Diagnosis of Gestational Diabetes in Early Pregnancy

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Objective: To determine whether glucose intolerance can be identified early in gestation in a high-risk population so that early intervention can be planned to prevent associated morbidity. Research Design and Methods: After appropriate dietary preparation, patients with a high risk for gestational diabetes underwent a 50-g oral glucose screening test during fasting. Patients were tested on enrollment and every 10 wk until delivery. Those with a 1-h plasma glucose value of ≥7.5 mM underwent a 100-g oral glucose tolerance test. Gestational diabetes was based on either a markedly abnormal 50-g screening test or abnormal 100-g oral glucose tolerance test. Results: Ten of 15 (66%) patients who developed gestational diabetes were diagnosed during the first half of the pregnancy. Six were diagnosed in the first trimester. If the definition of an abnormal 1-h plasma glucose value was lowered from 7.5 to 7.2 mM, an additional 2 patients could have been identified in the first trimester with an improvement in sensitivity from 70 to 91% with only a slight drop in specificity (from 91 to 88%). Diagnosis of gestational diabetes was not enhanced by measuring plasma insulin concentrations or insulin-glucose molar ratios. Conclusions: The diagnosis of gestational diabetes in a high-risk population can be made in the first half of pregnancy. Early diagnosis should permit evaluation of intervention strategies, which may result in improved perinatal outcome. *Diabetes Care* 14:288–94, 1991

Gestational diabetes mellitus not only places the mother at risk for developing overt diabetes at a later date (1) but it also increases the risk of perinatal morbidity and mortality by two- to fivefold (2,3). Screening programs coupled with intervention strategies (either diet or diet plus insulin) have reduced the perinatal morbidity and mortality associated with gestational diabetes (4–6). However, despite these interventions, the perinatal morbidity of gestational diabetes is still almost twice that of mothers with normal carbohydrate tolerance during pregnancy (7).

A possible explanation for the persistent morbidity in gestational diabetes may be late diagnosis. Current recommendations are to perform the glucose screening tests and oral glucose tolerance tests early in the third trimester (8–10). However, this leaves only a short time (~12–14 wk) to institute the appropriate interventions. Three studies that evaluated a 50-g glucose screening test before or at 20 wk of gestation diagnosed less than a quarter of the patients who developed gestational diabetes in the first half of pregnancy (10–12). The failure of these studies to detect gestational diabetes early in pregnancy may have been because a general clinic population was studied (10–12) or the test was performed in the fed state without proper dietary preparation (10,11).

The purpose of this study was to determine whether the diagnosis of gestational diabetes can be made early in pregnancy in a high-risk population, to determine the best cutoff values for a 50-g screening test for predicting gestational diabetes, and to determine whether plasma insulin values or insulin-glucose molar ratios can enhance the properties of this test in diagnosing gestational diabetes. A high-risk population was studied to examine the feasibility of testing in early pregnancy before evaluating it in a general population.

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RESEARCH DESIGN AND METHODS

High-risk pregnant patients who presented to MetroHealth Medical Center between June 1984 and June 1987 were evaluated for inclusion into the study. Patients were eligible if they met one of the following inclusion criteria: family history of diabetes in a first- or second-degree relative, past history of gestational diabetes (13), previous delivery of a neonate >4.1 kg, maternal weight >90 kg, maternal age ≥28 yr, or an unexplained intrauterine death (14). None of the patients enrolled had been diagnosed as having diabetes or being treated for gestational diabetes. This study was approved by our committee on investigations in humans, and after fully explaining the protocol, written informed consent was obtained from all participants.

All patients underwent a 50-g oral glucose screening test performed in the following manner: the patient was prescribed a diet containing a minimum of 300 g carbohydrate/day for 3 days before testing, and no food was eaten past midnight. Compliance with the diet was assessed by both a questionnaire and an interview. After documenting compliance with the diet, a 50-g oral glucose load was given during fasting. Blood samples for the measurement of glucose and insulin levels were obtained before ingesting the glucose load and at 1 and 2 h postingestion.

Blood samples were obtained in heparinized syringes from an indwelling intravenous catheter. The plasma was separated immediately and frozen at −20°C for later analysis. Plasma glucose was measured by the glucose oxidase method on a Beckman glucose analyzer (Fullerton, CA), and plasma insulin was measured by double-antibody radioimmunoassay (15). The lowest detectable plasma insulin level by this method was 13 pM.

