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The HAPO Study: Paving The Way For New Diagnostic Criteria For GDM

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Abstract

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study was performed in response to the need for internationally agreed upon diagnostic criteria for gestational diabetes, based upon their predictive value for adverse pregnancy outcome. Increases in each of the three values on the 75 gram, 2-hour oral glucose tolerance test are associated with graded increases in the likelihood of pregnancy outcomes such as large for gestational age, cesarean section, fetal insulin levels and neonatal fat content. Based upon an iterative process of decision making, a task force of the International Association of Diabetes in Pregnancy Study Groups (IADPSG) recommends that the diagnosis of gestational diabetes be made when any of the following three 75 gram 2-hour OGTT thresholds are met or exceeded: Fasting 92 mg/dL, one hour 180 mg/dL, two hours 153 mg/dL. Various authoritative bodies around the world are expected to deliberate the adoption of these criteria.

Keywords

Diagnostic OGTT criteria; Gestational diabetes; HAPO study

At present there is a lack of international consistency with regard to the diagnosis of gestational diabetes. While a glucose tolerance test is commonly employed, glucose challenge dosages vary and diagnostic threshold challenge is widely used throughout the world. The 75 gram glucose challenge is used throughout the world for diagnostic testing in the nonpregnant state. At the Third International Workshop-Conference on Gestational Diabetes in 1990¹ a series of recommendations were made which included universal employment of the 75 gram glucose challenge during pregnancy. Some sets of diagnostic criteria, such as those proposed by the World Health Organization, were simply based on criteria used in nonpregnant individuals, and did not take into account changes in carbohydrate metabolism brought about by the pregnant state. Others, such as the "O'Sullivan criteria"² in use in North America, were based on data from pregnant women, but were derived mathematically as being two standard

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deviations above the mean, and were validated for their predictive value for future diabetes in the mother, rather than on pregnancy outcomes. The organizers advocated for international agreement on all aspects of diagnostic testing, and for the development of criteria based on pregnancy outcomes.

Subsequently a group of investigators from the disciplines of obstetrics and gynecology, diabetology and neonatology, based in North America, Europe, Asia and the Middle East, met to plan a study to examine the relationship between maternal glucose and adverse neonatal outcomes. A 1992 workshop sponsored by NICHD and NIDDK³ supported the rationale behind this effort, concluding that carefully designed studies were critical in order to answer outstanding questions about the sensitivity, specificity and cost-effectiveness of efforts to diagnose and treat gestational diabetes to prevent adverse perinatal effects.

The Fourth International Workshop-Conference on Gestational Diabetes Mellitus⁴ in 1997 noted that the prevalence of gestational diabetes was increasing around the world, and that "... although... some progress has been made toward building consensus there remains a compelling need to develop diagnostic criteria for GDM that are based on the specific relationships between hyperglycemia and risk of adverse outcome."

Another area of controversy surrounded the potential benefit, or lack of benefit, of screening a population for gestational diabetes and treating when the diagnosis was made. As recently as 2008 the US Preventive Services Task Force *Guide To Clinical Preventive Service*⁵ recommended as follows: "The USPSTF concludes that the current evidence is insufficient to assess the benefits and harms of screening for gestational diabetes (GDM) either before or after 24 weeks gestation." The opposing view to this assertion is based upon studies showing increased perinatal morbidity even when only one glucose tolerance test value is elevated.⁶

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was designed to answer some of the questions posed above. While there was little or no argument that type 1 and type 2 diabetes increase the risk of any number of adverse pregnancy outcomes, HAPO sought to determine the level of glucose intolerance during pregnancy, short of overt diabetes, that is associated with adverse outcomes. The study design has been described in detail elsewhere.⁷ More than 25,000 non-diabetic gravidas were enrolled in 15 field centers located in 9 different countries. Each subject underwent a 75 gram, 2-hour oral glucose tolerance test at between 24 and 32 weeks gestation (mean gestational age 27.8 weeks); subjects and caregivers were blinded to the GTT results unless the fasting plasma glucose exceeded 105 mg/dl or the 2-hour value exceeded 200 mg/dl, in which case the caregiver was informed of the results and the subject was excluded from participation so that she could be treated as determined by the caregiver. As a safety precaution, a sample for random plasma glucose was collected at 34-37 weeks and unblinded if the value met or exceeded 160 mg/dl. Participants were also unblinded for any glucose value below 45 mg/dl.

