Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: An Overview

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2.1 Rationale for the HAPO Study

Gestational diabetes mellitus (GDM), defined as "glucose intolerance with onset or first recognition during pregnancy"[1, 2] has been the subject of considerable controversy. The initial criteria for the diagnosis of GDM that were established more than 40 years ago[3] remain in use today, with only minor modifications. The criteria were chosen to identify women at high risk for the development of diabetes following pregnancy,[4] or were derived from adaptation of criteria used for non-pregnant persons,[5] not to identify pregnant women at increased risk for adverse perinatal outcome. There is consensus that overt diabetes mellitus (DM) during pregnancy, whether or not accompanied by symptoms or signs of metabolic decompensation, is associated with a significant risk of adverse perinatal outcome; the risk of such outcomes associated with degrees of hyperglycemia less severe than overt DM is controversial. A number of factors contribute to this longstanding controversy.

The lack of international uniformity in the approach to ascertainment and diagnosis of GDM has been a major hurdle.[2] Some have attributed the risk of adverse outcomes associated with GDM to confounding characteristics such as obesity, advanced maternal age of subjects with GDM, or other medical complications, rather than glucose intolerance.[6–8] Bias of the caregiver toward the expectation of adverse outcomes may increase the likelihood of morbidity due to increased intervention.[9] Other reports suggest that the criteria currently used for the diagnosis of GDM[1] are too restrictive and that lesser degrees of hyperglycemia increase the risk of adverse perinatal outcomes.[10–15] Conversely, others believe that all systematic efforts to identify the condition should be stopped unless more data become available to link significant morbidities to specific degrees of glucose intolerance.[7] Finally, questions have been raised regarding the benefit of treating GDM. However, two recently reported randomized controlled trials found that treatment, achieved primarily by diet/lifestyle modification, resulted in reduced frequency of large-for-gestational age

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births and pre-eclampsia.[16,17] Notably, the most recent recommendations of the US Preventive Services Task Force, the UK National Health Service, and the Canadian Task Force on the Periodic Health Examination assert that there is not sufficient high level evidence to make a recommendation for, or against, screening for GDM.[18–20]

The objective of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study was to clarify the risk of adverse outcome associated with degrees of maternal glucose intolerance less severe than overt DM during pregnancy. Glucose tolerance was measured in a large, heterogeneous, multinational, multicultural, ethnically diverse cohort of women at 24–32 weeks gestation with medical caregivers "blinded" to status of glucose tolerance (except when predefined thresholds were met).[21]

In 1952, Jorgen Pedersen[22] postulated that maternal hyperglycemia led to fetal hyperglycemia that, in turn, evoked an exaggerated fetal insulin response. Fetal hyperinsulinemia was then responsible for the typical diabetic fetopathy such as macrosomia, neonatal hypoglycemia, perinatal trauma, and death. The hypothesis has represented the context in which associations between maternal glycemia and adverse perinatal outcome have been viewed for more than 50 years. In analyzing and reporting the results of the HAPO study, we considered the associations between maternal glycemia and the primary outcomes of increased size at birth, delivery by cesarean section, neonatal hypoglycemia and the presence of fetal hyperinsulinism within the framework of the Pedersen Hypothesis. Additional outcomes in HAPO included preterm delivery, shoulder dystocia and/or birth injury, sum of skinfolds >90th percentile, percent body fat >90th percentile, intensive neonatal care, hyperbilirubinemia, and pre-eclampsia.

2.2 Design of the HAPO Study

2.2.1 Participants and Exclusion Criteria

Participants were enrolled between July 2000 and April 2006. All pregnant women at each of 15 field centers in nine countries were eligible to participate unless they had one or more of the following exclusion criteria: age less than 18 years, planned delivery at a non-field center hospital, date of last menstrual period (LMP) not certain and no ultrasound (US) estimation from 6 to 24 weeks of gestational age available, unable to complete the oral glucose tolerance test (OGTT) within 32 weeks gestation, multiple pregnancy, conception using gonadotropin ovulation induction or by in vitro fertilization, glucose testing prior to recruitment or a diagnosis of diabetes during this pregnancy, diagnosis of diabetes antedating pregnancy requiring treatment with medication, participation in another study which might 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. Age and education level attained were ascertained for those women who declined to participate in the study.

Gestational age and the expected date of delivery (EDD) were determined from the date of the LMP, if the participant was certain of her dates. If the participant was unsure, the EDD was determined from an US performed between 6 and 24 weeks gestation. The final

EDD was also determined from US if: (1) the gestational dating from LMP differed from the US dating by more than 5 days, when the US was performed between 6 and 13 weeks gestation, or (2) if the dating differed by more than 10 days when the US was done between 14 and 24 weeks gestation.

2.2.2 Procedures

2.2.2.1 Glucose Testing

Participants underwent a standard 75-g OGTT between 24 and 32 weeks gestation and as close to 28 weeks as possible, following an overnight fast (8–14 h) and after at least 3 days of unrestricted diet and normal physical activity. Height, weight, and blood pressure were measured at the time of the OGTT. Data concerning smoking and use of alcohol during pregnancy, first degree family history of hypertension and/or diabetes, and demographic data were collected using standardized questionnaires. Race/ethnicity was self-identified by participants from a list read to them.

As a safety measure, a sample for random plasma glucose (RPG) was collected at 34–37 weeks gestation to reduce the unlikely possibility that undiagnosed diabetes may have evolved in late gestation. Participants could be retested under the blinded HAPO protocol at any time the managing clinician so requested.

