

## SELECTIVE SCREENING FOR GESTATIONAL DIABETES MELLITUS

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**ABSTRACT**

**Background** The usual approach to detecting gestational diabetes mellitus is to screen all pregnant women by measuring their plasma glucose after a 50-g oral glucose load at 24 to 28 weeks' gestation. Women are referred for an oral glucose-tolerance test if the plasma glucose concentration one hour later is  $\geq 140$  mg per deciliter (7.8 mmol per liter). We hypothesized that the efficiency of screening could be enhanced by considering women's risks of gestational diabetes on the basis of their clinical characteristics.

**Methods** We studied 3131 pregnant women who underwent both the screening and the diagnostic tests. We randomly selected data on half the women and used them to derive new screening strategies. We categorized each woman's risk of gestational diabetes mellitus on the basis of her age, body-mass index before pregnancy, and race. We developed strategies that entailed no screening for low-risk women, usual care for intermediate-risk women, and universal screening with lower thresholds — plasma glucose values of 130 mg per deciliter (7.2 mmol per liter) or 128 mg per deciliter (7.1 mmol per liter) — for high-risk women. The strategies were validated with data on the other half of the women.

**Results** The new strategies allowed a 34.6 percent reduction in the number of screening tests performed (95 percent confidence interval, 32.3 to 37.0 percent) and detected 81.2 to 82.6 percent of the women with gestational diabetes as compared with the 78.3 percent detected through usual care. The percentage of false positive screening tests was significantly reduced, from 17.9 percent with usual care to 16.0 percent ( $P=0.02$ ) or 15.4 percent ( $P<0.001$ ) with the new strategies, depending on the threshold values for high-risk women.

**Conclusions** Consideration of women's clinical characteristics allows efficient selective screening for gestational diabetes. (N Engl J Med 1997;337:1591-6.)

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**G**ESTATIONAL diabetes mellitus is defined as glucose intolerance first recognized during pregnancy.<sup>3</sup> It is usually diagnosed on the basis of an oral glucose-tolerance test, with plasma glucose values measured while fasting and hourly for three hours after the ingestion of 100 g of glucose. If two of the four values exceed the thresholds recommended by the National Diabetes Data Group (see the Methods section),<sup>4</sup> gesta-

tional diabetes is diagnosed. According to these criteria, 3 to 4 percent of pregnant women are affected. Gestational diabetes is associated with an excess incidence of fetal macrosomia, preeclampsia, and cesarean section in the index pregnancy,<sup>5-8</sup> and on long-term follow-up non-insulin-dependent diabetes mellitus develops in approximately one third of women who have ever had gestational diabetes.<sup>9</sup>

The results of randomized trials of dietary or insulin treatment of gestational diabetes have not conclusively demonstrated that treatment benefits either mothers or their infants.<sup>10,11</sup> Both the U.S. Preventive Services Task Force<sup>12</sup> and the Canadian Task Force on the Periodic Health Examination<sup>13</sup> have therefore recommended neither for nor against routine screening for gestational diabetes. However, universal screening for gestational diabetes with a glucose-challenge test has been endorsed by the American Diabetes Association<sup>14</sup> and the Second and Third International Workshop-Conferences on Gestational Diabetes<sup>15,16</sup> — a policy applicable to 4.3 million women annually in North America. The glucose-challenge test entails oral administration of 50 g of glucose at 24 to 28 weeks' gestation, regardless of the length of time since the last meal, with measurement of plasma glucose one hour later. Women with plasma glucose values  $\geq 140$  mg per deciliter (7.8 mmol per liter) are referred for a diagnostic 100-g oral glucose-tolerance test.<sup>4</sup> In a 1991 survey completed by the directors of 200 American obstetrical training programs, 97 percent of the respondents reported that they followed these guidelines.<sup>17</sup>

The glucose-challenge test as a screening method was first proposed by O'Sullivan et al. in 1973.<sup>18</sup> After administering both the glucose-challenge test and a 100-g oral glucose-tolerance test to 752 randomly selected pregnant women attending a maternity clinic in Boston, they found that the glucose challenge test had a sensitivity of 79 percent and a specificity of 87 percent for detecting gestational diabetes as defined by the criteria later adopted by the National Diabetes

