The 75-Gram Glucose Load in Pregnancy

Relation between glucose levels and anthropometric characteristics of infants born to women with normal glucose metabolism

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OBJECTIVE — To investigate, in pregnant women without gestational diabetes mellitus (GDM), the relation among obstetric/demographic characteristics; fasting, 1-h, and 2-h plasma glucose values resulting from a 75-g glucose load; and the risk of abnormal neonatal anthropometric features and then to verify the presence of a threshold glucose value for a 75-g glucose load above which there is an increased risk for abnormal neonatal anthropometric characteristics.

RESEARCH DESIGN AND METHODS — The study group consisted of 829 Caucasian pregnant women with singleton pregnancy who had no history of pregestational diabetes or GDM, who were tested for GDM with a 75-g, 2-h glucose load, used as a glucose challenge test, in two periods of pregnancy (early, 16–20 weeks; late, 26–30 weeks), and who did not meet the criteria for a GDM diagnosis. In the newborns, the following abnormal anthropometric characteristics were considered as outcome measures: cranial/thoracic circumference (CC/TC) ratio ≤10th percentile for gestational age (GA), ponderal index (birth weight/length^3 × 100) ≥90th percentile for GA, and macrosomia (birth weight ≥90th percentile for GA), on the basis of growth standard development for our population. For the first part of the objective, logistic regression models were used to identify 75-g glucose load values as well as obstetric and demographic variables as markers for abnormal neonatal anthropometric characteristics. For the second part, the receiver operating characteristic (ROC) curve was performed for the 75-g glucose load values to determine the plasma glucose threshold value that yielded the highest combined sensitivity and specificity for the prediction of abnormal neonatal anthropometric characteristics.

RESULTS — In both early and late periods, maternal age >35 years was a predictor of neonatal CC/TC ratio ≤10th percentile and macrosomia, with fasting 75-g glucose load values being independent predictors of neonatal CC/TC ratio ≤10th percentile. In both periods, 1-h values gave a strong association with all abnormal neonatal anthropometric characteristics chosen as outcome measures, with maternal age >35 years being an independent predictor for macrosomia. The 2-h, 75-g glucose load values were significantly associated in both periods with neonatal CC/TC ratio ≤10th percentile and ponderal index ≥90th percentile, whereas maternal age >35 years was an independent predictor of both neonatal CC/TC ratio ≤10th percentile and macrosomia. In the ROC curves for the prediction of neonatal CC/TC ratio ≤10th percentile for GA in both early and late periods of pregnancy, inflection points were identified for a 1-h, 75-g glucose load threshold value of 150 mg/dl in the early period and 160 mg/dl in the late period.

CONCLUSIONS — This study documented a significant association, seen even in the early period of pregnancy, between 1-h, 75-g glucose load values and abnormal neonatal anthropometric features, and provided evidence of a threshold relation between 75-g glucose load results and clinical outcome. Our results would therefore suggest the possibility of using a 75-g, 1-h oral glucose load as a single test for the diagnosis of GDM, adopting a threshold value of 150 mg/dl at 16–20 weeks and 160 mg/dl at 26–30 weeks.

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Abbreviations: CC/TC ratio, cranial/thoracic circumference; GA, gestational age; GCT, glucose challenge test; GDM, gestational diabetes; GTT, glucose tolerance test; OR, odds ratio; ROC, receiver operating characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

There is little permanent consensus on criteria for screening or specific screening strategies for gestational diabetes mellitus (GDM). The most commonly used criteria are those emanating from the American Diabetes Association, the International Workshop-Conference on Gestational Diabetes Mellitus, and the National Diabetes Data Group.

The recommendations from the Fourth International Workshop-Conference on Gestational Diabetes (1) suggested that the 75-g glucose tolerance test (GTT) could be used to diagnose GDM. However, the criteria for the 75-g GTT were not designed specifically for use in pregnant women, nor have they so far been validated for identifying pregnancies at increased risk for adverse outcome (2).

In recent years, the end point of GTTs in pregnancy has shifted from long-term maternal outcome to the prediction of short-term fetal and neonatal morbidity (3). Despite evidence of the continuous relationship between maternal glycemia during pregnancy and the risk of fetal macrosomia, no threshold of maternal glucose at glucose challenge test (GCT) has been observed to discriminate between high and low risk for neonatal macrosomia (4). Indeed, when neonatal macrosomia was used as an end point to validate the 75-g GTT in pregnancy, a clear threshold value could not be identified (3).

