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Maternal and Perinatal Outcomes in Women with Insulin Resistance

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Abstract

Objective—This study aims to estimate the risks of adverse maternal and perinatal outcomes in women with insulin resistance below the threshold of gestational diabetes mellitus (GDM).

Methods—This was a retrospective cohort study of 5,983 women with singleton pregnancies undergoing universal GDM screening between 24 and 28 weeks gestation. Subjects were divided into those with a normal 1-hour glucose challenge test (GCT), those with an elevated GCT with all normal values on a 3-hour glucose tolerance test (GTT), and those with an elevated GCT with one abnormal value on GTT. Outcomes included macrosomia, pregnancy-induced hypertension (PIH), cesarean section and operative delivery, shoulder dystocia, indicated-preterm birth, and other neonatal outcomes. Logistic regression was performed to compare outcomes among groups.

Results—The risk of macrosomia was increased for those with an elevated GCT and all normal values on GTT (adjusted odds ratio [aOR], 1.71; 95% confidence interval [CI]: 1.12, 1.97), and for those with an elevated GCT and one abnormal value (aOR, 2.69; 95% CI: 1.49, 4.83). Risks of PIH, cesarean section, and indicated-preterm birth were also increased in those with an elevated 1-hour GCT and no GDM.

Conclusion—There are increased risks of macrosomia, PIH, indicated-preterm birth, and cesarean section among those with insulin resistance even in the absence of GDM.

Keywords

insulin resistance; elevated 1-hour glucose challenge test; gestational diabetes mellitus; macrosomia

The American College of Obstetricians and Gynecologists (ACOG) continues to recommend a two-step screening and diagnostic process for gestational diabetes mellitus (GDM), with a 50-g glucose challenge test (GCT) for screening, followed by a diagnostic 100 g, 3-hour glucose tolerance test (GTT) for those with GCT results ≥ 130 to 140 mg/dL.[1] While several recent studies have suggested a continuous relationship between maternal glycemia and

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Conflict of Interest

The authors report no conflict of interest.

increasing risk of shoulder dystocia, hypertensive disorders, and increased birthweight, no clear threshold at which risks significantly increase has been established.[2–5] These studies are heterogeneous, use a varied approach to the diagnosis of GDM, and have been limited to populations that are predominantly Caucasian or Hispanic, limiting their external generalizability. Additionally, there are currently no guidelines for management of women with evidence of insulin resistance who fall short of a diagnosis of GDM.[1]

The objective of this study is to characterize the risk of adverse maternal and perinatal outcomes in women with evidence of insulin resistance but without evidence of GDM. We hypothesize that women with evidence of insulin resistance have increased risk for obstetric morbidity.

Material and Methods

We performed a retrospective cohort study of consecutive singleton pregnancies undergoing universal screening for GDM with a 1-hour, 50-g GCT and delivering at Barnes Jewish Hospital from 2004 to 2008. Institutional review board approval was obtained from Washington University School of Medicine in St. Louis, MO. Women were included in the study if they did not have preexisting diabetes and completed 1-hour GCT testing followed by a 3-hour GTT between 24 and 28 weeks of gestation.

At our institution, women with an elevated 1-hour GCT ≥ 140 mg/dL undergo prompt diagnostic testing with a 3-hour GTT. GDM is diagnosed by having two or more abnormal values using National Diabetes Data Group (NDDG) criteria (fasting ≥ 105 mg/dL, 1-hour ≥ 190 mg/dL, 2-hour ≥ 165 mg/dL, and 3-hour ≥ 145 mg/dL).[1] At our institution, those who do not have GDM on diagnostic testing return to routine prenatal care.

The cohort was divided into those with a normal GCT, those with an elevated GCT and all normal values on the GTT, and those with an elevated GCT and one abnormal value on the GTT. Those with a normal GCT were used as the reference group. To maximize external generalizability, analysis was also performed by dividing groups using more stringent Carpenter–Coustan (CC) criteria (fasting ≥ 95 mg/dL, 1-hour ≥ 180 mg/dL, 2-hour ≥ 155 mg/dL, and 3-hour ≥ 140 mg/dL).[1]

