The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 8, 2008 VOL. 358 NO. 19

Hyperglycemia and Adverse Pregnancy Outcomes

The HAPO Study Cooperative Research Group*

ABSTRACT

BACKGROUND

It is controversial whether maternal hyperglycemia less severe than that in diabetes mellitus is associated with increased risks of adverse pregnancy outcomes.

METHODS

A total of 25,505 pregnant women at 15 centers in nine countries underwent 75-g oral glucose-tolerance testing at 24 to 32 weeks of gestation. Data remained blinded if the fasting plasma glucose level was 105 mg per deciliter (5.8 mmol per liter) or less and the 2-hour plasma glucose level was 200 mg per deciliter (11.1 mmol per liter) or less. Primary outcomes were birth weight above the 90th percentile for gestational age, primary cesarean delivery, clinically diagnosed neonatal hypoglycemia, and cord-blood serum C-peptide level above the 90th percentile. Secondary outcomes were delivery before 37 weeks of gestation, shoulder dystocia or birth injury, need for intensive neonatal care, hyperbilirubinemia, and preeclampsia.

RESULTS

For the 23,316 participants with blinded data, we calculated adjusted odds ratios for adverse pregnancy outcomes associated with an increase in the fasting plasma glucose level of 1 SD (6.9 mg per deciliter [0.4 mmol per liter]), an increase in the 1-hour plasma glucose level of 1 SD (30.9 mg per deciliter [1.7 mmol per liter]), and an increase in the 2-hour plasma glucose level of 1 SD (23.5 mg per deciliter [1.3 mmol per liter]). For birth weight above the 90th percentile, the odds ratios were 1.38 (95% confidence interval [CI], 1.32 to 1.44), 1.46 (1.39 to 1.53), and 1.38 (1.32 to 1.44), respectively; for cord-blood serum C-peptide level above the 90th percentile, 1.55 (95% CI, 1.47 to 1.64), 1.46 (1.38 to 1.54), and 1.37 (1.30 to 1.44); for primary cesarean delivery, 1.11 (95% CI, 1.06 to 1.15), 1.10 (1.06 to 1.15), and 1.08 (1.03 to 1.12); and for neonatal hypoglycemia, 1.08 (95% CI, 0.98 to 1.19), 1.13 (1.03 to 1.26), and 1.10 (1.00 to 1.12). There were no obvious thresholds at which risks increased. Significant associations were also observed for secondary outcomes, although these tended to be weaker.

CONCLUSIONS

Our results indicate strong, continuous associations of maternal glucose levels below those diagnostic of diabetes with increased birth weight and increased cord-blood serum C-peptide levels.

The members of the Writing Group (Boyd E. Metzger, M.D., Lynn P. Lowe, Ph.D., Alan R. Dyer, Ph.D., Northwestern University Feinberg School of Medicine, Chicago; Elisabeth R. Trimble, M.D., Queen's University Belfast, Belfast, Northern Ireland; Udom Chaovarindr, M.D., Rajavithi Hospital, Bangkok, Thailand; Donald R. Coustan, M.D., Women and Infants' Hospital of Rhode Island–Brown University Medical School, Providence, RI; David R. Hadden, M.D., David R. McCance, M.D., Royal Jubilee Maternity Hospital, Belfast, Northern Ireland; Moshe Hod, M.D., Helen Schneider Hospital for Women, Rabin Medical Center–Sackler Faculty of Medicine, Tel-Aviv University, Petah-Tiqva, Israel; Harold David McIntyre, M.B., B.S., Jeremy J.N. Oats, M.D., Mater Misericordiae Mothers' Hospital–University of Queensland, Brisbane, Australia; Bengt Persson, M.D., Ph.D., Karolinska Institute, Stockholm, Sweden; Michael S. Rogers, M.D., Prince of Wales Hospital–Chinese University of Hong Kong, Hong Kong; and David A. Sacks, M.D., Kaiser Foundation Hospital, Bellflower, CA) of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group assume responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Metzger at the Northwestern University Feinberg School of Medicine, Endocrinology, 645 N. Michigan Ave., Suite 530-22, Chicago, IL 60611, or at bem@northwestern.edu.

*Members of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group are listed in the Appendix.

N Engl J Med 2008;358:1991-2002.

Gestational diabetes mellitus, defined as "glucose intolerance with onset or first recognition during pregnancy,"[1,2] has been the subject of considerable controversy. Criteria for the diagnosis were initially established more than 40 years ago[3] and, with minor modifications, remain in use today. These criteria are not designed to identify pregnant women who are at increased risk for adverse perinatal outcomes but rather women who are at high risk for the development of diabetes after pregnancy,[3,4] or they are the criteria used for the general population.[5]

Overt diabetes mellitus during pregnancy is associated with significantly increased risks of adverse perinatal outcomes. Whereas some data suggest that current diagnostic criteria for gestational diabetes mellitus[1] are too restrictive and that lesser degrees of hyperglycemia also increase risk,[6-11] risks associated with hyperglycemia that is less severe than that diagnostic of overt diabetes mellitus are uncertain for a number of reasons. First, there are no uniform international standards for the ascertainment and diagnosis of gestational diabetes mellitus.[2] In addition, the extent to which adverse outcomes associated with gestational diabetes mellitus may be explained by confounders (including obesity, advanced maternal age, or associated medical complications) is unclear.[12-14] Caregiver bias (i.e., an expectation of adverse outcomes due to gestational diabetes mellitus) may increase the likelihood of disorders or problems due to increased intervention.[15]

We conducted the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study to clarify the risks of adverse outcomes associated with various degrees of maternal glucose intolerance less severe than that in overt diabetes mellitus.

Methods

The protocol was approved by the institutional review board at each field center. All participants gave written informed consent. An external data and safety monitoring committee provided oversight. The study methods have been published previously.[16,17] A brief overview is presented here.

Participants

All pregnant women at a given center were eligible to participate unless they had one or more of the following exclusion criteria[16]: age younger than 18 years, a plan to undergo delivery at another hospital, an uncertain date of last menstrual period and no ultrasonographic estimation between 6 and 24 weeks of gestational age, inability to complete the oral glucose-tolerance test within 32 weeks of gestation, multiple pregnancy, conception by means of gonadotropin ovulation induction or in vitro fertilization, glucose testing before recruitment or a diagnosis of diabetes during the current pregnancy, diagnosis of diabetes before the current pregnancy and requiring treatment with medication, participation in another study that could interfere with the HAPO study, infection with the human immunodeficiency virus or hepatitis B or C virus, previous participation in the HAPO study, or inability to converse in the languages used on center forms without the aid of an interpreter. If glucose measurements were made outside the setting of the HAPO study after initial enrollment, participation was terminated. Age and education level were recorded for women who declined to participate.

Gestational age and expected date of delivery were determined from the date of the last menstrual period, if the date was certain. If the date was uncertain, the expected date of delivery was estimated by means of ultrasonography performed between 6 and 24 weeks of gestation. The final expected date of delivery was also determined with the use of ultrasonography if the gestational age estimated on the basis of the date of the last menstrual period differed by more than 5 days from that based on ultrasonography performed between 6 and 13 weeks of gestation or by more than 10 days from that based on ultrasonography performed between 14 and 24 weeks of gestation.