At the time of delivery, cord blood samples were obtained and analyzed at the Central Laboratory for glucose and for C-peptide. C-peptide was chosen as a marker for fetal insulin levels because, in the presence of hemolysis, it is much more stable than insulin in stored specimens. Neonatal anthropometric measurements were collected within 72 hours of delivery. These consisted of weight, length, head circumference and skinfold thickness measured at the flank, subscapular and triceps areas. Additional data were abstracted from maternal and neonatal medical records

The four primary outcomes for which the study was powered included macrosomia (birth weight >90th centile for gestational age, gender, parity, ethnicity and field center), primary cesarean delivery, clinical neonatal hypoglycemia (as noted in the medical record) and hyperinsulinemia (cord serum C-peptide >90th centile for the study group as a whole). A

number of secondary outcomes were also considered. These included preterm birth (defined as <37 weeks gestation), shoulder dystocia and/or birth injury, sum of skinfold thicknesses >90th centile for gestational age, gender, ethnicity, parity and field center, percent body fat >90th centile for gestational age (calculated from birth weight, length and flank skinfold8), admission for neonatal intensive care, hyperbilirubinemia and pre-eclampsia.

Participants were enrolled between July 2000 and April 2006. Data were analyzed, blinded to test results, for 23,316 mother-newborn pairs. The mean fasting plasma glucose value across all participants was 80.9 mg/dl. At 1 and 2 hours after the 75 gram oral glucose challenge the means were 134.1 mg/dl and 111 mg/dl, respectively. The average gestational age at delivery was 39.4 weeks; 6.9% of deliveries were pre-term. Participants were ethnically diverse, with 48% white non-hispanic, 12% black non-hispanic, 29% asian/oriental, 8% hispanic, and 3% other or unknown.⁹

For categorical analyses, fasting plasma glucose values were divided *a priori* into 7 categories in 5 mg/dl increments, with the lowest category being less than 75 mg/dl and the highest being ≥ 100 mg/dl. The one and two hour value categories were chosen to yield proportions of the population that were similar to those of the fasting plasma glucose categories. The lowest two categories contained approximately 50% of subjects. The highest two categories contained only 1% and 3% of subjects, in order to determine whether there was a threshold for any effects present. As shown in figure 1, the four primary outcomes were all related to each of the three glucose determinations in a continuous and graded manner. Clinical neonatal hypoglycemia, which occurred in only 2.1% of the total population in the study, showed the least robust association with fasting and other OGTT values, whereas the other three outcomes were more strongly related. For example, the prevalence of cord C-peptide above the 90th centile increased from 3.7% when fasting plasma glucose was below 75 mg/dl to 32.4% when it was 100 mg/dl or greater. When logistic models were constructed to account for potential confounders such as location (i.e., field center), age, body mass index and a number of other variables, the relationships described above held although they were somewhat attenuated.⁹

The relationship between OGTT values and each of the four primary outcomes was also evaluated using glucose as a continuous variable, and correcting for the potential confounders described above. As shown in table 1 these relationships were expressed as the odds ratio for a given outcome for each SD increase in glucose. The association between each of the OGTT values and each of the primary outcomes remained significant with the exception of that between both fasting plasma glucose and 2 hour plasma glucose with clinical neonatal hypoglycemia. A number of secondary outcomes were also evaluated. Both pre-eclampsia and shoulder dystocia/birth injury were significantly associated with each of the glucose values. Preterm delivery was associated with the one and two hour glucose values, but not with fasting plasma glucose.