2.2.2.2 Glucose Analysis

Glucose concentrations were measured by enzymatic methods on aliquots of plasma. The procedures used to assure comparability of results across the 15 field centers and the Central Laboratory were previously reported.[23] Samples were analyzed at the local field center laboratory for purposes of clinical decision making with respect to blinding or unblinding. To avoid confounding effects of center-to-center analytical variation, aliquots of all OGTT plasma glucose (PG) specimens (fasting, 1-, and 2-h) were analyzed at the Central Laboratory and these results were used in this report. Results subsequently obtained at the Central Laboratory did not reveal any bias in inclusion or exclusion due to methodological variations across the 15 field center laboratories.[23]

2.2.2.3 Unblinding

Aliquots of the fasting and 2-h OGTT plasma samples and the RPG sample were analyzed at the field center laboratory and values were unblinded only if the fasting plasma glucose (FPG) level exceeded 105 mg/dL (5.8 mmol/L), if the 2-h OGTT PG sample exceeded 200 mg/dL (11.1 mmol/L), if the RPG level was greater than or equal to 160 mg/dL

(8.9 mmol/L), or if any PG value was less than 45 mg/dL (2.5 mmol/L). Otherwise, the woman, her caregivers, and HAPO Study staff (except for laboratory personnel) remained blinded to her glucose values. Only women whose results were within these limits, with no additional glucose testing outside the HAPO protocol, were included in these analyses.

2.2.2.4 Prenatal Care and Delivery

Participants received prenatal care according to the usual practice at their field center. The timing of delivery was determined by standard practice for the individual field center. None of the field centers arbitrarily delivered their patients before full term or routinely performed cesarean delivery at a specified maternal or gestational age.

2.2.2.5 Cord Plasma Glucose and Serum C-Peptide Samples

Cord blood was collected at delivery for assessment of fetal β-cell function (C-peptide) and for glucose measurement. The samples were collected as soon as possible after the cord was clamped. The sample for cord PG measurement was placed in a tube containing sodium fluoride and placed in ice water to minimize glycolysis. The samples were separated within 60 min of collection. Aliquots of plasma from the glucose sample and serum from the C-peptide sample were prepared and frozen. These were analyzed at the Central Laboratory. A "Vitros 750" analyzer was used for glucose analysis and serum C-peptide was assayed on an Autodelfia instrument.[23] Fetal hyperinsulinism is typically assessed by measurements of insulin concentration in amniotic fluid or in cord blood serum or plasma. We used cord serum C-peptide (secreted in equimolar concentrations with insulin) as our index rather than insulin for the following reasons: first, insulin degradation is known to be increased in the presence of even small amounts of hemolysis; second, approximately 15% of cord samples show detectable hemolysis when serum or plasma is separated; and third, the concentration of C-peptide is not altered by hemolysis.[23]

2.2.2.6 Neonatal Care and Follow-Up

After delivery, customary routine neonatal care was carried out at each field center. Measurements of neonatal PG were performed at the field center for clinical indications at the discretion of the attending physician, if signs or symptoms suggested sustained or later development of hypoglycemia. Such measurements were performed without blinding in the local field center laboratory using a glucose enzymatic method. The need for other assessments, e.g., bilirubin and status of respiratory function, was determined by clinical indications.

Medical records were abstracted to obtain data regarding the prenatal, labor and delivery, postpartum, and newborn course. A questionnaire was administered to the participant between 4 and 6 weeks after delivery to collect follow-up information, including readmission of the mother or baby to the hospital.

2.2.2.7 Neonatal Anthropometrics

Neonatal anthropometrics were obtained within 72 h of delivery. Anthropometric measurements included weight, length, head circumference, and skinfold thickness at three sites (flank, subscapular, triceps). Two measurements were made; if results differed by more than a pre-specified amount (>10 g for weight, 0.5 cm for length and head circumference, or 0.5 mm for skinfolds, respectively), a third was done. For these analyses, the average of the two measurements was used, unless a third measurement was taken. In that case, if two of three measurements differed by less than the pre-specified amount, the average of those two was used; otherwise the average of all three was used.

Birth weight was obtained without diaper using a calibrated electronic scale. Length was measured on a standardized plastic length board constructed for use in the HAPO study. Head circumference was measured with a standard plastic measuring tape across the occipital fontanel. Skinfold thickness was measured with Harpenden (Baty, UK) skinfold calipers. Flank skinfold was measured on the left side just above the iliac crest on a diagonal fold on the mid axillary line. Triceps measurement was taken at the vertical fold over the triceps muscle half the distance between the acromion process and olecranon, and subscapular just below the lower angle of the scapula at about a 45° angle to the spine.

Mean coefficients of variation for anthropometric measurements were 0.04% for birth weight, 0.17% for length, 0.16% for head circumference, 2.91% for flank skinfold, 2.57% for subscapular skinfold, and 2.73% for triceps skinfold.

