International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy: *Diabetes Care February 27, 2010 vol. 33 no. 3 676-682*

1. International Association of Diabetes and Pregnancy Study Groups Consensus Panel*

1. Corresponding author: Boyd E. Metzger, bem@northwestern.edu.

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) was formed in 1998 as an umbrella organization to facilitate collaboration between the various regional and national groups that have a primary or significant focus on diabetes and pregnancy. The principal objectives of IADPSG are to foster an international approach to enhancing the quality of care, facilitating research, and advancing education in the field of diabetes in pregnancy.

During 11–12 June 2008, the IADPSG sponsored an International Workshop- Conference on Gestational Diabetes Diagnosis and Classification in Pasadena, California. More than 225 conferees from 40 countries reviewed published results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, additional unpublished HAPO study findings, and results of other work that examined associations of maternal glycemia with perinatal and long-term outcomes in offspring. Conferees then held regional caucuses to consider clinical implications of the information that had been presented. On 13 June 2008, the IADPSG Consensus Panel (with representation from the 10 member organizations of the IADPSG and other organizations with an interest in diabetes and pregnancy) was convened. Members of the IADPSG Consensus Panel are listed in the online-only appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc09-1848/DC1. Subsequently, the IADPSG Consensus Panel reviewed further HAPO study results. Through this process, the consensus summarized in this report was reached.

This report represents the opinions of individual members of the IADPSG Consensus Panel and does not necessarily reflect the position of the organizations they represent. It is expected that this report will be considered by diabetes, obstetric, and other organizations and will serve as the basis for internationally endorsed criteria for the diagnosis and classification of diabetes in pregnancy.

Gestational diabetes mellitus (GDM), a common medical complication of pregnancy, is defined as “any degree of glucose intolerance with onset or first recognition during pregnancy” (1,2). The initial criteria for its diagnosis were established more than 40 years ago (3) and, with modifications (4), remain in use today. These criteria were chosen to identify women at high risk for development of diabetes after pregnancy (5) or were derived from criteria used for nonpregnant individuals (6) and not necessarily to identify pregnancies with increased risk for adverse perinatal outcome. There is consensus that overt diabetes during pregnancy, whether symptomatic or not, is associated with significant risk of adverse perinatal outcome. The risk of adverse perinatal outcome associated with degrees of hyperglycemia less severe than overt diabetes is controversial. Several factors contribute to this longstanding controversy.

Some have attributed risks of adverse outcomes associated with GDM, such as birth weight that is large for gestational age (LGA), excess fetal adiposity, and higher rate of cesarean section, to confounding characteristics, such as obesity, more advanced maternal age, or other medical complications, rather than glucose intolerance (7–9). Bias of caregivers toward expectation of adverse outcomes may increase morbidity due to increased intervention (10). Some suggest that criteria currently in wide use for the diagnosis of GDM are too restrictive and that lesser degrees of hyperglycemia increase risk of adverse perinatal outcomes (11–16). Conversely, others believe that systematic efforts to identify GDM should be stopped unless data become available to link significant morbidities to specific degrees of glucose intolerance (8). Lack of international uniformity in the approach to ascertainment and diagnosis of GDM has been a major hurdle (2).

Questions have been raised regarding cost-effectiveness and benefit of detecting and treating GDM. Recent recommendations of the U.S. Preventive Services Task Force, the U.K. 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 (17–19). Recently, a cost-effectiveness study undertaken by the U.K. National Institute for Health and Clinical Excellence concluded that “screening, diagnosis, and treatment of gestational diabetes is cost-effective” (20).

As currently defined (1,2), GDM includes a subgroup with more severe hyperglycemia (similar to that seen in preexisting diabetes) that presents special issues concerning management during pregnancy and postpartum follow-up. The issues raised by inclusion of this subgroup with those with GDM are of greater concern because of the rising prevalence of obesity, type 2 diabetes, and other metabolic disturbances among younger age-groups (21–23).

