

# Clinical Outcomes of Pregnancies Complicated by Mild Gestational Diabetes Mellitus Differ by Combinations of Abnormal Oral Glucose Tolerance Test Values

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**OBJECTIVE** — To examine the association between levels of hyperglycemia, determined by each prenatal oral glucose tolerance test (OGTT) value (fasting, 1 and 2 h), and maternal and perinatal outcomes and to determine whether the risk for these outcomes differs for women whose value(s) equaled or exceeded the thresholds for gestational diabetes mellitus (GDM) established by the International Association of Diabetes in Pregnancy Study Groups (IADPSG).

**RESEARCH DESIGN AND METHODS** — This article discusses a retrospective study of 8,711 women, delivering at  $\geq 20$  weeks' gestation, who had a prenatal 2-h 75-g OGTT without a prior 50-g challenge and were not treated with insulin, glyburide, diet, and/or exercise during pregnancy. Associations between adverse outcomes and elevated OGTT values are reported.

**RESULTS** — After excluding treated women, 19.4% of the remaining women had IADPSG-defined GDM. Continuous fasting, 1- and 2-h OGTT measures, and GDM (yes/no) were significantly associated with most adverse outcomes. However, the magnitude and significance of risk for these outcomes differed by various combinations of abnormal glucose values. Women with normal fasting and elevated postload values were at higher risk for preterm delivery, gestational hypertension, and having an infant with hyperbilirubinemia, whereas women with elevated fasting and normal postload values were at higher risk of having a large-for-gestational-age infant, compared with women without GDM.

**CONCLUSIONS** — Risks for different adverse outcomes vary depending on which single or combined IADPSG-defined OGTT thresholds are equaled or exceeded. Prospective studies are needed to determine whether changing pre- and postprandial glucose targets during pregnancy will more uniformly reduce adverse outcomes.

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**G**estational diabetes mellitus (GDM) is defined as “any degree of glucose intolerance with onset or first recognition during pregnancy” (1). The diagnosis of GDM is typically based on the results of a 2-h 75-g or 3-h 100-g oral glucose tolerance test (OGTT), which measures maternal fasting plasma glucose (FPG) and postload glucose concentrations, administered between 24 and 28 weeks of gestation. American Diabetes Association (ADA) guidelines confer a

GDM diagnosis if at least two 75-g or 100-g OGTT values meet the following thresholds:  $\geq 95$  mg/dl FPG, 1-h glucose  $\geq 180$  mg/dl, 2-h glucose  $\geq 155$  mg/dl, and 3-h glucose  $\geq 140$  mg/dl (2). These thresholds were initially established to identify women at high risk for type 2 diabetes following pregnancy (3).

GDM is associated with increased risk for adverse maternal and perinatal outcomes, such as macrosomia, shoulder dystocia and birth injury, primary cesar-

ean delivery, preeclampsia, preterm delivery, and fetal and neonatal mortality (4–7). However, risk for these outcomes among women with modest hyperglycemia during pregnancy has only recently been studied. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study investigated quantitative associations between maternal glycemia and adverse outcomes and, after excluding women with FPG  $\geq 105$  and/or 2-h  $\geq 200$  mg/dl, reported significant associations between increasing glucose and adverse events, including birth weight  $>90$ th percentile, preterm delivery, shoulder dystocia/birth injury, primary cesarean delivery, preeclampsia, and hyperbilirubinemia (8,9). These findings formed the basis for the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations that GDM be identified by at least one abnormal 75-g 2-h OGTT value: FPG  $\geq 92$  mg/dl, 1-h glucose  $\geq 180$  mg/dl, or 2-h glu  $\geq 153$  mg/dl (10).

In the present study, we examined the association between each of the 75-g OGTT glucose values (fasting, 1-h and 2-h glucose) and several adverse maternal and perinatal outcomes in untreated women, taking into account differences in maternal demographics, prepregnancy BMI, and gestational weight gain. Additionally, we explored associations between adverse outcomes and categories of hyperglycemia that result in GDM diagnosis under IADPSG criteria to determine whether the level of risk is similar for each abnormal OGTT result and combinations thereof.

