the preservation of insulin sensitivity in women with IGT at 2 or 3 h. Conversely, like GDM, 1-h IGT is associated with a reduced adiponectin concentration. Because hypoadiponectinemia has been associated with the future development of type 2 diabetes in other populations (22–25), this observation raises the possibility that 1-h IGT, like GDM, may confer an increased risk of postpartum diabetes. Interestingly, in a study of 1,636 women with recent GDM undergoing an OGTT at 1–4 months after delivery, independent predictors of postpartum diabetes included (among others) higher AUC$_{glucose}$ from an OGTT during pregnancy, higher 1-h blood glucose result on a 50-g GCT, and a history of GDM before the index pregnancy (26). Indeed, in the present analysis, 1-h IGT was associated with each of these factors (Fig. 1 and Table 1). Accordingly, longitudinal evaluation of the postpartum consequences of 1-h IGT warrants study.

The cross-sectional nature of this study precludes inference on causal relationships. In particular, we are unable to address the relationship between the timing of IGT on an OGTT and either pregnancy outcome or postpartum diabetes. Nevertheless, these findings illustrate the metabolic heterogeneity of IGT and should lead to longitudinal studies of the impact of 1-h IGT on both pregnancy outcome and postpartum glucose metabolism. A second limitation is the absence of data on maternal diet in the days preceding the OGTT. It is conceivable that differences in carbohydrate intake on these days could have affected findings in women with IGT. It should also be noted that almost all study participants, including those comprising the NGT group, had a positive GCT result before recruitment.

Figure 3—*Mean adiponectin by glucose tolerance group.* A: *Adiponectin unadjusted. For the box-and-whisker plot, the line inside the box indicates the median, the upper and lower limits of the box indicate 75th and 25th percentiles, the upper and lower bars indicate maximum and minimum values, and + indicates the mean. Trend* P < 0.0009. *GDM vs. NGT:* P < 0.0001; *GDM vs. 2-h/3-h IGT:* P = 0.0058. B: *Adiponectin adjusted for age, weeks' gestation, prepregnancy BMI, weight gain during pregnancy, ethnicity, previous GDM, and family history of diabetes. Trend* P = 0.0024.

Thus, findings with this NGT group may not reflect a truly normal patient population (i.e., with normal screening GCT and normal results on a diagnostic OGTT). Nevertheless, with a truly normal NGT group, one would expect the differences between the 1-h IGT and NGT groups to be greater than those reported in this study and the observed differences between the IGT subgroups should still stand. Finally, another limitation is the relatively small number of subjects with IGT under study (15 with 1-h IGT and 23 with 2-h/3-h IGT). It is encouraging, however, that several consistent relationships between the IGT subgroups and severity of glycemia, insulin sensitivity, and adiponectin concentration were readily apparent, despite the modest sample size.

A further longitudinal study, with a larger sample size (and inclusion of individuals with isolated fasting hyperglycemia) is warranted.

In summary, the metabolic implications of IGT in pregnancy vary in relation to the timing of the abnormal glucose value from the diagnostic OGTT. IGT at 1 h is associated with greater hyperglycemia, higher insulin resistance, and lower adiponectin concentration than IGT at 2 or 3 h postchallenge. Furthermore, the metabolic phenotype associated with 1-h IGT resembles that of GDM, whereas that for IGT at 2 or 3 h exhibits similarity to that for NGT. From a clinical perspective, these findings raise the intriguing possibility that IGT at 1 h may identify women at risk of adverse pregnancy outcomes

and postpartum diabetes. A longitudinal study is needed to address this possibility.

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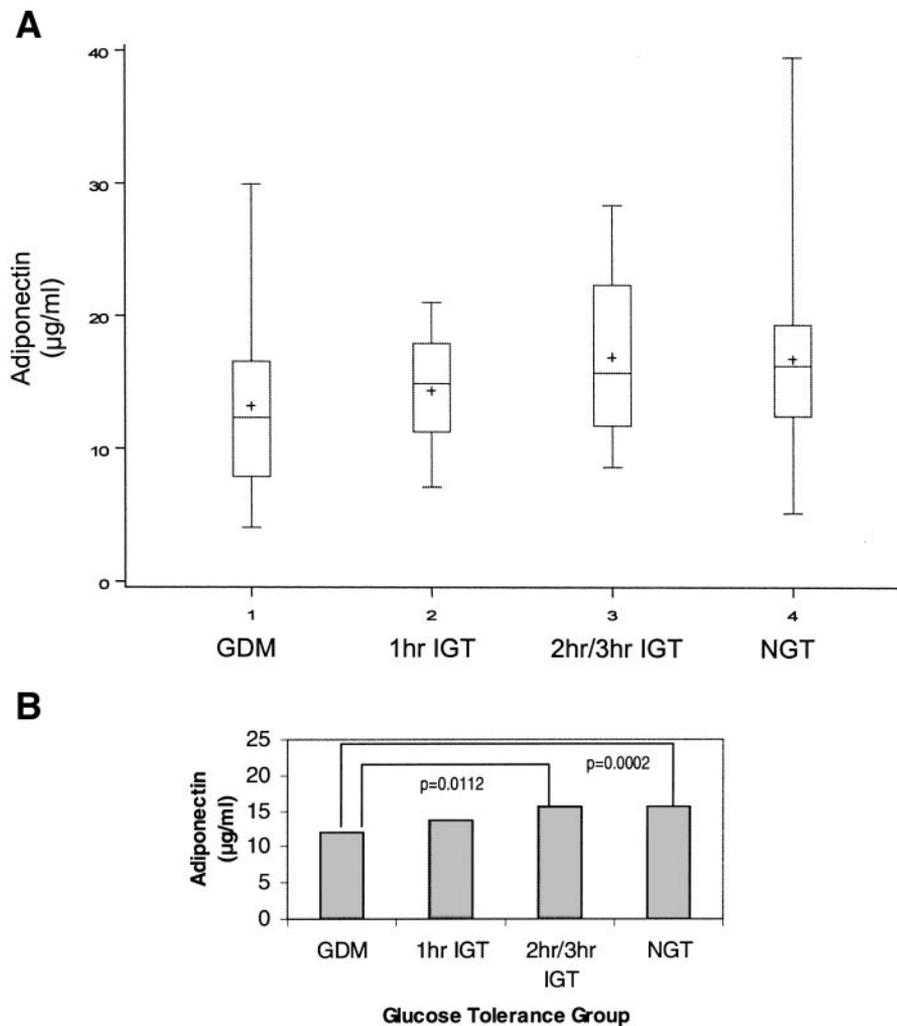
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