The HAPO study was designed to clarify risks of adverse outcome associated with degrees of maternal glucose intolerance less severe than those with overt diabetes during pregnancy (24). HAPO study results (25,26) were considered in depth in arriving at the recommendations for diagnosis of GDM presented in this report. Recommendations for detection of overt diabetes during pregnancy are based on the opinions of the IADPSG Consensus Panel members because information from prospective studies or appropriately designed clinical trials is not available.

THE HAPO STUDY

The objective of the HAPO study was to clarify associations of levels of maternal glucose lower than those diagnostic of diabetes with perinatal outcome (24,25). This was accomplished by performing a 75-g oral glucose tolerance test (OGTT) on a heterogeneous, multinational, multicultural, ethnically diverse cohort of □25,000 women in the third trimester of gestation. Medical caregivers were blinded to status of glucose tolerance except when predefined criteria were met (fasting plasma glucose [FPG] >5.8 mmol/l [105 mg/dl] and/or 2-h plasma glucose >11.1 mmol/l [200 mg/dl]) (24). It was anticipated that this would provide data on associations between maternal glycemia and risk of specific adverse outcomes that could be used to derive internationally acceptable criteria for diagnosis and classification of GDM.

Primary outcomes in the blinded HAPO cohort were birth weight >90th percentile, primary cesarean section delivery, clinically defined neonatal hypoglycemia, and cord C-peptide >90th percentile. Secondary outcomes were preclampsia, preterm delivery, shoulder dystocia/birth injury, hyperbilirubinemia, and intensive neonatal care.

Importantly, there were continuous graded relationships between higher maternal glucose and increasing frequency of the primary outcomes, independent of other risk factors (25). Similar associations were also observed for secondary outcomes (25,26). Associations did not differ among centers; thus, the results are applicable to all centers and can be used globally to develop outcome-based criteria for classifying glucose metabolism in pregnancy. Because associations were continuous with no obvious thresholds at which risks increased, it was concluded that a consensus was required to translate these results into clinical practice.

OTHER STUDIES REVIEWED

Data from numerous studies are consistent with HAPO study results. In Pima Indians, Pettitt et al. (27) found that maternal plasma glucose concentration during pregnancy (measured 2 h after a 75-g load) had a continuous association with adverse pregnancy outcomes (LGA and cesarean section). A Danish study of pregnant women with mild glucose intolerance but without GDM found a linear association between maternal 2-h glucose and cesarean delivery, spontaneous preterm delivery, shoulder dystocia, and macrosomia after adjustment for confounders (28). Another analysis of that cohort (11) showed a linear relationship between maternal fasting glucose and macrosomia. The Toronto Tri-Hospital Study showed continuous associations between maternal glycemia and adverse pregnancy outcomes (29). Sacks et al. (30) found associations between FPG and the 2-h value on a 75-g OGTT and macrosomia in a mixed ethnic U.S. cohort (61% Hispanic). In a multiethnic U.S. population, Ferrara et al. (16) found risk of severe macrosomia, neonatal hypoglycemia, and hyperbilirubinemia increased with increasing number of abnormal glucose values according to current American Diabetes Association cut points (2,5) among women who did not meet National Diabetes Data Group criteria for GDM (31).

There are studies relating maternal glycemia to long-term outcomes in offspring. Pima Indian data demonstrated a direct association between maternal glycemia (in women whose glucose concentrations were in the range found in the blinded HAPO cohort) and offspring's long-term relative weight and degree of glucose tolerance, and it was a risk factor for diabetes and/or impaired glucose tolerance during the female offspring's pregnancies (32). Hillier et al. (33) assessed offspring of mothers receiving care in a large, diverse health care practice. Adiposity in offspring at 5–7 years of age was significantly associated with measures of maternal glycemia (50-g glucose challenge and/or 100-g OGTT) during pregnancy. This suggests that we may expect similar outcomes in offspring from the HAPO study.

