Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study

Associations of maternal A1C and glucose with pregnancy outcomes

Lynn P. Lowe, phd[1]
Boyd E. Metzger, md[2]
Alan R. Dyer, phd[1]
Julia Lowe, mbchb[3]
David R. McCance, md[4]
Terence R.J. Lappin, phd[5]
Elisabeth R. Trimble, md[6]
Donald R. Coustan, md[7]
David R. Hadden, md[4]
Moshe Hod, md[8]
Jeremy J.N. Oats, md[9]
Bengt Persson, md, phd[10]
for the HAPO Study Cooperative Research Group*

OBJECTIVE—To compare associations of maternal glucose and A1C with adverse outcomes in the multinational Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study and determine, based on those comparisons, if A1C measurement can provide an alternative to an oral glucose tolerance test (OGTT) in pregnant women.

RESEARCH DESIGN AND METHODS—Eligible pregnant women underwent a 75-g OGTT at 24–32 weeks' gestation. A sample for A1C was also collected. Neonatal anthropometrics and cord serum C-peptide were measured. Associations with outcomes were assessed using multiple logistic regression with adjustment for potential confounders.

RESULTS—Among 23,316 HAPO Study participants with glucose levels blinded to caregivers, 21,064 had a nonvariant A1C result. The mean ± SD A1C was 4.79 ± 0.40%. Associations were significantly stronger with glucose measures than with A1C for birth weight, sum of skinfolds, and percent body fat >90th percentile and for fasting and 1-h glucose for cord C-peptide (all $P <$ 0.01). For example, in fully adjusted models, odds ratios (ORs) for birth weight >90th percentile for each measure higher by 1 SD were 1.39, 1.45, and 1.38, respectively, for fasting, 1-, and 2-h plasma glucose and 1.15 for A1C. ORs for cord C-peptide >90th percentile were 1.56, 1.45, and 1.35 for glucose, respectively, and 1.32 for A1C. ORs were similar for glucose and A1C for primary cesarean section, preeclampsia, and preterm delivery.

CONCLUSIONS—On the basis of associations with adverse outcomes, these findings suggest that A1C measurement is not a useful alternative to an OGTT in pregnant women.

Diabetes Care 35:574–580, 2012

The American Diabetes Association recently endorsed recommendations to use hemoglobin A1C (A1C) to diagnose diabetes and to identify people at increased risk for developing diabetes (1). They noted that A1C does not require a fasting state, reflects the usual level of glycemia for a period of 3–4 months, has low intraindividual variability, and is a good predictor of diabetes-related complications. However, these recommendations stipulate that the diagnosis of diabetes during pregnancy requires glucose testing since changes in erythrocyte turnover make the A1C assay problematic (2).

In overt diabetes, measurements of A1C are highly correlated with average glucose concentrations assessed by multiple daily measurements of capillary blood (3). Historically, A1C concentrations in preexisting diabetes have been associated with the risk of chronic complications and of adverse events during pregnancy, such as miscarriage, congenital malformations, or macrosomia (3). However, it has been shown that A1C measurements (4,5) and fructosamine levels (6,7) do not adequately separate women with normal pregnancy from those with gestational diabetes mellitus (GDM), even though A1C levels decline in normal pregnancy (8).

The objective of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study was to clarify the risk of adverse outcomes associated with degrees of glucose intolerance in pregnancy less severe than overt diabetes. Glucose tolerance was measured by a 75-g 2-h oral glucose tolerance test (OGTT) in a large, heterogeneous, international, ethnically diverse cohort of women at 24–32 weeks' gestation. Results of the HAPO Study on associations of maternal glucose levels below those diagnostic of diabetes with pregnancy outcomes have been reported (9).

The purpose of this report is to compare associations of maternal glucose and A1C measured at 24–32 weeks' gestation with adverse outcomes and to determine, based on those comparisons, if A1C can be used as an alternative to measurement of glucose in pregnant women.

RESEARCH DESIGN AND METHODS

—The protocol was approved by the institutional review board at all 15 field centers. All participants gave written informed consent. An external data monitoring committee provided oversight. Study methods have been published (9–11). A brief overview is presented here.

All pregnant women at each field center were eligible to participate unless they

From the [1]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; the [2]Division of Endocrinology, Metabolism, and Molecular Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; the [3]Department of Endocrinology, John Hunter Hospital, Newcastle, Australia; the [4]Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital Belfast, Belfast, Northern Ireland, U.K.; the [5]Department of Haematology, Queen's University Belfast, Belfast, Northern Ireland, U.K.; the [6]Department of Clinical Biochemistry, Queen's University Belfast, Belfast, Northern Ireland, U.K.; the [7]Division of Maternal Fetal Medicine, Warren Alpert Medical School, Brown University, Women & Infants Hospital of Rhode Island, Providence, Rhode Island; the [8]Department of Obstetrics and Gynecology, Helen Schneider Hospital for Women, Rabin Medical Center–Sackler Faculty of Medicine, Tel-Aviv University, Petah-Tiqva, Israel; the [9]Department of Obstetric Medicine, Mater Misericordiae Mothers' Hospital–University of Queensland, Brisbane, Australia; and the [10]Department of Pediatrics, Karolinska Institute, Stockholm, Sweden.
Corresponding author: Lynn P. Lowe, lplowe@northwestern.edu.
Received 31 August 2011 and accepted 4 December 2011.
DOI: 10.2337/dc11-1687
*A complete list of the members of the HAPO Study Cooperative Research Group can be found in ref. 9.