2.2.3 Outcomes

2.2.3.1 Primary Outcomes

a. *Birthweight >90th percentile for gestational age*: This was defined based on gender, ethnicity (Caucasian or other, Black, Hispanic, Asian), field center, gestational age (30–44 weeks only), and parity, using separate 90th percentile regression analyses for each of eight HAPO newborn gender-ethnic groups. A newborn was considered to have a birth weight >90th percentile, if the birth weight was greater than the estimated 90th percentile for HAPO newborns of the same gender, gestational age, ethnicity, field center, and maternal parity. Otherwise, the newborn was considered to have a birth weight ≤90th percentile.
b. *Primary cesarean delivery*: A cesarean delivery was defined as primary if it was the woman's first cesarean delivery.
c. *Clinical neonatal hypoglycemia*: Babies were categorized as having clinical neonatal hypoglycemia if the medical record contained a notation of neonatal hypoglycemia and there were symptoms and/or treatment with a glucose infusion or a local laboratory report of a glucose value ≤30.6 mg/dL (1.7 mmol/L) in the first 24 h and/or ≤45 mg/dL (2.5 mmol/L) after the first 24 h.[24]
d. *Hyperinsulinemia*: A cord serum C-peptide value >90th percentile of values for the total cohort of participants (1.7 ug/L) was defined as hyperinsulinemia.

2.2.3.2 Other Outcomes

a. *Preterm delivery*: Delivery prior to 37 weeks gestation was defined as preterm.
b. *Shoulder dystocia and/or birth injury*: Instances of shoulder dystocia and birth injury were reviewed without knowledge of glucose values and those that were confirmed were defined as having this outcome.
c. *Sum of skinfolds >90th percentile for gestational age*: 90th percentiles for gestational age (36–44 weeks only) were determined from 90th percentile regression analyses using eight newborn gender-ethnic groups (Caucasian or other, Black, Hispanic, Asian), with adjustment for field center, and parity (0, 1, 2+). A newborn was considered to have a sum of skinfolds >90th percentile if the sum was greater than the estimated 90th percentile for the baby's gender, gestational age, ethnicity, field center, and maternal parity. Otherwise, the newborn was considered to have a sum ≤90th percentile.
d. *Percent body fat >90th percentile for gestational age*: Fat mass was calculated from birthweight, length, and flank skinfold according to the equation given in Catalano et al[25] that was based on measurements of total body electrical conductivity (TOBEC). The derived formula was also prospectively validated with estimates of fat mass by TOBEC. Percent body fat was then calculated as 100 × fat mass/birthweight. Percent body fat >90th percentile for gestational age (36–44 weeks only) was defined using the same methods as for sum of skinfolds >90th percentile.
e. *Intensive neonatal care*: Admission to any type of unit for care more intensive than normal newborn care was classified as intensive neonatal care when the duration was greater than 24 h, or the baby died or was transferred to another hospital. Admissions where the only reason(s) for admission was (a) possible sepsis and sepsis was ruled out; (b) observation; or (c) feeding problems were not included.
f. *Hyperbilirubinemia*: If there was treatment with phototherapy after birth, or at least one laboratory report of a bilirubin level ≥20 mg/dL, or readmission for hyperbilirubinemia, the baby was categorized as having hyperbilirubinemia.
g. *Pre-eclampsia*: Hypertension present prior to 20 weeks that did not progress to pre-eclampsia was classified as chronic hypertension. After 20 weeks gestation, hypertension disorders in pregnancy were categorized according to International Society for the Study of Hypertension (ISSHP) guidelines.[26] Pre-eclampsia = systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg on two or more occasions a minimum of 6 h apart with proteinuria of ≥1+ dipstick or ≥300 mg/24 h. If the criteria for elevated BP but not proteinuria were met, this was classified as gestational hypertension.
h. *Birthweight <10th percentile for gestational age*: This was defined using the same methods that were used for birthweight >90th percentile for gestational age.

2.2.3.3 Possible Severe Adverse Outcomes

The field centers were asked to abstract additional data whenever a possible severe adverse event such as death, shoulder dystocia, birth injury, or major malformation was identified.

These data were reviewed by a subcommittee of the HAPO Steering Committee, blinded to the glycemic status of the mother. They confirmed whether the event was present. Perinatal deaths were classified according to the guidelines given in the "Australia and New Zealand Antecedent Classification of Perinatal Mortality".[27] Major malformations were classified according to ICD 10 coding.[28] The HAPO external Data Monitoring Committee also reviewed the adverse outcomes and deaths, but with full details of the OGTT and RPG levels.

2.2.4 Statistical Analyses

For unadjusted analyses of associations of glycemia with primary outcomes each glucose measurement was divided into seven categories, so that approximately 50% of all values were in the two lowest categories, and 3 and 1% were in the two highest categories, respectively. The smaller numbers in the higher categories for glucose variables were designed to allow us to assess whether or not there was a threshold effect with regard to each glycemia-outcome association, since we did not know, a priori, whether associations would be continuous and graded or whether risk might be increased only above a specific threshold. Thus, for these analyses FPG was categorized as <75, 75–79, 80–84, 85–89, 90–94, 95–99, and ≥100 mg/dL; 1-h PG as <105, 106–132, 133–155, 156–171, 172–193, 194–211, and ≥212 mg/dL; and 2-h PG as ≤90, 91–108,109–125, 126–139, 140–157, 158–177, ≥178 mg/dL (for cut-offs, see Fig. 2.1).