Oral Glucose-Tolerance Test

Participants underwent a standard oral glucose-tolerance test, with the use of a 75-g dose of glucose, between 24 and 32 weeks of gestation (target time of testing, 28 weeks). Height, weight, and blood pressure were measured at the test visit. Data concerning smoking and alcohol use, history of diabetes and hypertension among first-degree family members, and demographic characteristics were collected by means of standardized questionnaires. Race or ethnic group was self-reported by participants. A blood specimen was collected between 34 and 37 weeks of gestation for evaluation of the random plasma glucose level, as a safety measure to identify cases with hyperglycemia above a predefined threshold.

GLUCOSE ANALYSIS

For purposes of clinical decision making, plasma glucose levels were measured at center laboratories by means of enzymatic methods, with extensive quality control, as previously described.[17] To avoid the confounding effects of analytic variation among centers, aliquots of all oral glucose-tolerance test specimens were analyzed at the central laboratory of the HAPO study, and the results were used in the analyses reported here.

UNBLINDING OF DATA

Fasting and 2-hour specimens from the oral glucose-tolerance tests and the blood specimen taken for determination of the random plasma glucose level were analyzed at center laboratories. The data were unblinded if the 2-hour plasma glucose level was diagnostic of diabetes (i.e., >200 mg per deciliter [11.1 mmol per liter]) or, for ethical and safety reasons, if the fasting plasma glucose level exceeded 105 mg per deciliter (5.8 mmol per liter), the random plasma glucose level was 160 mg per deciliter (8.9 mmol per liter) or more, or any plasma glucose level was less than 45 mg per deciliter (2.5 mmol per liter). Otherwise, women, caregivers, and the staff of the HAPO study (except for laboratory personnel) remained unaware of the glucose values. Only women whose data were blinded and who did not undergo any additional glucose testing outside the HAPO study were included in our analyses.

CORD-BLOOD PLASMA GLUCOSE AND SERUM C-PEPTIDE LEVELS

Cord-blood specimens were collected at delivery for the measurement of serum C-peptide and plasma glucose levels. The specimens were analyzed at the central laboratory with the use of an immunoassay (AutoDELFIA, PerkinElmer) for serum C peptide and a chemical analyzer (Vitros 750, Ortho-Clinical Diagnostics) for plasma glucose.[17] Because approximately 15% of cord-blood samples have detectable hemolysis after serum or plasma is separated out, because hemolysis is known to increase insulin degradation but not to affect C-peptide level,[17] and because C peptide and insulin are secreted in equimolar levels, we used cord-blood serum C-peptide level rather than insulin level as our index of fetal β-cell function.

PRENATAL CARE, DELIVERY, AND NEONATAL CARE

Prenatal care, timing of delivery, and neonatal care were determined by means of the standard practice at each center. No center arbitrarily induced delivery before full term or routinely performed cesarean delivery at a specified maternal or gestational age. Medical records were abstracted to obtain data regarding the prenatal course, labor and delivery, the postpartum course, and the newborn course.

OUTCOMES

Primary and Secondary Outcomes

The four primary outcomes were birth weight above the 90th percentile for gestational age, primary cesarean delivery, clinical neonatal hypoglycemia, and cord-blood serum C-peptide level above the 90th percentile (fetal hyperinsulinemia). Secondary outcomes were premature delivery (before 37 weeks of gestation), shoulder dystocia or birth injury, need for intensive neonatal care, hyperbilirubinemia, and preeclampsia.

Possible Severe Adverse Outcomes

Additional data were abstracted at centers whenever a possible severe adverse event (e.g., death, shoulder dystocia, birth injury, and major malformation) was identified. Data were reviewed by the members of an outcome review committee, who were unaware of the mother's glycemic status, to confirm whether the event was present. Perinatal deaths were classified according to the Australian and New Zealand Antecedent Classification of Perinatal Mortality guidelines,[18] and major malformations were classified according to codes of the *International Classification of Diseases, Tenth Revision*.[19] The HAPO data and safety monitoring committee reviewed data regarding adverse outcomes and deaths after having been made aware of the results of the oral glucose-tolerance test and the random plasma glucose levels.

STATISTICAL ANALYSIS

Mean and standard deviation are reported for continuous variables, and number and percentage are reported for categorical variables. Pearson product-moment correlations were used to assess associations among glucose measures. For associations of glycemia with primary outcomes, as prespecified in the HAPO study protocol, each glucose measurement was considered as both a categorical and a continuous variable in multiple logistic-regression analyses. For secondary outcomes, only results for continuous variables are presented. For categorical analyses, each measure of glycemia was divided into seven categories, such that the

Table 1. Characteristics of the Study Participants and Their Newborns and Frequency of Outcomes.*

Characteristic or Outcome	No. of Participants (%)	Mean ±SD	Range of Means among Centers
Maternal characteristics			
Age (yr)	23,316 (100)	29.2±5.8	25.4–33.6
Body-mass index	23,316 (100)	27.7±5.1	24.4–29.9
Mean arterial pressure (mm Hg)	23,316 (100)	80.9±8.3	75.9–84.1
Plasma glucose (mg/dl)			
Fasting	23,316 (100)	80.9±6.9	78.2–83.7
1 hr	23,316 (100)	134.1±30.9	119.5–148.2
2 hr	23,316 (100)	111.0±23.5	99.6–120.9
Length of gestation at time of OGTT (wk)	23,316 (100)	27.8±1.8	25.9–29.5
Any prenatal smoking — %	1,581 (6.8)		0.2–23.7
Any prenatal alcohol use — %	1,612 (6.9)		0.1–26.5
Family history of diabetes — %	5,282 (22.7)		12.1–37.7
Parity (delivery ≥20 wk) at enrollment	12,233 (52.5)		34.8–68.9
Prenatal urinary tract infection — %	1,655 (7.1)		0.4–22.5
Hospitalization before delivery — %	3,271 (14.0)		2.3–33.2
Newborn characteristics			
Gestational age at delivery (wk)	23,316 (100)	39.4±1.7	38.7–39.9
Birth weight (g)	23,217 (99.6)	3292±529	3109–3526
Cord-blood serum C peptide (μg/liter)	19,885 (85.3)	1.0±0.6	0.9–1.2
Cord-blood plasma glucose (mg/dl)	19,859 (85.2)	81.5±19.6	74.2–90.4
Male sex — %	12,003 (51.5)		49.3–54.0
Obstetrical outcomes			
Cesarean delivery — %			
Primary	3,731 (16.0)		8.6–23.5
Repeat	1,792 (7.7)		3.3–11.8
Hypertension — %†			
Chronic hypertension	582 (2.5)		0.5–9.4
Gestational hypertension	1,370 (5.9)		0.7–17.7
Preeclampsia	1,116 (4.8)		1.4–11.4

1- and 2-hour plasma glucose measures reflected data for approximately the same number of women in each category as did the fasting plasma glucose measure. Categories for the fasting plasma glucose level were originally prespecified in the HAPO study protocol as 100 mg per deciliter (5.6 mmol per liter) or more, 95 to 99 (5.3 to 5.5), 90 to 94 (5.0 to 5.2), 85 to 89 (4.8 to 4.9), and less than 85. Subsequently, the category of less than 85 mg per deciliter was further subdivided into less than 75 mg per deciliter (4.2 mmol per liter), 75 to 79 (4.2 to 4.4), and 80 to 84 (4.5 to 4.7). The highest and second-highest categories for each glucose measure, accounting for 1% and 3% of participants, respectively, were specifically chosen to allow for assessment of whether there were threshold effects.