had one or more exclusion criteria (9): age <18 years, delivery planned at another hospital, date of last menstrual period not certain and no ultrasound estimation from 6 to 24 weeks of gestational age available, unable to complete the OGTT by 32 weeks' gestation, multiple pregnancy, conception using gonadotropin ovulation induction or by in vitro fertilization, glucose testing before recruitment or a diagnosis of diabetes during this pregnancy, diabetes antedating pregnancy requiring treatment with medication, participation in another study that may interfere with HAPO, known to be HIV positive or to have hepatitis B or C, prior participation in HAPO, or inability to converse in the languages used in field center forms without the aid of an interpreter. If glucose measurements were made outside of HAPO after initial enrollment, the participant was excluded from further participation.

Methods to determine gestational age and expected date of delivery have been described previously (9).

Glucose tolerance

Participants underwent a 75-g OGTT between 24 and 32 weeks' gestation (as close to 28 weeks as possible). Samples were collected fasting and at 1 and 2 h following the glucose load. A sample for random plasma glucose (RPG) was collected at 34–37 weeks' gestation as a safety measure to identify cases with hyperglycemia above a predefined threshold.

Glucose analysis and unblinding

Aliquots of fasting and 2-h OGTT and RPG samples were analyzed at field center laboratories. Values were unblinded if fasting plasma glucose (FPG) was >5.8 mmol/L, if 2-h OGTT plasma glucose (PG) was >11.1 mmol/L, if RPG was ≥8.9 mmol/L, or if any PG value was <2.5 mmol/L. Otherwise, women, caregivers, and HAPO Study staff (except for laboratory personnel) remained blinded to glucose values. To avoid confounding effects of center-to-center analytical variation, aliquots of all OGTT specimens were analyzed at the HAPO Central Laboratory (Belfast, Northern Ireland, U.K.) using a chemical analyzer (Vitros 750; Ortho Clinical Diagnostics, Rochester, NY), and those results are used here. Only data from women whose results remained blinded, with no additional glucose testing outside the HAPO protocol, are included in these analyses.

A1C analysis

Blood was drawn for analysis of A1C at the OGTT visit and stored frozen before transfer to the Central Laboratory where all A1C measurements were made. Previous large clinical trials such as the Diabetes Control and Complications Trial (DCCT) and the Diabetes Prevention Program (DPP) analyzed A1C on fresh, unfrozen samples shipped frequently to a central laboratory (all within the U.S.). This approach was not feasible in the HAPO Study involving 15 centers on four continents. A new method of sample storage and maintenance was developed before the study that gave reproducible results over several months for samples stored frozen (11).

A1C was measured by a high-performance liquid chromatography method on the Biomen HA 8140 instrument that gives an elution profile in which the glycated and nonglycated hemoglobin components are resolved in a time-dependent manner. Inspection of the elution profile for each participant sample allowed the detection of hemoglobin variants, such as HbS, HbC, or HbE. Women with variant hemoglobin are not included in this report. The coefficient of variation ranged from 2.8 to 5.0% across the range of A1C values. For external quality control, the Central Laboratory participated in the European Reference Laboratory (ERL) Program, which allows standardization to DCCT values, and the U.K. National Glycation Standardization Program, which involves certification of the high-performance liquid chromatography analytical procedure (11).

Cord serum C-peptide and PG levels

Cord blood was collected at delivery and analyzed for C-peptide and glucose at the central laboratory (11). Cord serum C-peptide (secreted in equimolar concentrations with insulin) was used as the index of fetal β-cell function; in contrast to insulin, C-peptide is not degraded by hemolysis, which occurs in ~15% of cord samples (12). Functional sensitivity of the assay was 0.2 μg/L. Cord PG was also measured at the central laboratory.

Demographic data

Height, weight, and blood pressure were measured at the OGTT visit using standardized procedures and calibrated equipment. Data concerning smoking and alcohol use, first-degree family history of diabetes and hypertension, and demographics were collected using standardized questionnaires. Race/ethnicity was self-identified by participants.

Prenatal care and delivery

Prenatal care and timing of delivery were determined by standard field center practice. No field center arbitrarily delivered patients before full term or routinely performed cesarean delivery at a specified maternal or gestational age.

Neonatal care and anthropometrics

After delivery, infants received customary routine care. Medical records were abstracted to obtain data regarding prenatal, labor and delivery, postpartum, and newborn course.

Neonatal anthropometrics were obtained within 72 h of delivery. Anthropometric measurements included weight, length, head circumference, and skinfold thickness at three sites (flank, subscapular, and triceps) (13). Birth weight was obtained without a diaper using a calibrated electronic scale. Length was measured on a standardized plastic length board constructed for use in the HAPO Study. Skinfold thickness was measured with Harpenden skinfold calipers (Baty International, West Sussex, U.K.).