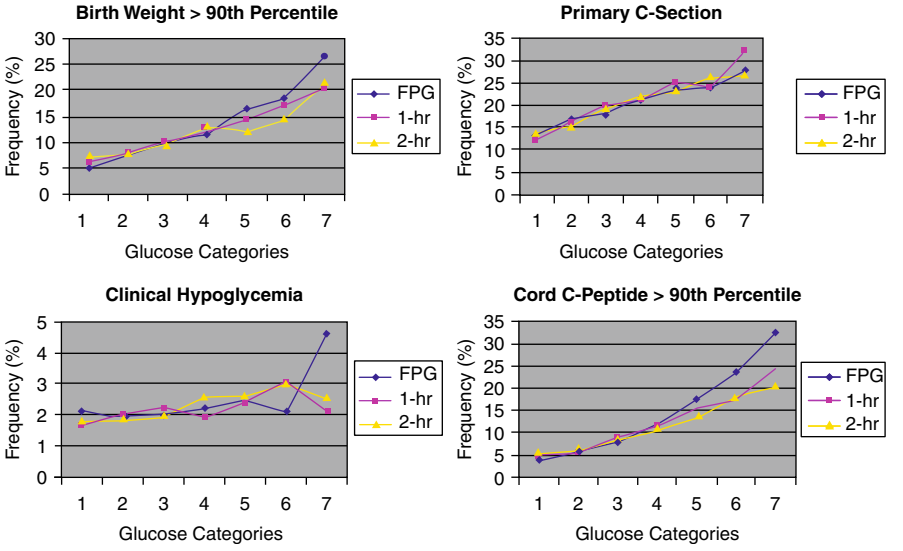

Fig. 2.1 Frequency of primary outcomes across categories of glucose. Fasting: Category 1 = <75, 2 = 75–79, 3 = 80–84, 4 = 85–89, 5 = 90–94, 6 = 95–99, 7 = ≥100 mg/dL. One hour oral glucose tolerance test (OGTT): Category 1 = ≤105, 106–132, 133–155, 156–171, 172–193, 194–211, ≥212. Two hour OGTT: Category 1 = ≤90, 91–108, 109–125, 126–139, 140–157, 158–177, ≥178

To make categorical analyses of neonatal anthropometric outcomes for cord serum C-peptide comparable to those that had previously been done for maternal glycemia, we also divided cord serum C-peptide into seven categories so that approximately 50% of the values were in the two lowest categories, and 3 and 1% were in the two highest categories respectively.[29] Thus, for these analyses cord serum C-peptide was categorized as ≤0.5, 0.6–0.8, 0.9–1.2, 1.3–1.5, 1.6–2.1, 2.2–3.0, ≥3.1 ug/L. In these analyses, the lowest cord serum C-peptide category was used as the referent category.

Each glucose measure was also considered as a continuous variable in multiple logistic regression analyses, with odds ratios calculated for each of the three glucose determinations (fasting, 1-, and 2-h PG) increased by one standard deviation. To assess whether or not the log of the odds of each outcome was linearly related to glucose, we added squared terms in each glucose measure. We also examined cord C-peptide as a continuous variable with both linear and squared terms for each outcome. However, because the squared term was significant ($p < 0.001$) for each anthropometric outcome, indicating significant nonlinearity, only categorical multiple logistic analyses are reported here for cord C-peptide.

For the results of the multiple logistic analyses reported here, associations with outcomes for each glycemia measure and cord serum C-peptide were adjusted for field center, maternal age, maternal body mass index (BMI) and height calculated from measurements taken at the OGTT visit, smoking and alcohol use during pregnancy, hospital admission during the prenatal period (except in the analyses for pre-eclampsia), family history of diabetes, mean arterial blood pressure at the OGTT (except in the analyses for pre-eclampsia), gestational age at the OGTT, parity (except in the analyses for cesarean delivery), gender of the neonate, maternal urinary tract infection and family history of high blood pressure for the outcome of pre-eclampsia, and cord PG for the outcome of fetal hyperinsulinemia. Ethnicity was not included as an additional potential confounder in these analyses except for the fetal adiposity measures in which it was included in the definition, since there was strong overlap with field center, and there was little or no contribution of ethnicity for the other outcomes when dummy variables for field center were included. In the continuous glucose analyses, we also tested for interactions of glucose with field center, age, BMI, and maternal height in relation to outcomes. In the analyses of the relationship between maternal glucose and delivery by primary cesarean, women who delivered by repeat cesarean were excluded altogether.

2.3 Results

2.3.1 Research Participants

A total of 53,295 women were found to be eligible and of these 28,562 (54%) agreed to participate between July 2000 and April 2006. The average age of participants was 29.0 years, compared with 28.5 among those who declined; the average number of years of education was 12.9 vs. 12.5 among those who agreed and declined, respectively. These differences, although statistically significant, were small. A total of 25,505 women

underwent an OGTT and of these, 746 or 2.9% were unblinded for at least one PG result outside of the threshold ranges (OGTT or RPG values) and excluded from the main study. A total of 1,412 women were dropped from the study due mainly to non-HAPO glucose testing or delivery in a non-field center hospital. Thirty-one women were excluded due to missing data on birth weight, gestational age at delivery, maternal age, BMI, mean arterial pressure at the OGTT, or 1- or 2-h PG, or for having a gestational age >44 weeks at delivery (which was assumed to be erroneous). A total of 23,316 women remained in the main study and this is the group for which results have been reported.[29, 30]

Selected characteristics of HAPO participants and their newborns are shown in Table 2.1. In this cohort of blinded participants, the mean FPG was 80.9 mg/dL (4.5 mmol/L); the mean 1-h PG was 134.1 mg/dL (7.4 mmol/L) and the mean 2-h PG was 111 mg/dL (6.2 mmol/L). Of the participants, 48.3% were white, non-Hispanic. The remainder were from several other ethnic groups. Approximately 23% reported a first degree family history of diabetes and 36% reported a first degree family history of hypertension.

The mean gestational age at delivery was 39.4 weeks. Mean birthweight of the newborns was 3,292 g (standard deviation 529 g) and the mean varied by more than 400 g among the field centers (data not shown). The mean cord glucose was 81.5 mg/dL (4.5 mmol/L). A total of 51.5% of the babies were male, and 6.9% were delivered preterm (prior to 37 weeks).