For continuous-variable analyses, odds ratios were calculated for a 1-SD increase in fasting, 1-hour, and 2-hour plasma glucose levels. As prespecified, to assess whether the log of the odds of each outcome was linearly related to glucose level, we added squared terms for glucose level for each adverse pregnancy outcome to assess whether there were significant quadratic associations. For each outcome, two logistic models were fit.

Table 1. (Continued.)

Characteristic or Outcome	No. of Participants (%)	Mean ±SD	Range of Means among Centers
Newborn outcomes			
Birth weight >90th percentile — %‡	2,221 (9.5)		9.0–9.9
Clinical neonatal hypoglycemia — %§	480 (2.1)		0.3–6.4
Cord-blood serum C peptide >90th percentile — %¶	1,671 (8.4)		5.9–15.1
Premature delivery (before 37 wk) — %	1,608 (6.9)		3.9–9.1
Shoulder dystocia or birth injury	311 (1.3)		0.1–3.4
Intensive neonatal care — %‖	1,855 (8.0)		3.0–28.8
Hyperbilirubinemia — %**	1,930 (8.3)		3.0–25.4

* The body-mass index (the weight in kilograms divided by the square of the height in meters), mean arterial pressure, and glucose levels were obtained at the oral glucose-tolerance test (OGTT). To convert the values for glucose to millimoles per liter, multiply by 0.05551. For additional characteristics of the participants, see Table A in the Supplementary Appendix.

† Chronic hypertension was defined as hypertension that was present before 20 weeks of gestation and that did not progress to preeclampsia. Hypertension disorders occurring during pregnancy after 20 weeks of gestation were categorized according to the International Society for the Study of Hypertension guidelines.[20] Preeclampsia was defined as systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two or more occasions a minimum of 6 hours apart and proteinuria of 1+ or more on a dipstick test or a protein level in the urine of 300 mg or more for a 24-hour period. If the criteria for elevated blood pressure were met but those for proteinuria were not, the hypertension was classified as gestational hypertension.

‡ For birth weight above the 90th percentile, the 90th percentiles for gestational age (30 to 44 weeks only) were determined with the use of quantile regression analyses for each of eight groups of newborns based on infant's sex and race or ethnic group (white or other, black, Hispanic, or Asian), with adjustment for gestational age, field center, and parity (0, 1, or ≥2). A newborn was considered to have a birth weight above the 90th percentile if the birth weight was greater than the estimated 90th percentile for the infant's sex, gestational age, race or ethnic group, field center, and maternal parity. Otherwise, the newborn was considered to have a birth weight at or under the 90th percentile. Birth weights were available for 23,217 newborns.

§ Clinical neonatal hypoglycemia was defined as being present if there was a notation of neonatal hypoglycemia in the medical record and there were symptoms or treatment with a glucose infusion or a local laboratory report of a glucose value of 30.6 mg per deciliter (1.7 mmol per liter) or less in the first 24 hours after birth or 45.0 mg per deciliter (2.5 mmol per liter) or less after the first 24 hours.[21]

¶ A cord-blood serum C-peptide level above the 90th percentile was defined on the basis of the 19,885 newborns for whom data were available.

‖ Intensive neonatal care was defined by admission to any type of unit for care more intensive than normal newborn care and lasting more than 24 hours or by death of the baby or transfer to another hospital. Data were excluded for admissions that were only for possible sepsis or sepsis, observation, or feeding problems.

** Hyperbilirubinemia was defined by treatment with phototherapy after birth, at least one laboratory report of a bilirubin level of 20 mg per deciliter (342 μmol per liter) or more, or readmission for hyperbilirubinemia.

Model I included adjustment for center or the variables used in estimating the 90th percentile for birth weight for gestational age (infant's sex, race or ethnic group, center, and parity). Model II included adjustment for multiple potential prespecified confounders, including age, body-mass index (BMI), smoking status, alcohol use, presence or absence of a family history of diabetes, gestational age at the oral glucose-tolerance test, sex of the infant, parity (0, 1, or ≥2, except for primary cesarean deliveries), mean arterial pressure and presence or absence of hospitalization before delivery (except for preeclampsia), and presence or absence of a family history of hypertension and maternal urinary tract infection (for analysis of preeclampsia only). Height was also included as a potential confounder, on the basis of post hoc findings of an association with birth weight greater than the 90th percentile, and two prespecified confounders (maternal urinary tract infection and previous prenatal death) were excluded from primary and secondary outcome analyses when neither was found to be related to any primary outcome or to affect primary outcome–glucose associations. Squared terms for age, BMI, and mean arterial pressure were prescreened for possible inclusion in model II adjustment when only the center had been included (i.e., models without glucose or other covariates); these terms were included in model II when significant. Only

the fully adjusted model results are presented in this report. (Results for all models are given in Tables B through F in the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

In post hoc analyses, we tested for interactions of each glucose measure with center in models I and II (except with regard to the outcomes of clinical neonatal hypoglycemia and shoulder dystocia or birth injury, owing to small numbers in some centers [a total of 42 tests]). We also tested for interactions of each glucose measure with BMI, age, height, and mean arterial pressure in model II (105 tests). P values less than 0.001 were considered to indicate statistical significance for squared terms for glucose, age, BMI, and mean arterial pressure and interaction terms for all outcomes, except neonatal hypoglycemia and shoulder dystocia or birth injury, for which P values less than 0.05 were considered to indicate statistical significance, owing to the smaller numbers of babies with these outcomes.

All analyses were conducted in SAS version 9.1 or Stata 10.0. All reported P values are two-sided and were not adjusted for multiple testing.

RESULTS

PARTICIPANTS

Among 53,295 eligible women (from 15 centers in nine countries; see the Appendix), 28,562 (53.6%) agreed to participate in this blinded study, between July 2000 and April 2006. Among the women who agreed to participate and those who refused to participate, the mean age and years of education were 29.0 and 12.9 years and 28.5 and 12.5 years, respectively. A total of 25,505 women completed an oral glucose-tolerance test: 746 (2.9%) were excluded because their data were unblinded, 1412 (5.5%) were excluded primarily because they had undergone glucose testing or delivery outside the context of the HAPO study, and 31 (0.1%) were excluded owing to missing key data or an implausible gestational age (>44 weeks); data from the remaining 23,316 were available for analyses. Of these 23,316 patients, 48.3% were self-reported to be white, 11.6% to be black, 8.5% to be Hispanic, 29.0% to be "Asian or Oriental," and 2.6% to be of other races or ethnic groups.

