Lack of Relationship Between Glucose Tolerance and Complications of Pregnancy in Nondiabetic Women

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Recent studies suggest that gestational diabetes mellitus (GDM) is underdiagnosed. To test this hypothesis, we examined the relationship of perinatal complications to glucose tolerance during the third trimester. Our population consisted of 287 women evaluated at ~28 wk gestation who had normal fasting (<5.9 mM) and 2-h (<9.2 mM plasma glucose) levels after a 100-g glucose load. Glycosylated hemoglobin and glycosylated plasma protein were also measured. Study subjects were stratified into three groups based on 2-h plasma glucose values: group 1 (n = 59) <5.6 mM, group 2 (n = 112) 5.6–6.0 mM, and group 3 (n = 116) 6.7–9.2 mM. There were statistically significant but low correlations (r < 0.20) between 2-h plasma glucose levels and mother's age, body mass index, infant weights, and Apgar scores. There was a significant increasing trend in the proportion of overweight and obese women from groups 1 to 3 (P < 0.02). There was also a significant trend toward higher birth weights (P = 0.013) and larger proportions of large for gestational age (LGA) babies (P = 0.02) from groups 1 to 3, and women with LGA infants showed higher fasting and 2-h plasma glucose levels than women with non-LGA infants (P = 0.032). However, there was no significant difference in perinatal complications or infant morbidity or mortality between groups. Percentage of glycosylated hemoglobin or glycosylated plasma protein did not differ between groups. In conclusion, mother and infant size are significantly related to 2-h plasma glucose, but we found no increased risk of perinatal complications with increased 2-h plasma glucose if <9.2 mM, suggesting that the current criteria for GDM are adequate for detecting women at risk for complications in our patient population. ***Diabetes Care*** **13:483–87, 1990**

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Received for publication 11 September 1989 and accepted in revised form 5 December 1989.

It is widely recognized that patients with gestational diabetes mellitus (GDM) are at increased risk of perinatal mortality and morbidity and that this risk can be reduced by identification and treatment of the disease (1–5). Accordingly, it is essential that cases be identified for institution of treatment aimed at achieving normoglycemia. The best documented and most commonly used criteria for diagnosis of GDM are those proposed by O'Sullivan and Mahan (6) based on a 100-g 3-h oral glucose tolerance test (OGTT).

It has been recommended that all pregnant women be screened for GDM between the 24th and 28th wk of pregnancy (7). This glucose challenge test usually consists of 50 g oral glucose given without regard to prandial state, with determination of plasma glucose 1 h later. Cutoff values of 7.3–8.4 mM are currently used as an indication for a 3-h OGTT, which is considered the definitive diagnostic test.

The relationship between hyperglycemia and complications of pregnancy in diabetic women is well documented (8–11). Recent studies have suggested that current criteria for GDM are not adequate and that women with more subtle levels of hyperglycemia may also be at increased risk for maternal and perinatal complications (12–17).

The purpose of this study was to examine the relationship of complications of pregnancy and fetal outcome to glucose tolerance during the third trimester.

RESEARCH DESIGN AND METHODS

Subjects for this study were drawn consecutively from all prenatal women evaluated at the obstetrical clinic of the University of Missouri Health Sciences Center, Columbia, Missouri, over a 16-mo period from 1987 to 1988. For purposes of this study, women were tested for GDM at ~28 wk gestation with a 100-g OGTT; venous blood was drawn in the fasting state and 2 h after ingestion of the 100-g glucose load (1- and 3-h samples were not obtained). The subjects did not receive a 50-g glucose challenge test before the 100-g screen. There were 347 women screened. Only women with normal plasma glucose values by O'Sullivan and Mahan's (6) criteria (fasting plasma glucose <5.9 mM and 2-h plasma glucose <9.2 mM) were enrolled in our study. Twenty-five subjects were excluded because a 2-h sample could not be obtained. An additional 12 were excluded due to delivery at another location; thus, records on delivery and newborns were not available. Twenty-three women were excluded because either their fasting or 2-h plasma glucose value was abnormal. The remaining 287 women comprised the basis of this investigation.