TRANSLATION OF HAPO STUDY RESULTS FOR DIAGNOSIS OF GDM

Some studies cited above and others were presented at the IADPSG Pasadena meeting. The results were consistent with HAPO findings indicating that associations between maternal glycemia and adverse outcomes are continuous across the range of glucose concentrations below levels diagnostic of diabetes (25,26). As a result of the extensive efforts used to standardize procedures for participant enrollment (24,25), laboratory analyses (34), data collection (24,25), and analysis of results (25,26), HAPO data were used as the basis for the new GDM diagnostic thresholds recommended in this report.

HAPO data show strong linear associations of risks for >90th percentiles of birth weight, cord C-peptide, and percent body fat with each of three measures of maternal glucose (FPG, 1-h, and 2-h post–75-g load). In determining the recommendations for diagnostic thresholds, associations with these outcomes were used to select glucose concentrations as potential diagnostic threshold values (supplemental Fig. 1). Published data support this decision. Fetal macrosomia (LGA) is a major indicator of the effects of hyperglycemia during pregnancy (12,35,36). Associations of LGA and excess adiposity with fetal hyperinsulinemia are strong and independent of confounders (26,37,38). This is supported by experiments in pregnant monkeys (39). Risks of difficult delivery and maternal/neonatal damage associated with fetal macrosomia (9,40) were confirmed in large populations (41,42). Long-term risks associated with fetal macrosomia in infants of women with GDM (independent of confounders) include childhood overweight (43,44) and metabolic factors that may increase risk of cardiovascular disease (CVD) (45).

In the HAPO study, frequencies of study outcomes were compared across the entire distribution of glucose concentrations, with the lowest glucose concentration ranges used as the reference for calculation of odds ratios (ORs) (25). However, the IADPSG Consensus Panel decided that for selection of diagnostic thresholds, mean values for FPG, 1-h, and 2-h OGTT plasma glucose concentrations (4.5, 7.4, and 6.2 mmol/l, respectively) for the entire study cohort should be used as reference. Concentrations at which ORs for specific outcomes in adjusted models reached predefined values, with glucose modeled as a continuous variable, were then determined. After review of these data, the IADPSG Consensus Panel concluded that the predefined value for the OR at the threshold relative to the mean should be 1.75 (ORs 1.5 and 2.0 were also considered, see other considerations below). Finally, proportions of participants who would be identified by measurement of FPG only, FPG plus 1-h glucose concentration, and FPG plus both 1-h and 2-h plasma glucose concentrations were considered.

Diagnostic recommendations

The stepwise consideration of the HAPO study data described above led to the recommendation of the values for FPG, 1-h, and 2-h plasma glucose concentration (*Si* and conventional) indicated in Table 1 as diagnostic thresholds. These thresholds are the average glucose values at which odds for birth weight >90th percentile, cord C-peptide >90th percentile, and percent body fat >90th percentile reached 1.75 times the estimated odds of these outcomes at mean glucose values, based on fully adjusted logistic regression models. At least one of these thresholds must be equaled or exceeded to make a diagnosis of GDM. Measuring FPG alone identified 8.3% of the cohort as having GDM. Adding measurement of the 1-h plasma glucose identified an additional 5.7%; adding the 2-h plasma glucose measurement identified another 2.1% of the cohort. Among the HAPO cohort, 11.1% had only one elevated result, 3.9% had two elevated results, and 1.1% had elevation of all three results. In addition, 1.7% of the cohort was unblinded due to an FPG or 2-h plasma glucose value on the enrollment OGTT above predefined values of 5.8 mmol/l (105 mg/dl) or 11.1 mmol/l (200 mg/dl), respectively (25). Thus, by these new criteria, the total incidence of GDM was 17.8%; the FPG plus 1-h plasma glucose levels identified a large majority of these individuals.