Characteristics of the mothers and newborns and pregnancy outcomes are summarized in Table 1. The mean age of participants was 29.2 years, and the mean fasting, 1-hour, and 2-hour plasma glucose levels were 80.9 mg per deciliter (4.5 mmol per liter), 134.1 mg per deciliter (7.4 mmol per liter), and 111.0 mg per deciliter (6.2 mmol per liter), respectively. Correlations among these three glucose measures were as follows: 0.38 for the fasting plasma glucose level and the 1-hour plasma glucose level, 0.30 for the fasting plasma glucose level and the 2-hour plasma glucose level, and 0.68 for the 1-hour plasma glucose level and the 2-hour plasma glucose level (P<0.001 for all three comparisons). There were 2 maternal deaths (1 due to pulmonary embolism, the other due to respiratory failure secondary to pneumonia), 14 cases of eclampsia, 321 cases of major malformation of the newborn, and 130 perinatal deaths (89 fetal and 41 neonatal or infant) (incidence, 5.6 per 1000) among the 23,316 deliveries.

GLYCEMIA AND PREGNANCY OUTCOMES

Categorical Analyses

The frequency of each primary outcome across the seven glucose categories is shown in Figure 1. With increasing maternal glucose levels, the frequency of each primary outcome increased, although less so for clinical neonatal hypoglycemia than for the other outcomes. For example, for the fasting plasma glucose level, frequencies in the lowest and highest categories, respectively, were 5.3% and 26.3% for birth weight above the 90th percentile, 13.3% and 27.9% for primary cesarean section, 2.1% and 4.6% for clinical neonatal hypoglycemia, and 3.7% and 32.4% for C-peptide level above the 90th percentile.

Table 2 shows the associations of maternal glucose as a categorical variable with each primary outcome, including odds ratios and 95% confidence intervals for each category, as compared with the lowest category, with adjustment for confounders. There were strong associations with birth weight above the 90th percentile that increased across the increasing glycemia categories. Differences in mean birth weight between the lowest and highest categories of the fasting, 1-hour, and 2-hour plasma glucose levels were 242 to 305 g when birth weight was modeled as a continuous variable, with adjustment for multiple confounders (data not shown). The odds ratio for primary cesarean section increased across categories of maternal glycemia and was 1.86 in the highest category of 1-hour plasma glucose; the odds ratio in the highest category of 2-hour plasma

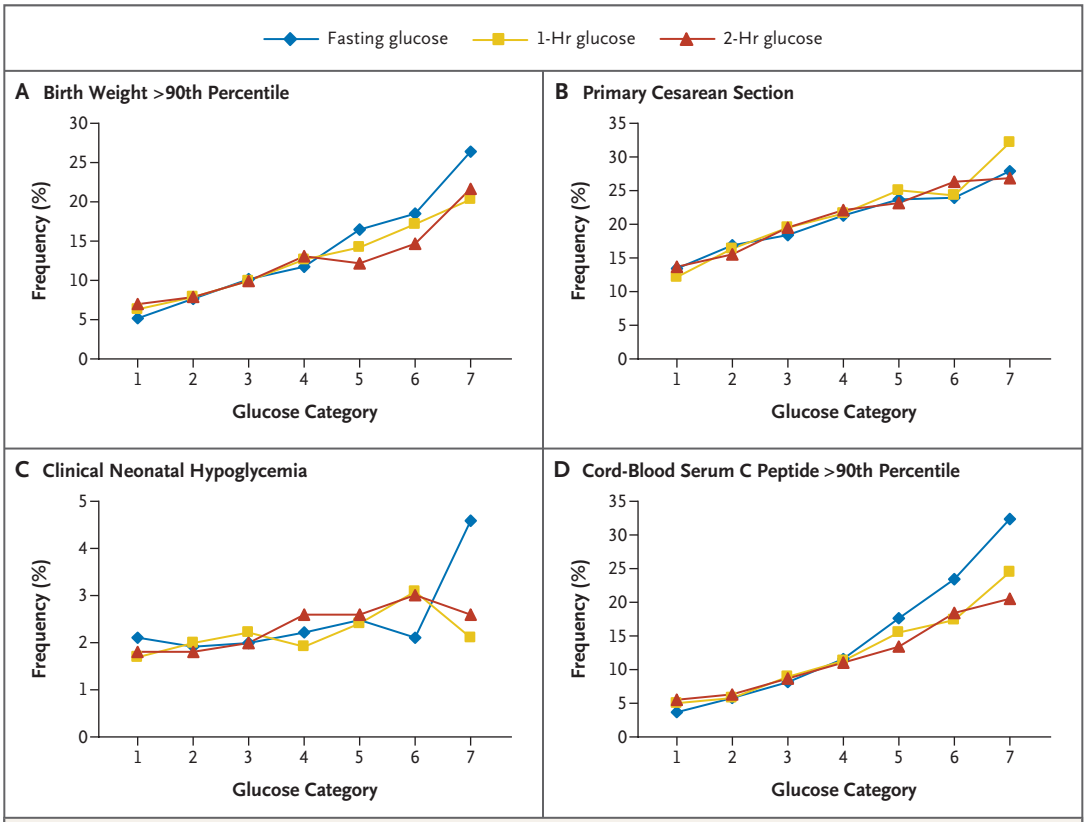

Figure 1. Frequency of Primary Outcomes across the Glucose Categories.

Glucose categories are defined as follows: fasting plasma glucose level — category 1, less than 75 mg per deciliter (4.2 mmol per liter); category 2, 75 to 79 mg per deciliter (4.2 to 4.4 mmol per liter); category 3, 80 to 84 mg per deciliter (4.5 to 4.7 mmol per liter); category 4, 85 to 89 mg per deciliter (4.8 to 4.9 mmol per liter); category 5, 90 to 94 mg per deciliter (5.0 to 5.2 mmol per liter); category 6, 95 to 99 mg per deciliter (5.3 to 5.5 mmol per liter); and category 7, 100 mg per deciliter (5.6 mmol per liter) or more; 1-hour plasma glucose level — category 1, 105 mg per deciliter (5.8 mmol per liter) or less; category 2, 106 to 132 mg per deciliter (5.9 to 7.3 mmol per liter); category 3, 133 to 155 mg per deciliter (7.4 to 8.6 mmol per liter); category 4, 156 to 171 mg per deciliter (8.7 to 9.5 mmol per liter); category 5, 172 to 193 mg per deciliter (9.6 to 10.7 mmol per liter); category 6, 194 to 211 mg per deciliter (10.8 to 11.7 mmol per liter); and category 7, 212 mg per deciliter (11.8 mmol per liter) or more; and 2-hr plasma glucose level — category 1, 90 mg per deciliter (5.0 mmol per liter) or less; category 2, 91 to 108 mg per deciliter (5.1 to 6.0 mmol per liter); category 3, 109 to 125 mg per deciliter (6.1 to 6.9 mmol per liter); category 4, 126 to 139 mg per deciliter (7.0 to 7.7 mmol per liter); category 5, 140 to 157 mg per deciliter (7.8 to 8.7 mmol per liter); category 6, 158 to 177 mg per deciliter (8.8 to 9.8 mmol per liter); and category 7, 178 mg per deciliter (9.9 mmol per liter) or more.

glucose did not differ significantly from 1.00. The adjusted odds ratios for clinical neonatal hypoglycemia were substantially attenuated, and none of the odds ratios for the highest glucose categories were significantly different from 1.00. After adjustment for confounders, there was a strong association between cord-blood serum C-peptide level above the 90th percentile and maternal glycemia, with the association increasing with increasing glycemia category; the odds ratio was 7.65 (95% confidence interval [CI], 5.17 to 11.32) for the highest category of the fasting plasma glucose.