Maternal outcomes included cesarean section, operative delivery, and pregnancy-induced hypertension (PIH). PIH was defined as new-onset hypertension with systolic blood pressure ≥ 140 mm Hg or diastolic ≥ 90 mm Hg on two occasions at least 6 hours apart, with or without proteinuria after 20 weeks gestation based on 2002 ACOG diagnostic criteria.[6] PIH also included those with chronic hypertension diagnosed with superimposed preeclampsia with new-onset proteinuria, sudden increase in proteinuria or hypertension, or the development of HELLP (hemolysis, elevated liver enzymes, and low platelet counts) syndrome.[6]

Neonatal outcomes included macrosomia (birthweight ≥ 4,000 g, 4,500 g, and 5,000 g), shoulder dystocia as documented by the delivering physician, Apgar score at 5 minutes of life of < 7, acidemia defined as arterial cord pH ≤ 7.10, admission to the neonatal intensive care unit (NICU), stillbirth or neonatal death, and indicated preterm birth before 37 weeks.

Indicated preterm birth was defined as preterm delivery after induction for any medical indication before 37 weeks.

Baseline maternal characteristics were compared between the groups using Student *t*-test or Wilcoxon rank sum test as appropriate for continuous variables and chi-square test for categorical variables. A p value < 0.05 was considered statistically significant. Backward, step-wise multivariable logistic regression was used to estimate the association between increasing insulin resistance and maternal and neonatal outcomes while adjusting for confounders, including advance maternal age ≥ 35 years (AMA), obesity with body mass index (≥ 30.0 kg/m^2), African American race/ethnicity, and history of chronic hypertension or gestational age at delivery as appropriate.

Results

There were 5,983 women eligible for the study, of whom 5,230 (87.4%) had a normal GCT (reference group), 454 (7.6%) had an elevated GCT with normal GTT, 134 (2.2%) had an elevated GCT with one abnormal value on the GTT, with 165 (2.8%) diagnosed with GDM using NDDG criteria. When the CC criteria were used, 377 (6.3%) had an elevated GCT with all normal values on the GTT, 126 (2.1%) had an elevated GCT with one abnormal value on the GTT, and 250 (4.2%) had GDM.

The cohort was 66.2% African American, 23.9% Caucasian, 6.1% Hispanic, 2.3% Asian, and 1.5% other races or ethnic groups. Baseline demographics of the groups are shown in ▶**Table 1.** Those with an elevated GCT and all normal values on the GTT and those with an elevated GCT and one abnormal value on the GTT were more likely to be AMA (p < 0.001), obese (p < 0.001), and to have a history of GDM (p < 0.001) than those with a normal GCT. They were less likely to be African American than the remainder of the cohort (p < 0.001). Rates of primiparity were similar between groups.

The relationships between insulin resistance and maternal and neonatal morbidities are seen in ▶**Table 2.** Women with an elevated GCT and all normal values on a GTTwere at an increased risk of PIH (adjusted odds ratio [aOR], 1.45; 95% confidence interval [CI], 1.11, 1.88), cesarean section (aOR, 1.28; 95% CI 1.05, 1.58), macrosomia ≥ 4,000 g (aOR, 1.77; 95% CI, 1.22, 2.60), macrosomia ≥ 4,500 g (aOR, 2.68; 95% CI, 1.27, 5.66), shoulder dystocia (aOR, 1.88; 95% CI, 1.17, 2.99), and indicated preterm birth (aOR, 2.59; 95% CI, 1.37, 4.92) when compared with those with a normal 1-hour GCT (▶**Table 2**). Those with one abnormal value on the 3-hour GTT were at an increased risk of PIH (aOR, 1.66; 95% CI, 1.06, 2.58), cesarean section (aOR, 1.67; 95% CI, 1.17, 2.38), and macrosomia ≥ 4,000 g (aOR, 2.70; 95% CI, 1.50, 4.87) (▶**Table 2**). Risks for low Apgar score, arterial cord pH ≤ 7.10, NICU admission, stillbirth or neonatal death, and indicated preterm birth were similar between groups (▶**Table 2**). When analysis was repeated using CC criteria, rates of PIH, cesarean section, macrosomia ≥ 4,000 g, macrosomia ≥ 4,500 g, shoulder dystocia, and indicated preterm birth were also increased in those with an elevated 1-hour GCT and all normal values on the GTT compared with those with a normal 1-hour GCT (▶**Table 3**). For patients with an elevated 1-hour GCT and one abnormal value on the GTT using CC criteria,

risks for cesarean section, and macrosomia ≥ 4,000 g were increased compared with those with a normal 1-hour GCT (▶**Table 3**).