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Table 1

Threshold values for diagnosis of GDM or overt diabetes in pregnancy

Adjusted ORs and 95% CIs for associations between maternal glucose and HAPO study outcomes are in supplemental Table A. ORs are for the difference in glucose between the mean glucose value and the recommended threshold. In addition to the outcomes used to determine the thresholds, there were strong associations between maternal glucose and preeclampsia (ORs 1.40–1.57) and shoulder dystocia and/or birth injury (1.30–1.43).

The frequencies of HAPO study outcomes when all three glucose measures were below threshold values and when any one or more values were greater than or equal to threshold concentration were compared (supplemental Table B). The frequency of birth weight, C-peptide, or percent infant body fat >90th percentile was approximately twofold greater when any of the glucose values were greater than or equal to the threshold. The frequency of preeclampsia was twofold higher when one or more glucose values met or exceeded threshold, and frequencies of preterm delivery and primary cesarean section were >45% higher.

Other considerations

Measurement of glucose.

The frequencies and ORs for outcomes on which the recommended diagnostic thresholds are based increase substantially over relatively small changes in glucose concentration (supplemental Fig. 1 and Table A). Therefore, to achieve reliable diagnosis and classification of hyperglycemia in pregnancy, clinical laboratories must measure venous plasma or serum glucose using an enzymatic method with high accuracy and precision. This includes proper sample collection and processing to minimize pre-analytic glycolysis and proper laboratory analysis (34,46). Capillary and venous plasma glucose concentrations differ and are not interchangeable, and conversion factors do not accurately estimate equivalent values (46).

Alternative OR/threshold combinations.

Consideration was given to glucose values and outcome frequencies for adjusted ORs of 1.5 and 2.0. The threshold OR of 1.5 identified 25% of the cohort with one or more glucose values that met or exceeded the threshold. The proportion of the cohort with FPG equal to or greater than threshold at ORs of 1.5, 1.75, or 2.0 (5.0, 5.1, and 5.3 mmol/l or 90, 92, or 95 mg/dl, respectively) differed substantially, representing □12, 8, and 4%, respectively. At ORs of 2.0, frequencies of birth weight, cord serum C-peptide, or percent infant body fat >90th percentile in those meeting threshold were modestly higher than those for OR 1.75 (supplemental Table B), but the number of participants meeting threshold decreased from 16.1 to 8.8%, meaning that the higher thresholds would fail to identify many cases with nearly comparable risk of adverse outcomes.

Rounding threshold values to easy-to-remember numbers.

Values such as 5.0 and 9.0 mmol/l (90 and 155 mg/dl, respectively) for FPG and 2-h plasma glucose would be somewhat easier to remember than those indicated in Table 1. However, this strategy is not feasible. First, as indicated above, arbitrarily choosing an FPG threshold of 5.0 mmol/l (90 mg/dl) would substantially affect the proportion of women meeting a diagnostic threshold. Second, both *Si* and standard units are widely used, and the numbers are not equally easy or difficult to remember for both units of measure. The values in Table 1 represent the best choice from a clinical perspective, and they meet the predefined strength of association from an epidemiological perspective.

Randomized treatment trials and choice of threshold values.

Two randomized controlled trials comparing active treatment versus standard obstetric care for mild GDM have been conducted during the years in which the HAPO study was carried out (47,48). In both randomized controlled trials, treatment, achieved primarily by diet/lifestyle modification, resulted in reduced birth weight and frequency of LGA births and preeclampsia. Recruitment processes and glycemic values of participants were not identical in the randomized controlled trials and the HAPO observational study. However, there was substantial overlap between glucose values used for inclusion in the randomized controlled trials and those recommended in this report as new threshold values. Furthermore, frequencies of outcomes such as LGA or birth weight >90th percentile and preeclampsia in usual care versus treatment arms of the randomized controlled trials are similar to those observed in the HAPO study among women with one or more glucose values that meet or exceed the threshold, compared with those with all values below threshold (supplemental Table B). Although not directly comparable, it was concluded that results of the two randomized controlled trials (47,48) and HAPO (25,26) are highly complementary.