Continuous Analyses

Results for analyses of glucose level as a continuous variable, with model II adjustment for both primary and secondary outcomes, are shown in Table 3. Among the primary outcomes, odds ratios for an increase in the glucose level by 1 SD were highest for birth weight greater than the 90th percentile (range, 1.38 to 1.46) and cord-blood serum C-peptide level above the 90th percentile (range, 1.37 to 1.55). For primary cesarean section and clinical neonatal hypoglycemia, the associations were weaker and the associations of

Table 2. Adjusted Odds Ratios for Associations between Maternal Glucose as a Categorical Variable and Primary Outcomes.*

Glucose Category†	Plasma Glucose Level					
	Fasting		At 1 Hr		At 2 Hr	
	total no. (no. with outcome)	*odds ratio (95% CI)*	*total no. (no. with outcome)*	*odds ratio (95% CI)*	*total no. (no. with outcome)*	*odds ratio (95% CI)*
Birth weight >90th percentile						
1	4035 (213)	1.00	4177 (268)	1.00	4264 (297)	1.00
2	7501 (572)	1.37 (1.16–1.62)	7524 (584)	1.21 (1.04–1.41)	7422 (587)	1.11 (0.96–1.30)
3	6168 (622)	1.72 (1.46–2.03)	6003 (593)	1.65 (1.41–1.93)	5865 (580)	1.51 (1.30–1.75)
4	2741 (323)	1.95 (1.62–2.35)	2768 (352)	2.27 (1.91–2.71)	3024 (396)	2.15 (1.82–2.54)
5	1883 (310)	2.73 (2.25–3.31)	1858 (264)	2.66 (2.19–3.21)	1720 (210)	2.10 (1.73–2.56)
6	672 (124)	3.00 (2.34–3.86)	645 (111)	3.50 (2.72–4.50)	690 (101)	2.68 (2.08–3.45)
7	217 (57)	5.01 (3.54–7.09)	242 (49)	4.49 (3.16–6.39)	232 (50)	4.46 (3.15–6.33)
Primary cesarean section‡						
1	3721 (495)	1.00	3826 (458)	1.00	3903 (535)	1.00
2	6806 (1151)	1.19 (1.06–1.34)	6792 (1113)	1.21 (1.07–1.36)	6664 (1032)	0.97 (0.86–1.09)
3	5483 (1014)	1.21 (1.07–1.37)	5311 (1032)	1.26 (1.11–1.42)	5201 (1017)	1.11 (0.99–1.26)
4	2378 (506)	1.33 (1.15–1.54)	2425 (522)	1.31 (1.13–1.52)	2650 (583)	1.15 (1.00–1.32)
5	1601 (380)	1.44 (1.23–1.69)	1623 (407)	1.48 (1.26–1.74)	1506 (350)	1.17 (0.99–1.37)
6	560 (134)	1.39 (1.11–1.75)	547 (132)	1.30 (1.04–1.64)	615 (162)	1.32 (1.08–1.63)
7	183 (51)	1.60 (1.12–2.27)	208 (67)	1.86 (1.35–2.57)	193 (52)	1.28 (0.91–1.81)
Clinical neonatal hypoglycemia						
1	4043 (83)	1.00	4183 (72)	1.00	4266 (78)	1.00
2	7503 (144)	0.91 (0.69–1.21)	7523 (153)	1.12 (0.84–1.49)	7421 (134)	0.87 (0.66–1.17)
3	6164 (122)	0.92 (0.68–1.23)	6003 (131)	1.24 (0.92–1.68)	5868 (117)	0.96 (0.71–1.30)
4	2744 (59)	1.00 (0.70–1.43)	2772 (54)	1.11 (0.77–1.62)	3027 (80)	1.23 (0.88–1.71)
5	1884 (48)	1.19 (0.81–1.75)	1860 (45)	1.48 (0.99–2.22)	1720 (44)	1.13 (0.76–1.68)
6	672 (14)	1.01 (0.55–1.84)	643 (20)	2.17 (1.28–3.69)	693 (21)	1.36 (0.81–2.28)
7	217 (10)	1.98 (0.97–4.05)	243 (5)	1.29 (0.51–3.31)	232 (6)	1.12 (0.47–2.67)

clinical neonatal hypoglycemia with the fasting plasma glucose level and the 2-hour plasma glucose level were not significant.

Twelve of the 15 analyses of secondary outcomes showed significant positive associations with maternal glycemia, after adjustment for confounders (Table 3). The strongest associations were found for preeclampsia, for which the odds ratio for each 1-SD increase in each glucose measure ranged from 1.21 to 1.28; corresponding odds ratios for shoulder dystocia or birth injury were approximately 1.20. Premature delivery, intensive neonatal care, and hyperbilirubinemia were significantly related to the 1-hour and 2-hour plasma glucose levels but not to the fasting plasma glucose level.

The only significant quadratic (nonlinear) association found in these analyses was for the fasting plasma glucose level with clinical neonatal hypoglycemia ($P=0.01$). Among the 147 tests for interactions, 7 were significant: the fasting plasma glucose level with field center, in relation to primary cesarean delivery, in both models I and II ($P<0.001$); age with the fasting, 1-hour, and 2-hour plasma glucose levels, with regard to clinical neonatal hypoglycemia ($P=0.05$, $P=0.03$, and $P=0.001$, respectively); BMI and 1-hour plasma glucose level, for clinical neonatal hypoglycemia ($P<0.001$); and mean arterial pressure with fasting plasma glucose level, for premature delivery ($P<0.001$).

We also examined associations of glucose measures with birth weight below the 10th percentile for gestational age, using the same methods to estimate the 10th percentiles as were used to es-

Table 2. (Continued.)