The 50-g screening test was repeated every 10 wk until the patient delivered or had an abnormal test result, which was defined as a 1-h plasma glucose value of ≥7.5 mM. If the 1-h plasma glucose value was abnormal, the patient underwent a 100-g oral glucose tolerance test. The 100-g oral glucose tolerance test was performed in the same manner as the 50-g screening test, except that an additional plasma sample was obtained 3 h after ingestion of the glucose load. If the 100-g oral glucose tolerance test was not diagnostic for gestational diabetes, the patients were retested every 10 wk with the 100-g oral glucose tolerance test until term or until they were diagnosed to have gestational diabetes.

The diagnosis of gestational diabetes was made if any two of the glucose values from either the 50-g screening test or the 100-g oral glucose tolerance test were greater than or equal to: fasting, 5.28 mM; 1 h, 10 mM; 2 h, 8.61 mM; and 3 h, 7.78 mM (16). These abnormal plasma glucose values were defined by Carpenter and Coustan (16) in their interpretation of O'Sullivan and Mahan's (17) original study, which used the Somogyi-Nelson method for measuring whole-blood reducing sugars.

All infants underwent the Ballard modification of the Dobowitz examination within the first 48 h of life to assess their gestational age (18). The k-score, a method for adjusting the birth weight in grams by the infant's gestational age, was calculated for each infant. A k-score of 1 represents the 90th percentile for weight, whereas scores of 0 and −1 represent the 50th and 10th percentiles for that gestational age, respectively. Infants with a k-score ≥1 were considered to be large for gestational age. Infants born to mothers with gestational diabetes or infants who were large for gestational age had their blood glucose concentrations monitored by Chemstrip bG (Boehringer Mannheim, Indianapolis, IN) every hour for the first 6 h of life followed by every 4 h during the first day of life. Infants were considered to have hypoglycemia if their blood glucose levels were ≤1.4 mM.

Postpartum testing was left to the discretion of the patient's attending physician. On reviewing the medical records of our patients, three patients remained glucose intolerant in the postpartum period requiring medical management.

Statistical analysis. The data were analyzed with the SPSS/PC+ V3.0 Statistical Package for the Social Sciences (Chicago, IL). Dichotomous variables were analyzed by χ^2-test with Yates correction. Interval variables were analyzed by the Mann-Whitney *U* test. The interval variables are reported as means ± SD. All statistical tests were two tailed. The receiver operating characteristic (ROC) curves for determining the best cutoff value for an abnormal test were performed by plotting the sensitivity on the *y*-axis and the false-positive rate (1 − specificity) on the *x*-axis for glucose, insulin, and insulin-glucose molar ratios (19). In interpreting the ROC curve, a sharp break point in the upper left-hand corner would represent an excellent cutoff point for defining an abnormal test result, whereas a test with an ill-defined cutoff point would produce a diagonal line through the origin of the graph. To determine whether the curves were statistically different from one another, the area under each curve was measured by the trapozoid rule and compared with others by calculating a critical ratio *Z* test (20). The area under each curve is reported as the percentage of the graph under the curve plus or minus the standard error. In addition, the 95% confidence intervals (CIs) for sensitivity and specificity were calculated for the best cutoff value for an abnormal test (21).

RESULTS

Forty-three patients were enrolled in the first trimester and an additional 32 were enrolled in the early second trimester. The median number of risk factors in both groups was two (Table 1). The characteristics of the patients enrolled in the first trimester versus the second trimester were similar.

Of the 43 patients enrolled during the first trimester (gestational age 11.4 ± 2.0 wk), 12 had an abnormal

TABLE 1
Characteristics of patients

Characteristics	First trimester enrollment (n = 43)	Second trimester enrollment (n = 32)
Family history of diabetes		
First generation	16 (37.2)	15 (46.9)
Second generation	15 (34.9)	8 (25.0)
Past obstetrical history		
Macrosomia (wt >4.1 kg)	8 (18.6)	6 (18.8)
Gestational diabetes	9 (20.9)	5 (15.6)
Unexplained fetal death	6 (14.0)	5 (15.6)
Maternal characteristics		
Age ≥28 yr	20 (46.5)	11 (34.4)
Obesity (wt >90 kg)	11 (25.6)	8 (25.0)

Percentage of total enrollment in parentheses. $P > 0.40$ for all variables by χ^2-test with Yates correction.