The aim of our study was to investigate the use of a 75-g glucose load in pregnant women without GDM to provide data on the specific relation among obstetric/demographic characteristics; fasting, 1-h, and 2-h plasma glucose values; and the risk of abnormal neonatal anthropometric features and then to verify the presence of a threshold glucose value for a 75-g glucose load above which there is an increased risk for abnormal neonatal anthropometric characteristics.

RESEARCH DESIGN AND METHODS

Subjects and methods

From January 1997 to December 1999, 1,061 consecutive Caucasian pregnant

Table 1—*Variables and outcome measures used in the logit models for the risk of abnormal anthropometric neonatal characteristics in the study population*

Variables	
n	829
Maternal age (years)	31.2 ± 4.6
Maternal age >35 years	175 (21.1)
Parity ≥2	245 (29.6)
BMI (kg/m^2)	22.5 ± 3.0
BMI ≥27 kg/m^2	44 (5.3)
Maternal macrosomia*	27 (3.3)
Previous macrosomia	17 (2.1)
Maternal weight gain (kg)	12.5 ± 4.6
Neonatal (male sex)	407 (49.1)
Early period 75-g glucose load (mg/dl)	
Fasting	84.1 ± 6.1
1-h	114.2 ± 27.4
2-h	99.3 ± 20.1
Late period 75-g glucose load (mg/dl)	
Fasting	84.7 ± 7.0
1-h	121.3 ± 30.1
2-h	103.3 ± 21.3
Outcome measures	
Neonatal (CC/CT ratio) ≤10th percentile for GA	112 (13.5)
Neonatal ponderal index ≥90th percentile for GA	109 (13.1)
Neonatal macrosomia	96 (11.6)

Data are *n*, *n* (%), or means ± SD. *Maternal macrosomia defined as maternal birth weight ≥4.000 g.

women with singleton pregnancy attending the Maternal-Fetal Medicine Unit of the Department of Gynecology, Perinatology and Human Reproduction of the University of Florence who had no history of pregestational diabetes or GDM were tested for GDM with a 75-g, 2-h glucose load, used as a GCT, in two periods of pregnancy: early (16–20 weeks) and late (26–30 weeks). All subjects with an early negative 75-g glucose load (plasma glucose level after 1 h <135 mg/dl) or with an early positive 75-g load followed by a negative 100-g GTT underwent a second 75-g GCT later in pregnancy.

Prior to the study, gestational age was determined by a first trimester dating scan. All plasma glucose determinations were performed at the clinical laboratory of the hospital using the glucose oxidase method.

GDM was diagnosed according to the criteria established by Carpenter and Coustan (5).

From the group of 1,061 women, we selected a study group of 829 women who did not meet criteria for a GDM diagnosis and delivered term (from 37 completed to 42 weeks), live-born infants with no evidence of congenital malformations. Among the women excluded, 44 discontinued the GDM screening/diagnosis program, 93 were diagnosed as having GDM (29 at 16–20 weeks and 64 at 26–30 weeks), 63 had a preterm delivery, and 13 had a fetal malformation detected during gestation or at birth. Complete data were not available from 19 women, 14 of whom delivered elsewhere.

In the newborns, the following abnormal anthropometric characteristics were considered as outcome measures: cranial/thoracic circumference (CC/TC) ratio ≤10th percentile for gestational age (GA), ponderal index (birth weight/length^3 × 100) ≥90th percentile for GA, and macrosomia (birth weight ≥90th percentile for GA), on the basis of growth standard development for our population (6). Cranial circumference was measured at the level of occipital-glabellar diameter by using a metric tape; thoracic circumference was determined as the mean value between inhalation and exhalation, taken by metric tape at the level of submammary line (6).

The study received ethical approval, and all subjects gave their informed consent.

Statistical analysis

For the first part of the objective, logistic regression models were used to identify 75-g glucose load values and personal, obstetric, and demographic variables that are markers for abnormal neonatal anthropometric characteristics.

For the second part, the receiver operating characteristic (ROC) curve was performed for the 75-g glucose load values to determine the plasma glucose threshold value that yielded the highest combined sensitivity and specificity for the prediction of abnormal neonatal anthropometric characteristics.

To identify cutoff values of the different 75-g load measures that best discriminate between the groups with normal or abnormal anthropometric characteristics, a binary logistic regression was performed. The predictive power of the binary logistic regression was assessed by evaluating sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio for an abnormal test corresponding to a cutoff level of 0.5 (7).

Two-tailed χ^2 or Fisher's exact tests were used for categoric variables, and the odds ratios (ORs) were calculated by cross-tabulation, with a 95% CI. Statistical significance was determined at $P < 0.05$. Statistical analyses were performed with Stata statistical software (Release 5.0; Stata Corporation, College Station, TX).