Glucose Category†	Plasma Glucose Level					
	Fasting		1 Hr		2 Hr	
	total no. (no. with outcome)	*odds ratio (95% CI)*	*total no. (no. with outcome)*	*odds ratio (95% CI)*	*total no. (no. with outcome)*	*odds ratio (95% CI)*
Cord-blood serum C peptide >90th percentile						
1	3546 (131)	1.00	3593 (176)	1.00	3599 (193)	1.00
2	6453 (378)	1.41 (1.15–1.74)	6372 (366)	1.07 (0.88–1.29)	6353 (401)	1.06 (0.88–1.27)
3	5255 (429)	1.75 (1.42–2.15)	5132 (458)	1.62 (1.34–1.95)	5039 (440)	1.44 (1.20–1.73)
4	2308 (266)	2.36 (1.88–2.97)	2424 (274)	1.95 (1.58–2.41)	2609 (286)	1.72 (1.40–2.11)
5	1592 (181)	3.62 (2.87–4.58)	1607 (251)	2.76 (2.21–3.43)	1495 (202)	2.21 (1.77–2.76)
6	561 (131)	4.46 (3.36–5.93)	549 (95)	2.91 (2.18–3.89)	596 (109)	2.86 (2.18–3.77)
7	170 (55)	7.65 (5.17–11.32)	208 (51)	4.65 (3.19–6.79)	194 (40)	3.48 (2.33–5.21)

* Associations were adjusted for the following variables: field center, age, body-mass index, height, smoking status, alcohol use, presence or absence of family history of diabetes, gestational age at oral glucose-tolerance test, infant's sex, presence or absence of hospitalization before delivery, mean arterial pressure (in all models), parity (0, 1, or ≥2; not included in the model for primary cesarean delivery), cord-blood plasma glucose level (included in the model for cord-blood serum C-peptide level >90th percentile only). Additional details are shown in Tables B, C, D, and E in the Supplementary Appendix.

† Glucose categories are defined as follows: fasting plasma glucose level — category 1, less than 75 mg per deciliter (4.2 mmol per liter); category 2, 75 to 79 mg per deciliter (4.2 to 4.4 mmol per liter); category 3, 80 to 84 mg per deciliter (4.5 to 4.7 mmol per liter); category 4, 85 to 89 mg per deciliter (4.8 to 4.9 mmol per liter); category 5, 90 to 94 mg per deciliter (5.0 to 5.2 mmol per liter); category 6, 95 to 99 mg per deciliter (5.3 to 5.5 mmol per liter); and category 7, 100 mg per deciliter (5.6 mmol per liter) or more; 1-hour plasma glucose level — category 1, 105 mg per deciliter (5.8 mmol per liter) or less; category 2, 106 to 132 mg per deciliter (5.9 to 7.3 mmol per liter); category 3, 133 to 155 mg per deciliter (7.4 to 8.6 mmol per liter); category 4, 156 to 171 mg per deciliter (8.7 to 9.5 mmol per liter); category 5, 172 to 193 mg per deciliter (9.6 to 10.7 mmol per liter); category 6, 194 to 211 mg per deciliter (10.8 to 11.7 mmol per liter); and category 7, 212 mg per deciliter (11.8 mmol per liter) or more; and 2-hr plasma glucose level — category 1, 90 mg per deciliter (5.0 mmol per liter) or less; category 2, 91 to 108 mg per deciliter (5.1 to 6.0 mmol per liter); category 3, 109 to 125 mg per deciliter (6.1 to 6.9 mmol per liter); category 4, 126 to 139 mg per deciliter (7.0 to 7.7 mmol per liter); category 5, 140 to 157 mg per deciliter (7.8 to 8.7 mmol per liter); category 6, 158 to 177 mg per deciliter (8.8 to 9.8 mmol per liter); and category 7, 178 mg per deciliter (9.9 mmol per liter) or more.

‡ Data for women who had had a previous cesarean section were excluded.

timate the 90th percentiles (Table 1). In the continuous-variable models, odds ratios for each 1-SD increase in glucose measures ranged from 0.77 to 0.80, with no evidence of nonlinear associations (data not shown) and little difference from the results from unadjusted models.

Although the HAPO study did not have the statistical power to permit examination of perinatal death as a primary outcome, with only 130 deaths, unadjusted analyses showed no increase in the risk of perinatal death with increasing glucose levels. Unadjusted odds ratios for perinatal death for each 1-SD increase in the fasting, 1-hour, and 2-hour plasma glucose levels, respectively, were 0.91 (95% CI, 0.76 to 1.08), 0.93 (95% CI, 0.78 to 1.11), and 0.99 (95% CI, 0.83 to 1.18), with no evidence of nonlinear associations.

DISCUSSION

In 1952, Jorgen Pedersen[22] postulated that maternal hyperglycemia led to fetal hyperglycemia, which evoked an exaggerated fetal response to insulin. Since then, the Pedersen hypothesis has formed the basis for understanding the pathophysiological consequences of diabetes during pregnancy. The objective of the HAPO study was to clarify risks of adverse outcomes associated with degrees of maternal glucose intolerance less severe than overt diabetes mellitus. The data presented here show associations between increasing levels of fasting, 1-hour, and 2-hour plasma glucose obtained on oral glucose-tolerance testing and birth weight above the 90th percentile and cord-blood serum C-peptide level above the 90th percentile, with weaker associations between glucose levels and primary cesarean delivery and clinical neonatal hypoglycemia. We also found positive associations between increasing plasma glucose levels and each of the five secondary outcomes examined: premature delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia, and preeclampsia.

Associations between maternal glycemia and

Table 3. Adjusted Odds Ratios for Associations between Maternal Glycemia as a Continuous Variable and Primary and Secondary Perinatal Outcomes.*

Outcome	Plasma Glucose Level		
	Fasting	At 1 Hr	At 2 Hr
	odds ratio (95% CI)		
Primary outcome			
Birth weight >90th percentile	1.38 (1.32–1.44)	1.46 (1.39–1.53)	1.38 (1.32–1.44)
Primary cesarean section†	1.11 (1.06–1.15)	1.10 (1.06–1.15)	1.08 (1.03–1.12)
Clinical neonatal hypoglycemia	1.08 (0.98–1.19)‡	1.13 (1.03–1.26)	1.10 (1.00–1.12)
Cord-blood serum C peptide >90th percentile	1.55 (1.47–1.64)	1.46 (1.38–1.54)	1.37 (1.30–1.44)
Secondary outcome			
Premature delivery (before 37 wk)	1.05 (0.99–1.11)	1.18 (1.12–1.25)	1.16 (1.10–1.23)
Shoulder dystocia or birth injury	1.18 (1.04–1.33)	1.23 (1.09–1.38)	1.22 (1.09–1.37)
Intensive neonatal care	0.99 (0.94–1.05)	1.07 (1.02–1.13)	1.09 (1.03–1.14)
Hyperbilirubinemia	1.00 (0.95–1.05)	1.11 (1.05–1.17)	1.08 (1.02–1.13)
Preeclampsia	1.21 (1.13–1.29)	1.28 (1.20–1.37)	1.28 (1.20–1.37)

* Odds ratios were for an increase in the glucose level of 1 SD (6.9 mg per deciliter [0.4 mmol per liter] for the fasting plasma glucose level, 30.9 mg per deciliter [1.7 mmol per liter] for the 1-hr plasma glucose level, and 23.5 mg per deciliter [1.3 mmol per liter] for the 2-hr plasma glucose level). The model for preeclampsia did not include adjustment for hospitalization or mean arterial pressure, and presence or absence of family history of hypertension or prenatal urinary tract infection was included in the model for preeclampsia only. See Table 2 for other details about adjustments in each model.
† Data for women who had had a previous cesarean section were excluded.
‡ The P value for the quadratic (nonlinear) association was 0.013.

adverse outcomes generally remained significant after adjustment for multiple potential confounders — 10 of 12 associations for primary outcomes and 12 of 15 for secondary outcomes — and were generally consistent across centers, except the association for the fasting plasma glucose level and primary cesarean delivery. Furthermore, findings with respect to cord-blood serum C-peptide levels, and hence fetal insulin levels, support Pedersen's proposed mechanism to explain the propensity for excessive growth in fetuses of mothers with hyperglycemia. When associations between maternal glucose level and birth weight were estimated with the use of birth weight as a continuous variable, the difference in mean birth weight between the lowest and highest glucose categories was in the range of 240 to 300 g, even after full adjustment for potential confounders.