There were two maternal deaths, one due to pulmonary embolism and the other to respiratory failure secondary to pneumonia. In the postpartum period, 187 or 0.8% of mothers experienced a major hemorrhage requiring transfusion or operative treatment. A total of 26 women required transfer to intensive care for treatment and 172 or 0.74% of mothers were readmitted to hospital after initial post delivery discharge. There were 130 perinatal deaths among the 23,316 deliveries, or 5.6/1,000. These were comprised of 89 fetal and 41 neonatal/infant deaths.

2.3.2 Glycemia and Outcomes

The frequency of each primary outcome across categories of glucose is shown in Fig. 2.1. With higher levels of maternal glycemia, the frequency of each primary outcome rose, although to a lesser extent for clinical neonatal hypoglycemia than for the other outcomes. Using FPG categories as an example, frequencies in the lowest and highest categories were: birthweight above the 90th percentile 5.3 and 26.3%; primary cesarean section 13.3 and 27.9%; clinical neonatal hypoglycemia 2.1 and 4.6%; and C-peptide above the 90th percentile 3.7 and 32.4%.

Results for glucose as a continuous variable with adjustment for confounders for both primary and other outcomes are shown in Table 2.2. For primary outcomes, odds ratios for glucose higher by 1 standard deviation were largest for birthweight and cord C-peptide and ranged from 1.38 to 1.46 for birthweight >90th percentile and from 1.37 to 1.55 for cord C-peptide >90th percentile. For primary cesarean section and clinical neonatal hypoglycemia, associations were weaker and the associations of clinical neonatal hypoglycemia with FPG and 2-h PG were not statistically significant.

Table 2.1 Characteristics of HAPO participants and frequency of outcomes

Maternal characteristics	*N*	*Mean*	*SD*
Age (years)	23,316	29.2	5.8
Body mass index (BMI)[a]	23,316	27.7	5.1
Mean arterial pressure (MAP) (mmHg)[a]	23,316	80.9	8.3
Fasting plasma glucose (FPG) (mg/dL)[a]	23,316	80.9	6.9
1-h plasma glucose (PG) (mg/dL)[a]	23,316	134.1	30.9
2-h plasma glucose (mg/dL)[a]	23,316	111.0	23.5
Gestational age* (weeks)	23,316	27.8	1.8
	N	*%*	
Ethnicity			
White, non-Hispanic	11,265	48.3	
Black, non-Hispanic	2,696	11.6	
Hispanic	1,984	8.5	
Asian/oriental	6,757	29.0	
Other or unknown	614	2.6	
Prenatal smoking (any)	1,581	6.8	
Prenatal alcohol use (any)	1,612	6.9	
Family history of diabetes	5,282	22.7	
Parity (prior delivery ≥20 weeks)	12,233	52.5	
Prenatal urinary tract infection	1,655	7.1	
Hospitalization prior to delivery	3,271	14.0	
Newborn characteristics	*N*	*Mean*	*SD*
Gestational age (weeks)	23,316	39.4	1.7
Birthweight (g)	23,267	3,292	529
Cord serum C-peptide (ug/L)	19,885	1.0	0.6
Cord plasma glucose (mg/dL)	19,859	81.5	19.6
	N	*%*	
Sex – Male	12,003	51.5	
Obstetric outcomes	*N*	*%*	
Cesarean section delivery			
Primary	3,731	16.0	
Repeat	1,792	7.7	
Hypertension[2]			
Chronic hypertension	582	2.5	
Gestational hypertension	1,370	5.9	
Pre-eclampsia	1,116	4.8	
Newborn outcomes	*N*	*%*	
Birthweight >90th percentile[3]	2,221	9.6	
Clinical neonatal hypoglycemia[4]	480	2.1	
Cord C-peptide >90th percentile[5]	1,671	8.4	
Preterm delivery (before 37 weeks)	1,608	6.9	
Shoulder dystocia and/or birth injury	311	1.3	
Intensive neonatal care[6]	1,855	8.0	
Hyperbilirubinemia[7]	1,930	8.3	

[a]Measured at the OGTT

[b]Hypertension: Hypertension present prior to 20 weeks which did not progress to pre-eclampsia was classified as chronic hypertension. After 20 weeks gestation, hypertension disorders in

pregnancy were categorized according to International Society for the Study of Hypertension (ISSHP) guidelines (26). Pre-eclampsia = systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg on 2 or more occasions a minimum of 6 hours apart and proteinuria of > 1+ dipstick or > 300 mg per 24 hours. If the criteria for elevated BP but not proteinuria were met, this was classified as gestational hypertension.

[c]Birthweight > 90th percentile: 90th percentiles for gestational age (30-44 weeks only) were determined using quantile regression analyses for each of 8 newborn gender-ethnic groups (Caucasian or Other, Black, Hispanic, Asian), with adjustment for gestational age, field center, and parity (0, 1, 2+). A newborn was considered to have a birthweight > 90th percentile if the birthweight was greater than the estimated 90th percentile for the baby's gender, gestational age, ethnicity, field center, and maternal parity. Otherwise, the newborn was considered to have a birthweight < 90th percentile.

[d]Clinical neonatal hypoglycemia: Clinical neonatal hypoglycemia was defined as present if there was notation of neonatal hypoglycemia in the medical record and there were symptoms and/or treatment with a glucose infusion or a local laboratory report of a glucose value < 30.6 mg/dL (1.7 mmol/L) in the first 24 hours and/or < 45 mg/dL (2.5 mmol/L) after the first 24 hours after birth (24).