1-h plasma glucose value (≥7.5 mM; Fig. 1). In these 12 patients, 4 met the criteria for gestational diabetes based on a markedly abnormal 50-g screening test. In the remaining 8 patients, 2 had an abnormal 100-g oral glucose tolerance test. Results from the 50-g screening test are shown in Table 2.

In the second trimester (gestational age 20.0 ± 0.8 wk), 23 patients returned for a second 50-g screening test, of whom 3 had an abnormal 1-h plasma glucose value. Two of 3 had an abnormal 100-g oral glucose tolerance test. Both of the patients had a first trimester 1-h plasma glucose value of 7.44 mM on the first trimester 50-g screening test.

In the third trimester (gestational age 31.2 ± 2.5 wk), 22 patients returned for a third 50-g screening test, of whom 2 had an abnormal 1-h plasma glucose value. Both patients had a normal 100-g oral glucose tolerance test. An additional 5 patients had a third trimester 100-g oral glucose tolerance test, of whom 3 had an abnormal 100-g oral glucose tolerance test. Two of 3 had an abnormal 1-h glucose value on the 50-g oral glucose tolerance test in the first trimester.

An additional 32 patients were enrolled in the second trimester (gestational age 19.8 ± 1.9 wk), of whom 10 had an abnormal 1-h plasma glucose value (Fig. 2). Of the 10 patients, 2 were diagnosed as having gestational diabetes (1 abnormal 100-g oral glucose tolerance test and 1 markedly abnormal 50-g screening test). Because the patient characteristics were the same in the patients enrolled in the first and second trimester (Table 1), the results of the second trimester 50-g oral glucose tolerance test for both the first and second trimester enrollees were combined (Table 3).

In the third trimester (gestational age 30.5 ± 2.9 wk), 16 patients who were enrolled in the second trimester returned for a repeat 50-g screening test, of whom 4 had an abnormal 1-h plasma glucose value. One of 4 patients had an abnormal 100-g oral glucose tolerance test. An additional 5 patients had a third trimester 100-g oral glucose tolerance test, of whom 1 had an abnormal 100-g oral glucose tolerance test. The one with the abnormal 100-g oral glucose tolerance test had an abnormal second trimester 1-h plasma glucose value.

Of 15 patients who had gestational diabetes, 10 were diagnosed in the first half of pregnancy (Table 4). Three of the remaining 5 patients who were diagnosed in the third trimester had an abnormal 1-h plasma glucose value in the first half of pregnancy (2 at 10 wk and 1 at 20 wk). The 2 patients who were not identified in the first half of pregnancy had second trimester 1-h plasma glucose values of 5.61 and 6.94 mM. Of 15 patients with gestational diabetes, 2 had a fasting blood glucose value >7.2 mM with an additional 3 having a fasting glucose level between 5.8 and 7.2 mM.

Of all the patients enrolled in the study, 48 of 65 (74%) patients without gestational diabetes returned in the third trimester for an oral glucose tolerance test (38