Primary outcomes

Birth weight >90th percentile. The 90th percentiles for gestational age (30–44 weeks) were determined for eight newborn sex-ethnic groups (Caucasian or Other, Black, Hispanic, and Asian), with adjustment for gestational age, field center, and parity (0, 1, 2+) using quantile regression. A newborn was considered to have a birth weight >90th percentile if birth weight was greater than the estimated 90th percentile for the baby's sex, gestational age, ethnicity, field center, and maternal parity. Otherwise, the newborn was considered to have a birth weight ≤90th percentile.

Primary cesarean section. If the delivery was the first by cesarean, it was defined as primary.

Clinical neonatal hypoglycemia. Clinical neonatal hypoglycemia was defined by one or more clinical criteria: a notation of neonatal hypoglycemia in the medical record and symptoms or treatment with a glucose infusion or a laboratory-reported glucose value ≤1.7 mmol/L in the first 24 h after birth or ≤2.5 mmol/L after the first 24 h (14). Meter measurements of glucose were not included in this determination.

Cord C-peptide >90th percentile. The 90th percentile for the total HAPO cohort (1.7 μg/L) was used.

Secondary outcomes

Preeclampsia. Hypertension that was present before 20 weeks' gestation that

did not progress to preeclampsia was classified as chronic hypertension. Hypertensive disorders occurring after 20 weeks were categorized according to the International Society for the Study of Hypertension guidelines (15). Preeclampsia was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on two or more occasions at least 6 h apart and proteinuria ≥1+ on dipstick or ≥300 mg on 24-h urine collection. If the criteria for elevated blood pressure were met without proteinuria, this was classified as gestational hypertension.

Preterm delivery. Preterm delivery was defined as delivery prior to 37 weeks' gestation.

Sum of skinfolds >90th percentile. Sum of skinfolds >90th percentile for gestational age (36–44 weeks only) was defined using the same methods as for birth weight >90th percentile.

Percent body fat >90th percentile. Fat mass was calculated from birth weight, length, and flank skinfold according to the equation given in Catalano et al. (16) that was based on measurements of total body electrical conductivity. The derived formula was also prospectively validated with estimates of fat mass by total body electrical conductivity. Percent body fat was then calculated as 100 × fat mass/birth weight. Percent body fat >90th percentile for gestational age (36–44 weeks only) was defined using the same methods as for birth weight >90th percentile.

Statistical analyses

Descriptive statistics include means and SDs for continuous variables and numbers and percentages for categorical variables. For analyses of associations of A1C with primary outcomes, A1C was considered as both a categorical and continuous variable in multiple logistic regression analyses. For other outcomes and maternal glucose, only continuous variable results are presented. In categorical analyses, A1C was divided into seven categories with ~50% of all values in the two lowest categories and 3 and 1% in the two highest categories, respectively. These categories were selected to provide numbers in each category that were similar to those previously reported for maternal glucose (9).

We also created a composite OGTT measure that used all three glucose measures. This variable was created by calculating *z*-scores for FPG, 1-h PG, and 2-h PG by subtracting the appropriate HAPO mean from each woman's glucose measurements, dividing by the corresponding SD, and then summing the three resulting *z*-scores for each woman. For continuous variable analyses, odds ratios (ORs) were calculated for each measure (A1C, FPG, 1-h PG, 2-h PG, and the composite OGTT measure) higher by 1 SD. To assess whether the log of the odds of each outcome was linearly related to A1C and glucose measures, we added squared terms in each measure. Because of the large sample size in HAPO and the generally large number of women with each outcome, squared terms were considered statistically significant and included in logistic models only for $P < 0.001$.

For each outcome included in the A1C categorical analyses, three logistic models (1, 2, and 3) were fit. Model 1 included adjustment for the variables used to define the 90th percentile for the neonatal anthropometric measures, and model 2 included additional adjustment for multiple potential confounders that had been prespecified. Potential confounders included in model 2 were maternal age, BMI, height, gestational age, and mean arterial

Table 1—*Characteristics of study participants with measurement of A1C*

	No. of participants	Mean ± SD or *n* (%)
Maternal characteristics		
Age (years)	21,064	29.3 ± 5.8
BMI (kg/m^2)[1]	21,064	27.7 ± 5.1
MAP (mmHg)[1]	21,064	81.0 ± 8.3
PG (mmol/L)[1]		
FPG	21,064	4.5 ± 0.4
1-h	21,064	7.4 ± 1.7
2-h	21,064	6.2 ± 1.3
z-score sum[2]	21,064	0.0 ± 2.4
A1C (%)[1]	21,064	4.79 ± 0.40
Ethnicity		
White	21,064	10,586 (50.3)
Black	21,064	2,228 (10.6)
Hispanic	21,064	1,850 (8.8)
Asian	21,064	5,833 (27.7)
Other	21,064	567 (2.7)
Prenatal smoking (any)	21,064	1,490 (7.1)
Prenatal alcohol use (any)	21,064	1,513 (7.2)
Family history of diabetes	21,064	4,876 (23.2)
Parity (any prior delivery ≥20 weeks)	21,064	6,248 (29.7)
Any hospitalization prior to delivery	21,064	2,975 (14.1)
Prenatal urinary tract infection	21,064	1,526 (7.2)
Neonatal characteristics		
Gestational age at delivery (weeks)	21,064	39.4 ± 1.7
Birth weight (g)	21,022	3,299 ± 530
Cord serum C-peptide (μg/L)	17,868	1.01 ± 0.60
Cord PG (mmol/L)	17,845	4.5 ± 1.1
Sex (male)	21,064	10,849 (51.5)
Obstetric outcomes		
Primary cesarean section	18,698	3,370 (18.0)
Preeclampsia	19,270	1,020 (5.3)
Newborn outcomes		
Birth weight >90th percentile	20,979	2,018 (9.6)
Clinical neonatal hypoglycemia	20,983	434 (2.1)
Cord C-peptide >90th percentile	17,868	1,522 (8.5)
Sum of skinfolds >90th percentile	17,457	1,686 (9.7)
Percent body fat >90th percentile	17,396	1,724 (9.9)
Preterm delivery (<37 weeks)	21,064	1,442 (6.8)

