

# The Relationship Between Maternal Glycemia and Perinatal Outcome

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**OBJECTIVE:** To examine the relationship between varying degrees of maternal hyperglycemia and pregnancy outcomes.

**METHODS:** This was a secondary analysis of a treatment trial for mild gestational diabetes including four cohorts: 1) 473 women with untreated mild gestational diabetes; 2) 256 women with a positive 50-g screen and one abnormal oral glucose tolerance test (OGTT) value; 3) 675 women with a positive screen and no abnormal OGTT values; and 4) 437 women with a normal 50-g screen. Groups were compared by test of trend for a composite perinatal outcome (neonatal hypoglycemia, hyperbilirubinemia, elevated cord C-peptide level, and perinatal trauma or death), frequency of large for gestational age neonates, shoulder dystocia, and pregnancy-related hypertension. Three-hour OGTT levels (fasting, 1-, 2-, and 3-hour) levels were divided into categories and analyzed for their relationship to perinatal and maternal outcomes.

**RESULTS:** There were significant trends by glycemic status among the four cohorts for the composite and all other outcomes ( $P < .001$ ). Analysis for trend according to OGTT categories showed an increasing relationship between fasting and all postload levels and the various outcomes ( $P < .05$ ). Fasting glucose 90 mg/dL or greater and 1 hour 165 mg/dL or greater were associated with an increased risk for the composite outcome (odds ratios and 95% confidence intervals of 2.0 [1.03–4.15] and 1.46 [1.02–2.11] to 1.52 [1.08–2.15] for the fasting and 1 hour, respectively). A 1 hour glucose 150 mg/dL or greater was associated with an increased risk for large for gestational age (odds ratios, 1.8 [1.02–3.18] to 2.35 [1.35–4.14]); however, 2- and 3-hour glucose levels did not increase the risk for the composite or large for gestational age until well beyond current gestational diabetes diagnostic thresholds.

**CONCLUSION:** A monotonic relationship exists between increasing maternal glycemia and perinatal morbidity. Current OGTT criteria require reevaluation in determining thresholds for the diagnosis and treatment of gestational diabetes.

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**LEVEL OF EVIDENCE: II**



Gestational diabetes mellitus represents a health-care burden that can be expected to rise as the frequency of obesity increases worldwide.<sup>1</sup> The lack of uniform criteria for diagnosis and the reliance on observational data drawing on historic controls has limited the accurate determination of the relationship between mild degrees of hyperglycemia and perinatal outcomes.<sup>2</sup> The recent Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study confirmed that a strong continuous relationship exists between maternal glucose concentrations and increasing birth weight, cord blood serum C-peptide levels, and other markers of perinatal complications.<sup>3</sup> However, inconsistent results have been reported with respect to postglucose load levels and the risk for outcomes such as macrosomia.<sup>4</sup> Using patients enrolled in a blinded trial of treatment for mild gestational diabetes, we sought to examine the relationship between varying degrees of maternal glycemia and pregnancy outcomes.

## MATERIALS AND METHODS

This study is a secondary analysis of the Maternal-Fetal Medicine Units Network randomized clinical trial for the treatment of mild gestational diabetes.<sup>5</sup> The study group consists of 1,841 women enrolled between 24 weeks 0 days and 30 weeks 6 days of gestation. For this analysis, three groups are considered, consisting of 1) 473 women in the untreated arm of the randomized trial with mild gestational diabetes defined as a fasting glucose less than 95 mg/dL with two or more post 100-g glucose load measurements meeting or exceeding established cutoffs<sup>6</sup>; 2) an observational cohort of 931 women matched one-to-one to the randomized patients with respect to clinical center, race or ethnicity, and body mass index (BMI, calculated as weight (kg)/[height (m)]<sup>2</sup> classified as less than 27 or 27 or greater, with an elevated 50-g screen (135 mg/dL or greater) but normal oral glucose tolerance test (OGTT) results (for some analyses, this group is further divided into those with one abnormal value [n=256] compared with those with no abnormal OGTT values [n=675]); and 3) an observational cohort of 437 women matched one-to-one to the untreated group with respect to clinical center, race or ethnicity, and BMI classified as less than 27 or 27 or greater, with a screening value less than 120 mg/dL and thus unlikely to have gestational diabetes. A 3-hour OGTT was not performed for this group. To analyze for trend between glycemia and outcomes for patients who underwent an OGTT test, five categories were created according to 5-mg increments for the fasting values and in 15-mg increments for the 1-, 2-,

and 3-hour time points of the OGTT. Fasting cutoffs were chosen based on the HAPO study,<sup>3</sup> whereas postprandial cutoffs were based on accepted OGTT thresholds with 15-g increments selected to provide for adequate sample size for analysis.