One of the most critical observations of the HAPO Study was that the associations of various adverse outcomes with OGTT results were continuous, and no clear inflection points could be identified. The relationships held even down to the most “normal” maternal glucose levels. This led to two conclusions: (1) the relationship between maternal glucose levels and fetal growth and fetal outcome appears to be a basic biological phenomenon, and not a clearly demarcated disease state; (2) the construction of diagnostic criteria for a condition called “gestational diabetes” was not going to be easily accomplished directly from the configuration of significant associations between maternal glycemia and outcomes. It was clear that the results of HAPO were applicable to all the involved field centers since the associations did not vary significantly across field centers, even though the prevalence of adverse outcomes differed among them. Thus the HAPO results should be applicable globally to develop outcome based criteria for classifying glucose metabolism in pregnancy.

The HAPO investigators did not make specific recommendations for diagnostic criteria. Because there were not obvious inflection points in the associations, and because it was important that any recommended diagnostic criteria be accepted internationally, a committee of experts was convened to develop a consensus regarding appropriate diagnostic criteria. This task was undertaken by the International Association of Diabetes and Pregnancy Study Groups (IADPSG, www.iadpsg.org), an umbrella organization which was formed to encourage and facilitate research and advance education in the field of diabetes in pregnancy, and which aims to facilitate an international approach to enhancing the quality of care for women with diabetes in pregnancy. IADPSG's affiliated organizations include the Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes, the Japanese Association of Diabetes and Pregnancy, the Australasian Diabetes in Pregnancy Society, the West Coast USA DPSG, the Diabetes in Pregnancy Society of India and the Canadian Special Interest Group for Diabetes and Pregnancy. Associated organizations include the European Association of Perinatal Medicine, the Society for Maternal Fetal Medicine of the USA, the Pregnancy and Reproductive Health Interest Group of the American Diabetes Association and the Saredia International Association.

The IADPSG convened a workshop/conference in June of 2008. There were presentations of data from HAPO and other studies, and discussion of these data by the 220 delegates from approximately 40 different countries. This was followed by caucuses of the various groups who were present. Then a consensus development session was held, in which approximately 50 delegates representing the IADPSG organizations such as ACOG, WHO, ADA, EASD, IDF, and CDC as well as a number of "at large" delegates took the first steps to reach consensus around international recommendations. A smaller steering committee and writing group was appointed.

The delegates agreed that the choice of thresholds would have to be somewhat arbitrary since inflection points in these continuous and graded relationships were not apparent. The group decided that the various adverse outcomes were not equally important in devising diagnostic thresholds, and that some outcomes such as macrosomia and cesarean section were inter-related. The outcomes of large for gestational age, and fat or hyperinsulinemic babies comprise the primary basis for the recommended diagnostic criteria. It would have simplified matters if a single glucose determination, such as fasting plasma glucose, would be sufficient for the diagnosis, so as to preclude the need for a full OGTT. Therefore, the relative independent contributions of the fasting, 1-hour and 2-hour glucose values were considered. As described below, each of the three samples contributed at least partially independently as a predictor of adverse pregnancy outcome, and the group decided to recommend the full 2-hour 75 gram oral glucose tolerance test, leaving open the possibility that a particular professional organization might opt to eliminate one or more of the three tests, thereby reducing the sensitivity of the process but also decreasing the cost and inconvenience.

The mean glucose value at each of the three time points was chosen as the reference value, against which proposed thresholds would be compared. Thresholds which yielded odds ratios of 1.5, 1.75 and 2.0 times the likelihood of adverse outcomes at mean glucose levels were considered (Table 2). Setting thresholds at an odds ratio of 1.5 identifies more than 20% of the cohort with one or more glucose values that met or exceeded the threshold. Using an odds ratio of 1.75 rather than 2.0 increased the yield of cases with similar risks of adverse outcome by 83%, and identifies 16.1% of the population as having gestational diabetes (Table 3). The thresholds recommended represent odds ratios of 1.75, and are fasting plasma glucose 92 mg/dl (5.1 mmol/L), 1-hour after the 75 gram challenge 180 mg/dl (10 mmol/L), and 2 hours 153 mg/dl (8.5 mmol/L).