## RESEARCH DESIGN AND METHODS

### Population and data sources

The Kaiser Permanente Southern California (KPSC) Medical Care Program is a large, prepaid, group-practice, managed-health care organization with  $>3.3$  million members in 2010. Members receive their health care in KPSC-owned facilities

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throughout the seven-county region. This study was approved by the KPSC Institutional Review Board.

The study population consisted of women who had a live singleton birth at  $\geq 20$  weeks' gestation at the KPSC Bellflower Medical Center between 1 October 2005 and 31 March 2010, who underwent a prenatal 2-h 75-g OGTT with no prior 50-g oral glucose challenge test and had prepregnancy and delivery anthropometric data ( $n = 9,199$ ). In this medical center, routine clinical practice involved treating women whose prenatal 75-g OGTT results met at least two thresholds: FPG  $\geq 100$  mg/dl, 1-h glucose  $\geq 195$  mg/dl, and 2-h glucose  $\geq 160$  mg/dl with diet and exercise therapy. Of these, women whose FPG was consistently  $\geq 105$  mg/dl or 1-h postprandial glucose was  $\geq 140$  mg/dl were treated with insulin or glyburide in addition to diet and exercise. This practice is based on the analyses of OGTT results and pregnancy outcomes published by Sacks et al. (11). After excluding women who received any form of treatment during pregnancy ( $n = 488$ ), we used OGTT results to identify women with GDM based on IADPSG guidelines (10). For untreated women with more than one OGTT during pregnancy, outcomes are reported based on the test result within or nearest to 24–28 weeks' gestation. For women with more than one birth during the study period, only data from the first pregnancy were analyzed.

Maternal age at delivery, race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, Asian/Pacific Islander, and other/multiple races), and parity (0, 1, and  $\geq 2$ ) were obtained from infant birth certificates. Information on prenatal smoking was obtained from the electronic health record (EHR) during prenatal encounters. Infant sex, gestational age at birth, birth weight, and birth length were obtained from the birth certificate or EHR. Ponderal index was calculated as birth weight/height<sup>3</sup>  $\times 100$  (12).

### Categorization of OGTT results

Based on the results of the 2-h 75-g OGTT, we categorized women into five mutually exclusive categories: no glucose impairment (no GDM), single isolated impaired glucose tolerance (*i*-IGT<sub>1</sub>) if either 1-h glucose  $\geq 180$  mg/dl or 2-h glucose  $\geq 153$  mg/dl and FPG  $< 92$  mg/dl, isolated impaired fasting glucose (*i*-IFG) if FPG  $\geq 92$  mg/dl and both 1-h glucose  $< 180$  mg/dl and 2-h glucose  $< 153$  mg/dl, double-isolated impaired glucose

tolerance (*i*-IGT<sub>2</sub>) if both 1-h glucose  $\geq 180$  mg/dl and 2-h glucose  $\geq 153$  mg/dl but FPG  $< 92$  mg/dl, and combined IFG and IGT (IFG+IGT) if FPG  $\geq 92$  mg/dl and either 1-h glucose  $\geq 180$  mg/dl and/or 2-h glucose  $\geq 153$  mg/dl.

### Measures of prepregnancy BMI and gestational weight gain

Prepregnancy BMI and weight gain during pregnancy both have been shown to be associated with the development of GDM (13–15) as well as adverse outcomes independent of GDM (16–19). Maternal prepregnancy weight and height were obtained from the EHR ( $n = 7,894$  [90.6%]) or from the infant's birth certificate if not available from the EHR ( $n = 817$  [9.4%]). Among those with data available from the EHR, identification of measured prepregnancy weight was contingent upon the timing of the clinical visit closest to last menstrual period (LMP). To establish the LMP date, infant gestational age at delivery (in days) was subtracted from infant delivery date. Height and prepregnancy weight were selected hierarchically, if available, 0–3 months prior to LMP ( $n = 3,046$  [38.6%]), 0–3 months after LMP ( $n = 4,690$  [59.4%]), or 3–6 months prior to LMP ( $n = 158$  [2.0%]). Delivery weight was obtained within 30 days prior to delivery; 96.1% were measured within 14 days of delivery. Prepregnancy BMI was classified as normal (BMI  $< 25$  kg/m<sup>2</sup>), overweight ( $25 \leq$  BMI  $< 30$  kg/m<sup>2</sup>), or obese (BMI  $\geq 30$  kg/m<sup>2</sup>) (20). Gestational weight gain was calculated as the difference between prepregnancy and delivery weight. The 2009 Institute of Medicine (IOM) guidelines were used to classify excessive weight gain during pregnancy based on categories of prepregnancy BMI (normal:  $> 35$  lb, overweight:  $> 25$  lb, or obese:  $> 20$  lb) (21).