The primary study outcome consisted of a composite outcome that included perinatal mortality, hypoglycemia, hyperbilirubinemia, elevated cord blood C-peptide level, and birth trauma.<sup>5</sup> Other outcomes assessed in this analysis included the frequency of large for gestational age neonates (birth weight greater than the 90th centile of a U.S. reference population), shoulder dystocia, gestational hypertension, preeclampsia, or gestational hypertension coupled with preeclampsia.<sup>5</sup> Trained study personnel collected antepartum, intrapartum, and postdelivery data for enrolled women and their newborns at the time of discharge from the hospital. All cases of hypertensive disorders and shoulder dystocia underwent masked central review by two of the authors to ensure accurate diagnosis.

For statistical analysis, baseline categorical variables were analyzed using chi square or Fisher's exact test. Continuous variables were analyzed using the Wilcoxon rank sum test or the Kruskal-Wallis test. The Cochran Armitage test was used to test for trends between OGTT category as defined previously and the outcomes of interest.<sup>7</sup> Multiple logistic regression analysis was performed examining the relationship of higher OGTT glucose categories compared with the lowest OGTT glucose category to assess whether a trend or threshold was associated with increasing glucose levels and the outcome of interest while adjusting for other potential confounders. In addition to glucose categories, regression models included maternal age, gestational age at enrollment and at delivery, parity, BMI, and race or ethnicity. Adjusted odds ratios and profile likelihood 95% confidence intervals were calculated.

A nominal two-sided *P* value <.05 was considered to indicate statistical significance. This study was approved by the Institutional Review Boards of all participating centers.

## RESULTS

The demographics of the study population are shown in Table 1. Among the three groups, there was a significant increase in maternal age with greater degrees of carbohydrate intolerance. There were no significant differences in parity, race, or BMI among the three groups.

Figure 1 illustrates a significant increasing trend (all *P*<.002) of the composite perinatal outcome as well as the frequency of large for gestational age neonates,



**Table 1. Demographic Information**

	50-g Screen			P
	Less Than 120 mg (No OGTT)	135 mg or Higher (Normal OGTT)	Untreated GDM	
No.	437	931	473	
Age (y)	25.1±5.3	27.4±5.5	28.9±5.6	<.001
Nulliparous	37.3	31.9	35.3	.12
Race				.70
African American	12.8	12.4	11.4	
Hispanic	58.6	58.3	56	
White or other	28.6	29.3	32.6	
BMI at entry (kg/m <sup>2</sup> )	29.9±5.8	30.1±5.3	30.2±5.1	.23

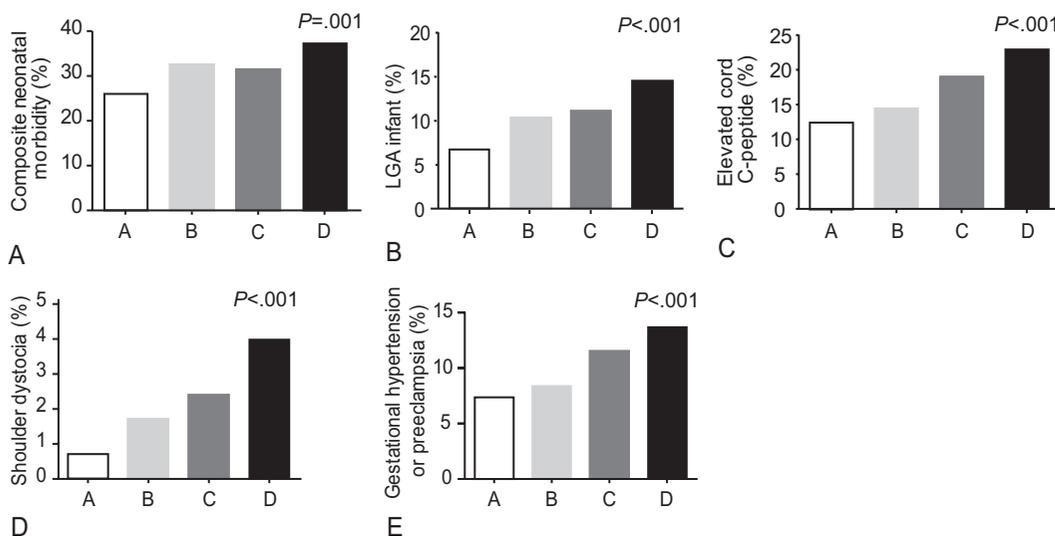
OGTT, oral glucose tolerance test; GDM, gestational diabetes mellitus; BMI, body mass index. Data are mean±standard deviation or % unless otherwise specified.