DETECTION AND DIAGNOSIS OF OVERT DIABETES DURING PREGNANCY

The International Workshop-Conferences on GDM have defined the condition as “any degree of glucose intolerance with onset or first recognition during pregnancy” (1,2). The definition has applied whether or not insulin is used for treatment or hyperglycemia persists after pregnancy. The possibility that unrecognized glucose intolerance antedated the pregnancy is not excluded. This facilitates a uniform strategy for detection and classification of GDM but has limitations. As ongoing epidemics of obesity and diabetes result in more type 2 diabetes in young women, the number who are undiagnosed (before pregnancy) is increasing (49,50). The need to identify these women and address perinatal risks that may be particular to their greater degree of hyperglycemia is becoming more important. The IADPSG Consensus Panel reviewed the current knowledge base during the June 2008 IADPSG meeting. The recommendations summarized below are the opinions of the IADPSG Consensus Panel.

The issue of classification of women with likely prepregnancy diabetes (overt diabetes) first noted during pregnancy was addressed via presentations by experienced clinicians/researchers (Yasue Omori, Lois Jovanovic, Elisabeth Mathiesen, and Siri Kjos), accompanied by interactive discussion. Several arguments were made for identifying as a distinct group women with overt diabetes:

- Increased risk of congenital anomalies in offspring (51).
- Risk of diabetes complications (nephropathy and retinopathy) requiring treatment during pregnancy (52).
- Need for rapid treatment and close follow-up during pregnancy to ensure prompt restoration of normal glycemia (53,54).
- Need to ensure confirmation and appropriate treatment of diabetes after pregnancy.

Identification of overt diabetes

When and how to identify women with overt diabetes during pregnancy (not previously diagnosed) and how to define overt diabetes were considered during the IADPSG Pasadena meeting and subsequently. There was uniform agreement that this assessment should be made during the initial visit for prenatal care. There was debate about performing universal early testing or limiting testing to those women classified as high risk according to locally defined criteria. It was acknowledged that background population prevalence of diabetes in young women and extent of previous testing for metabolic disturbances vary greatly in different regions. Furthermore, it has not been determined whether universal testing early in pregnancy to detect overt diabetes is either of clinical value or cost-effective.

IADPSG Consensus Panel members favored use of any available certified laboratory measure of glucose (FPG, random plasma glucose, or A1C) for initial detection of possible cases. An expert committee recently recommended that an A1C value ≥6.5% (measured in a laboratory standardized/aligned with the Diabetes Control and Complications Trial [DCCT]/UK Prospective Diabetes Study [UKPDS] assay) be used for diagnosis of diabetes outside pregnancy (55). Although many IADPSG Consensus Panel members favored using A1C for detection of overt diabetes in pregnancy, it was not feasible to recommend a single test to use exclusively. Cost and standardization of A1C testing are issues for consideration, and hemoglobin variants are prevalent in some populations. Attending the first prenatal visit in the fasting state is impractical in many settings. Consensus thresholds recommended for the individual glycemia measures are indicated in Table 1. A tentative diagnosis of overt diabetes based on measurement of random plasma glucose must be confirmed with either an FPG or A1C value greater than or equal to the threshold using a DCCT/UKPDS standardized/aligned method (56).

Other considerations

Timing of the initial test.

It is desirable to detect overt diabetes in pregnancy as early as possible to provide an opportunity to optimize pregnancy outcome. However, there is variability in time of enrollment for prenatal care beyond the control of health care providers. Accordingly, no limit is placed on the timing of initial

assessment for detection of overt diabetes in pregnancy. However, if enrollment is at 24 weeks' gestation or later and overt diabetes is not found, the initial test should be followed by a 75-g OGTT.

Indeterminate results of initial testing.