As shown in Table 4, at the proposed threshold of 92 mg/dl for fasting plasma glucose, 8.3% of the HAPO population was identified and 19.5% of the babies were large for gestational age. Adding the 1 hour threshold of 180 mg/dl identified an additional 5.7% of the population who did not have an elevated fasting value and a total of 16.5% of identified pregnancies delivered babies with LGA. Adding the 2 hour threshold of 153 mg/dl identified an additional 2.1% of the population, and a cumulative total of 16.2% with LGA. The proportion with LGA babies decreased with the addition of patients identified by only the one hour and/or two hour thresholds because the positive predictive value (PPV) of these thresholds was slightly lower than that of the fasting, which did not preclude values for 1-hr and/or 2-hr also above threshold.

It may be stated that the IADPSG recommendations are based on pregnancy outcomes, but do not take into account the predictive values for maternal well-being or long term neonatal outcomes. The original O'Sullivan criteria were based on the likelihood of subsequent diabetes in the mother. HAPO does not include follow-up data on either mothers or offspring. However, we have examined and to date reported some of our data on maternal outcomes. In the NEJM article⁹ we report two maternal deaths, both of which would not have had GDM by the recommended thresholds, among over 23,000 pregnancies. Outcomes like C-section and preeclampsia are outcomes for both mother and offspring and we have reported those findings as well.

The proposed thresholds identify gravidas having an increased risk, compared to the general population, of adverse outcomes such as large, fat and hyperinsulinemic babies, and cesarean section. Secondary outcomes such as shoulder dystocia or birth injury, preterm delivery and pre-eclampsia were also increased in these individuals.⁹ However, it would be important to be able to demonstrate that identification of gestational diabetes by these criteria and intervention can prevent such adverse outcomes. The ACHOIS investigators¹⁰ demonstrated improvement in outcomes when subjects with a 2 hour value on the 75 gram OGTT between 140 and 200 mg/dl were treated for gestational diabetes with diet and insulin as needed, compared to controls who were not screened for GDM. A recent randomized trial of screening and treatment of mild gestational diabetes (fasting below 95 mg/dl, 2 of the other three 100 gram, 3-hour OGTT values meeting or exceeding 180, 155 and/or 140 mg/dl respectively) by the NICHD sponsored Maternal-Fetal Medicine Units Network¹¹ demonstrated a significant reduction in macrosomia, neonatal fat mass, shoulder dystocia, pre-eclampsia and cesarean section. These data strongly suggest that intervention in mild forms of gestational diabetes will be beneficial. Importantly, only 20% of treated ACHOIS subjects and 8% of MFMU subjects required insulin, implying that dietary intervention will be effective in the great majority of mild GDM.

While the current ADA recommendations for the 75 gram OGTT (12) require two elevated values, the proposed thresholds require only a single elevated value. It is of significant concern that the recommended thresholds will result in 16.1% of the population being identified as having gestational diabetes. In fact, an additional 1.7% of HAPO study participants were unblinded because of glucose values exceeding predetermined limits, so that 17.8% of HAPO participants would meet the new thresholds. However, current population trends in both gestational diabetes and type 2 diabetes render the above projections biologically plausible. Getahun et al¹³ demonstrated that the rate of diagnosed gestational diabetes more than doubled in the US between 1989 and 2004, with the rate in gravidas age 35 years or more exceeding 8%. This is consistent with the current epidemic of obesity and diabetes in this country, with the rate of diagnosed and undiagnosed diabetes among adults over the age of 20 years 10.2% and rising in 2006.¹⁴ Gestational diabetes bears a similarity to "prediabetes," defined as impaired fasting glucose (fasting plasma glucose 100-125 mg/dl) or impaired glucose tolerance (2 hour, 75 gram OGTT plasma glucose value 140-199 mg/dl), short of the diagnostic criteria for diabetes. The American Diabetes Association estimates that in 2007 57 million Americans, or 19% of the adult population had prediabetes¹⁵. Combining this figure with the NHANES

estimate of 10.2% of the population with diabetes results in the estimate that 29% of the US adult population has prediabetes or diabetes. Consequently, it should not be a great surprise that 18% of the pregnant population might have GDM.