RESULTS — Personal, obstetric, and demographic characteristics of the 829 patients enrolled in the study, along with the 75-g glucose load results and abnormal anthropometric characteristics considered as outcome measures, are listed in Table 1.

First objective

Results from the logistic regression models to determine independent risk factors for abnormal neonatal anthropometric features are shown in Tables 2 (early period) and 3 (late period). Only significant risk factors are listed in these tables.

In the early period, maternal age >35 years and fasting 75-g glucose load values were independent predictors of neonatal CC/TC ratio ≤10th percentile; maternal age >35 years also predicted macrosomia (Table 2). The 1-h values gave a strong association with all abnormal neonatal anthropometric characteristics chosen as outcome measures, and in particular with a neonatal CC/TC ratio ≤10th percentile, with an area under the ROC curve of 0.7705 (Table 2, Fig. 1*A*). Maternal age

Table 2—*Significant risk factors from the logit models for abnormal anthropometric neonatal characteristics in early period (16–20 weeks' gestation)*

Variables	Neonatal CC/CT ratio ≤10th percentile for GA	Neonatal ponderal index ≥90th percentile for GA	Macrosomia
Logit model with fasting 75-g glucose load values			
Maternal age >35 years	1.65 (1.14–2.38)	1.50 (1.00–2.23)	2.13 (1.38–3.27)
Fasting 75-g glucose load value	1.05 (1.02–1.07)	1.02 (0.99–1.05)	1.03 (1.00–1.06)
Area under ROC Curve	0.6371	0.5986	0.6429
Logit model with 1-h, 75-g glucose load values			
Maternal age >35 yrs	1.31 (0.86–1.99)	1.17 (0.76–1.79)	1.04 (1.04–1.05)
Maternal macrosomia	1.02 (1.01–1.04)	0.73 (0.45–1.20)	0.32 (0.70–1.50)
1-h, 75-g glucose load value	1.81 (1.15–2.83)	1.03 (1.02–1.03)	1.02 (1.01–1.03)
Area under ROC curve	0.7705	0.7358	0.7210
Logit model with 2-h, 75-g glucose load values			
Maternal age >35 years	1.02 (1.01–1.03)	1.30 (0.86–1.97)	1.03 (1.01–1.04)
2-h, 75-g glucose load value	1.03 (1.02–1.04)	1.03 (1.02–1.04)	1.02 (1.00–1.03)
Area under ROC curve	0.7011	0.6834	0.6804

Data are *n* or adjusted ORs (95% CI).

>35 years and maternal macrosomia were independent predictors for macrosomia and neonatal CC/TC ratio ≤10th percentile, respectively. The 2-h values were significantly associated with neonatal CC/TC ratio ≤10th percentile and ponderal index ≥90th percentile, whereas maternal age >35 years was an independent predictor of both neonatal CC/TC ratio ≤10th percentile and macrosomia (Table 2).

In the late period, maternal age >35 years was a predictor of neonatal CC/TC ratio ≤10th percentile and macrosomia, and fasting 75-g glucose load values were independent predictors of CC/TC ratio ≤10th percentile and ponderal index ≥90th percentile (Table 3). Also in this case, the 1-h plasma glucose values gave the strongest association with abnormal neonatal anthropometric characteristics, and in particular with a neonatal CC/TC ratio ≤10th percentile, with an area under the ROC curve of 0.8154 (Fig. 1*B*). Maternal age >35 years was significantly associated with macrosomia. Again, the 2-h values were significantly associated with neonatal CC/TC ratio ≤10th percentile and ponderal index ≥90th percentile, whereas maternal age >35 years was an independent predictor of both a neonatal CC/TC ratio ≤10th percentile and macrosomia (Table 3).

Interestingly, there were significant differences between pregnancies with a neonatal CC/TC ratio ≤10th percentile or >10th percentile in the rates of cesarean section (38/112 [33.9%] vs. 119/717 [16.6%]; $P < 0.001$; OR 3.93, CI 2.6–5.9) and shoulder dystocia (6/112 [5.4%] vs. 1/717 [0.1%]; $P < 0.0003$; OR 6.65, CI 4.6–9.4).