elevated cord C-peptide level, shoulder dystocia, and hypertensive disorders of pregnancy among four groups (women with an abnormal screen have been subdivided into those with or without one abnormal OGTT value). For example, the frequency of large for gestational age increased from 6.7% in women with a normal screening value to 14.5% in untreated gestational diabetes. We did not observe a significant trend for either neonatal hypoglycemia or hyperbilirubinemia considered as a separate outcome.

Figure 2 demonstrates direct comparisons between groups. An abnormal glucose screen was associated with an increased risk for both the composite

outcome and large for gestational age neonates compared with a normal glucose screening test. Women with gestational diabetes (two or more abnormal values on GTT) demonstrated an increased risk for large for gestational age, elevated C-peptide, and shoulder dystocia compared with those with an abnormal screening test only. There were no statistically significant differences in the frequency of any of the outcomes in women with one abnormal value compared with those with untreated gestational diabetes.

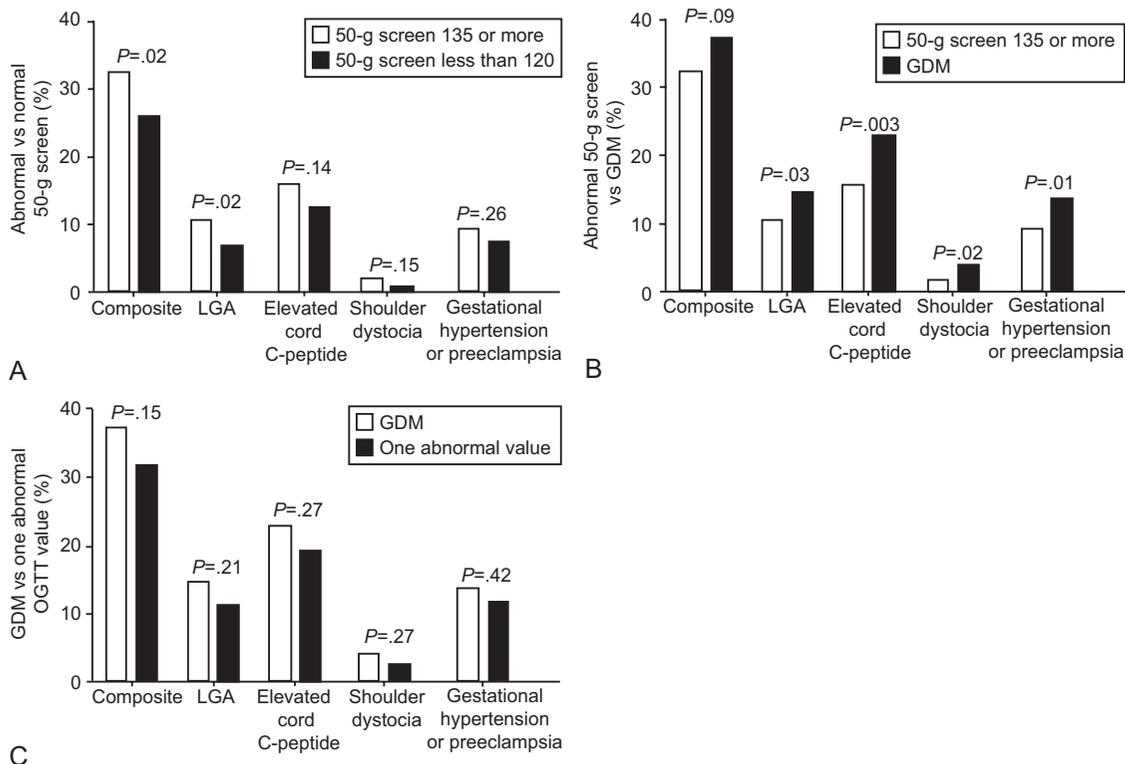
The distribution of subjects in the five glucose categories created from the OGTT is shown in Table 2. Significant trends for increasing frequency for large