[1]Maternal BMI, MAP, PG, and A1C were measured at the OGTT visit. [2]The OGTT *z*-score sum was created by calculating *z*-scores for FPG, 1-h PG, and 2-h PG by subtracting the appropriate HAPO mean from each woman's glucose measurements, dividing by the corresponding SD, and then summing the three resulting *z*-scores for each woman.

Table 2—*Relationship between maternal A1C and primary outcomes*

	In A1C category			Model 1		Model 2		Model 3	
A1C (%)	Total (*n*)	With outcome (*n*)	With outcome (%)	OR	95% CI	OR	95% CI	OR	95% CI
Birth weight >90th percentile									
<4.5	3,684	269	7.3	1.00		1.00		1.00	
4.5–4.7	5,944	541	9.1	1.27	(1.09–1.48)	1.19	(1.02–1.39)	1.15	(0.98–1.34)
4.8–5.0	6,363	619	9.7	1.37	(1.18–1.59)	1.22	(1.05–1.42)	1.08	(0.92–1.26)
5.1–5.2	2,578	255	9.9	1.39	(1.16–1.67)	1.22	(1.02–1.47)	0.95	(0.78–1.14)
5.3–5.4	1,400	186	13.3	1.95	(1.60–2.37)	1.66	(1.35–2.04)	1.25	(1.01–1.54)
5.5–5.7	777	107	13.8	2.03	(1.60–2.57)	1.66	(1.30–2.13)	1.10	(0.85–1.42)
≥5.8	233	41	17.6	2.71	(1.89–3.88)	1.93	(1.34–2.80)	1.09	(0.74–1.60)
Primary cesarean section[a]									
<4.5	3,362	493	14.7	1.00		1.00		1.00	
4.5–4.7	5,395	900	16.7	1.21	(1.08–1.37)	1.17	(1.04–1.33)	1.16	(1.02–1.31)
4.8–5.0	5,665	1,054	18.6	1.41	(1.25–1.59)	1.24	(1.10–1.40)	1.20	(1.06–1.35)
5.1–5.2	2,224	437	19.6	1.49	(1.28–1.72)	1.20	(1.03–1.40)	1.12	(0.97–1.31)
5.3–5.4	1,199	277	23.1	1.84	(1.55–2.18)	1.40	(1.17–1.66)	1.29	(1.08–1.54)
5.5–5.7	661	167	25.3	2.04	(1.66–2.51)	1.48	(1.20–1.83)	1.33	(1.07–1.65)
≥5.8	192	42	21.9	1.79	(1.25–2.57)	1.15	(0.80–1.67)	0.98	(0.67–1.43)
Clinical neonatal hypoglycemia									
<4.5	3,683	64	1.7	1.00		1.00		1.00	
4.5–4.7	5,940	102	1.7	0.97	(0.71–1.33)	0.94	(0.68–1.30)	0.93	(0.67–1.28)
4.8–5.0	6,372	136	2.1	1.26	(0.93–1.71)	1.17	(0.86–1.60)	1.13	(0.83–1.55)
5.1–5.2	2,578	65	2.5	1.51	(1.06–2.16)	1.35	(0.93–1.94)	1.26	(0.87–1.83)
5.3–5.4	1,397	39	2.8	1.67	(1.11–2.53)	1.45	(0.95–2.21)	1.34	(0.87–2.07)
5.5–5.7	779	24	3.1	1.87	(1.15–3.03)	1.66	(1.00–2.73)	1.50	(0.90–2.49)
≥5.8	234	4	1.7	0.86	(0.31–2.40)	0.73	(0.26–2.06)	0.62	(0.22–1.78)
Cord serum C-peptide >90th percentile									
<4.5	3,196	182	5.7	1.00		1.00		1.00	
4.5–4.7	5,092	332	6.5	1.16	(0.96–1.40)	1.13	(0.93–1.37)	1.06	(0.88–1.29)
4.8–5.0	5,437	468	8.6	1.56	(1.30–1.87)	1.37	(1.14–1.65)	1.19	(0.99–1.44)
5.1–5.2	2,150	238	11.1	2.09	(1.70–2.57)	1.65	(1.33–2.05)	1.29	(1.03–1.60)
5.3–5.4	1,161	163	14.0	2.79	(2.22–3.51)	2.11	(1.66–2.69)	1.57	(1.22–2.01)
5.5–5.7	642	95	14.8	3.03	(2.31–3.97)	2.19	(1.64–2.91)	1.43	(1.07–1.93)
≥5.8	190	44	23.2	5.10	(3.50–7.42)	3.38	(2.27–5.03)	1.82	(1.20–2.75)