Second objective

The ROC curves for the prediction of neonatal CC/TC ratio ≤10th percentile for GA in both early and late periods of pregnancy were then constructed for 1-h, 75-g glucose load values (Fig. 1*A* and *B*). Inflection points were identified for a threshold value of 150 mg/dl in the early period and 160 mg/dl in the late period. The performance of the binary logistic re-

Table 3—*Significant risk factors from the logit models (with fasting, 1-h, and 2-h values of 75-g glucose load) for abnormal anthropometric neonatal characteristics in late period (26–30 weeks' gestation)*

Variables	Neonatal CC/CT ratio ≤10th percentile for GA	Neonatal ponderal index ≥90th percentile for GA	Macrosomia
Logit model with fasting 75-g glucose load values			
Maternal age >35 years	1.57 (1.08–2.28)	1.48 (1.00–2.21)	2.09 (1.36–3.21)
Fasting 75-g glucose load value	1.07 (1.05–1.10)	1.04 (1.01–1.06)	1.03 (1.00–1.06)
Area under ROC curve	0.6683	0.6214	0.6540
Logit model with 1-h, 75-g glucose load values			
Maternal age >35 years	1.36 (0.88–2.11)	1.25 (0.81–1.91)	1.05 (1.04–1.05)
1-h, 75-g glucose load value	1.86 (1.19–2.91)	1.03 (1.02–1.03)	1.02 (1.01–1.03)
Area under ROC curve	0.8154	0.7499	0.7313
Logit model with 2-h, 75-g glucose load values			
Maternal age >35 years	1.05 (1.03–1.06)	1.37 (0.90–2.09)	1.99 (1.28–3.09)
2-h, 75-g glucose load value	1.04 (1.03–1.05)	1.03 (1.02–1.04)	1.02 (1.00–1.03)
Area under ROC curve	0.7244	0.7102	0.6996

Data are *n* or adjusted ORs (95% CI).

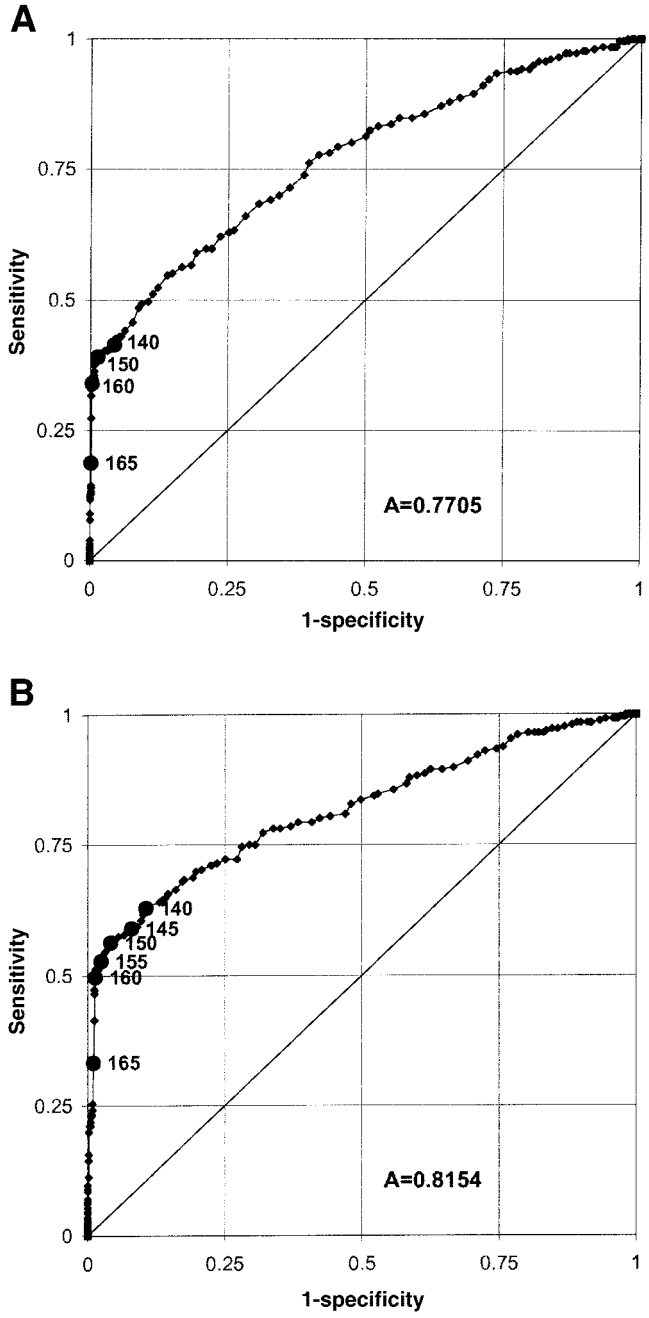

Figure 1—*ROC curves for the prediction of neonatal CC/TC ratio ≤10th percentile in early* (A) *and late* (B) *periods of pregnancy for 1-h, 75-g glucose load values.*

gression for these threshold values is shown in Table 4.