### Maternal and infant outcomes

Large-for-gestational-age (LGA) infants were defined as sex-, race-, and gestational age-specific birth weight  $> 90$ th percentile. Consistent with the methods used by the HAPO Study Group (11), percentiles for birth weight were determined by quantile regression stratified by sex and race/ethnicity, with adjustment for gestational age and maternal parity. An infant was considered to have a birth weight  $> 90$ th percentile if the birth weight was greater than the estimated 90th percentile for the infant's sex, gestational age, race/ethnicity, and maternal

parity. Delivery by primary cesarean section was obtained from infant birth certificates; data for women who had a previous cesarean section ( $n = 963$ ) were excluded from analysis of this outcome. Preterm delivery was defined as any delivery prior to 37 weeks of gestation. We identified hyperbilirubinemia based on ICD-9 codes 774.0–774.7 within the first week of birth. Shoulder dystocia/birth injury was defined by ICD-9 codes 653.4, 653.5, 660.4, 767.0–767.9, or 959.0–959.9 at delivery. We identified women with gestational hypertensive disorders by ICD-9 codes 642.3–642.6 and/or 642.9 during pregnancy. In analyses of gestational hypertension, we excluded women with pregestational hypertension (ICD-9 codes 401–405.9, 642.0–642.2, and/or 642.7;  $n = 323$ ).

### Statistical analyses

We examined the associations between maternal demographic, clinical, and anthropometric characteristics; adverse clinical outcomes; and GDM subtypes (*i*-IGT<sub>1</sub>, *i*-IFG, *i*-IGT<sub>2</sub>, and IFG+IGT). Associations between categorical variables and GDM subtype were assessed using  $\chi^2$  tests; differences in mean continuous variables by subtype were evaluated using ANOVA with Tukey honestly-significant-difference adjustment for multiple comparisons. Pearson product-moment correlations were used to assess associations among OGTT measures. Multiple logistic regression models were used to calculate adjusted odds ratios (AORs) and corresponding 95% CIs for a 1-SD increase in continuous fasting and 1-h and 2-h glucose levels associated with adverse outcomes, after controlling for maternal age, race/ethnicity, parity, prepregnancy BMI, and gestational weight gain. AORs were also calculated for the association between GDM and all adverse clinical outcomes. All analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC).

**RESULTS**— The study population consisted of 9,199 women, of which 2,179 (23.7%) met the IADPSG criteria for GDM (10). After excluding 488 women who received any form of treatment (5.3% of the population; 22.4% of all women with GDM), the remaining sample for this analysis was comprised of 8,711 untreated women with a mean age of  $29.1 \pm 5.9$  years, the majority of whom were Hispanic (Table 1). Among all women, the mean prepregnancy BMI was  $27.5 \pm 6.1$  kg/m<sup>2</sup>, which exceeds the threshold for overweight, and the mean

Table 1—Maternal characteristics and frequency of maternal and infant outcomes by GDM subtype