Model 1: Adjusted for field center or those variables used to define the 90th percentile for birth weight. Model 2: Additional adjustment for age, BMI, height, smoking, alcohol use, hospitalization prior to delivery, any family history of diabetes, MAP, gestational age at OGTT, parity (except primary cesarean section), and cord glucose (cord C-peptide >90th percentile only). Model 3: Additional adjustment for the sum of the *z*-scores for FPG, 1-h PG, and 2-h PG. [a]Data for women who had a previous cesarean section were excluded.

pressure (MAP) at the OGTT (except preeclampsia); parity (except primary cesarean section); family history of diabetes; family history of hypertension (preeclampsia only); hospitalization prior to delivery (except preeclampsia); smoking status; alcohol use; and maternal urinary tract infection (preeclampsia only). Model 3 included additional adjustment for the composite glucose measure. Squared terms for age, BMI, and MAP were prescreened for possible inclusion in model 2 and model 3 adjustment in models that included only linear and squared terms for these variables. Squared terms were included if $P < 0.001$.

For the four glucose measures in the continuous variable analyses, we fit three logistic models, with models 1 and 2 the same as for A1C and model 3 including adjustment for A1C, which yielded associations of A1C, adjusting in turn for FPG, 1-h PG, 2-h PG, and the composite glucose measure. To determine whether the associations of A1C with each outcome were significantly different from those of the four glucose measures, we compared the model 3 logistic regression coefficients for A1C with those of FPG, 1-h PG, 2-h PG, and the composite measure. All analyses were conducted in SAS version 9.1 or Stata 11.2.

RESULTS—Pregnancies in 23,316 women with glucose values blinded, birth weight recorded, gestational age determined, and obstetric and neonatal records available were in the initial report (9); A1C results were available for 21,909 of these pregnancies. Hemoglobinopathies were found in 845 or 3.9% of the participants, and the results from these pregnancies were removed leaving 21,064 for these analyses. Characteristics of these participants and frequency of outcomes are shown in Table 1. Correlations of A1C with FPG, 1-h PG, 2-h PG, and the composite measure were 0.290, 0.254, 0.227, and 0.324, respectively (all $P < 0.001$).

Table 2 shows associations of maternal A1C with each of the prespecified primary outcomes, including ORs and 95% CIs for each category of A1C compared with the lowest or referent category. With higher levels of maternal A1C, the frequencies of birth weight >90th percentile, primary cesarean section, and cord serum C-peptide >90th percentile were greater. For example, the frequency of cord serum C-peptide >90th percentile rose from 5.7% in the lowest category of A1C (<4.5%) to 23.2% in the highest (≥5.8%). In model 1, the OR was 2.71, 1.79, and 5.10 in the highest compared with the lowest category of A1C for birth weight >90th percentile, primary cesarean section, and cord serum C-peptide >90th percentile, respectively. Associations were attenuated with adjustment for model 2 confounders but remained significant for birth weight and cord serum C-peptide >90th percentile with ORs of 1.93 and 3.38, respectively. The odds of clinical neonatal hypoglycemia rose through the first six categories of A1C but were lower in the highest category. With adjustment for the composite glucose measure in model 3, there was no independent association of A1C with birth weight >90th percentile or clinical neonatal hypoglycemia. The associations with primary cesarean section and cord C-peptide were further attenuated with this adjustment for PG.

Results from continuous variable models 1 and 2 for the associations between A1C, the four glucose measures, and outcomes are shown in Table 3. In model 1 analyses, there were significant associations of A1C and PG with all of the primary and secondary outcomes. For birth weight, cord C-peptide, sum of skinfolds, and percent body fat >90th percentile, the ORs for A1C were smaller than those for PG. Associations were somewhat attenuated with adjustment for model 2 confounders but remained significant. Again, ORs for A1C were somewhat smaller than those for PG for birth weight, cord C-peptide, sum of skinfolds, and percent body fat >90th percentile. Associations with the other outcomes were generally similar for PG and A1C. In general, the composite measure of PG indicated by the PG *z*-score was more strongly associated with risk of the outcomes than individual measures of PG alone.

Table 4 shows the independent associations of the glucose measures with adjustment for A1C and the associations of A1C adjusted for each of the glucose

Table 3—*Relationship[a] between maternal glucose, A1C, and primary and secondary outcomes*