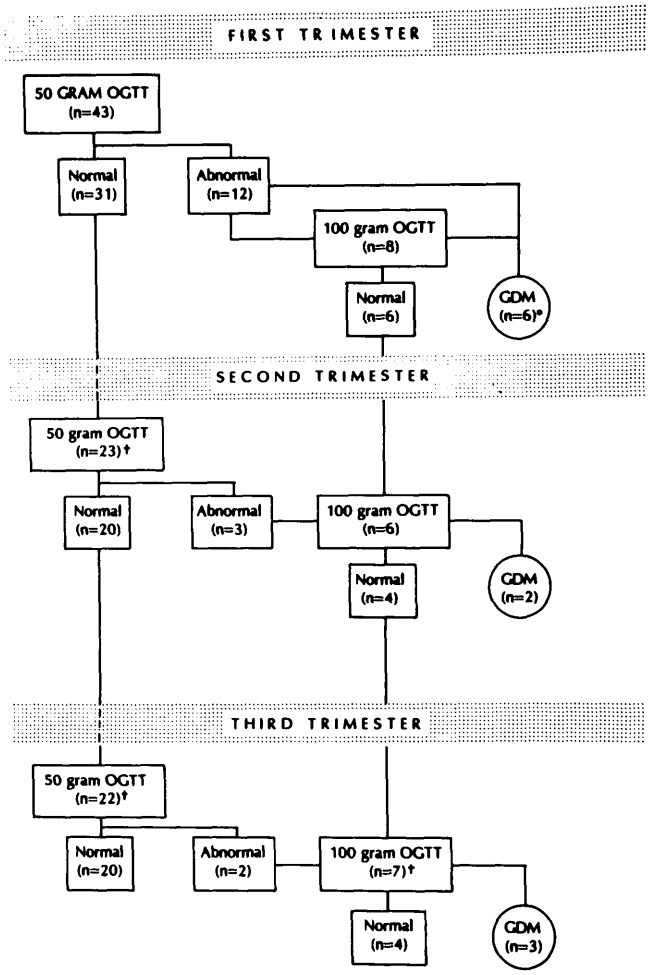

FIG. 1. Diagram of when oral glucose tolerance tests (OGTTs) were performed in patients who were enrolled in 1st trimester. *Of 6 patients with gestational diabetes (GDM), 4 were diagnosed with markedly abnormal 50-g screening test. †Five patients who missed 2nd trimester testing returned for 3rd trimester studies (4 for 50-g screening test and 1 for 100-g OGTT).

TABLE 2
Results of first trimester 50-g glucose tolerance test

	Normal 1-h glucose (<7.5 mM; n = 31)	Abnormal 1-h glucose (≥7.5 mM)	
		Normal 100-g OGTT (n = 6)	Abnormal 100-g OGTT (n = 6)
Gestational age (wk)	11.1 ± 1.8	11.8 ± 2.6	12.5 ± 1.9
Glucose (mM)			
Fasting	4.47 ± 0.33	4.40 ± 0.32	6.66 ± 1.94†‡
1 h	5.16 ± 1.21	8.10 ± 0.52*	12.08 ± 3.45†‡
2 h	4.31 ± 1.11	4.02 ± 0.59*	8.61 ± 2.87†‡
Insulin (pM)			
Fasting	44 ± 53	47 ± 43	70 ± 47
1 h	271 ± 181	434 ± 299	601 ± 452
2 h	126 ± 175	140 ± 76	426 ± 241†
Insulin-glucose ratio (pmol/mmol)			
Fasting	9.9 ± 12.0	10.4 ± 8.7	11.7 ± 8.4
1 h	52.2 ± 33.2	53.6 ± 38.4	58.7 ± 53.0
2 h	25.3 ± 29.3	36.1 ± 20.8	59.4 ± 41.9†
Birth weight (g)	3356 ± 780	3320 ± 508	3418 ± 1388
k-Score	0.258 ± 1.203	0.117 ± 0.617	0.688 ± 1.467
Macrosomia (>4 kg)	8/30 (26.7%)§	1/6 (16.7%)	2/5 (40%)§

Data reported as means ± SD. OGTT, oral glucose tolerance test.
*P < 0.05 vs. abnormal 1-h value and normal 100-g OGTT with normal 1-h value.
†P < 0.05 vs. abnormal 1-h value and abnormal 100-g OGTT with normal 1-h value.
‡P < 0.05 vs. abnormal 1-h test and normal vs. abnormal 100-g OGTT.
§Denominator reduced secondary to fetal death.

for 50-g screening test and 10 for 100-g oral glucose tolerance test; Table 4). Patients who dropped out of the study and those who were retested in the third trimester had similar first and second trimester 50-g screening test results, risk factors for gestational diabetes, and neonatal results except that patients who dropped out of the study had a higher first trimester 1-h plasma glucose value (6.56 ± 1.55 vs. 5.27 ± 1.47 mM, P = 0.048) and delivered heavier infants when the birth weight was adjusted for gestational age (k-score 0.757 ± 1.187 vs. 0.135 ± 0.97, P = 0.06). Of the six large for gestational age infants delivered by the mothers who dropped out of the study, one developed hypoglycemia (jitteriness with a blood glucose value of 1.44 mM) in the 1st day of life.

The insulin response to the first trimester 50-g screening test in patients with gestational diabetes and those with a normal 1-h plasma glucose value were similar except for the 2nd-h insulin value (Table 2). In the second trimester, the insulin values were similar among all three groups (Table 3).