**Fig. 1.** Frequencies of various outcomes according to glucose groupings. Group A, 50-g screen less than 120 mg/dL; B, 50-g screen 135 mg/dL or more with normal oral glucose tolerance test (OGTT); C, 50-g screen 135 mg/dL or more with one abnormal OGTT value; D, gestational diabetes mellitus (GDM; two or three abnormal OGTT values). Number of participants in each outcome: Composite (Panel A): A, 407; B, 626; C, 238; D, 440; large for gestational age (LGA) infant (Panel B): A, 421; B, 652; C, 251; D, 454; elevated C-Peptide (Panel C): A, 365; B, 549; C, 211; D, 403; shoulder dystocia (Panel D): A, 423; B, 653; C, 252; D, 455; gestational hypertension (Panel E): A, 423; B, 653; C, 252; D, 455.

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**Fig. 2.** Comparisons of outcomes between glucose groups. A. Abnormal versus normal 50-gram screen: Composite, 279/864 (abnormal screen) and 105/407 (normal screen); large for gestational age (LGA) infant, 95/903 (abnormal screen) and 28/421 (normal screen); elevated C-peptide, 119/760 (abnormal screen) and 45/365 (normal screen); shoulder dystocia, 17/905 (abnormal screen) and 3/423 (normal screen); gestational hypertension or preeclampsia, 83/905 (abnormal screen) and 31/423 (normal screen). B. Abnormal screen versus gestational diabetes mellitus (GDM): Composite, 279/864 (abnormal screen) and 163/440 (GDM); LGA, 95/903 (abnormal screen) and 66/454 (GDM); elevated C-peptide, 119/760 (abnormal screen) and 92/403 (GDM); shoulder dystocia, 17/905 (abnormal screen) and 18/455 (GDM); gestational hypertension or preeclampsia, 83/905 (abnormal screen) and 62/455 (GDM). C. GDM versus one abnormal oral glucose tolerance test (OGTT) value: Composite, 163/440 (GDM) and 75/238 (one abnormal OGTT); LGA, 66/454 (GDM) and 28/251 (one abnormal OGTT); elevated C-peptide, 92/403 (GDM) and 40/211 (one abnormal OGTT); shoulder dystocia, 18/455 (GDM) and 6/252 (one abnormal OGTT); gestational hypertension or preeclampsia, 62/455 (GDM) and 29/252 (one abnormal OGTT).

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for gestational age neonates were present across the five glucose categories of the fasting, 1-hour, 2-hour, and 3-hour determinations (Fig. 3). Similar trends were apparent for the composite outcome (all  $P < .05$ ), elevated cord C-peptide level (all  $P < .02$ ) with the trends only being significant for the 1- and 2-hour glucose in relation to shoulder dystocia ( $P < .01$ ). A

significant trend was present for all three postglucose load times for hypertensive disorders (all  $P < .03$ ).