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\*The Toronto Trihospital Gestational Diabetes Project Investigators are listed in Sermer et al.<sup>1</sup> and Naylor et al.<sup>2</sup>

Data Group.<sup>18,19</sup> Subsequent studies have attempted to refine the glucose-challenge test, but they have not included both screening and diagnostic tests for all women. In contrast, in the Toronto Trihospital Gestational Diabetes Project<sup>1,2,20</sup> the diagnostic glucose-tolerance test was administered to more than 3000 consenting women regardless of the results of the screening glucose-challenge test. We have used this unique data source to derive and validate a new approach to screening for gestational diabetes. Given the continuing uncertainty about the merits of detecting and treating this condition, our primary goal was to reduce the burden of screening on women and the health care system while maintaining rates of detection similar to those of usual care.

## METHODS

### Overview

This was a secondary analysis drawing on data from our published prospective study of 3131 pregnant women.<sup>1,2,20</sup> We randomly divided the women on a post hoc basis into two groups of similar size — a derivation group and a validation group. We used only the data from the derivation group to develop new screening strategies for gestational diabetes. These strategies were then tested in the validation group by comparing their effectiveness and efficiency with those of usual care. The low incidence of gestational diabetes (3.5 percent) limited the statistical power to detect and specify the relation between clinical characteristics and the risk of gestational diabetes. Milder forms of gestational glucose intolerance are also associated with adverse maternal and fetal outcomes,<sup>2,20-23</sup> and the combined incidence of diabetes and milder forms of glucose intolerance in the derivation group was 10 percent. Therefore, we used multivariate analysis to develop a simple scoring system that specified women's risks of gestational glucose intolerance on the basis of clinical factors (e.g., age, race, and body-mass index [the weight in kilograms divided by the square of the height in meters]). We confirmed that the scoring system remained valid for predicting gestational diabetes alone.

Clinical scores were then used to assign each woman to one of three risk subgroups. For efficiency and ease of use, we aimed to forgo screening altogether in low-risk women, retain the usual screening-test thresholds if possible for intermediate-risk women, and set new, lower plasma glucose thresholds for high-risk women. Increased rates of detection in high-risk women would then offset cases missed in the unscreened low-risk women.

Strategies showing high detection rates and low false positive rates in the derivation group were validated in the second group of women (the validation group). Finally, we examined whether the specificity of screening could be further enhanced by taking into account the length of time since the woman's last meal.<sup>1</sup>

### Setting, Research Methods, and Study Subjects

Data were drawn from a study that enrolled consenting pregnant women without known diabetes mellitus, 24 years of age or older, presenting before 24 weeks' gestation, from September 1989 to March 1992 at three teaching hospitals in Toronto. Each woman was interviewed by study nurses for information on her obstetrical history and family history of diabetes. The length of time since the last meal was recorded. The women were then given a standard one-hour 50-g glucose-challenge test at 26 weeks' gestation ( $\pm 1$  week). A three-hour 100-g oral glucose-tolerance test was scheduled for 28 weeks ( $\pm 1$  week); 90 percent of the women had this test. Women delivering before 28 weeks' gestation were excluded. Of 3152 women with data available from both screening and diagnostic tests, 3131 (99.3 percent) had singleton deliveries and data sufficiently complete for analysis.

### Clinical Risk Factors

Each woman's body-mass index immediately before pregnancy was calculated from her self-reported height and most recent weight before conception. On the basis of the data relating the risk of diabetes to body-mass index,<sup>24</sup> the index was categorized as follows:  $\leq 22.0$ , 22.1 to 25.0, and  $\geq 25.1$ .

The incidence of gestational diabetes varies with race.<sup>25,26</sup> Race, information on which was obtained during the interviews, was categorized simply as white, black, Asian, or other. "Other" included women of Hispanic, South Asian (e.g., from India, Pakistan, Sri Lanka, and Bangladesh), and Middle Eastern origins. The remaining clinical risk factors, shown in Table 1, are self-explanatory.