Plasma glucose was measured by a glucose oxidase procedure (Beckman glucose analyzer). Average glucose levels during the few weeks or months before testing were evaluated by measurement of glycosylated plasma protein and glycosylated hemoglobin (GHb), respectively. GHb was measured in all samples by two different methods: *1*) HbA_{1c} was measured by an automated ion-exchange high-performance liquid chromatography method (Diamat; Bio-Rad, Richmond, CA) and *2*) total GHb was measured by a boronate affinity chromatography test kit (Pierce, Rockford, IL). All GHb values were standardized to a reference ion-exchange high-performance liquid chromatography method to increase assay precision and to allow direct comparison of results by the two methods (18). Both GHb assay methods showed excellent precision (coefficient of variation [C.V.] <5%) over the study period, as assessed by assays of high- and low-level control samples in each run. Glycosylated plasma protein or fructosamine was also measured by two different methods: *1*) boronate affinity chromatography (Pierce) with measurement of protein in bound and nonbound fractions by Coomassie blue dye reduction reagent (Pierce protein assay reagent)—assay precision was adequate with interassay C.V.s <8%, and *2*) nitroblue tetrazolum reduction (RoTAG fructosamine assay; Roche, Nutley, NJ). Interassay C.V.s for the fructosamine assay were <5%. All of the above measurements were performed in our laboratory.

Our study subjects were divided into three groups based on 2-h plasma glucose values: group 1, 2-h plasma glucose <5.6 mM; group 2, 2-h plasma glucose 5.6–6.6 mM; and group 3, 2-h plasma glucose 6.7–9.2 mM.

These study groups were patterned after Tallarigo et al. (17). Group 3 corresponds with the category of impaired gestational glucose tolerance suggested by the National Diabetes Data Group report (19).

Statistics. In addition to summary statistics giving means, standard deviations, and proportions, the primary statistical methods used were group comparisons. Three groups were defined based on 2-h plasma glucose values. For categorical variables (including type of delivery, characteristics of the baby, e.g., large for gestational age [LGA], or complications) the groups were compared with a χ^2-test for homogeneity of proportions. In cases where it was necessary to test for a trend on increasing or decreasing proportions across the groups, a test for trend as described by Rosner was used (20). For variables on an interval scale (including age, height, or other characteristics of the mother), the groups were compared with one-way analysis of variance (ANOVA). In most cases, data were normally distributed, justifying the use of parametric analysis. For data that were not normal, the use of parametric analysis was justified on the basis of the large sample sizes. If the variable of interest was measured on an ordinal scale (e.g., Apgar scores), the Kruskal-Wallis nonparametric ANOVA test was used. In cases where only two groups were compared, either a two-sample *t* test or Wilcoxon's rank-sum test was used. In addition, approximations to the error made in estimating the differences in proportions between groups were found.

Clinical data. Subjects' weights were based on self-reported prepregnancy weights. Mother's weight, height, and age; gestational age; mode of delivery; complications at delivery; newborn weights; and newborn evaluations were obtained from hospital charts. Hypoglycemia was defined as plasma glucose <2.2 mM. Shoulder dystocia was judged by subjective report of one or several of the following criteria: prolonged time from delivery of fetal head to fetal shoulders, excessive traction required for delivery of fetal shoulders, additional maneuvers required for delivery of fetal shoulders (e.g., Wood's or McRobert's maneuver), and/or delivery of posterior shoulder after inability to deliver anterior shoulder. Congenital anomalies included both major and minor malformations identified by the examining pediatrician at the newborn exam. A woman was considered to be overweight if the body mass index (BMI) was >25 kg/m^2 and obese if BMI was >30 kg/m^2. Babies were considered to be LGA if their weight was >90th percentile for gestational age (21).

RESULTS

Some characteristics of our study population are shown in Table 1. Approximately 90% of the women were White.

Figures 1 and 2 show the distribution of 2-h plasma glucose values in the 287 study subjects. Group 1 included only 21% of the women in our study (Fig. 2*A*) in contrast to Tallarigo et al. (17) who found that >60%

TABLE 1
Characteristics of study population (n = 287)

Age (yr)	23.0 ± 5.0
Height (cm)	163.8 ± 7.2
Weight (kg)	63.5 ± 16.2
Body mass index (kg/m^2)	23.6 ± 5.5
Fasting plasma glucose (mM)	4.7 ± 0.4
Two-hour plasma glucose (mM)	6.5 ± 1.1
Gestation (wk)	29.5 ± 2.4

Values are means ± SD.

of subjects had 2-h plasma glucose values <5.6 mM (Fig. 2*B*).