[e]Cord C-Peptide > 90th %ile: Defined from the total HAPO cohort with a C-peptide result.

[f]Intensive Neonatal Care: Admission to any type of unit for care more intensive than normal newborn care when the duration was greater than 24 hours, or the baby died or was transferred to another hospital. Admissions for only: (a) possible sepsis and sepsis was ruled out; (b) observation; or (c) feeding problems were excluded.

[g]Hyperbilirubinemia: Treatment with phototherapy after birth, or at least 1 laboratory report of a bilirubin level > 20mg/dL, or readmission for hyperbilirubinemia.

Table 2.2 Adjusted[a] odds ratios and 95% confidence intervals for associations between maternal glucose as a continuous variable and perinatal outcomes

Outcome	FPG		1-h PG		2-h PG	
	OR[b]	95% CI	OR	95% CI	OR	95% CI
Birthweight >90th percentile	1.38	(1.32–1.44)	1.46	(1.39–1.53)	1.38	(1.32–1.44)
Primary cesarean delivery[c]	1.11	(1.06–1.15)	1.10	(1.06–1.15)	1.08	(1.03–1.12)
Clinical neonatal hypoglycemia	1.08[d]	(0.98–1.19)	1.13	(1.03–1.26)	1.10	(1.00–1.12)
Cord C-peptide >90th percentile	1.55	(1.47–1.64)	1.46	(1.38–1.54)	1.37	(1.30–1.44)
Preterm delivery (<37 weeks)	1.05	(0.99–1.11)	1.18	(1.12–1.25)	1.16	(1.10–1.23)
Shoulder dystocia and/or birth injury	1.18	(1.04–1.33)	1.23	(1.09–1.38)	1.22	(1.09–1.37)
Sum of skinfolds >90th percentile	1.39	(1.33–1.47)	1.42	(1.35–1.49)	1.36	(1.30–1.43)
Percent body fat >90th percentile	1.35	(1.28–1.42)	1.44	(1.37–1.52)	1.35	(1.29–1.42)

Table 2.2 (continued)

Outcome	FPG		1-h PG		2-h PG	
	OR[b]	95% CI	OR	95% CI	OR	95% CI
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)
Pre-eclampsia	1.21	(1.13–1.29)	1.28	(1.20–1.37)	1.28	(1.20–1.37)

[a]Associations were adjusted for field center, age, BMI, height, smoking status, alcohol use, family history of diabetes, gestational age at OGTT, infant's gender, hospitalization prior to delivery, mean arterial pressure, parity (not included in the model for primary cesarean delivery), cord plasma glucose (included in the model for cord serum C-peptide >90th percentile only), pre-eclampsia did not include adjustment for hospitalization or mean arterial pressure, and family history of hypertension and prenatal urinary tract infection were included only in the model for pre-eclampsia

[b]Odds ratios for glucose higher by 1 standard deviation (6.9 mg/dL for FPG, 30.9 mg/dL for 1-h PG, 23.5 mg/dL for 2-h PG) (mmol/L = mg/dL/18)

[c]Excluding those with a prior cesarean section

[d]Nonlinear relationship

There were also strong associations with pre-eclampsia, where the odds ratios for each 1 standard deviation increase in each glucose measure ranged from 1.21 to 1.28; corresponding odds ratios for shoulder dystocia and/or birth injury were approximately 1.2. Premature delivery, intensive neonatal care, and hyperbilirubinemia were significantly related to 1- and 2-h PG, but not to FPG.

Odds ratios for associations of glycemia with percent body fat >90th percentile and sum of skinfolds >90th percentile were similar in size to those for birthweight >90th percentile.

2.3.3 Cord C-peptide and Neonatal Anthropometrics

Associations between cord C-peptide and neonatal anthropometrics are shown in Table 2.3. With higher levels of cord C-peptide, frequency of each measure of size and adiposity rose. For example, the frequency of birthweight >90th percentile ranged from 4.5 to 25.6% across categories of cord C-peptide. With adjustment only for field center, odds ratios for the three measures ranged from 5.97 to 7.31 in the highest category of cord C-peptide (data not shown). In the fully adjusted logistic regression models, odds ratios were modestly attenuated, but strong graded associations remained.

When cord C-peptide was examined in relationship to birthweight, sum of skinfolds, percent body fat and fat free mass as continuous dependent variables in multiple regression analyses, mean differences between the highest and lowest categories for cord C-peptide were 345 g for birth weight, 2.0 mm for sum of skinfolds, 2.7% for percent fat, and 221 g for fat free mass (all $p < 0.001$) (data not shown).