In the first trimester, the insulin-glucose molar ratios at time 0 and 1 h during the 50-g screening test were similar in all three groups. The 2nd-h insulin-glucose ratio was higher in the patients with gestational diabetes versus those with a normal 1-h plasma glucose value (Table 2). In the second trimester, the insulin-glucose molar ratios were similar among all three groups.

Among the three ROC curves for the first trimester 50-g screening test, the 1-h plasma glucose value resulted in the curve with the sharpest break point (point A 7.2 mM; Fig. 3). The area under this curve was significantly greater than that under the insulin curve (0.923 ± 0.045 vs. 0.617 ± 0.106, P = 0.004) and the insulin-glucose molar ratio curve (0.923 ± 0.045 vs. 0.436 ± 0.108, P = 0.0001). There was no statistical difference between the insulin and insulin-glucose molar ratio curves. If the definition of an abnormal 1-h plasma glucose result had been lowered from 7.5 to 7.2 mM, the sensitivity would improve from 70% (95% CI 43–97) to 91% (95% CI 74–100) with only a slight drop in specificity from 91% (95% CI 81–100) to 88% (95% CI 77–99).

Of the ROC curves for second trimester screening test, the area under the glucose curve was significantly greater than the insulin curve (0.856 ± 0.101 vs. 0.464 ± 0.134, P = 0.011) and the insulin-glucose curve (0.856 ± 0.101 vs. 0.304 ± 0.109, P = 0.0001). The 1-h glucose value of 6.86 mM gave the best cutoff value with a sensitivity of 85% (95% CI 56–100) and a specificity of 79% (95% CI 68–90). When the value was increased to 7.5 mM, the sensitivity fell to 71% (95% CI 35–97) with an increase in specificity to 83% (95% CI 73–93).

CONCLUSIONS

In contrast to previous studies (10–12), our data show that the diagnosis of gestational diabetes can be made in the early part of pregnancy in a high-risk population. The key finding of this study is that we were able to

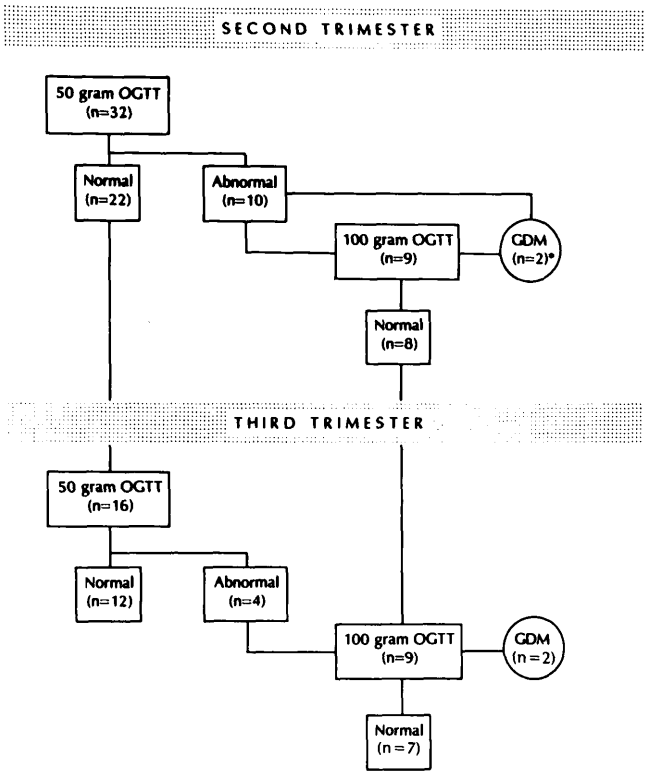

FIG. 2. Diagram of when oral glucose tolerance tests (OGTTs) were performed in patients who were enrolled in 2nd trimester. *Of 2 patients with gestational diabetes (GDM), 1 was diagnosed with markedly abnormal 50-g screening test.

diagnose 10 of 15 patients with gestational diabetes in the first half of pregnancy. Of the patients who were enrolled in the first trimester, 10 of 11 (91%) patients who developed gestational diabetes were identified by a 1-h plasma glucose value of ≥7.2 mM from a first trimester 50-g glucose screening test.