CONCLUSIONS — Strategies for the screening and diagnosis of GDM vary greatly in different countries. For example, many European centers, following World Health Organization recommendations, use a 75-g, 2-h load and the same criteria as for diabetes in the nonpregnant state (8), whereas a 100-g, 3-h oral GTT is commonly used in the U.S., with diagnostic thresholds based on the mothers' likelihood of developing diabetes in later life (9).

The reasons for the use of a 75-g test have been clearly outlined by Coustan (9). First, if it is standard to use the 75-g, 2-h oral GTT in nonpregnant individuals, then using a different test in pregnant women might be confusing for the laboratory as to the application of the proper diagnostic criteria. Second, a more widespread use of a 75-g, 2-h oral glucose load in pregnancy, once pregnancy-based diagnostic criteria are validated, would simplify worldwide comparison of data.

So far, however, the 75-g glucose load has not been validated as a test for the screening or diagnosis of GDM in the absence of a specific threshold relation between glucose load results and clinical outcome (2,3). In fact, the failure to demonstrate such a threshold relation might be attributable to the misleading selection of the outcome measure; for example, macrosomia defined merely in terms of birth weight does not allow discrimination between fetal overgrowth from exposure to hyperglycemia in utero and overgrowth that is genetically determined. Indeed, infants born to diabetic mothers also differ in terms of their anthropometric features and body proportions when compared with neonates of mothers with normal glucose metabolism (10). This tendency toward disproportionate growth of insulin-sensitive tissue has also been clearly demonstrated for minor degrees of maternal glucose intolerance (11), and a positive correlation between third trimester maternal glucose levels and fetal abdominal circumference has been found even in pregnant women with normal glucose metabolism (12).

Moving from this premise, we decided to explore the relation between the results of a 75-g glucose load and neonatal CC/TC ratio in addition to other traditional criteria, such as ponderal index and macrosomia. Our reasoning for this was that the CC/TC ratio is a parameter that can reveal the different growth pattern of insulin-sensitive tissues and therefore appears more appropriate than birth weight or ponderal index in defining body proportion (11,12).

With respect to our first objective, the 1-h glucose load value showed the strongest association with abnormal anthropometric features and particularly with a neonatal CC/TC ratio ≤10th percentile; interestingly, this association was present already in the early period of pregnancy.

Regarding the second objective, we found an inflection point for a threshold 1-h value of 150 mg/dl at 16–20 weeks in the ROC curve for the prediction of neonatal CC/TC ratio ≤10th percentile, but for 26–30 weeks, found a threshold 1-h value of 160 mg/dl. This finding, obtained with a noninvasive procedure, confirms

Table 4—*Performance of the binary logistic regression for selected 75-g glucose load thresholds*

	Threshold of 150 mg/dl (early period)	Threshold of 160 mg/dl (late period)
OR (95% CI)	112.3 (8.3–422.7)	67.4 (32.2–141.2)
True positive	66	71
False negative	46	35
False positive	9	7
True negative	708	710
Sensitivity (%)	58.9	68.8
Specificity (%)	98.7	99.02
Positive predictive value (%)	88	91.7
Negative predictive value (%)	93.9	93.3
Likelihood ratio (abnormal)	45.3	70.2

Data are *n* or %.

those achieved invasively by Weiss (13), who established a threshold of 160 mg/dl for 1-h glucose values to define an increased risk of fetal hyperinsulinemia.

A major result of our study was represented by the ORs obtained by the binary regression. In the early period of pregnancy, the nonadjusted OR for the CC/TC ratio ≤10th percentile, in the case of 1-h glucose load values >150 mg/dl, was as high as 112.3 (CI 8.3–422.7); in the late period, the nonadjusted OR for 1-h glucose load values >160 mg/dl was 67.4 (CI 32.1–141.2).

With the use of our suggested 75-g glucose load threshold values for the diagnosis of GDM in our study population, 75 cases would have been diagnosed in the early period and 78 in the later period; 59 cases had already been diagnosed in the early period. Thus the overall rate of positive diagnosis was 11.3% (94 GDM cases out of 829 women screened), similar to that found in our population with the traditional two-step screening/diagnosis strategy.

In conclusion, our study documented a significant association, already seen in the early period of pregnancy, between 75-g glucose load values and abnormal neonatal anthropometric features, and provided evidence of a threshold relation between 75-g glucose load results and perinatal outcome. Our results would therefore suggest the possibility of using a 75-g, 1-h oral glucose load as a single test for the diagnosis of GDM, adopting a threshold value of 150 mg/dl at 16–20 weeks and 160 mg/dl at 26–30 weeks.

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