Characteristics	GDM subtypes according to IADPSG thresholds					P *
	All women	No GDM	i-IGT <sub>1</sub>	i-IFG	i-IGT <sub>2</sub>	
<i>n</i>	8,711	7,020	391	886	83	331
<b>Maternal characteristics</b>						
Mean age (years)	29.1 ± 5.9	28.6 ± 5.9†§¶¶	32.1 ± 5.4†§	30.4 ± 5.6†¶¶¶	32.3 ± 5.2†§	32.0 ± 5.1†§
Race/ethnicity (%)#						
Non-Hispanic white	626 (7.2)	507 (7.2)	28 (7.2)	53 (6.0)	5 (6.0)	33 (10.0)
Hispanic	6,484 (74.4)	5,216 (74.3)	273 (69.8)	691 (78.0)	59 (71.1)	245 (74.0)
Black	880 (10.1)	741 (10.6)	29 (7.4)	85 (9.6)	2 (2.4)	23 (7.0)
Asian	641 (7.4)	493 (7.0)	53 (13.6)	49 (5.5)	17 (20.5)	29 (8.8)
Other	80 (0.9)	63 (0.9)	8 (2.1)	8 (0.9)	0 (0.0)	1 (0.3)
Parity (%)#						
0	3,492 (40.1)	2,924 (41.7)	130 (33.3)	317 (35.8)	29 (34.9)	92 (27.8)
1	2,675 (30.7)	2,151 (30.6)	121 (31.0)	272 (30.7)	30 (36.1)	101 (30.5)
≥2	2,479 (28.5)	1,888 (26.9)	137 (35.0)	294 (33.2)	24 (28.9)	136 (41.1)
Unknown	65 (0.7)	57 (0.8)	3 (0.8)	3 (0.3)	0 (0.0)	2 (0.60)
Mean pregravid BMI (kg/m <sup>2</sup> )	27.5 ± 6.1	26.9 ± 5.8†§¶	28.1 ± 5.6†§¶	30.8 ± 7.1†¶¶	27.5 ± 4.7§¶	31.8 ± 7.0†¶¶
<b>Pregravid BMI (%)#</b>						
Normal	3,497 (40.1)	3,096 (44.1)	127 (32.5)	188 (21.2)	29 (34.9)	57 (17.2)
Overweight	2,733 (31.4)	2,187 (31.2)	145 (37.1)	271 (30.6)	31 (37.4)	99 (29.9)
Obese	2,481 (28.5)	1,737 (24.7)	119 (30.4)	427 (48.2)	23 (27.7)	175 (52.9)
Unknown	28.7 ± 13.9	29.0 ± 13.7	27.1 ± 14.5	27.8 ± 15.2	26.4 ± 11.6	27.8 ± 14.8
<b>Gestational weight gain (%)#</b>						
Less than or equal to IOM recommendations	4,490 (51.5)	3,664 (52.2)	225 (57.5)	413 (46.6)	45 (54.2)	143 (43.2)
More than IOM recommendations	4,221 (48.5)	3,356 (47.8)	166 (42.5)	473 (53.4)	38 (45.8)	188 (56.8)
<b>Mean OGTT values (mg/dl)</b>						
Fasting	83.5 ± 8.0	81.0 ± 5.6	84.5 ± 5.6	97.0 ± 7.1	85.0 ± 4.6	97.5 ± 5.5
1 h	132.1 ± 30.8	124.6 ± 26.3	179.9 ± 20.1	143.8 ± 23.5	190.6 ± 9.8	186.9 ± 17.9
2 h	107.8 ± 23.1	103.0 ± 19.7	139.3 ± 25.4	114.3 ± 18.5	165.6 ± 13.5	138.9 ± 22.9
<b>Prenatal smoking (%)</b>						
No	8,031 (92.2)	6,490 (92.4)	352 (90.0)	819 (92.5)	73 (88.0)	297 (89.7)
Yes	217 (2.5)	172 (2.5)	11 (2.8)	19 (2.1)	4 (4.8)	11 (3.3)
Unknown	463 (5.3)	358 (5.1)	28 (7.2)	48 (5.4)	6 (7.2)	23 (7.0)
<b>Infant characteristics</b>						
Mean gestational age at OGTT (weeks)	26.7 ± 2.9	26.7 ± 2.7	26.8 ± 3.3	26.6 ± 3.4	26.7 ± 3.0	26.7 ± 3.6
Mean gestational age at delivery (weeks)	38.9 ± 1.8	39.0 ± 1.8†¶	38.3 ± 2.5§¶	38.8 ± 1.8†	38.3 ± 1.8†	38.7 ± 1.9†
Mean birth weight (g)	3,356 ± 534	3,334 ± 516§¶	3,318 ± 652§¶	3,487 ± 563†¶¶	3,303 ± 568§¶	3,514 ± 593†¶¶
Mean ponderal index**	2.71 ± 0.33	2.70 ± 0.33§¶	2.73 ± 0.34¶	2.75 ± 0.33†¶	2.79 ± 0.45	2.83 ± 0.32††§
<b>Sex (%)</b>						
Male	4,512 (51.8)	3,654 (52.0)	187 (47.8)	450 (50.8)	48 (57.8)	173 (52.3)
Female	4,199 (48.2)	3,366 (48.0)	204 (52.2)	436 (49.2)	35 (42.2)	158 (47.7)