	Model 1		Model 2	
Outcome	OR	95% CI	OR	95% CI
Primary				
Birth weight >90th percentile				
A1C	1.22	(1.16–1.28)	1.15	(1.09–1.21)
FPG	1.49	(1.43–1.56)	1.39	(1.32–1.46)
1-h PG	1.38	(1.32–1.45)	1.45	(1.38–1.52)
2-h PG	1.31	(1.26–1.37)	1.38	(1.32–1.45)
PG *z*-score sum	1.51	(1.45–1.58)	1.55	(1.48–1.63)
Primary cesarean section[b]				
A1C	1.20	(1.15–1.24)	1.09	(1.04–1.13)
FPG	1.25	(1.21–1.30)	1.11	(1.07–1.16)
1-h PG	1.27	(1.22–1.32)	1.12	(1.08–1.17)
2-h PG	1.22	(1.17–1.27)	1.08	(1.04–1.13)
PG *z*-score sum	1.32	(1.27–1.37)	1.14	(1.09–1.19)
Clinical neonatal hypoglycemia				
A1C	1.18	(1.07–1.30)	1.13	(1.02–1.25)
FPG	1.16	(1.06–1.28)	1.08	(0.97–1.20)
1-h PG	1.26	(1.14–1.39)	1.16	(1.04–1.29)
2-h PG	1.20	(1.09–1.32)	1.11	(1.00–1.23)
PG *z*-score sum	1.25	(1.14–1.38)	1.15	(1.04–1.28)
Cord serum C-peptide >90th percentile				
A1C	1.47	(1.39–1.56)	1.32	(1.25–1.40)
FPG	1.79	(1.70–1.89)	1.56	(1.47–1.65)
1-h PG	1.63	(1.54–1.72)	1.45	(1.37–1.54)
2-h PG	1.50	(1.42–1.58)	1.35	(1.28–1.43)
PG *z*-score sum	1.83	(1.74–1.92)	1.62	(1.53–1.71)
Secondary				
Preeclampsia				
A1C	1.42	(1.33–1.52)	1.27	(1.19–1.37)
FPG	1.46	(1.37–1.55)	1.21	(1.13–1.30)
1-h PG	1.40	(1.32–1.50)	1.30	(1.21–1.40)
2-h PG	1.37	(1.29–1.46)	1.31	(1.22–1.40)
PG *z*-score sum	1.53	(1.44–1.63)	1.36	(1.27–1.46)
Preterm delivery (<37 weeks)				
A1C	1.17	(1.11–1.23)	1.17	(1.10–1.24)
FPG	1.08	(1.02–1.14)	1.05	(0.99–1.11)
1-h PG	1.22	(1.15–1.28)	1.19	(1.12–1.26)
2-h PG	1.21	(1.15–1.27)	1.17	(1.11–1.24)
PG *z*-score sum	1.21	(1.15–1.28)	1.18	(1.11–1.25)
Sum of skinfolds >90th percentile				
A1C	1.18	(1.12–1.24)	1.09	(1.03–1.15)
FPG	1.53	(1.46–1.60)	1.40	(1.33–1.48)
1-h PG	1.46	(1.39–1.53)	1.44	(1.36–1.51)
2-h PG	1.40	(1.33–1.46)	1.39	(1.32–1.46)
PG *z*-score sum	1.60	(1.53–1.68)	1.56	(1.48–1.65)
Percent body fat >90th percentile				
A1C	1.22	(1.16–1.29)	1.15	(1.09–1.21)
FPG	1.47	(1.40–1.54)	1.35	(1.28–1.43)
1-h PG	1.41	(1.35–1.48)	1.44	(1.37–1.52)
2-h PG	1.33	(1.27–1.39)	1.36	(1.29–1.43)
PG *z*-score sum	1.53	(1.45–1.60)	1.53	(1.45–1.61)

Model 1: Adjusted for field center or those variables used to define the 90th percentile for birth weight, sum of skinfolds, and percent body fat. Model 2: Adjusted for field center, age, BMI, height, parity (except primary cesarean section), smoking, alcohol use, hospitalization prior to delivery (except preeclampsia), any family history of diabetes, MAP (except preeclampsia), gestational age at OGTT, cord glucose (cord C-peptide >90th percentile only), maternal urinary tract infection (preeclampsia only), and any family history of hypertension (preeclampsia only). [a]Continuous variable analysis, glucose higher by 1 SD 0.4% for A1C, 0.4 mmol/L for FPG, 1.7 mmol/L for 1-h PG, and 1.3 mmol/L for 2-h PG. [b]Data for women who had a previous cesarean section were excluded.

measures. Associations were significantly stronger for each of the glucose measures than for A1C for birth weight, sum of skinfolds, and percent body fat >90th percentile (all $P < 0.001$). In addition, with adjustment for the composite measure, A1C was not significantly related to birth weight and percent body fat >90th percentile, and A1C was not significantly related to sum of skinfolds >90th percentile with adjustment for each of the four glucose measures. Associations were also significantly stronger for fasting, 1-h PG, and the composite measure than for A1C for cord C-peptide >90th percentile. There were no significant differences between the glucose measures and A1C for the associations with primary cesarean section, clinical neonatal hypoglycemia, and preeclampsia. A1C showed a stronger association than FPG for preterm delivery ($P = 0.003$) but no difference compared with 1- or 2-h PG or the composite measure.

CONCLUSIONS—Historically, A1C measurements (4,5) and fructosamine levels (6,7) did not adequately separate women with normal pregnancy from those with GDM, even though A1C levels decline in normal pregnancy (8). However, none of these reports involved a sample size approaching that of the HAPO Study cohort.

In the HAPO Study cohort, we found significant correlations of A1C with the individual OGTT glucose measures (FPG correlation being the largest), as well as the composite measure, which was larger than the individual glucose measures. There were also significant associations between higher levels of A1C and all of the primary and secondary HAPO Study outcomes, when the associations were not adjusted for glucose.

The new criteria for the diagnosis of GDM promulgated by the International Association of Diabetes in Pregnancy Study Groups (IADPSG) (17) were based on associations seen between glucose and birth weight, cord C-peptide, and percent body fat >90th percentile. These outcomes were selected because fetal macrosomia is a major indicator of hyperglycemia in pregnancy and because of the known associations between macrosomia and excess adiposity with fetal hyperinsulinemia (17).