Table 2 shows characteristics of subjects grouped according to 2-h plasma glucose values. Our results show a statistically significant relationship between the size of the mother and infant and mother's plasma glucose within the normal range of 2-h plasma glucose. Correlations between mother's weight or BMI and infant weight were low (r < 0.20), but there was a statistically significant increasing trend in the proportion of overweight mothers (P = 0.005, trend test) and obese mothers (P = 0.016, trend test) from groups 1 to 3. Overweight women and obese women had a significantly higher 2-h plasma glucose than women whose weight was normal (P = 0.01, t test). There were no statistically significant differences in age, height, weight, BMI, fasting plasma glucose, GHb, or glycosylated plasma protein among the three groups.

Table 3 shows the outcome of pregnancy by group. There was a statistically significant trend toward higher birth weight (P < 0.013, ANOVA) and larger proportions of LGA babies and babies >4000 g from groups 1 to 3 (P < 0.025, trend test). Women with LGA infants had higher fasting and 2-h plasma glucose values than women with non-LGA infants (P = 0.03, t test). However, trend analyses showed no significant differences in perinatal complications or infant morbidity or mortality among groups as measured by gestational age, percentage cesarean sections, percentage cephalopelvic disproportion (CPD), percentage fetal distress, 1- and 5-min Apgar scores, percentage hypoglycemia, and percentage congenital anomalies. Although no significant differences between groups were found, e.g., for proportions of cesarean sections, CPD, or fetal distress, it may be that sample sizes in this study were inadequate to detect small differences. To give an indication of the possible errors or margin of error due to sampling variability, we approximated the error that might be made in estimating differences in proportions between the groups. Based on these calculations we can be 95% confident that the differences between true proportions and observed sample proportions in the groups is <0.16 for primary cesarean sections, <0.11 for CPD and LGA, <0.10 for fetal distress, <0.08 for hypoglycemia, and <0.05 for shoulder dystocia and anomalies.

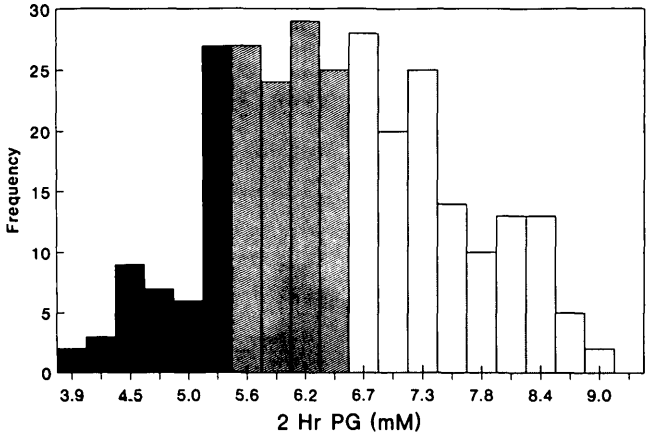

FIG. 1. Distribution of 2-h plasma glucose (PG) in 287 subjects. *Solid*, group 1 (plasma glucose <5.6 mM); *hatched*, group 2 (plasma glucose 5.6–6.6 mM); and *stippled*, group 3 (plasma glucose 6.7–9.2 mM) *bars* correspond to stratification by 2-h plasma glucose.