Outcomes	792 (9.1)	528 (7.5)	39 (10.0)	148 (16.7)	9 (10.8)	68 (20.5)	<0.0001
LGA (%)#	1,448 (18.7)	1,112 (17.7)	69 (20.2)	179 (23.0)	19 (25.7)	69 (25.5)	<0.0001
Primary cesarean section (%)#††	635 (7.3)	465 (6.6)	50 (12.8)	81 (9.1)	15 (18.1)	27 (8.2)	<0.0001
Preterm delivery (%)#	364 (4.2)	268 (3.8)	18 (4.6)	50 (5.6)	5 (6.0)	23 (7.0)	0.007
Shoulder dystocia/birth injury (%)#	674 (8.0)	490 (7.2)	36 (9.8)	90 (10.8)	11 (13.6)	47 (15.4)	<0.0001
Gestational hypertension (%)#††	1,243 (14.3)	980 (14.0)	72 (18.4)	128 (14.4)	18 (21.7)	45 (13.6)	0.042
Hyperbilirubinemia (%)#							

\*P values based on  $\chi^2$  test, with Fisher exact test used for variables with any cell count <10. ANOVA adjusted with Tukey honestly significant difference for continuous variables,  $P < 0.05$ ; †significantly different than *i*-IGT<sub>1</sub>; ‡significantly different than *i*-IFG; §significantly different than IFG+IGT; ¶significantly different than no GDM. #The distribution of each variable within the population is shown as a column percent. \*\*Ponderal index was available for 5,893 infants. ††Data for women who had pre-gestational hypertension were excluded.

weeks of gestation at which OGTT was performed was  $26.7 \pm 2.9$ . Mean fasting and 1-h and 2-h glucose levels were  $83.4 \pm 7.9$ ,  $131.8 \pm 30.7$ , and  $107.6 \pm 23.0$  mg/dl, respectively. Correlations among these three glucose measures were 0.39 for FPG and 1-h glucose, 0.30 for FPG and 2-h glucose, and 0.62 for 1-h and 2-h glucose ( $P < 0.0001$  for each comparison).

Of these women, 1,691 (19.4%) had IADPSG-defined GDM. Compared with women without GDM, those with GDM tended to be slightly older, more parous, have higher mean prepregnancy BMI, and have relatively similar mean gestational weight gain (Table 1). Among women with GDM, ~52% were based on *i*-IFG, 23% on *i*-IGT<sub>1</sub>, 5% on *i*-IGT<sub>2</sub>, and 20% on IFG+IGT. Of 391 women with *i*-IGT<sub>1</sub>, 131 (33.5%) had an abnormal 2-h glucose value only (7.7% of all women with GDM). Of those with IFG+IGT ( $n = 331$ ), only 55 had three abnormal OGTT results (0.6% of GDM women), reflecting the fact that women with the most abnormal OGTT results were treated and therefore excluded from these analyses.

As shown in Table 1, women in the *i*-IGT<sub>1</sub> group had significantly lower prepregnancy BMI than those with *i*-IFG or IFG+IGT; BMI for these women was similar to those with *i*-IGT<sub>2</sub>. On average, weight gain for the *i*-IGT<sub>1</sub> group was similar to women of all other GDM subtypes. Women with *i*-IFG had significantly higher prepregnancy BMI than those with *i*-IGT<sub>1</sub> or *i*-IGT<sub>2</sub>; BMI was similar to those with IFG+IGT. Mean weight gain for these women was similar to those with *i*-IGT<sub>1</sub>, *i*-IGT<sub>2</sub>, or IFG+IGT. Among all GDM subtypes, prepregnancy BMI and gestational weight gain were highest for women with *i*-IFG and IFG+IGT.