Comment

We found a dose–response relationship between all categories of insulin resistance and macrosomia. In addition to macrosomia, there were increasing risks of PIH, cesarean section, shoulder dystocia, and indicated preterm birth among women with an elevated 1-hour GCT followed by a normal GTT when using both NDDG and CC criteria for diagnosis. There were increasing rates of PIH, cesarean section, and indicated preterm birth among those with an elevated 1-hour GCT followed by one abnormal value on the GTT using NDDG criteria and increasing rates of cesarean section for those with one abnormal value on the GTT using CC criteria. These findings suggest that patients with abnormal glucose testing below the threshold of GDM diagnosis are at risk of adverse obstetric outcomes.

Our results confirm and add a U.S. clinical context to existing literature regarding glucose intolerance and pregnancy outcomes. The hyperglycemia and adverse pregnancy outcomes study was a large, multicentered international trial evaluating rates of large for gestational age (LGA) birthweight, primary cesarean section, neonatal hypoglycemia, and cord blood c-peptide level among women without GDM and found a strong and continuous association of increasing hyperglycemia with increased rates of LGA, rates of primary cesarean section, and elevated cord blood c-peptide. This study used a 75-g, 2-hour GTT for diagnosis, had a largely Caucasian and Asian cohort, and also showed increased rates of shoulder dystocia and preeclampsia.[2] Similarly, in a secondary analysis of the Australian carbohydrate intolerance study in pregnancy, women with an elevated 1-hour 50-g GCT and mild glucose intolerance but no GDM on a 2-hour 75-g GTT, patients with mild fasting hyperglycemia had increased risks of preeclampsia, shoulder dystocia, and neonatal hypoglycemia.[3] Finally, in a secondary analysis of the maternal and fetal medicine units network trial of the treatment of mild gestational diabetes, women with a normal 1-hour 50-g screen were compared with women with varying levels of insulin resistance. There were increasing rates of a composite outcome which included hypoglycemia, hyperbilirubinemia, cord blood c-peptide, and birth trauma as well as of LGA, and shoulder dystocia across increasing groups of insulin resistance.[5] The cohort in this study differed from our cohort because it was 59% Hispanic and the analysis focused primarily on neonatal outcomes whereas our cohort was 66.2% African American and focused on both maternal and neonatal outcomes.

Despite mounting evidence of risks, there are no clear guidelines for counseling and management of patients with hyperglycemia that do not meet these diagnostic criteria for GDM. In many practices, including ours, patients who do not meet official criteria for GDM return to routine obstetric care with the assumption that they are normal. Data from this study and others suggest that in fact the relationship between abnormal glycemic controls and adverse outcomes is continuous with an increased risk for adverse outcomes even in women who demonstrate insulin resistance that falls short of the diagnosis of GDM.

Strengths of this study include the size and ethnic diversity of the cohort. This study confirms findings of adverse outcomes in those with an elevated 1-hour GCT without the

diagnosis of GDM in an urban, predominantly African American population. The larger sample size allowed us to stratify into both those with all normal values and those with one abnormal value on the GTT. Additionally, this robust cohort contained data allowing evaluation of both maternal and neonatal outcomes. Finally, our results are generalizable to common U.S. diagnostics practices as we examined subdiagnostic thresholds using the common two-step approach (50-g screening followed by 100-g diagnostic test) as well as demonstrated increased risk for adverse outcomes using both NDDG and CC criteria.

This study is not without limitations that should be considered. The overall rate of obesity in our cohort was 54.3%, which may limit the external generalizability of this study to populations with lower rates of obesity. In spite of these high rates of obesity, the rates of insulin resistance in this cohort were relatively lower than in previously reported studies, with 8.9% having an elevated GCT and all normal GTT and 2.2% having an elevated GCT and one abnormal value on the GTT. This may, therefore, underestimate the population at risk of adverse outcomes compared with populations with higher prevalences of insulin resistance. Additionally, there were still low rates of shoulder dystocia, acidemia, and stillbirth or neonatal death in the cohort, which limit power to detect differences in these outcomes.

In conclusion, this study suggests that patients with an elevated 1-hour GCT who do not have GDM warrant counseling regarding increased risks of macrosomia, PIH, and cesarean section. Such patients may benefit from an ultrasound in the third trimester to evaluate fetal growth, although further research is needed to evaluate the impact of third trimester ultrasounds on rates of adverse outcomes. Future studies should evaluate if interventions less aggressive than those used for women with GDM such as counseling and dietary modifications will reduce these risks.