Two primary outcomes — birth weight above the 90th percentile and cord-blood serum C-peptide level above the 90th percentile — though strongly associated with maternal glycemia, could be viewed as physiological consequences of maternal glycemia rather than as true disorders or problems. However, the other two primary outcomes (primary cesarean delivery and clinical neonatal hypoglycemia) and the five secondary outcomes reported (premature delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia, and preeclampsia) also showed continuous linear associations with the 1-hour plasma glucose level (seven analyses), the 2-hour plasma glucose level (six analyses), and the fasting plasma glucose level (three analyses). These are well-recognized complications of pregnancies in mothers with preexisting or gestational diabetes, as currently defined.

Questions have been raised regarding the benefits of treating "mild" gestational diabetes mellitus.[13,23,24] However, one recently published randomized clinical trial, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), found reduced perinatal morbidity and mortality when standard contemporary treatment of gestational diabetes mellitus was compared with no intervention[25]; another study on treatment of "mild" gestational diabetes mellitus is ongoing.[26] Taken together, the current results and results of the ACHOIS trial[25] indicate that maternal hyperglycemia less severe than that used to define overt diabetes is related to clinically important perinatal disorders or problems and that their

effects can be reduced by means of treatment, although a threshold for the need for treatment is not established.

The individual measures from the oral glucose-tolerance tests were not highly correlated, and no single measure was clearly superior in predicting the primary outcomes. When adjusted for potential confounders, relative increases in each glucose measure were similarly predictive of birth weight above the 90th percentile. When the glucose measures were analyzed as continuous variables, each was a significant predictor of primary cesarean delivery, with 1-SD increases in glucose level being associated with an increase of 8 to 11% in the odds of delivery by cesarean section. Clinical neonatal hypoglycemia was infrequent (overall incidence, 2.1%), and when adjusted for confounders, only the 1-hour plasma glucose level remained a significant predictor of this outcome. All three measures of plasma glucose were highly predictive of cord-blood serum C-peptide values, with the fasting plasma glucose level being the strongest predictor.

Our study had some limitations. The nutritional status and gestational weight gain of the participants could affect fetal growth and other perinatal outcomes; we do not have data on these variables. Some confounders, such as previous gestational diabetes mellitus, maternal BMI, or previous macrosomia, may have influenced clinical decisions such as the choice of route of delivery. Because of the observational design of our study, we cannot conclude that maternal glycemia is causally related to the adverse outcomes observed; however, such a relationship is plausible. Although the rate of participation in this blinded study was 54%, we believe this is unlikely to materially affect our estimates of associations. Differences in age and education level were small between those who agreed to participate and those who did not.

The broad inclusion criteria, the large number and the geographic distribution of centers involved, and the similarity across centers in the associations we found between maternal glycemia and outcomes provide support that our results can be generalized to develop outcome-based criteria for classifying glucose metabolism in pregnancy that can be applied worldwide. Lack of clear thresholds for risk and the fact that the four primary outcomes are not necessarily of equal clinical importance make direct translation of our results into clinical practice challenging. However, our findings of significant associations between adverse outcomes and higher levels of maternal glucose within what is currently considered a nondiabetic range indicate the need to reconsider current criteria for diagnosing and treating hyperglycemia during pregnancy.

Supported by grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Diabetes and Digestive and Kidney Diseases (R01-HD34242 and R01-HD34243); the National Center for Research Resources (M01-RR00048 and M01-RR00080); and the American Diabetes Association; and grants to local field centers from Diabetes UK (RD04/0002756), Kaiser Permanente Medical Center, KK Women's and Children's Hospital, Mater Mother's Hospital, Novo Nordisk, the Myre Sim Fund of the Royal College of Physicians of Edinburgh, and the Howard and Carol Bernick Family Foundation.

Dr. Metzger reports receiving an educational grant from Novo Nordisk; Dr. Hadden, an honorarium from Novo Nordisk; Dr. McCance, an honorarium from Takeda; and Dr. Persson, honoraria from Novo Nordisk. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The members of the HAPO Study Cooperative Research Group were as follows: **North American Field Centers —** *Kaiser Foundation Hospital, Bellflower, CA:* M. Contreras, D.A. Sacks, W. Watson (deceased); *Prentice Women's Hospital of Northwestern Memorial Hospital–Northwestern University Feinberg School of Medicine, Chicago:* S.L. Dooley, M. Foderaro, C. Niznik; *MetroHealth Medical Center–Case Western Reserve University, Cleveland:* J. Bjaloncik, P.M. Catalano, L. Dierker, S. Fox, L. Gullion, C. Johnson, C.A. Lindsay, H. Makovos, F. Saker; *Women and Infants' Hospital of Rhode Island–Brown University Medical School, Providence:* M.W. Carpenter, J. Hunt, M.H. Somers; *Sunnybrook and Women's College Health Sciences Centre–University of Toronto, Toronto:* K.S. Amankwah, P.C. Chan, B. Gherson, E. Herer, B. Kapur, A. Kenshole, G. Lawrence, K. Matheson, L. Mayes, K. McLean, H. Owen; **European–Caribbean Field Centers —** *Queen Elizabeth Hospital–School of Clinical Medicine and Research, University of the West Indies, Barbados:* C. Cave, G. Fenty, E. Gibson, A. Hennis, G. McIntyre, Y.E. Rotchell, C. Spooner, H.A.R. Thomas; *Royal Jubilee Maternity Hospital, Belfast, Northern Ireland:* J. Gluck, D.R. Hadden, H. Halliday, J. Irwin, O. Kearney, J. McAnee, D.R. McCance, M. Mousavi, A.I. Traub; *St. Mary's Hospital–Manchester University, Manchester, United Kingdom:* J.K. Cruickshank, N. Derbyshire, J. Dry, A.C. Holt, F. Khan, C. Lambert, M. Maresh, F. Prichard, C. Townson; *University Hospital–University Medical Center Utrecht, Utrecht, the Netherlands:* T.W. van Haeften, A.M.R. van de Hengel, G.H.A. Visser, A. Zwart; **Middle Eastern–Asian Field Centers —** *Rajavithi Hospital, Bangkok, Thailand:* U. Chaovarindr, U. Chotigeat, C. Deerochanawong, I. Panyasiri, P. Sanguanpong; *Soroka Medical Center–Ben-Gurion University, Beersheba, Israel:* D. Amichay, A. Golan, K. Marks, M. Mazor, J. Ronen, A. Wiznitzer; *Helen Schneider Hospital for Women, Rabin Medical Center–Sackler Faculty of Medicine, Tel-Aviv University, Petah-Tiqva, Israel:* R. Chen, D. Harel, N. Hoter, N. Melamed, J. Pardo, M. Witshner, Y. Yogev; **Australasian Field Centers —** *Mater Misericordiae Mothers' Hospital–University of Queensland, Brisbane, Australia:* F. Bowling, D. Cowley, P. Devenish-Meares, H.G. Liley, A. McArdle, H.D. McIntyre, B. Morrison, A. Peacock, A. Tremellen, D. Tudehope; *Prince of Wales Hospital–Chinese University of Hong Kong, Hong Kong:* K.Y. Chan, N.Y. Chan, L.W. Ip, S.L. Kong, Y.L. Lee, C.Y. Li, K.F. Ng, P.C. Ng, M.S. Rogers, K.W. Wong; *John Hunter Hospital, Newcastle, Australia:* M. Edgar, W. Giles, A. Gill, R. Glover, J. Lowe, F. Mackenzie, K. Siech, J. Verma, A. Wright; *KK Women's and Children's Hospital, Singapore City, Singapore:* Y.H. Cao, J.J. Chee, A. Koh, E. Tan, V.J. Rajadurai, H.Y. Wee,