In summary, the HAPO study provides an opportunity to revise diagnostic criteria for gestational diabetes. The proposed criteria for the 75 gram, 2-hour OGTT are that any one or more of the following thresholds be met or exceeded:

- Fasting plasma glucose 92 mg/dl (5.1 mmol/L)
- One hour plasma glucose 180 mg/dl (10 mmol/L)
- Two hour plasma glucose 153 mg/dl (8.5 mmol/L)

These proposed diagnostic criteria are based upon their predictive value for adverse pregnancy outcomes, are based on multi-national data and international consensus, allow the diagnosis to be made with a single elevated value, and treatment has been demonstrated to be efficacious at similar glucose levels. The proposal from the IADPSG has been published¹⁶ and various professional organizations around the world are now considering whether to adopt them.

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1.

Frequency of primary outcomes across the glucose categories. Reprinted, with permission, from the New England Journal of Medicine⁹

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 OGTT: Category 1 = < 105, 2 = 106 – 132, 3 = 133 – 155, 4 = 156 – 171, 5 = 172 – 193, 6 = 194 – 211, 7 = > 212 mg/dL

Two Hour OGTT: Category 1 = < 90, 2 = 91 – 108, 3 = 109 – 125, 4 = 126 – 139, 5 = 140 – 157, 6 = 158 – 177, 7 = > 178 mg/dL

Table 1

Adjusted¹ 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 ²	95% CI	OR	95% CI	OR	95% CI
Birthweight > 90 th %ile	1.38	(1.32 – 1.44)	1.46	(1.39 – 1.53)	1.38	(1.32 – 1.44)
Primary Cesarean delivery ³	1.11	(1.06 – 1.15)	1.10	(1.06 – 1.15)	1.08	(1.03 – 1.12)
Clinical neonatal hypoglycemia	1.08 ⁴	(0.98 – 1.19)	1.13	(1.03 – 1.26)	1.10	(1.00 – 1.12)
Cord C-peptide > 90 th %ile	1.55	(1.47 – 1.64)	1.46	(1.38 – 1.54)	1.37	(1.30 – 1.44)
Preterm delivery (< 37 wks)	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 > 90 th percentile	1.39	(1.33 – 1.47)	1.42	(1.35 – 1.49)	1.36	(1.30 – 1.43)
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)	(1.05 – 1.17)	1.11	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)

¹ 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.

² 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)

³ Excluding those with a prior Cesarean section

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Table 2

Plasma glucose concentrations at specified odds ratios.¹

Sample Time	Odds Ratio		
	1.5	1.75	2.0
	Plasma Glucose (mg/dl)		
FPG	90	92	95
1-HOUR PG	167	180	191
2-HOUR PG	142	153	162

¹ Plasma glucose values represent the mean of threshold values for odds ratio for increased neonatal body fat, LGA and cord serum C-peptide >90th centile.

Table 3

Pregnancies meeting glucose thresholds and positive predictive values for outcomes.

Glucose Thresholds (mg/dl)	% Subjects $\geq$ Threshold	PPV for BW $>90^{\text{th}}$ Centile ¹	PPV for C-Peptide $>90^{\text{th}}$ Centile ²	PPV for %Body Fat $>90^{\text{th}}$ Centile ³
92/180/153	16.1	16.2	17.5	16.6
95/191/162	8.8	17.6	19.7	18.8

¹ 9.6% of total population had birth weight $>90^{\text{th}}$ centile

² 8.4% of total population had C-peptide above 90th centile

³ 9.8% of total population had neonatal %body fat 7gt;90th centile

Table 4

Contributions of each sample interval to diagnosis and LGA frequencies

Sample Time	Glucose (mg/dl)	Percent of Subjects (cumulative %)	LGA Babies (cumulative %) ^I
Fasting	92	8.3	19.5
1-hour	180	14.0	16.5
2-hour	153	16.1	16.2

^I Cumulative percentage of LGA babies reflects both numerator increases and denominator increases when additional subjects are identified.