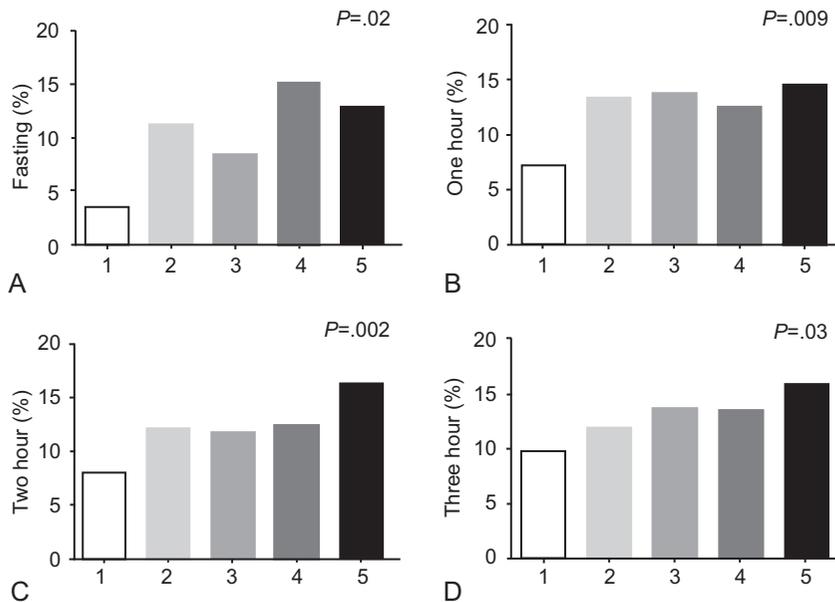
Logistic regression analysis controlling for maternal age, gestational age at enrollment and at delivery, parity, BMI, and race and ethnicity for each glucose category was performed in which adjusted odds ratios were generated comparing higher glucose categories

**Table 2. Glucose Categories (mg/dL)**

	1	2	3	4	5
Fasting	<75 (57)	75–79 (171)	80–84 (322)	85–89 (426)	90–94 (382)
1-h	<150 (362)	150–164 (233)	165–179 (275)	180–194 (254)	≥195 (234)
2-h	<125 (365)	125–139 (240)	140–154 (236)	155–169 (234)	≥170 (283)
3-h	<110 (535)	110–124 (296)	125–139 (236)	140–154 (171)	≥155 (120)

Number of women in each glucose grouping is shown in parentheses.





**Fig. 3.** Percentage of neonates who were large for gestational age by oral glucose tolerance test (OGTT) glucose level. A. Fasting OGTT (mg/dL). Group 1, glucose levels less than 75; Group 2, levels between 75 and 79; Group 3, levels between 80 and 84; Group 4, levels between 85 and 89; Group 5, levels between 90 and 94. B. One-hour OGTT (mg/dL). Group 1, glucose levels less than 150; Group 2, levels between 150 and 164; Group 3, levels between 165 and 179; Group 4, levels between 180 and 194; Group 5, levels of 195 or more. C. Two-hour OGTT (mg/dL). Group 1, glucose levels less than 125; Group 2, levels between 125 and 139; Group 3, levels between 140 and 154; Group 4, levels between 155 and 169; Group 5, levels of 170 or more. D. Three-hour OGTT (mg/dL). Group 1, glucose levels less than 110; Group 2, levels between 110 and 124; Group 3, levels between 125 and 139; Group 4, levels between 140 and 154; Group 5, levels of 155 or more.

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with the lowest to assess whether a trend or threshold was associated with increasing glucose levels and outcomes (Table 3). For fasting glucose, an increased risk for both elevated C-peptide and large for gestational age were evident at 85–89 mg/dL and for the composite at 90–94 mg/dL. For the 1-hour value, an increased risk for the composite, large for gestational age, and hypertensive disorders was evident at levels less than 180 mg/dL. A 1-hour value of 165–179 mg/dL was associated with an increased risk for the composite outcome, 1-hour values of 150–164 mg/dL and 165–179 mg/dL was associated with an increased risk for large for gestational age, and a 1-hour value of 165–179 mg/dL was associated with an increased risk of hypertensive disorders. The highest 2-hour values were not associated with an increased risk for the composite, and the risk for large for gestational age was not apparent until glucose exceeded 170 mg/dL. Similarly, for the 3-hour value, an increased risk for several outcomes was present only in the highest glucose category.

## DISCUSSION

We found a significant relationship between increasing levels of maternal glycemia and perinatal morbidity.

This graded increase in adverse maternal–fetal outcomes is observed across the spectrum of carbohydrate intolerance and includes glucose values below current cutoffs for the diagnosis of gestational diabetes.<sup>2,3,8</sup> This observation provides additional information as experts continue to debate what constitutes appropriate thresholds for the diagnosis of gestational diabetes.