### Definitions of Gestational Diabetes and Glucose Intolerance

Gestational diabetes was diagnosed if two or more values on the 100-g oral glucose-tolerance test met or exceeded the following thresholds: fasting, 105 mg per deciliter (5.8 mmol per liter); one hour, 190 mg per deciliter (10.5 mmol per liter); two hours, 165 mg per deciliter (9.2 mmol per liter); and three hours, 145 mg per deciliter (8.0 mmol per liter). The broader category of gestational glucose intolerance applied if one or more of the values met or exceeded these thresholds and if two or more values met or exceeded alternative thresholds proposed by Carpenter and Coustan.<sup>27</sup> With the latter criteria, the thresholds are reduced, respectively, to 95 mg per deciliter (5.3 mmol per liter), 180 mg per deciliter (10.0 mmol per liter), 155 mg per deciliter (8.6 mmol per liter), and 140 mg per deciliter (7.8 mmol per liter).

### Analysis Plan

#### Clinical Scoring System

The women's clinical characteristics were entered into a multivariate logistic-regression analysis if, on univariate analysis, they were nonrandomly associated ( $P < 0.05$ ) with the incidence of gestational glucose intolerance. Predictive accuracy was assessed by measuring the area under a receiver-operating-characteristic curve. The results of the logistic-regression analysis were used to create an additive clinical scoring system<sup>28</sup> for independent predictors of gestational glucose intolerance.

The incidence of gestational glucose intolerance was determined for women with each clinical score. Two or more single-score subgroups were combined when the incidences of gestational glucose intolerance were similar across scores. To validate the scoring system and grouping, we confirmed that a graded relation between the clinical scores and the incidence of gestational diabetes (rather than gestational glucose intolerance) was present for the women in the validation group.

#### Development of New Screening Strategies

We assumed that women with low scores would not be screened. Plasma glucose thresholds for a positive screening test among women with intermediate and high scores were chosen on the basis of three simple criteria. First, neither the detection rate nor the false positive rate for any new strategy could be significantly worse than those of usual care — i.e., universal screening with a single threshold of 140 mg per deciliter. McNemar's test was used for these paired comparisons. Second, to facilitate the introduction of these new screening strategies into clinical practice, the current plasma glucose threshold of 140 mg per deciliter was to be retained for intermediate-risk women, if possible. Third, we rejected any new screening strategy that showed both lower detection rates and higher false positive rates than other potential new strategies, even if those differences were not statistically significant.

Although current guidelines state that fasting is unnecessary before the glucose-challenge test, the results do vary with the

length of time since the last meal or snack.<sup>18,29</sup> Earlier, we found that the specificity of the test is improved, with minimal loss of sensitivity, by changing the single threshold of 140 mg per deciliter to thresholds of 148, 142, and 150 mg per deciliter (8.2, 7.9, and 8.3 mmol per liter, respectively), for postprandial times of less than two hours, two to three hours, and more than three hours, respectively.<sup>18</sup> In designing this study, we planned that our previously derived adjustments for the length of time since the last meal would be explored if a threshold value of 140 mg per deciliter was retained for the intermediate-risk group.

**Validation of the New Screening Strategies**

The new screening strategies were tested in the validation group. McNemar's test was used to compare the rates of detection and false positive tests of usual care and the new strategies, and the paired 95 percent confidence intervals for absolute differences in rates of detection and false positive tests were calculated.

**Statistical Analysis**

Analyses were performed with SAS software (SAS Institute, Cary, N.C.). Stata 4.0 (Stata, College Station, Tex.) was used to generate confidence intervals for paired data.

RESULTS

**Clinical Scoring System for Predicting Gestational Glucose Intolerance and Diabetes**

The relations between each risk factor and the incidences of gestational glucose intolerance in the derivation group are shown in Table 1. In a multivariate analysis, the independent clinical predictors of gestational glucose intolerance were age, race, and body-mass index. As Table 2 shows, points in the scoring system accrue for greater age or body-mass index and for race other than white or black. The predictive performance and excellent model fit were maintained after odds ratios were converted to additive clinical scores (Table 2).