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Table 1

Baseline characteristics of women with varying degrees of insulin resistance compared with those with normal 1-h GCT (using National Diabetes Data Group criteria)

Total Cohort *N* = 5,983 (Includes 165 women diagnosed with GDM)	**Reference Normal 1-h GCT *N* = 5,230 (87.4%)**	**Elevated 1-h GCT, all normal values on 3-h GTT *N* = 454 (8.9%)**	**Elevated 1-h GCT, one abnormal value on 3-h GTT *N* = 134 (2.2%)**	***p* Value**
Maternal age Median (IQR)	24 (20, 29)	27 (23, 32)	28 (24, 33)	0.018
AMA	380 (7.3%)	59 (13.0%)	26 (19.4%)	< 0.001
Primiparity	1,608 (30.8%)	121 (26.7%)	36 (26.9%)	0.116
BMI, mean ± SD	32.3 ± 7.6	33.4 ± 8.0	35.3 ± 7.6	0.283
Obese (BMI ≥ 30.0 kg/m^2)	2,872 (56.4%)	275 (62.2%)	100 (75.8%)	< 0.001
African American	3,575 (68.4%)	232 (51.1%)	67 (50.0%)	< 0.001
Chronic hypertension	207 (4.0%)	20 (4.4%)	5 (3.7%)	0.886
History of GDM	33 (0.6%)	26 (5.7%)	48 (35.8%)	< 0.001
Smoking	914 (17.5%)	76 (16.7%)	21 (15.7%)	0.804

Abbreviation: AMA, advanced maternal age; BMI, body mass index; GCT, glucose challenge test; GDM, gestational diabetes mellitus; GTT, glucose tolerance test; IQR, interquartile range; SD, standard deviation. Note: Significant *p* values < 0.05 are given in bold.

Table 2

Maternal and perinatal outcomes in women with an elevated 1-h GCT and either all normal values or one abnormal value on 3-h GTT compared with those with normal 1-h GCT (using National Diabetes Data Group)

Total cohort *N* = 5,983 (Includes 165 women diagnosed with GDM)	**Reference Normal 1-h GCT *N* = 5,230**		**Elevated 1-h GCT, all normal values on 3-h GTT *N* = 454**		**Elevated 1-h GCT, one abnormal value on 3-h GTT *N* = 134**	
	***n* (%)**	**aOR (95% CI)**	***n* (%)**	**aOR (95% CI)**	***n* (%)**	**aOR (95% CI)**
Pregnancy-induced hypertension[a]	683 (13.1%)	Ref	78 (17.2%)	1.45 (1.11, 1.88)	27 (20.2%)	1.66 (1.06, 2.58)
Cesarean section[b]	1640 (31.4%)	Ref	184 (40.5%)	1.28 (1.05, 1.58)	69 (51.5%)	1.67 (1.17, 2.38)
Operative delivery[b]	436 (8.3%)	Ref	30 (6.6%)	0.83 (0.57, 1.23)	5 (3.7%)	0.50 (0.20, 1.24)
Macrosomia						
≥ 4,000 g[b]	278 (5.3%)	Ref	39 (8.6%)	1.77 (1.22, 2.60)	18 (13.4%)	2.70 (1.50, 4.87)
≥ 4,500 g[b]	41 (0.8%)	Ref	9 (2.0%)	2.68 (1.27, 5.66)	4 (3.0%)	2.71 (0.80, 9.24)
≥ 5,000 g[b]	5 (0.1%)	Ref	1 (0.2%)	2.30 (0.25, 21.00)	1 (0.8%)	5.29 (0.55, 50.59)
Shoulder dystocia[b]	157 (3.0%)	Ref	23 (5.1%)	1.88 (1.17, 2.99)	4 (3.0%)	1.16 (0.42, 3.22)
5-min Apgar score < 7[b]	123 (2.4%)	Ref	13 (2.9%)	0.92 (0.49, 1.73)	5 (3.7%)	0.99 (0.37, 2.59)
Arterial cord pH ≤ 7.10[b]	89 (1.8%)	Ref	9 (2.1%)	1.15 (0.57, 2.32)	1 (0.8%)	0.41 (0.06, 2.97)
NICU admission[b]	229 (4.4%)	Ref	25 (5.5%)	0.79 (0.48, 1.29)	10 (6.4%)	0.75 (0.35, 1.65)
Stillbirth or neonatal death[b]	24 (0.5%)	Ref	2 (0.4%)	0.52 (0.11, 2.53)	0 (0.0)	n/a
Indicated preterm birth[c]	55 (1.1%)	Ref	12 (2.6%)	2.59 (1.37, 4.92)	1 (0.8%)	0.73 (0.10, 5.36)

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; GCT, glucose challenge test; GTT, glucose tolerance test; n/a, not applicable; NICU, neonatal intensive care unit; Ref, reference.