G.S.H. Yeo; **Regional Centers —** *Providence, RI:* D. Coustan, B. Haydon; *Belfast, Northern Ireland:* A. Alexander, D.R. Hadden; *Petah-Tiqva, Israel:* O. Attias-Raved, M. Hod; *Brisbane, Australia:* J.J.N. Oats, A.F. Parry; **Clinical Coordinating Center —** *Northwestern University Feinberg School of Medicine, Chicago:* A. Collard, A.S. Frank, L.P. Lowe, B.E. Metzger, A. Thomas; **Data Coordinating Center —** *Northwestern University Feinberg School of Medicine, Chicago:* T. Case, P. Cholod, A.R. Dyer, L. Engelman, M. Xiao, L. Yang; **Central Laboratory —** *Queen's University Belfast, Belfast, Northern Ireland:* C.I. Burgess, T.R.J. Lappin, G.S. Nesbitt, B. Sheridan, M. Smye, E.R. Trimble; **Steering Committee —** *Providence, RI:* D. Coustan; *Chicago:* A.R. Dyer; *Belfast, Northern Ireland:* D.R. Hadden; *Petah-Tiqva, Israel:* M. Hod; *Chicago:* B.E. Metzger, L.P. Lowe (ex officio); *Brisbane, Australia:* J.J.N. Oats; *Stockholm:* B. Persson; *Belfast, Northern Ireland:* E.R. Trimble; **Data and Safety Monitoring Committee —** G.R. Cutter, S.G. Gabbe, J.W. Hare, L.E. Wagenknecht; **Consultants —** Y. Chen, J. Claman, J. King.

REFERENCES

1. American Diabetes Association. Clinical practice recommendations 2001: gestational diabetes mellitus. Diabetes Care 2001;24:Suppl 1:S77-S79.
2. Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 1998;21:Suppl 2:B161-B167.
3. O'Sullivan JB, Mahan C. Criteria for oral glucose tolerance test in pregnancy. Diabetes 1964;13:278-85.
4. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 2007;30:Suppl 2: S251-S260. [Erratum, Diabetes Care 2007; 30:3154.]
5. WHO Expert Committee on Diabetes Mellitus: second report. World Health Organ Tech Rep Ser 1980;646:1-80.
6. Jensen DM, Damm P, Sorensen B, et al. Clinical impact of mild carbohydrate intolerance in pregnancy: a study of 2904 nondiabetic Danish women with risk factors for gestational diabetes. Am J Obstet Gynecol 2001;185:413-9.
7. Yang X, Hsu-Hage B, Zhang H, Zhang C, Zhang Y, Zhang C. Women with impaired glucose tolerance during pregnancy have significantly poor pregnancy outcomes. Diabetes Care 2002;25:1619-24.
8. Vambergue A, Nuttens MC, Verier-Mine O, Dognin C, Cappoen JP, Fontaine P. Is mild gestational hyperglycemia associated with maternal and neonatal complications? The Diagest Study. Diabet Med 2000;17:203-8.
9. Langer O, Brustman L, Anyaegbunam A, Mazze R. The significance of one abnormal glucose tolerance test value on adverse outcome in pregnancy. Am J Obstet Gynecol 1987;157:758-63.
10. Sacks DA, Greenspoon JS, Abu-Fadil S, Henry HM, Wolde-Tsadik G, Yao JFF. Toward universal criteria for gestational diabetes: the 75-gram glucose tolerance test in pregnancy. Am J Obstet Gynecol 1995;172:607-14.
11. Sermer M, Naylor CD, Gare DJ, et al. Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without gestational diabetes. Am J Obstet Gynecol 1995;173:146-56.
12. Jarrett RJ. Reflections on gestational diabetes mellitus. Lancet 1981;2:1220-1.
13. Hunter DJS, Keirse MJNC. Gestational diabetes. In: Chalmers I, Enkin M, Kierse M, eds. Effective care in pregnancy and childbirth. Oxford, England: Oxford University Press, 1989:403-10.
14. Spellacy WN, Miller S, Winegar A, Peterson PQ. Macrosomia: maternal characteristics and infant complications. Obstet Gynecol 1985;66:158-61.
15. Coustan DR. Management of gestational diabetes: a self-fulfilling prophecy? JAMA 1996;275:1199-200.
16. HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Int J Gynecol Obstet 2002;78:69-77.
17. HAPO Study Cooperative Research Group, Nesbitt GS, Smye M, Sheridan B, Lappin TR, Trimble ER. 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.
18. Chan A, King JF, Flenady V, Haslam R, Tudehope D. Classification of perinatal deaths: development of the Australian and New Zealand classifications. J Paediatr Child Health 2004;40:340-7.
19. International statistical classification of diseases and related health problems, 10th revision: ICD-10. Geneva: World Health Organization, 1992.
20. 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.
21. 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;23:115-9.
22. Pedersen J. Diabetes and pregnancy: blood sugar of newborn infants. (Ph.D. thesis. Copenhagen: Danish Science Press, 1952:230.)
23. Brody SC, Harris RH, Whitener BL, et al. Screening for gestational diabetes: systematic evidence review. Rockville, MD: Agency for Healthcare Research and Quality, 2003.
24. Tuffnell DJ, West J, Walkinshaw SA. Treatments for gestational diabetes and impaired glucose tolerance in pregnancy. Cochrane Database Syst Rev 2003;3: CD003395.
25. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes on pregnancy outcomes. N Engl J Med 2005;352:2477-86.
26. Landon MB, Thom E, Spong CY, et al. The National Institute of Child Health and Human Development Maternal-Fetal Medicine Unit Network randomized clinical trial in progress: standard therapy versus no therapy for mild gestational diabetes. Diabetes Care 2007;30:Suppl 2: S194-S199.