Assessed independently in the validation group, the incidences of gestational diabetes ranged from 0.9 percent among the 544 women with scores of 0 or 1, to 18.7 percent among the 91 women with scores  $\geq 6$  (Table 3). Thus, the clinical scores successfully differentiated women according to their risk of gestational diabetes.

**Development of New Screening Strategies**

We developed a strategy whereby women with scores of 0 to 1 were not screened but the remainder were all screened with the glucose-challenge test. As compared with usual care, excluding women with scores of 0 or 1 allowed 34.7 percent of the women to avoid screening altogether (95 percent confidence interval, 32.3 to 37.4). We retained the current threshold value of 140 mg per deciliter for women with scores of 2 or 3. We found that threshold values of either 128 mg per deciliter (7.1 mmol per liter) or 130 mg per deciliter (7.2 mmol per liter) could be applied to women with clinical scores above 3. As Table 4 shows, the detection rates and false positive rates of selective screening with these new strategies were similar to those of usual care.

**TABLE 1. INCIDENCE OF GLUCOSE INTOLERANCE ACCORDING TO RISK FACTORS IN THE 1560 PREGNANT WOMEN IN THE DERIVATION GROUP.\***

RISK FACTOR	INCIDENCE (%)	NO. OF WOMEN	P VALUE
Age (yr)			0.02
$\leq 30$	8.8	760	
31–34	8.8	476	
$\geq 35$	14.2	324	
Race			<0.001
White	8.3	1271	
Black	7.3	82	
Asian	25.0	140	
Other	11.9	67	
Body-mass index			<0.001
$\leq 22.0$	7.4	824	
22.1–25.0	9.9	415	
$\geq 25.1$	16.5	321	
Parity			0.01
0	10.4	868	
1	9.9	525	
2	4.4	137	
$\geq 3$	23.3	30	
Family history of diabetes†			0.15
Yes	12.8	226	
No	9.5	1323	
Adverse obstetrical history‡			0.03
Yes	14.5	200	
No	9.3	1360	

\*The group included women with gestational diabetes according to the criteria of the National Diabetes Data Group,<sup>4</sup> those with gestational diabetes according to the criteria of Carpenter and Coustan,<sup>27</sup> and those with one abnormal value according to the National Diabetes Data Group criteria.

†Information about family history was unavailable for 11 women.

‡An adverse obstetrical history was defined as a history of gestational diabetes during one or more pregnancies, an unexplained stillbirth, fetal anomalies, fetal macrosomia, or preeclampsia.

**TABLE 2. INDEPENDENT CLINICAL RISK FACTORS FOR GESTATIONAL GLUCOSE INTOLERANCE, WITH ODDS RATIOS AND CORRESPONDING SCORES FROM A MULTIPLE LOGISTIC-REGRESSION MODEL IN THE DERIVATION GROUP.\***

RISK FACTOR	ODDS RATIO (95% CI)	P VALUE	SCORE
Age (reference category, $\leq 30$ yr)			0
31–34 yr	1.0 (0.7–1.5)	0.95	1
$\geq 35$ yr	1.6 (1.1–2.5)	0.02	2
Body-mass index (reference category, $\leq 22.0$ )			0
22.1–25.0	1.8 (1.1–2.7)	0.01	2
$\geq 25.1$	3.2 (2.1–4.8)	<0.001	3
Race (reference category, white)			0
Black	0.7 (0.3–1.7)	0.44	0
Asian	4.8 (3.0–7.6)	<0.001	5
Other	1.6 (0.7–3.5)	0.24	2

\*Scores were derived from rounded odds ratios. The original model has a receiver-operating-characteristic (ROC) curve area of 0.68, with  $P=0.93$  for the Hosmer–Lemeshow test statistic. Substituting patient-specific scores for regression coefficients, the ROC curve area is 0.69, with  $P=0.86$  for the Hosmer–Lemeshow test statistic. CI denotes confidence interval.

**TABLE 3.** INCIDENCE GRADIENT FOR GESTATIONAL DIABETES ACCORDING TO CLINICAL SCORE IN THE VALIDATION GROUP OF 1571 PREGNANT WOMEN.