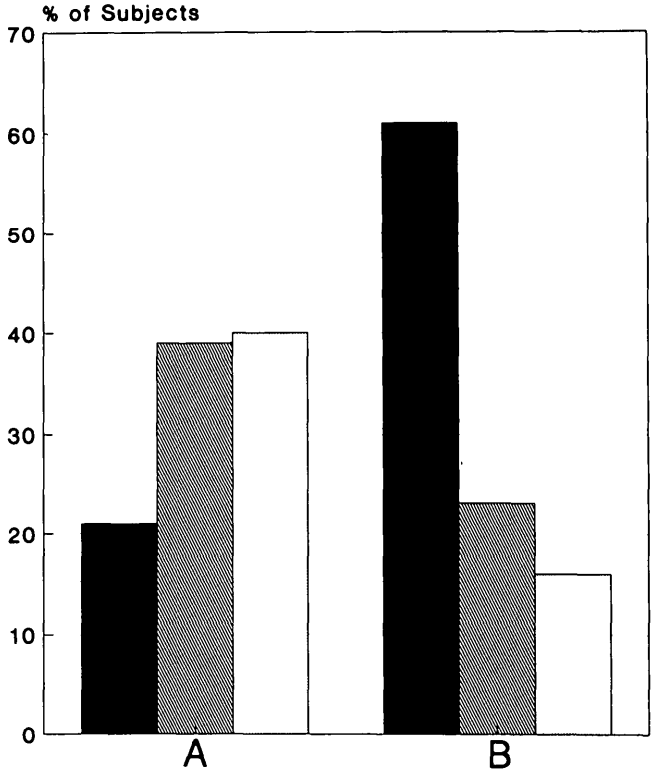

FIG. 2. Histograms showing number of subjects (percentage of total) in each 2-h glucose group. *A*, 287 subjects from this study; *B*, 249 subjects from Tallarigo et al. (17). *Solid bars*, group 1 (plasma glucose <5.6 mM); *hatched bars*, group 2 (plasma glucose 5.6–6.6 mM); *stippled bars*, group 3 (plasma glucose 6.7–9.2 mM).

DISCUSSION

Because hyperglycemia during pregnancy is a major cause of morbidity and mortality, any degree of maternal hyperglycemia could have some adverse effect. The most widely used diagnostic criteria for GDM are those of O'Sullivan and Mahan (6),

TABLE 2
Characteristics of study population by 2-h plasma glucose group

	Groups		
	1 (n = 59)	2 (n = 112)	3 (n = 116)
Age (yr)	21.9 ± 4.4	22.8 ± 5.2	23.8 ± 5.1
Height (cm)	165.1 ± 6.8	164.4 ± 7.4	162.4 ± 7.0
Weight (kg)	61.1 ± 12.1	63.5 ± 14.2	64.7 ± 19.5
Body mass index (kg/m²)	22.4 ± 4.1	23.5 ± 4.9	24.4 ± 6.6
Overweight (%)	13.6 ± 4.5	31.0 ± 4.4	35.3 ± 4.4
Obese (%)	5.1 ± 2.9	10.7 ± 2.9	17.2 ± 3.5
Fasting plasma glucose (mM)	4.6 ± 0.4	4.7 ± 0.3	4.8 ± 0.4
Two-hour plasma glucose (mM)	5.1 ± 0.4	6.1 ± 0.3	7.6 ± 0.6
Gestation (wk)	29.3 ± 2.4	29.6 ± 2.6	29.5 ± 2.3
GHb (%)	4.9 ± 0.3	4.9 ± 0.3	4.9 ± 0.3
HbA_{1c} (%)	4.5 ± 0.3	4.7 ± 0.4	4.6 ± 0.4
Glycosylated plasma protein (%)	10.4 ± 0.6	10.4 ± 0.8	10.4 ± 1.0
Fructosamine	1.8 ± 0.1	1.8 ± 0.1	1.7 ± 0.1

Values are means ± SD. Group 1, 2-h plasma glucose <5.6 mM; group 2, 2-h plasma glucose 5.6–6.6 mM; group 3, 2-h plasma glucose 6.7–9.2 mM.

which are based on predicting the risk of an individual developing established diabetes later in life. The use of such criteria serves to exclude patients who may have a lesser degree of hyperglycemia but still may have undesirable pregnancy outcome (22). It has been assumed that the same criteria would be suited to both of these objectives, i.e., predicting subsequent diabetes and as a prognostic indicator for pregnancy outcome.

Several studies have reported an increase in perinatal complications with subtle degrees of maternal hyperglycemia not diagnosable as GDM. Jovanovic and Peterson (12), Frisoli et al. (13), Forsbach et al. (14), and Leiken et al. (15) have shown that a high percentage (12–28%) of women with abnormal 50-g 1-h glucose challenge tests but normal 3-h OGTTs have babies weighing >4000 g. Some of these study samples, however, were not randomly selected (13,15).