It was recognized that any assessment of glycemia in early pregnancy would also result in detection of milder degrees of hyperglycemia short of overt diabetes. Recently, it was reported that higher first-trimester FPG levels (lower than those diagnostic of diabetes) are associated with increased risks of later diagnosis of GDM and adverse pregnancy outcomes (57). However, there have not been sufficient studies performed to know whether there is benefit of generalized testing to diagnose and treat GDM before the usual window of 24–28 weeks' gestation. Therefore, the IADPSG Consensus Panel does not recommend routinely performing OGTTs before 24–28 weeks' gestation. It is recommended that an FPG value in early pregnancy ≥5.1 mmol/l (92 mg/dl) also be classified as GDM.

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SUMMARY OF DETECTION STRATEGY

The overall strategy recommended by the IADPSG Consensus Panel for detection and diagnosis of hyperglycemic disorders in pregnancy is summarized in Table 2. Two discrete phases are included. The first is detection of women with overt diabetes not previously diagnosed or treated outside of pregnancy. Universal early testing in populations with a high prevalence of type 2 diabetes is recommended, especially if metabolic testing in this age-group is not commonly performed outside of pregnancy. Well-designed studies should be conducted to determine whether it is beneficial and cost-effective to perform an OGTT in women who do not have overt diabetes at early testing but have indeterminate nondiagnostic results. The second phase is a 75-g OGTT at 24–28 weeks' gestation in all women not previously found to have overt diabetes or GDM.

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Table 2

Strategy for the detection and diagnosis of hyperglycemic disorders in pregnancy*

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CONCLUSIONS

Immediate implications

These recommendations have widespread implications. The strategy outlined in Table 2 will finally lead to using a 75-g glucose dose for an OGTT in all clinical settings in or outside of pregnancy. In some regions and/or countries, this represents a substantial change in long-established practices. Glucose testing early in pregnancy to detect overt diabetes and again with a 75-g OGTT at 24–28 weeks' of gestation in all pregnancies not already diagnosed with overt diabetes or GDM by early testing represents fundamental changes in strategies for detection and diagnosis of hyperglycemia in pregnancy. In most areas, using the outcome-linked diagnostic criteria in Table 1 and the detection strategy in Table 2 will substantially increase the frequency of hyperglycemic disorders in pregnancy. However, this is consistent with the high prevalence of obesity and disorders of glucose metabolism in the general population of young adults (21,22) and with recent reports of a rising prevalence of GDM and preexisting overt diabetes in pregnant women (49).

Future considerations

In future clinical practice, simpler and more cost-effective strategies that do not require performing an OGTT on most pregnant women may be developed. In the HAPO study, risks of some adverse outcomes were low when FPG was ≤4.4 mmol/l (80 mg/dl). However, it was thought that using FPG to potentially identify pregnancies at very low risk for GDM and for adverse outcomes requires further evaluation. Similarly, further evaluation of A1C results from the HAPO study, results from other populations, or new integrated tests of glycemia with a shorter timeframe than A1C might serve this purpose.

The HAPO study was a basic epidemiological investigation that for the first time conclusively identified strong continuous associations of maternal glucose levels below those diagnostic of diabetes with several perinatal outcomes. It was not a clinical trial, but two randomized controlled trials of treatment of mild GDM have been carried out successfully in participants with glucose values that overlap with the thresholds recommended in this report. However, it is likely that additional well-designed randomized controlled trials and other clinical studies will be needed to determine *1*) cost-effective therapeutic strategies for treatment of GDM diagnosed by the IADPSG Consensus Panel–recommended criteria; *2*) optimal glycemic treatment targets; *3*) appropriate follow-up of mothers to determine risks for later development of diabetes, other metabolic disorders, or CVD risk factors; and *4*) follow-up of children to assess potential associations of maternal glycemia with long-term risks of obesity, altered glucose metabolism, and CVD risk factors.

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