Table 2.3 Relationship between cord C-peptide and neonatal anthropometrics

Cord C-peptide (ug/L)	*N*	#	%	OR[a]	95% CI
Birthweight >90th percentile[b]					
≤0.5	2,911	131	4.5	1.00	(1.03–1.55)
0.6–0.8	6,530	392	6.0	1.26	(1.82–2.70)
0.9–1.2	5,899	614	10.4	2.21	(2.32–3.60)
1.3–1.5	2,077	283	13.6	2.89	(3.77–5.82)
1.6–2.1	1,639	333	20.3	4.68	(4.31–7.33)
2.2–3.0	571	140	24.5	5.62	(4.75–9.51)
≥3.1	242	62	25.6	6.72	
Total	19,869	1,955	9.8		
Sum of skinfolds >90th percentile[b]					
≤0.5	2,412	117	4.9	1.00	(1.03–1.58)
0.6–0.8	5,647	369	6.5	1.27	(1.56–2.37)
0.9–1.2	5,145	513	10.0	1.92	(2.26–3.57)
1.3–1.5	1,821	267	14.7	2.84	(2.97–4.72)
1.6–2.1	1,409	265	18.8	3.74	(2.99–5.36)
2.2–3.0	485	101	20.8	4.00	(3.78–8.21)
≥3.1	181	46	25.4	5.57	
Total	17,100	1,678	9.8		
Percent body fat >90th percentile[b]					
≤0.5	2,399	119	5.0	1.00	(1.00–1.54)
0.6–0.8	5,630	370	6.6	1.24	(1.52–2.31)
0.9–1.2	5,140	513	10.0	1.87	(2.30–3.62)
1.3–1.5	1,817	276	15.2	2.88	(2.99–4.75)
1.6–2.1	1,403	269	19.2	3.77	(3.79–6.66)
2.2–3.0	485	121	25.2	5.02	(3.41–7.52)
≥3.1	181	43	23.8	5.06	
Total	17,050	1,726	10.0		

[a]Associations were adjusted for the variables used in estimating 90th percentiles, age, BMI, height, mean arterial blood pressure, gestational age at the OGTT, smoking, alcohol use, hospitalization prior to delivery, any family history of diabetes

[b]Defined based on gender, ethnicity, field center, gestational age (36–44 weeks for skinfolds and body fat), and parity

N total number in the cord C-peptide category (excluding births with gestational age <30 weeks and fetal deaths); # number in the cord C-peptide category with the outcome; % proportion in the cord C-peptide category with the outcome

2.3.4 Frequency of Birthweight >90th and <10th Percentile

Figure 2.2 shows the frequencies of babies with a birthweight <10th percentile and >90th percentile across categories of FPG, 1-, and 2-h PG. The change in the frequency of birthweight <10th percentile shows a smaller decline across increasing categories of glucose, compared with the change in the increased frequency of birthweight >90th percentile across glucose categories.

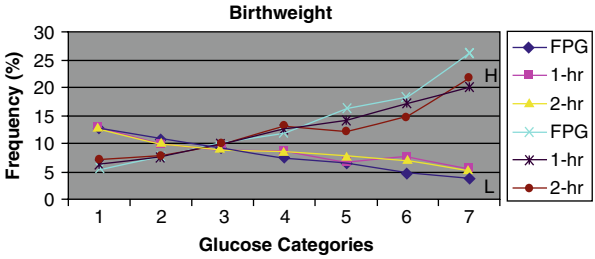

Fig. 2.2 Frequency of birthweight <10th percentile (L) and >90th percentile (H) across categories of glucose

2.4 Clinical Implications

The objective of the HAPO study was to clarify the risk of adverse outcome associated with degrees of maternal glucose intolerance less severe than overt DM. The data published in the initial reports[29,30] demonstrate associations between higher fasting, 1- and 2-h OGTT PG concentrations and birthweight >90th percentile and cord serum C-peptide >90th percentile. Weaker associations were found between glucose levels and primary cesarean delivery and clinical neonatal hypoglycemia. We also found positive associations between increasing PG levels and each of the five secondary outcomes: preterm delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia, and preeclampsia, as well as with newborn adiposity.[30]

The associations were examined with adjustments made for potential confounders that included field center, age, BMI, height, mean arterial pressure measured at the time of the OGTT, gestational age at the OGTT, smoking, drinking, family history of diabetes, parity, hospitalization pre-delivery, and neonatal gender. In general, the adjustments resulted in small to moderate attenuation of most of the field center or unadjusted associations, and associations generally did not differ among field centers. Thus, the influence of maternal glycemia on various maternal/fetal outcomes appears to be a basic biologic phenomenon, and not an epiphenomenon related to the confounders described above. The Pedersen Hypothesis has formed the basis for understanding the pathophysiology of diabetic pregnancy over the past 50+ years. The associations between maternal glucose at concentrations less than those diagnostic of diabetes and outcomes such as birthweight greater than the 90th percentile, fetal hyperinsulinemia (cord C-peptide >90th percentile) and infant adiposity (percent body fat >90th percentile) are strongly supportive of the Pedersen hypothesis.

The lack of differences across field centers for all of the associations described above confirms their applicability to all of the centers. Thus, the results can be used to develop "outcome based" criteria for classifying glucose metabolism in pregnancy that apply globally.

Because the associations of maternal glycemia with perinatal outcomes were continuous with no obvious thresholds at which risks increased, it is evident that a consensus is required to translate these results into clinical practice. Other issues must be addressed as well. For example, is it important to have all three OGTT glucose measurements (fasting, 1-, and 2-h-post load values)? The individual OGTT glucose measures were not highly correlated, and no single measure was clearly superior in predicting the primary

outcomes. Can a single glucose value that is equal to or greater than a certain threshold value represent GDM, or must thresholds be met for more than one value? Which of the primary or secondary outcomes should be used to identify the level of glycemia that will be considered GDM, that is to say, the threshold at or above which the risk of adverse outcome is too high?