For the outcomes used to derive the IADPSG criteria, in models that included both glucose and A1C, the four glucose measures had significantly stronger associations with birth weight, sum of skinfolds, and percent body fat >90th percentile, and

Table 4—*Relationship[a] between maternal glucose, A1C, and primary and secondary outcomes in Model 2 with inclusion of A1C in each glucose model*

	Glucose		A1C			
Outcome	OR	95% CI	OR	95% CI	z[c]	*P* value
Primary						
Birth weight >90th percentile						
FPG	1.37	(1.30–1.44)	1.07	(1.01–1.12)	6.18	<0.001
1-h PG	1.43	(1.36–1.50)	1.06	(1.01–1.12)	7.36	<0.001
2-h PG	1.36	(1.30–1.43)	1.08	(1.03–1.13)	5.95	<0.001
PG *z*-score sum	1.54	(1.48–1.63)	1.02	(0.97–1.07)	9.95	<0.001
Primary cesarean section[b]						
FPG	1.09	(1.05–1.14)	1.06	(1.02–1.11)	0.83	0.41
1-h PG	1.11	(1.06–1.16)	1.06	(1.02–1.11)	1.20	0.23
2-h PG	1.07	(1.03–1.12)	1.07	(1.03–1.12)	−0.05	0.96
PG *z*-score sum	1.12	(1.08–1.17)	1.05	(1.01–1.10)	1.83	0.067
Clinical neonatal hypoglycemia						
FPG	1.05	(0.94–1.17)	1.12	(1.01–1.24)	−0.71	0.48
1-h PG	1.13	(1.02–1.27)	1.10	(0.99–1.23)	0.33	0.38
2-h PG	1.09	(0.98–1.21)	1.11	(1.00–1.24)	−0.30	0.77
PG *z*-score sum	1.12	(1.01–1.25)	1.10	(0.99–1.22)	0.25	0.81
Cord serum C-peptide >90th percentile						
FPG	1.49	(1.41–1.58)	1.19	(1.12–1.27)	4.61	<0.001
1-h PG	1.39	(1.31–1.47)	1.23	(1.16–1.31)	2.54	0.011
2-h PG	1.29	(1.22–1.37)	1.26	(1.19–1.34)	0.60	0.55
PG *z*-score sum	1.55	(1.46–1.64)	1.17	(1.10–1.24)	5.65	<0.001
Secondary						
Preeclampsia						
FPG	1.15	(1.07–1.24)	1.23	(1.14–1.32)	−1.04	0.30
1-h PG	1.25	(1.16–1.34)	1.21	(1.12–1.30)	0.53	0.60
2-h PG	1.26	(1.17–1.35)	1.21	(1.13–1.31)	0.65	0.52
PG *z*-score sum	1.30	(1.21–1.40)	1.18	(1.09–1.27)	1.63	0.10
Preterm delivery (<37 weeks)						
FPG	1.01	(0.95–1.07)	1.17	(1.10–1.24)	−2.99	0.003
1-h PG	1.16	(1.09–1.23)	1.13	(1.07–1.20)	0.46	0.64
2-h PG	1.15	(1.09–1.22)	1.14	(1.07–1.21)	0.26	0.79
PG *z*-score sum	1.14	(1.08–1.22)	1.13	(1.06–1.20)	0.31	0.75
Sum of skinfolds >90th percentile						
FPG	1.40	(1.33–1.48)	1.00	(0.95–1.06)	7.63	<0.001
1-h PG	1.43	(1.36–1.51)	1.01	(0.95–1.06)	8.17	<0.001
2-h PG	1.39	(1.31–1.46)	1.02	(0.97–1.08)	7.31	<0.001
PG *z*-score sum	1.58	(1.49–1.67)	0.96	(0.91–1.01)	11.04	<0.001
Percent body fat >90th percentile						
FPG	1.33	(1.26–1.40)	1.07	(1.02–1.13)	4.91	<0.001
1-h PG	1.42	(1.35–1.50)	1.07	(1.01–1.13)	6.65	<0.001
2-h PG	1.34	(1.27–1.41)	1.09	(1.03–1.15)	5.01	<0.001
PG *z*-score sum	1.51	(1.43–1.60)	1.03	(0.97–1.09)	8.65	<0.001

Model 2: Adjusted for field center, age, BMI, height, parity (except primary cesarean section), smoking, alcohol use, hospitalization prior to delivery (except preeclampsia), any family history of diabetes, MAP (except preeclampsia), gestational age at OGTT, cord glucose (cord C-peptide >90th percentile only), maternal urinary tract infection (preeclampsia only), and any family history of hypertension (preeclampsia only). [a]Continuous variable analysis, glucose higher by 1 SD 0.4% for A1C, 0.4 mmol/L for FPG, 1.7 mmol/L for 1-h PG, and 1.3 mmol/L for 2-h PG. [b]Data for women who had a previous cesarean section were excluded. [c]*z* and *P* value for comparison of coefficients for glucose and A1C in model containing both.

only 2-h glucose did not have a significantly stronger association with cord C-peptide >90th percentile. In addition, with adjustment for the composite glucose measure, A1C was not significantly associated with any of the neonatal anthropometric outcomes. For example, the model 3 adjusted OR per SD difference for birth weight >90th percentile was 1.36–1.54 for glucose versus 1.02–1.08 for A1C, and the association for A1C was not significant with adjustment for the PG *z*-score sum. The only instance where A1C had a significantly stronger association was for FPG for preterm delivery. But there were no significant differences compared with the other three glucose measures. And there were no significant differences between A1C and glucose for primary cesarean delivery, clinical neonatal hypoglycemia, and preeclampsia.