### Glucose values and adverse outcomes

Associations between adverse outcomes and continuous fasting and 1-h and 2-h glucose values, as well as glucose dichotomized at IADPSG cut points, are shown in Table 2. Odds ratios for each continuous glucose measure are expressed as risk per 1-SD increase above the mean. Odds ratios presented are adjusted for maternal age, race/ethnicity, parity, prepregnancy BMI, gestational weight gain, infant sex, and gestational age at OGTT. Results were similar after additional adjustment for maternal prenatal smoking. When modeled separately, we found a significant association between each continuous

OGTT value and LGA, primary cesarean, preterm delivery, and gestational hypertension. We additionally observed significant associations between the continuous 1-h and 2-h postglucose challenge values and shoulder dystocia/birth injury, as well as hyperbilirubinemia. Odds ratios for significant risk of adverse outcomes categorized by IADPSG cut points for each glucose measure were relatively consistent with those of the continuous measures, except that those with 1-h glucose  $\geq 180$  mg/dl were not at significantly increased risk for primary cesarean section or hyperbilirubinemia, compared with women with 1-h glucose <180 mg/dl. Similarly, women with 2-h glucose  $\geq 153$  mg/dl were not at significantly increased risk for LGA, shoulder dystocia/birth injury, or hyperbilirubinemia, compared with those with 2-h glucose <153 mg/dl. Women with GDM, as defined by IADPSG guidelines, were at significantly increased risk for all outcomes except infant hyperbilirubinemia.

### GDM subtypes and adverse outcomes

Associations between GDM subtype (*i*-IGT<sub>1</sub>, *i*-IFG, *i*-IGT<sub>2</sub>, and IFG+IGT) and each adverse outcome, adjusting for maternal age, race/ethnicity, parity, prepregnancy BMI, and gestational weight gain are presented in Table 3. We did not observe statistically significant associations between *i*-IGT<sub>1</sub> and LGA, primary cesarean, and shoulder dystocia/birth injury. Women classified as having GDM based on a single abnormal postload glucose value were at significantly increased risk for preterm delivery, gestational hypertension, and infant hyperbilirubinemia. Conversely, women with *i*-IFG were twice as likely to have an LGA infant (95% CI 1.62–2.45) and 45% more likely to have shoulder dystocia/birth injury at delivery (1.05–2.00) than those with no glucose impairment. Women with *i*-IFG were also 29% more likely to have gestational hypertension (1.04–1.72) compared with women without GDM. Women with the *i*-IGT<sub>2</sub> GDM subtype were 2.33 times as likely to develop gestational hypertension (1.20–4.51) than women without GDM, and infants born to these women were 2.85 times as likely to be delivered preterm (1.59–5.10) than infants of mothers without GDM. Women with IFG+IGT were more than twice as likely to have gestational hypertension (1.42–2.84), 87% more likely to have shoulder dystocia/birth injury during de-

Table 2—Adjusted odds ratios\* and 95% CIs for the association of adverse outcomes with OGTT values and GDM

	Fasting glucose		1-h glucose		2-h glucose	
	Continuous, per 1 SD from the mean	<92 vs. ≥92 mg/dl	Continuous, per 1 SD from the mean	<180 vs. ≥180 mg/dl	Continuous, per 1 SD from the mean	<153 vs. ≥153 mg/dl
LGA	1.32 (1.23–1.42)	2.04 (1.70–2.44)	1.31 (1.22–1.42)	1.52 (1.19–1.94)	1.26 (1.17–1.36)	1.36 (0.96–1.95)
Primary cesarean section	1.07 (1.01–1.14)	1.20 (1.01–1.43)	1.13 (1.06–1.21)	1.02 (0.81–1.29)	1.20 (1.13–1.28)	1.41 (1.04–1.92)
Preterm delivery	1.12 (1.03–1.21)	1.35 (1.07–1.69)	1.23 (1.13–1.34)	1.57 (1.19–2.08)	1.19 (1.10–1.30)	1.84 (1.31–2.60)
Shoulder dystocia/birth injury	1.09 (0.98–1.21)	1.51 (1.14–2.00)	1.17 (1.05–1.31)	1.55 (1.08–2.22)	1.23 (1.11–1.38)	1.25 (0.73–2.14)
Gestational hypertension	1.14 (1.05–1.23)	1.41 (1.14–1.74)	1.31 (1.20–1.42)	1.70 (1.30–2.23)	1.27 (1.16–1.38)	1.94 (1.35–2.80)
Hyperbilirubinemia	0.98 (0.92–1.05)	0.99 (0.82–1.18)	1.13 (1.06–1.21)	1.14 (0.91–1.43)	1.07 (1.00–1.14)	1.27 (0.94–1.71)