VARIABLE	SCORE				
	0-1	2	3	4-5	≥6
No. in group	544	322	284	330	91
Incidence of gestational diabetes — % (no.)	0.9 (5)	3.7 (12)	3.9 (11)	7.3 (24)	18.7 (17)

**Validation of the New Strategies**

In the validation group, the new strategies performed more strongly still (Table 5). As compared with usual care, selective screening again allowed more than a third of the women (34.6 percent; 95 percent confidence interval, 32.3 to 37.0) to avoid the glucose-challenge test altogether. The new two-threshold approaches (strategies A and B, Table 5) both detected similar proportions of women with gestational diabetes and led to significant but small reductions in false positive rates as compared with usual care.

For women at intermediate risk (scores of 2 or 3), we examined the effect of adjusting the screening threshold of 140 mg per deciliter for the length of time since the last meal (strategies C and D, Table 5). Detection rates remained similar to those with usual care, but there were further decreases in false positive rates.

**DISCUSSION**

We have developed and validated a selective approach to screening for gestational diabetes that, as compared with the standard care endorsed by leaders of American obstetrics,<sup>17</sup> could annually spare hundreds of thousands of women the need to undergo a screening blood test. Our strategy hinges on a simple clinical scoring system that groups pregnant women according to their risk of gestational diabetes. Its efficiency is achieved by not screening women in the low-risk group, maintaining the current threshold value (or a postprandial modification thereof) for considering a glucose-challenge test positive in intermediate-risk women, and applying lower thresholds for women in the high-risk group. This approach is not associated with a significant reduction in the numbers of women identified as having gestational diabetes but is associated with significant reductions in the number of unnecessary oral glucose-tolerance tests caused by false positive screening tests. It also provides evidence in support of a new recommendation for selective screening that was made in mid-1997 by an expert committee of the American Diabetes Association.<sup>30</sup>

The scoring system and the two-threshold approach are easy for practitioners to use. However, implementing the more complex algorithms with adjustments for postprandial status will require cooperation between clinicians and laboratories. For example, the woman's test requisition might note the risk category (intermediate risk, score of 2 or 3; high risk, score above 3), and the length of time since the last snack or meal could be recorded by the venipuncturist for the intermediate-risk group. Any lab-

**TABLE 4.** RATES OF DETECTION AND OF FALSE POSITIVE TESTS WITH USUAL CARE AND WITH THE NEW SELECTIVE-SCREENING STRATEGIES IN THE DERIVATION GROUP.\*

STRATEGY	NO. TO BE SCREENED	DETECTION RATE†	P VALUE	FALSE POSITIVE RATE‡	P VALUE
		% (no.)		% (no.)	
Usual care (test 100% of patients; 1 threshold of 140 mg/dl)	1560	72.7 (32)		16.7 (253)	
Selective screening (test threshold of 140 mg/dl for scores 2-3, 128 mg/dl for scores >3)	1016	65.9 (29)	0.34	16.0 (242)	0.34
Selective screening (test threshold of 140 mg/dl for scores 2-3, 130 mg/dl for scores >3)	1016	61.4 (27)	0.10	15.4 (233)	0.070

\*P values are for the comparison of selective screening with usual care.

†Values are based on a total of 44 true positive results and false negative results.

‡Values are based on a total of 1516 false positive results and true negative results.

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TABLE 5. RATES OF DETECTION AND OF FALSE POSITIVE TESTS WITH USUAL CARE AND WITH SELECTIVE TESTING.\*