We cannot determine why, with adjustment for glucose measures, A1C is associated with some pregnancy outcomes but not others. A1C reflects average glycemia over an interval of several preceding weeks. Since A1C was associated with cesarean delivery, preeclampsia, and preterm delivery, it might be speculated that risks of these outcomes are influenced by glycemia earlier in pregnancy, whereas anthropometric outcomes are more strongly associated with glycemia later in pregnancy.

Our findings are consistent with the new IADPSG recommendations. These findings, based on its associations with pregnancy outcomes with adjustment for glucose, suggest that measurement of A1C is not a useful alternative to an OGTT in pregnant women. Furthermore, the generally stronger associations between a single measure of glucose at an average of 28 weeks' gestation with pregnancy outcome than the associations of A1C with the same outcomes counter the concerns about basing the diagnosis of GDM on a single abnormal glucose measurement performed on only one occasion (18,19).

Acknowledgments—This study was funded by grants R01-HD-34242 and R01-HD-34243 from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Diabetes and Digestive and Kidney Diseases; by the National Center for Research Resources (M01-RR-00048 and M01-RR-00080); and by the American Diabetes Association. Support has also been provided to local field centers by Diabetes UK (RD04/0002756), Southern California Permanente Medical Group, KK Women's and Children's Hospital, Mater Mother's Hospital, Novo Nordisk, and the Howard and Carol Bernick Family Foundation. No other potential conflicts of interest relevant to this article were reported.

L.P.L., B.E.M., A.R.D., and D.R.H. researched data, contributed to discussion, and wrote, reviewed, and edited the manuscript. J.L. contributed to discussion and reviewed and edited the manuscript. J.J.N.O., D.R.M., D.R.C., E.R.T., and D.R.H. researched data, contributed to discussion, and reviewed and edited the manuscript. T.R.J.L. reviewed and edited the manuscript. M.H. and B.P. researched data and reviewed and edited the manuscript. L.P.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors would like to give special thanks to the late Geraldine Savage (Department of Haematology, Queen's University Belfast, Belfast, Northern Ireland, U.K.) who performed the majority of the A1C assays.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1):S62–S69
2. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334
3. Metzger BE, Phelps RL. Diabetes mellitus and pregnancy. In *Endocrinology*. 6th ed. Jameson JL, DeGroot LJ, Eds. Philadelphia, Saunders, 2010, p. 2644–2661
4. Cousins L, Dattel BJ, Hollingsworth DR, Zettner A. Glycosylated hemoglobin as a screening test for carbohydrate intolerance in pregnancy. Am J Obstet Gynecol 1984;150:455–460
5. Shah BD, Cohen AW, May C, Gabbe SG. Comparison of glycohemoglobin determination and the one-hour oral glucose screen in the identification of gestational diabetes. Am J Obstet Gynecol 1982;144:774–777
6. Vermes I, Zeyen LJJM, van Roon E, Brandts H. The role of serum fructosamine as a screening test for gestational diabetes mellitus. Horm Metab Res 1989;21:73–76
7. Hughes PF, Agarwal M, Newman P, Morrison J. An evaluation of fructosamine estimation in screening for gestational diabetes mellitus. Diabet Med 1995;12:708–712
8. Kurishita M, Nakashima K, Kozu H. Glycated hemoglobin of fractionated erythrocytes, glycated albumin, and plasma fructosamine during pregnancy. Am J Obstet Gynecol 1992;167:1372–1378
9. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002
10. HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Intl J Gynaecol Obstet 2002;78:69–77
11. Nesbitt GS, Smye M, Sheridan B, Lappin TRJ, Trimble ER; HAPO Study Cooperative Research Group. Integration of local and central laboratory functions in a worldwide multicentre study: Experience from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Clin Trials 2006;3:397–407
12. O'Rahilly S, Burnett MA, Smith RF, Darley JH, Turner RC. Haemolysis affects insulin but not C-peptide immunoassay. Diabetologia 1987;30:394–396
13. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. Diabetes 2009;58:453–459
14. Alkalay AL, Sarnat HB, Flores-Sarnat L, Elashoff JD, Farber SJ, Simmons CF. Population meta-analysis of low plasma glucose thresholds in full-term normal newborns. Am J Perinatol 2006;23:115–119
15. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001;20:IX–XIV
16. Catalano PM, Thomas AJ, Avallone DA, Amini SB. Anthropometric estimation of neonatal body composition. Am J Obstet Gynecol 1995;173:1176–1181
17. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676–682
18. Ryan EA. Diagnosing gestational diabetes. Diabetologia 2011;54:480–486
19. Long H. Diagnosing gestational diabetes: can expert opinions replace scientific evidence? Diabetologia 2011;54:2211–2213