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) sponsored an "International Workshop Conference on Gestational Diabetes Diagnosis and Classification" in Pasadena, CA on June 11–12, 2008 to initiate the process of consensus development. The IADPSG, an umbrella organization, was formed in 1998 to facilitate collaboration between the various regional and national groups that have a primary or significant focus on diabetes and pregnancy. More than 225 conferees from 40 countries reviewed the published results of the HAPO Study, additional unpublished HAPO Study findings and results of other published and unpublished work that examined associations of maternal glycemia with perinatal and long-term outcomes in offspring. Following the presentation and review of data, conferees held regional caucuses to consider the clinical implications of the large body of information that had been presented.

On the following day, June 13, 2008, the IADPSG Consensus Panel (with representation from the ten member organizations of the IADPSG, together with representatives from other organizations with an interest in diabetes and pregnancy) was convened to begin the process of moving from dialog to consensus. Subsequently, with coordination from the Consensus Panel Steering Committee/Writing Group, the Panel reviewed further HAPO Study results provided by the HAPO Study Data Coordinating Center. Through this process the Consensus Panel has formulated "Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy" which were recently published[31]. These new thresholds for the diagnesis of GDM are shown in Table 2.4. It is expected that this report will be considered by all of the major diabetes organizations and will serve as the basis for internationally endorsed criteria for the diagnosis and classification of diabetes in pregnancy.

Table 2.4 Threshold Values for Diagnosis of GDM and Cumulative Proportion of HAPO Cohort Equaling or Exceeding those Thresholds

Glucose Measure	Glucose Concentration Threshold+		Percent ≥ Threshold
	mmol/l	mg/dl	Cumulative
FPG	5.1	92	8.3
1-h PG	10.0	180	14.0
2-h PG	8.5	153	16.1*

+One or more of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of GDM.

*In addition, 1.7% of participants in the initial cohort were unblinded because of a FPG >5.8 mmol/l (105 mg/dl) or 2-h OGTT values >11.1 mmol/l (200 mg/dl) bringing the total to 17.8%.

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2.5 Appendix: HAPO Study Cooperative Research Group

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Clinical Coordinating Center: A Collard, AS Frank, LP Lowe, BE Metzger, A Thomas (Northwestern University Feinberg School of Medicine, Chicago).

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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; 13:278-285.
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.
5. World Health Organization. WHO Expert Committee on Diabetes Mellitus: second report. *World Health Organ Tech Rep Ser*. 1980;646:1-80.
6. Jarrett RJ. Reflections on gestational diabetes. *Lancet*. 1981;28:1220-1221.
7. Hunter DJS, Keirse MJNC. Gestational diabetes in effective care. In: Chalmers I, Enkin M, Kierse M, eds. *Pregnancy and Childbirth*. Oxford: Oxford University Press; 1989:403-410.
8. Spellacy WN, Miller S, Winegar A, et al. Macrosomia: maternal characteristics and infant complications. *Obstet Gynecol*. 1985;66:158-161.
9. Coustan DR. Management of gestational diabetes: a self-fulfilling prophecy? [editorial]. *JAMA*. 1996;275:1199-1200.
10. 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;185:413-419.
11. Yang X, Zhang C, Hsu-Hage B, et al. Women with impaired glucose tolerance during pregnancy have significantly poor pregnancy outcomes. *Diabetes Care*. 2002;25:1619-1624.
12. 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;17:203-208.

13. 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;157:758-763.
14. Sacks DA, Abu-Fadil S, Greenspoon JS, Fotheringham N. Do the current standards for glucose tolerance testing in pregnancy represent a valid conversion of O'Sullivan's original criteria? *Am J Obstet Gynecol*. 1989;161:638-641.
15. Ferrara A, Weiss NS, Hedderson MM, et al. Elevations in pregnancy plasma glucose levels below the National Diabetes Data group thresholds for gestational diabetes mellitus are associated with an increased risk of neonatal macrosomia, hypoglycemia and hyperbilirubinemia. *Diabetologia*. 2007;50:298-306.
16. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes on pregnancy outcomes. *N Engl J Med*. 2005;352:2477-2486.
17. Landon MB, Spong CY, Thom E, et al. A multicenter randomized trial of treatment for mild gestational diabetes. *N Engl J Med*. 2009;361:1339-1348.
18. U.S. Preventive Services Task Force. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2008;148:759-765.
19. Scott DA, Loveman E, McIntyre L, Waugh N. Screening for gestational diabetes: a systematic review and economic evaluation. *Health Technol Assess*. 2002;6(11):1-161.
20. Canadian Task Force on the Periodic Health Examination. *The Canadian Guide to Clinical Preventive Health Care*. Ottawa: Health Canada; 1994:15-23.
21. HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Int J Gynaecol Obstet*. 2002;78:69-77.
22. Pedersen J. *Diabetes and Pregnancy. Blood Sugar of Newborn Infants* [Copenhagen]. 1952:230.
23. Nesbitt GS, Smye M, Sheridan B, Lappin TRJ, Trimble ER for the 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.
24. 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.
25. Catalano PM, Thomas AJ, Avallone DA, Amini SB. Anthropometric estimation of neonatal body composition. *Am J Obstet Gynecol*. 1995;173:1176-1181.
26. Brown MA, Lindheimer MD, deSwiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001;20:ix-xiv.
27. Chan A, King J, Flenady V, Haslam R, Tudehope D. Classification of perinatal deaths: development of the Australian and New Zealand classifications. *J Paediatr Child Health*. 2004; 40:340-347.
28. WHO. *Tenth International Statistical Classification of Diseases and Related Health Problems (ICD-10)*. Geneva, Switzerland: WHO; 1992.
29. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes*. 2009;58:453-459.
30. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcomes. *N Engl J Med*. 2008;358:1991-2002.
31 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.

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