\*Odds ratios for OGTT measures are for an increase in glucose level of 1 SD (7.99 mg/dl for FPG, 30.84 mg/dl for 1-h glucose, and 23.08 mg/dl for 2-h glucose) and are adjusted for maternal age, race/ethnicity, parity, prepregnancy BMI, gestational weight gain, infant sex, and gestational age at OGTT.

livery (1.18–2.96), and 2.32 times as likely to have an LGA infant (1.72–3.13) than women without GDM.

LGA was more strongly associated with GDM subtypes defined by an abnormal fasting glucose (*i*-IFG and IFG+IGT) than those based on abnormal postload glucose values only. Additionally, while risk for shoulder dystocia/birth injury was elevated in all four GDM subtype groups, the outcome was only significantly associated with *i*-IFG and IFG+IGT. In contrast, preterm delivery, gestational hypertension, and hyperbilirubinemia appeared to be more strongly associated with categories of GDM involving elevated postload glucose (*i*-IGT<sub>1</sub> and/or *i*-IGT<sub>2</sub>). In fact, women with *i*-IGT<sub>2</sub> had the highest risk for preterm delivery and gestational hypertension among all GDM subtypes.

**CONCLUSIONS**— In this sample of 8,711 untreated women, 19.4% of whom had GDM by IADPSG criteria, we found a significant association between adverse maternal and perinatal outcomes and increasing fasting and 1- and 2-h OGTT glucose values. The magnitude and significance of these associations were consistent with those reported by the HAPO Study Group (8). As IADPSG guidelines for diagnosis of GDM were determined by the average glucose values in the HAPO study, at which the adjusted risk for selected adverse outcomes increased by 75% compared with the risk at mean glucose levels overall, it was not surprising that we additionally observed significant association between GDM status and all adverse outcomes, even after adjusting for confounders such as prepregnancy BMI and gestational weight gain, which were not included in the analyses conducted by the HAPO Study Group.

However, the formulation of the new guidelines, whereby a single abnormal fasting and 1-h or 2-h value is sufficient to diagnose GDM, implies that each glucose value contributes a significant independent effect on adverse outcomes and that such effects are equally important for outcome development. Models that examine only the associations between a single glucose measure and outcome, with or without adjustment for multiple confounders, do not account for the underlying correlation between fasting and 1-h and 2-h OGTT values. We observed significant correlations of moderate magnitude among the three glucose measures (range 0.30–0.62) that are consistent with those

reported by HAPO investigators (8), suggesting that a woman's response to glucose is at least partially associated with her FPG levels. Therefore, we examined various combinations of abnormal values, categorized women according to one of four combinations that result in a diagnosis of GDM under IADPSG guidelines (*i*-IGT<sub>1</sub>, *i*-IFG, *i*-IGT<sub>2</sub>, and IFG+IGT) and investigated group-specific risk for adverse outcomes compared with women without GDM.

Our results suggest that women with *i*-IGT<sub>1</sub> may have modestly elevated risk for primary cesarean delivery, shoulder dystocia/birth injury, or having an LGA infant, compared with women without GDM, but these risks were not statistically significant. Most importantly, women diagnosed with GDM based on *i*-IFG may have different risks for specific outcomes, compared with women with GDM based on abnormal 1-h and 2-h OGTT results. For example, LGA and shoulder dystocia appear to be more strongly associated with categories of GDM based on abnormal fasting values; the risk for LGA among those with elevated fasting glucose may be further compounded by abnormal postload glucose. In contrast, preterm delivery, gestational hypertension, and hyperbilirubinemia appear to be more closely related to elevated postload glucose than abnormal fasting values, with the highest risks observed among women with normal fasting and two elevated postload glucose values.