In the three previous studies that evaluated the 50-g screening test at or before 20 wk gestation, two found that early screening was unsuccessful in identifying patients at risk for gestational diabetes (10,11). In both of these studies, a low-risk population was evaluated, and the screening test was performed in the fed state. A possible explanation for their failure in identifying patients with carbohydrate intolerance during pregnancy may be because they performed the glucose screening test in the fed state. In the study by Coustan et al. (22), the rise in plasma glucose during the 50-g screening test in patients with gestational diabetes was less when the test was performed in the fed versus the fasting state. Coustan et al. recommend that a cutoff value of 7.2 mM be used when the test is performed in the fed state. This value is lower than the one used in the two studies stated above. In the third study, Benjamin et al. (12) were able to identify seven of eight patients with gestational diabetes with a 50-g glucose screening test performed at 10 wk gestation. In this study, a high-risk population was evaluated, and the test was performed in the fasting state. With a cutoff value of 7.8 mM, their sensitivity and specificity values were similar to our study (cutoff value of 7.2 mM) with a sensitivity of 88% (95% CI 65–100) versus 91% (95% CI 74–100) and a specificity of 73% (95% CI 64–81) versus 88% (95% CI 77–99), respectively. If Benjamin et al. used a cutoff value of 7.2 mM, all of their cases of gestational diabetes would have been identified in the first trimester.

Although Benjamin et al. identified 7 of 8 patients with gestational diabetes in the first trimester, they were able to confirm only 2 of 8 with a second trimester 100-g oral glucose tolerance test using the criteria of O'Sullivan and Mahan (17). In our study, we were able to confirm 10 of 15 patients in the second trimester. In 3 of the remaining 5 patients, the plasma glucose values from their 100-g second trimester oral glucose tolerance test were elevated but did not reach the modified cutoff values from O'Sullivan and Mahan until the third trimester. This highlights the importance of developing criteria for each trimester for the glucose tolerance test rather than the use of one set of values for all three trimesters (23,24).

A limitation of this study in evaluating sensitivity and specificity should be recognized. In evaluating a screening test, the true prevalence of the disease (i.e., gestational diabetes) should be determined by applying a standardized test (i.e., 100-g oral glucose tolerance test) to the entire population. In our study, only patients with a 1-h plasma glucose value ≥7.5 mM had a 100-g oral glucose tolerance test. It is possible that a patient with glucose intolerance could have been missed by not testing those who had a 1-h glucose value of <7.5 mM. As described by Carpenter and Coustan (16), the probability of this occurring, based on larger studies, is negligible.

In comparing the ROC curves for the 1-h plasma and insulin-glucose values from the first trimester 50-g glucose screening test, the area under the glucose curve was significantly greater than either the insulin or insulin-glucose molar ratio curves. The best break point on the glucose curve occurred at 7.2 mM, which is similar to the results of Carpenter and Coustan (7.5 mM; 16) when they performed the 50-g oral glucose screening test in the early third trimester. The ability to diagnose gestational diabetes was not enhanced by the use of insulin or insulin-glucose molar ratios.

In this pilot study, a high-risk population was examined. The incidence of gestational diabetes in our population was 20%, which is ~4–5 times the incidence in the general population (16). This high-risk population was chosen to examine the feasibility and diagnostic properties of this test in early gestation. Before these findings can be used in a general obstetrical practice, the results need to be replicated in that group of subjects. Because of the lack of preconception screening and postnatal testing programs, it is possible that some of these patients could have had preexisting diabetes (25). However, on enrollment into the study, none of the patients were diagnosed as having diabetes or being treated for diabetes.