Previous studies have documented that an abnormal glucose screening test alone is an independent predictor of macrosomia.<sup>9,10</sup> In addition to an increased risk for large for gestational age neonates, we have also documented a risk exists for other neonatal morbidities as well as shoulder dystocia in this group of women. Because of a perceived intermediate risk for fetal macrosomia, some have advocated follow-up diagnostic testing or close surveillance for fetal overgrowth during the third trimester for women with an abnormal screening test (and normal OGTT) discovered between 24 and 28 weeks of gestation.<sup>11</sup> Recently, a small randomized trial has shown a reduction in large neonates in women with abnormal screening results receiving nutritional intervention compared with control subjects.<sup>12</sup>

Although our sample size is relatively small, our findings support the hypothesis of an increased risk of



**Table 3. Adjusted Odds Ratios for Outcomes by Oral Glucose Tolerance Test Glucose Levels**

Outcome (No. of Events/ No. of Patients)	Oral Glucose Tolerance Test Glucose Level				
	Less than 75	75–79	80–84	85–89	90–94
Fasting glucose level (mg/dL)					
Composite (442/1,304)	1.0	1.40 (0.69–3.01)	1.36 (0.70–2.84)	1.63 (0.84–3.37)	2.00* (1.03–4.15)
Large-for-gestational age (161/1,357)	1.0	3.27 (0.89–21.09)	2.16 (0.61–13.72)	3.98* (1.18–24.85)	3.67* (1.07–23.05)
Elevated C-peptide (211/1,163)	1.0	2.41 (0.78–10.59)	1.64 (0.55–7.11)	3.34* (1.15–14.18)	3.76* (1.29–15.99)
Shoulder dystocia (35/1,360)		1.0 <sup>†</sup>	3.21 (0.81–21.33)	2.53 (0.66–16.58)	3.35 (0.90–21.73)
Gestational hypertension or preeclampsia (145/1,360)	1.0	1.35 (0.46–4.97)	1.38 (0.50–4.91)	0.98 (0.36–3.47)	1.61 (0.60–5.62)
1-h glucose level (mg/dL)					
Composite (442/1,304)	1.0	1.17 (0.81–1.70)	1.52* (1.08–2.15)	1.27 (0.89–1.82)	1.46* (1.02–2.11)
Large-for-gestational-age (161/1,357)	1.0	1.80* (1.02–3.18)	1.90* (1.11–3.30)	1.60 (0.91–2.83)	2.35* (1.35–4.14)
Elevated C-peptide (211/1,163)	1.0	1.09 (0.64–1.85)	1.52 (0.95–2.44)	1.60 (0.99–2.58)	2.01 (1.26–3.24)
Shoulder dystocia (35/1,360)	1.0	2.33 (0.65–9.39)	2.83 (0.83–11.02)	2.26 (0.63–9.05)	5.44* (1.81–20.10)
Gestational hypertension or preeclampsia (145/1,360)	1.0	1.43 (0.76–2.69)	1.88* (1.06–3.38)	1.91* (1.07–3.44)	1.94* (1.09–3.52)
2-h glucose level (mg/dL)					
Composite (442/1,304)	1.0	1.29 (0.90–1.85)	1.27 (0.88–1.82)	1.22 (0.85–1.75)	1.40 (0.99–1.98)
Large-for-gestational age (161/1,357)	1.0	1.58 (0.90–2.76)	1.47 (0.83–2.59)	1.66 (0.94–2.91)	2.53* (1.51–4.28)
Elevated C-peptide (211/1,163)	1.0	1.55 (0.93–2.58)	1.51 (0.90–2.52)	2.01* (1.23–3.30)	2.36* (1.49–3.77)
Shoulder dystocia (35/1,360)	1.0	4.10 (0.86–29.15)	6.37* (1.49–43.58)	6.46* (1.51–44.30)	11.39* (3.02–74.65)
Gestational hypertension or preeclampsia (145/1,360)	1.0	0.81 (0.43–1.49)	1.27 (0.72–2.23)	1.31 (0.74–2.29)	1.33 (0.79–2.27)
3-h glucose level (mg/dL)					
Composite (442/1,304)	1.0	0.92 (0.67–1.26)	1.28 (0.92–1.78)	1.16 (0.80–1.68)	1.41 (0.92–2.15)
Large-for-gestational age (161/1,357)	1.0	1.29 (0.80–2.05)	1.54 (0.94–2.51)	1.69 (0.97–2.89)	2.24* (1.21–4.02)
Elevated C-peptide (211/1,163)	1.0	1.08 (0.70–1.65)	1.66* (1.08–2.53)	1.01 (0.60–1.66)	1.94* (1.13–3.28)
Shoulder dystocia (35/1,360)	1.0	1.38 (0.53–3.43)	1.91 (0.72–4.83)	1.67 (0.51–4.72)	0.96 (0.15–3.75)
Gestational hypertension or preeclampsia (145/1,360)	1.0	1.53 (0.91–2.57)	2.06* (1.21–3.50)	2.21* (1.24–3.86)	2.23* (1.13–4.23)