We acknowledge several limitations of this study. First, we observed considerable variation in sample sizes for specific GDM subgroups, which is largely attributed to the fact that women with the most abnormal results were likely to be treated and thus excluded from our analyses. The smaller numbers of women in *i*-IGT<sub>1</sub> and *i*-IGT<sub>2</sub> categories reduced our power to detect statistically significant differences for some outcomes in these groups. Additionally, given that data used for these analyses were collected during the course of clinical care, there was some variability in the timing of ascertainment of prepregnancy and delivery weight. Among women with prepregnancy weight extracted from the EHR, there was little variability in the mean prepregnancy BMI by timing of measurement (mean BMI ± SD: 0–3 months prior to LMP 27.69 ± 6.20 kg/m<sup>2</sup>; 0–3 months after LMP 27.69 ± 6.14 kg/m<sup>2</sup>; and 3–6 months before LMP 27.03 ± 5.90 kg/m<sup>2</sup>). Additionally, delivery weight was ascer-

Table 3—Adjusted odds ratios\* with 95% CIs for the association between adverse outcomes and GDM subtype

	i-IGT <sub>1</sub> vs. no GDM (95% CI)	i-IFG vs. no GDM (95% CI)	i-IGT <sub>2</sub> vs. no GDM (95% CI)	IFG+IGT vs. no GDM (95% CI)
LGA	1.25 (0.87–1.77)	2.00 (1.62–2.45)	1.51 (0.74–3.05)	2.32 (1.72–3.13)
Primary cesarean section	1.03 (0.77–1.38)	1.16 (0.95–1.41)	1.39 (0.78–2.46)	1.36 (1.00–1.85)
Preterm delivery	1.90 (1.38–2.63)	1.50 (1.16–1.95)	2.85 (1.59–5.10)	1.33 (0.87–2.03)
Shoulder dystocia/birth injury	1.31 (0.80–2.16)	1.45 (1.05–2.00)	1.72 (0.68–4.35)	1.87 (1.18–2.96)
Gestational hypertension	1.49 (1.03–2.16)	1.29 (1.01–1.66)	2.33 (1.20–4.51)	2.01 (1.42–2.84)
Hyperbilirubinemia	1.33 (1.02–1.74)	1.04 (0.85–1.27)	1.56 (0.92–2.65)	0.96 (0.69–1.33)

\*Odds ratios are adjusted for maternal age, race/ethnicity, parity, prepregnancy BMI, gestational weight gain, infant sex, and gestational age at OGTT.

tained 2–4 weeks prior to delivery for 3.9% of the women with measurements in the EHR ( $31.36 \pm 5.88 \text{ kg/m}^2$ ) and is likely an underestimate of their true weight at delivery (for women measured within 2 weeks of delivery:  $32.72 \pm 5.84 \text{ kg/m}^2$ ), as is delivery weight by self-report ( $31.74 \pm 5.72 \text{ kg/m}^2$ ). Moreover, we abstracted gestational age from the EHR or infant birth certificate, which is largely based on date of LMP rather than estimates from first or midtrimester ultrasound dates. This may have resulted in some misclassification of preterm delivery, which in turn may have influenced our estimates of preterm delivery risk for the various GDM subtypes. Lack of ultrasound data, as well as the lack of high-quality information on maternal behaviors and family history, precluded us from controlling for additional confounders which may have affected some outcomes.

The utilization of clinical and administrative information allowed for the identification and characterization of women with GDM based on standard laboratory test (75-g 2-h OGTT) results, which allowed us to disaggregate potential subgroups of GDM using OGTT values. In addition, we were able to exclude women who were treated with diet, exercise, and/or pharmacotherapy for GDM during pregnancy, which provided an opportunity to examine outcomes for untreated women with modestly elevated glycemia. This afforded us an opportunity to examine the relationship between glucose measures in untreated women, including those who meet contemporary criteria for GDM, and adverse clinical outcomes.

As more women with mild hyperglycemia will be diagnosed with GDM under IADPSG criteria, examining this cohort allowed us to assess outcomes for these women if left untreated. Our data suggest that the risks for different adverse maternal and perinatal outcomes vary depend-

ing on which single or combined IADPSG-defined OGTT thresholds are equaled or exceeded. Prospective studies are needed to determine whether changing pre- and postprandial glucose targets will more uniformly reduce adverse outcomes for women whose pregnancies are complicated by mild GDM.

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