TABLE 3
Results of second trimester 50-g glucose tolerance test

	Normal 1-h glucose (<7.5 mM; *n* = 42)	Abnormal 1-h glucose (≥7.5 mM)	
		Normal 100-g OGTT (*n* = 9)	Abnormal 100-g OGTT (*n* = 4)
Gestational age (wk)	20.1 ± 1.5	19.4 ± 1.1	18.8 ± 2.2
Glucose (mM)			
Fasting	4.24 ± 0.73	4.73 ± 0.28	5.81 ± 2.15
1 h	5.34 ± 1.06	9.00 ± 0.98*	10.65 ± 1.76†‡
2 h	4.56 ± 1.48	6.20 ± 2.64*	7.47 ± 2.03
Insulin (pM)			
Fasting	55 ± 55	64 ± 41	58 ± 33
1 h	348 ± 223	524 ± 342	312 ± 226
2 h	201 ± 192	217 ± 181	225 ± 145
Insulin-glucose ratio (pmol/mmol)			
Fasting	12.2 ± 10.4	13.5 ± 8.6	10.2 ± 5.6
1 h	67.0 ± 52.2	57.1 ± 33.5	30.5 ± 23.6
2 h	40.1 ± 35.7	31.7 ± 22.3	32.6 ± 24.2
Birth weight (g)	3367 ± 734	3346 ± 843	3717 ± 410
k-Score	0.208 ± 1.067	0.579 ± 0.880	0.906 ± 0.780
Macrosomia (>4 kg)	10/42 (24%)	2/9 (22%)	2/4 (50%)

Data reported as means ± SD. OGTT, oral glucose tolerance test.
*$P < 0.05$ vs. abnormal 1-h value and normal 100-g OGTT with normal 1-h value.
†$P < 0.05$ vs. abnormal 1-h value and abnormal 100-g OGTT with normal 1-h value.
‡$P < 0.05$ vs. abnormal 1-h value and normal vs. abnormal 100-g OGTT.

Seventy-four percent of our patients returned for a third trimester glucose tolerance test. The patients who did not return tended to have a higher first trimester 1-h plasma glucose value and delivered heavier babies (k-score) than those who were retested in the third trimester. It is possible that some of these patients could have become carbohydrate intolerant in the third trimester (10,11). The latter would have lowered the sensitivity (i.e., those originally classified as not having gestational diabetes would be reclassified as having a negative test but having diabetes) with little change in specificity.

We conclude that the diagnosis of gestational diabetes can be made in a high-risk population during the first half of pregnancy. Future studies are needed to address the cost-effectiveness and usefulness of such a program in a general obstetrical population and to determine whether earlier diagnosis coupled with various intervention strategies can reduce the persistent morbidity associated with gestational diabetes.

TABLE 4
Summary of oral glucose tolerance test (OGTT) results

	1st trimester enrollees (*n* = 43)	2nd trimester enrollees (*n* = 32)	Total (*n* = 75)
Diagnosis of gestational diabetes			
1st trimester	6		6
2nd trimester	2	2	4
3rd trimester	3	2	5
3rd trimester OGTT (not gestational diabetes)			43
Attrition (no 3rd trimester OGTT)			17
Total			75

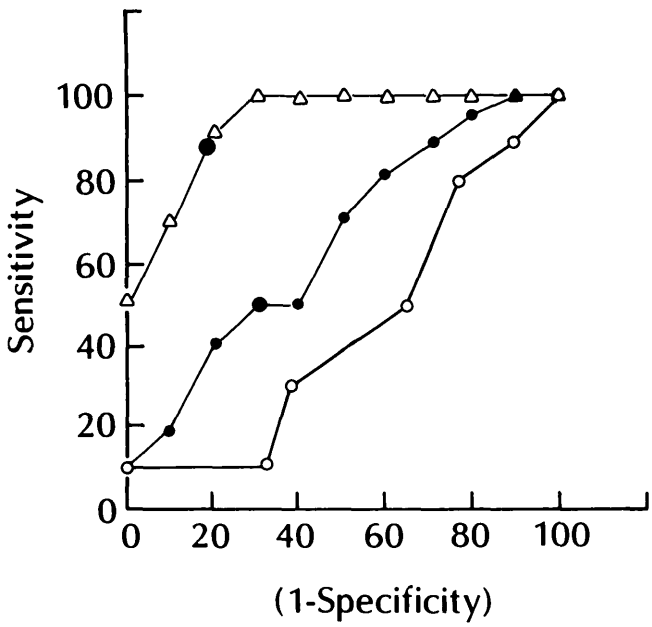

FIG. 3. Of 3 receiver operating characteristic curves for 1st trimester 50-g screening test, area under 1-h glucose curve (△) was significantly greater than either 1-h insulin curve (●; *P* = 0.004) or 1-h molar insulin-glucose ratio curve (○; *P* = 0.0001). Glucose curve had sharper break point (△; 7.2 mM) in predicting abnormal 100-g oral glucose tolerance test than either insulin curve (●; 382 pM) or insulin-glucose curve (○; 144 pmol/mmol).

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