Langer et al. (16) found that in women referred for an OGTT, there were more large babies born to women with one abnormal value on a 3-h OGTT than to those with no abnormal values or to those with treated GDM.

Tallarigo et al. (17) reported that among women with 2-h plasma glucose values between 6.7 and 9.2 mM (the upper end of normal) there was a greater incidence of fetal and maternal complications of pregnancy. Tallarigo et al. concluded that more stringent criteria may be necessary to define GDM. However, Weiss (23) suggests that the population studied by Tallarigo et al. may not have been representative of a normal population because it consisted of women with poor reproductive histories and with infants judged to be abnormal in >40% of the subjects' previous pregnancies.

Because threshhold values for this study group were patterned after the Tallarigo et al. study it seems appropriate to make certain comparisons. The most striking difference is in the distribution of 2-h plasma glucose values. In the Tallarigo et al. study >60% of the women had 2-h plasma glucose values <5.6 mM. Only 21% of women in our study had values in this range, suggesting significant differences in the patient population. Furthermore, unlike Tallarigo et al., we did not find increased complications in the higher glucose group.

Other studies also show population differences in glucose tolerance during pregnancy. In a study of OGTT in pregnant Nigerian women Famuyiwa et al. (24) showed that, unlike in White women, there was improvement

TABLE 3
Outcome of pregnancy by 2-h plasma glucose group

	Groups		
	1 (n = 59)	2 (n = 112)	3 (n = 116)
Gestational age (wk)	39.1 ± 1.7	38.8 ± 1.8	39.2 ± 1.6
Cesarean sections (primary; %)	22.0 ± 5.4	21.2 ± 3.9	19.8 ± 2.7
Cephalopelvic disproportion (%)	8.5 ± 3.6	7.1 ± 2.4	9.5 ± 2.7
Fetal distress (%)	6.8 ± 3.3	4.5 ± 2.0	8.6 ± 2.6
Birth weight (g)	3188.6 ± 508.3	3208.2 ± 531.18	3371.6 ± 502
Shoulder dystocia (%)	1.7 ± 1.7	0.9 ± 0.9	0.9 ± 0.9
Large for gestational age (%)	6.8 ± 3.3	12.5 ± 3.1	19.0 ± 3.6
Apgar			
1 min	8,7–9	8,7–9	8,7–9
5 min	9,9–9	9,9–9	9,9–9
Hypoglycemia (%)*	1.7 ± 1.7	7.1 ± 2.4	5.2 ± 2.1
Anomalies (%)	1.7 ± 1.7	1.8 ± 1.3	2.6 ± 1.5

Values are means ± SD except for Apgar scores, which are median, interquartile values. Group 1, 2-h plasma glucose <5.6 mM; group 2, 2-h plasma glucose 5.6–6.6 mM; group 3, 2-h plasma glucose 6.7–9.2 mM.
*Diagnosed by plasma glucose <2.2 mM.

in glucose tolerance in the second and third trimesters. Similar findings were also reported among Kenyan women (25). Whether these disparities are related to genetic, dietary, or activity differences among Kenyan women has not been determined.

Srinivasan et al. (26) found that in pregnant Indian women during the third trimester the levels of plasma glucose at fasting and at 1, 2, and 3 h after 100-g oral glucose were lower than those described by O'Sullivan and Mahan (6) in a White population. They also suggest that the criteria for diagnosis of GDM may require modifications to avoid underdiagnosis in certain populations.

In our study, we did not see any significant increase in perinatal complications, morbidity, or mortality in women with higher 2-h plasma glucose values that remained within the normal range. Furthermore, glycosylation measurements (both hemoglobin and plasma proteins) do not reflect subtle differences in glucose tolerance as measured by the OGTT. Thus, these assays would not be useful diagnostic tools for detecting subtle perturbations in glucose tolerance during pregnancy. We conclude that current criteria for diagnosis of GDM are appropriate for detecting women at risk for complications in our patient population.

ACKNOWLEDGMENTS

Measurement of fructosamine was funded by Roche Diagnostic Systems, a division of Hoffman-La Roche, Nutley, New Jersey.

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