STRATEGY	DETECTION RATE†	ABSOLUTE DIFFERENCE	P VALUE	FALSE POSITIVE RATE‡	ABSOLUTE DIFFERENCE	P VALUE
	% (no.)	% (95% CI)		% (no.)	% (95% CI)	
Usual care: test 100% of patients; 1 threshold of 140 mg/dl	78.3 (54)	—	—	17.9 (269)	—	—
Selective screening: test 65% of patients						
Two threshold values						
Strategy A: 140 mg/dl for scores 2–3, 128 mg/dl for scores >3	82.6 (57)	+4.3 (–4.5 to +13.2)	0.26	16.0 (240)	–1.9 (–3.6 to –0.3)	0.02
Strategy B: 140 mg/dl for scores 2–3, 130 mg/dl for scores >3	81.2 (56)	+2.9 (–5.5 to +11.3)	0.41	15.4 (231)	–2.5 (–4.1 to –0.9)	0.001
Strategy C: postprandial threshold values for scores 2–3, 128 mg/dl for scores >3	79.7 (55)	+1.4 (–8.5 to +11.4)	0.74	13.6 (205)	–4.2 (–6.0 to –2.4)	<0.001
Strategy D: postprandial threshold values for scores 2–3, 130 mg/dl for scores >3	78.3 (54)	0 (–9.5 to +9.5)	1.00	13.0 (196)	–4.9 (–6.6 to –3.1)	<0.001

\*Absolute differences are derived from comparisons of selective screening strategies with usual care. CI denotes confidence interval.

†Values are based on a total of 69 true positive results and false negative results.

‡Values are based on a total of 1502 false positive results and true negative results.

ratory computer could instantaneously assimilate the scoring information and postprandial status and generate a recommendation about whether a follow-up oral glucose-tolerance test was indicated.

Clinicians, laboratorians, and policy makers can choose among the four suggested strategies, weighing sensitivities, the simplicity of application of the two-threshold strategies, and the greater specificity achieved when the threshold for intermediate-risk patients is adjusted for the length of time since the last meal.

The clinical consequences of the new strategies cannot be compared with those of usual care, since all the women in our original study underwent an oral glucose-tolerance test and those with gestational diabetes were treated. However, by definition the selective strategy detects more cases of gestational diabetes among older women with higher body-mass indexes and misses more cases among younger women with lower body-mass indexes. It is very unlikely that this shift in detection patterns is harmful.

Apart from age, clinical factors have been rejected in most other studies for their lack of sensitivity in identifying women at risk for gestational diabetes.<sup>31–34</sup> In one nonrandomized comparative study,<sup>35</sup> screening based on risk factors allowed the use of the glucose-challenge test to be reduced dramatically, but the threshold for a positive glucose-challenge test was high. In contrast to the methods of the Toronto Trihospital Gestational Diabetes Project, oral glucose-tolerance tests in these studies were performed only in women with positive screening tests,

and threshold adjustments of the type validated here could not be made.

Some potential limitations of the current study bear mention. First, unlike other variables in the scoring system, race or ethnicity as a clinical characteristic is difficult to define. Asian, first-generation Hispanic, South Asian, and Middle Eastern women have lower glucose tolerance during gestation, whereas blacks and whites have comparatively higher glucose tolerance.<sup>25,26,36,37</sup> Our analysis mirrors these findings. For the present, we believe it is clinically useful to incorporate race as a factor in the scoring system, notwithstanding the difficulty of defining distinct groups. Second, our cohort included only women 24 years of age or older. It is possible that the scoring system would be modified slightly if data were available for younger women. Third, the generalizability of the strategies should ideally be confirmed in other populations with various clinical and demographic characteristics.

In conclusion, these new strategies represent an opportunity to redefine the approach to screening for gestational diabetes in a fashion that reduces the burden of testing for hundreds of thousands of pregnant women each year while maintaining detection rates similar to those obtained with current standards of practice.

Supported by an operating grant (02650) from the Ontario Ministry of Health. Dr. Naylor is supported in part by an Ontario Ministry of Health Career Scientist award.

We are indebted to the many women who volunteered to participate; to the study coordinators, Michelle Bailey, R.N., Vicki Bowden, R.N., and Elizabeth Peloso, R.N.; to the study secretaries, Ms. Angela Anderson, Ms. Audra Duncan, and Ms. Tracey Harrison; to Ms. Mona Shaw of the Institute for Clinical Evaluative Sciences, Toronto, for assistance in manuscript production; and to the investigators of the Toronto Trihospital Gestational Diabetes Project for their vital contributions.

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