Note: Significant p values < 0.05 are given in bold.

[a]Controlled for maternal age ≥ 35, BMI ≥ 30.0, race/ethnicity, and history of chronic hypertension.

[b]Controlled for maternal age ≥ 35, BMI ≥ 30.0, race/ethnicity, and gestational age at delivery.

[c]Controlled for maternal age ≥ 35, BMI ≥ 30.0, and race/ethnicity.

Table 3

Maternal and perinatal outcomes in women with an elevated 1-h GCT and either all normal values or one abnormal value on 3-h GTT compared with those with normal 1-h GCT (using Carpenter–Coustan criteria)

Total cohort *N* = 5,983 (Includes 250 women diagnosed with GDM)	**Reference Normal 1-h GCT *N* = 5,230**		**Elevated 1-h GCT, all normal values on 3-h GTT *N* = 377**		**Elevated 1-h GCT, one abnormal value on 3-h GTT *N* = 126**	
	***n* (%)**	**aOR (95% CI)**	***n* (%)**	**aOR (95% CI)**	***n* (%)**	**aOR (95% CI)**
Pregnancy-induced hypertension[a]	683 (13.1%)	Ref	66 (17.5%)	1.49 (1.12, 1.97)	19 (15.1%)	1.17 (0.69, 1.94)
Cesarean section[b]	1,640 (31.4%)	Ref	146 (38.7%)	1.19 (1.05, 1.49)	61 (48.4%)	1.70 (1.17, 2.46)
Operative delivery[b]	436 (8.3%)	Ref	25 (6.6%)	0.83 (0.54, 1.27)	6 (4.8%)	0.59 (0.26, 1.37)
Macrosomia						
≥ 4,000 g[b]	278 (5.3%)	Ref	29 (7.7%)	1.71 (1.12, 2.61)	19 (15.1%)	2.69 (1.49, 4.83)
≥ 4,500 g[b]	41 (0.8%)	Ref	7 (1.9%)	2.59 (1.13, 5.95)	4 (3.2%)	2.70 (0.79, 9.20)
≥ 5,000 g[b]	5 (0.1%)	Ref	1 (0.3%)	2.91 (0.32, 26.72)	1 (0.8%)	6.75 (0.72, 63.62)
Shoulder dystocia[b]	157 (3.0%)	Ref	19 (5.0%)	1.89 (1.13, 3.14)	7 (5.6%)	2.07 (0.94, 4.59)
5-min Apgar score < 7[b]	123 (2.4%)	Ref	13 (3.5%)	1.10 (0.59, 2.09)	2 (1.6%)	0.55 (0.13, 2.33)
Arterial cord pH ≤ 7.10[b]	89 (1.8%)	Ref	8 (2.2%)	1.24 (0.59, 2.60)	1 (0.8%)	0.44 (0.06, 3.23)
NICU admission[b]	229 (4.4%)	Ref	21 (5.6%)	0.73 (0.43, 1.26)	8 (6.4%)	1.11 (0.49, 2.50)
Stillbirth or neonatal death[b]	24 (2.1%)	Ref	2 (0.5%)	0.57 (0.12, 2.79)	0 (0.0)	n/a
Indicated preterm birth[c]	55 (1.1%)	Ref	12 (2.6%)	3.09 (1.62, 5.87)	1 (0.8%)	0.79 (0.11, 5.78)

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; GCT, glucose challenge test; GTT, glucose tolerance test; n/a, not applicable; NICU, neonatal intensive care unit; Ref, reference.

Note: Significant p values < 0.05 are given in bold.

[a] Controlled for maternal age ≥ 35, BMI ≥ 30.0, race/ethnicity, and history of chronic hypertension.

[b] Controlled for maternal age ≥ 35, BMI ≥ 30.0, race/ethnicity, and gestational age at delivery.

[c] Controlled for maternal age ≥ 35, BMI ≥ 30.0, and race/ethnicity.