Data are odds ratio (95% confidence interval).

\* Confidence interval does not include 1.

<sup>†</sup> Reference category for fasting OGTT is less than 80.0 for regression model for shoulder dystocia.

perinatal outcomes with one abnormal OGTT value compared with the normal OGTT group both in the trend analysis and in the comparison with the untreated mild gestational diabetes (at least two abnormal OGTT values) group. The finding of similar frequencies of various perinatal outcomes among women with one abnormal OGTT value compared with untreated mild gestational diabetes is important because some previous studies have compared this group with treated gestational diabetes subjects and thus have been unable to estimate their true level of risk.<sup>13</sup> Originally, O’Sullivan and Mahan<sup>14</sup> required two values to be abnormal on the diagnostic OGTT to minimize misclassification resulting from rapid glucose absorption or laboratory error. An analysis from the HAPO study demonstrating independent risks at each timed OGTT value has suggested that the criteria for the diagnosis of gestational diabetes should be based on the presence of one abnormal OGTT value. In an effort to define gestational diabetes, Sacks and colleagues<sup>8</sup> were among the first to attempt to quantitate the relationship between maternal glucose

levels and birth weight centiles. However, within the ranges of glucose studied in over 3,000 women, these authors could not establish a “clinically meaningful” threshold for diagnosis. The HAPO study also failed to yield any apparent inflection points when comparing maternal glycemia with both perinatal and maternal outcomes. Thus, any proposed thresholds for diagnosis, as Sacks predicted, will rely on expert opinion and be based on a consideration of relative risk.<sup>8</sup> Our analysis revealed that the risk for large for gestational age and other morbidities is present at fasting and 1-hour levels below the current criteria for the diagnosis of gestational diabetes. However, risks for large for gestational age did not become significant until 2- and 3-hour values exceeded the Carpenter-Coustan thresholds.<sup>6</sup> After controlling for confounders, Sermer and colleagues reported that only fasting glucose could be related to macrosomia (birth weight greater than 4,000 g), whereas others have suggested that the 1-hour postprandial level, representing the peak of the glucose response curve, is most significant.<sup>2</sup>



We do note several limitations of this secondary analysis. First, we were able to only consider OGTT data from a cohort of women who failed the 50-g glucose screen. These individuals likely have an intermediate level of carbohydrate intolerance and also appear to have an increased risk for adverse perinatal outcomes compared with women with normal screening. We chose to generate odds ratios for outcomes in comparison to the lowest glucose categories for this reason. Thus, our finding of increased 2- and 3-hour OGTT thresholds for several outcomes among such women may actually be considered even more significant. Our study also used the 3-hour, 100-g OGTT, which, although standard for use in pregnancy in the United States, is not the diagnostic test common in many areas of the world. This limits direct comparisons to 75-g, 2-hour OGTT data found in other reports.<sup>8</sup> Although we analyzed outcomes in relation to greater than 1,000 OGTTs, our treatment trial did not include a sample size sufficient to suggest precise cutoffs for the diagnosis of gestational diabetes. Current proposed recommendations for new diagnostic criteria for gestational diabetes, if adopted, will substantially increase the frequency of this diagnosis.<sup>15</sup> Although two randomized controlled trials now demonstrate a treatment benefit to women meeting specific OGTT criteria, evidence is lacking concerning treating women with thresholds outside those we studied as well as one abnormal 75-g OGTT value.<sup>5,16</sup> The results of treatment trials as well as the current analysis will hopefully further aid professional organizations as they consider the most cost-effective approach to the diagnosis and treatment of gestational diabetes.

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