A Study of Glucose Tolerance and Screening Criteria in 752 Unselected Pregnancies

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Although many factors influencing the standard glucose tolerance test have been adequately described, those pertaining to pregnancy continue to cause confusion.[1] Since such confusion is largely due to disagreement on the level at which the test itself should be considered abnormal, workers seeking to clarify the situation must either work with preselected and strictly defined criteria, or survey a random group of subjects so large that a representative range of glucose determinations and tolerance levels can be obtained, allowing examination of the behavior and distribution of the mean values. The objective of our study was an examination of blood sugar behavior in standard glucose tolerance tests among a large, unselected group of pregnant women; we chose the latter approach.

We also took the opportunity, however, to apply a specifically defined criterion of abnormality in order to evaluate various methods of screening for the "prediabetic" state which often becomes recognizable during pregnancy.

MATERIAL AND METHODS

This study includes all prenatal registrants at Boston City Hospital between Dec. 12, 1956, and April 19, 1957. Patients were first classified as having screened negative or positive on the basis of meeting one or more of the following criteria:

1. A venous blood sugar value of 130 mg. or more per 100 ml. one hour after 50 gm. of glucose orally;
2. A history of diabetes in the family;
3. A history of having borne a baby 9 lbs. (4.1 kg.) or more; and
4. A history of fetal death, neonatal death, congenital anomaly, prematurity, toxemia (excessive weight gain, hypertension, or proteinuria) in two or more previous pregnancies.

Appointments were then given for the women to return for a standard, three-hour, 100 gm. oral glucose tolerance test (GTT) during each trimester under our observation. All patients were instructed to take 250 gm. of carbohydrate daily for three days prior to the test, and to avoid eating or drinking after midnight on the day before the test. For the minimal criterion of abnormality two or more of the following glucose levels had to be met or exceeded: Fasting, 100 mg.; at one hour 170 mg.; at two hours 120 mg.; and at three hours 110 mg. per 100 ml., using Somogyi-Nelson determinations on venous blood specimens.

RESULTS

During the period under review 986 prenatal patients were screened, and 752 (76.3 per cent) satisfactorily completed one or more glucose tolerance tests. The remaining 23.7 per cent were either uncooperative (213 patients), had incomplete tests (eighteen patients), or had previously known diabetes (three patients). In order to assess any bias due to their exclusion, the women not receiving glucose tolerance tests were compared with those in the study as to age, parity, screening criteria, and week of gestation at the time of selection. Application of the chi square technic indicated no statistically significant difference except with regard to the last item, there being proportionately more women not having a glucose tolerance test presenting in the last part of the third trimester. The group which did receive glucose tolerance tests may thus be considered a reasonably unbiased sample of pregnancies in the population studied.

Each of the 752 patients received at least one glucose tolerance test, 215 were tested in two successive trimesters and thirteen were tested in all three. In order to remove the bias introduced by not having complete data on all patients, most of the analyses deal with the first glucose tolerance test obtained on each person. Of these, forty-seven reached the defined criterion of abnormality. Distribution of these tests by trimester is shown in table 1. To complete the picture, it might

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TABLE 1

Distribution of age, week of gestation, and number of previous pregnancies with first glucose tolerance tests in 752 unselected pregnancies

	Normal		Abnormal*		
	No.	Per cent distribution	No.	Per cent distribution	Per cent abnormal
Week of gestation					
Total	705	100.0	47	100.0	6.2
1-13	20	2.8	0	0	0
14-25	256	36.3	13	27.7	4.8
26 and over	429	60.9	34	72.3	7.3
Number of previous pregnancies					
Total	705	100.0	47	100.0	6.2
0	145	20.6	5	10.6	3.3
1	131	18.6	7	14.9	5.1
2	115	16.3	4	8.5	3.4
3	96	13.6	3	6.4	3.0
4	75	10.6	6	12.8	7.4
5	51	7.2	4	8.5	7.3
6	30	4.3	3	6.4	9.1
7	24	3.4	9	19.2	27.3
8	16	2.3	3	6.4	15.8
9 or more	22	3.1	3	6.4	12.0
Age					
All ages	705	100.0	47	100.0	6.2
—20	132	18.7	0	0	0
20-24	249	35.4	10	21.3	3.9
25-29	156	22.1	9	19.1	5.5
30-34	96	13.6	13	27.7	11.9
35-39	50	7.1	9	19.1	15.3
40-44	22	3.1	6	12.8	21.4

*See "Methods" for criteria.

be added that by consideration of the 228 repeated glucose tolerance tests, eleven additional persons could have been classified abnormal.

Glucose tolerance results

Mean blood sugar readings in the 752 initial glucose tolerance tests are shown in table 2; the fasting and three postglucose hourly readings were 69.3, 103.6, 91.7 and 79.4 mg. per 100 ml., respectively. Standard deviation for each period is also recorded. As indicated by closeness of the means and medians, all blood sugar values approached symmetrical distribution. The postglucose values were, however, approximately twice as variable as the fasting ones. Distribution of glucose values for the tests' four hourly readings is presented in table 3. In addition, this table contains the cumulative percentage of patients exceeding each group of glucose levels. These percentages represent the empirical probability of a woman in this or a similar popula-

TABLE 2

Median and mean blood glucose values,* standard deviations and coefficients of variations, by hour of test, based on glucose tolerance tests in 752 unselected pregnancies

	Hour of glucose tolerance test			
	Fasting	One	Two	Three
Median	68.4	100.8	87.8	77.7
Mean	69.3	103.6	91.7	79.4
Standard deviation	10.4	30.8	25.8	24.0
Coefficient of variation (Standard deviation at per cent of mean)	15.0	29.7	28.1	30.2

*Mg. per 100 ml.

TABLE 3

Distribution of glucose tolerance test values at different time intervals with cumulative number and per cent exceeding specified values of blood glucose

Values of blood glucose mg. per 100 ml.	Fasting	Fasting Cumulative*		One-hour	One-hour Cumulative*		Two-hour	Two-hour Cumulative*		Three-hour	Three-hour Cumulative*	
	No.	No.	per cent	No.	No.	per cent	No.	No.	per cent	No.	No.	per cent
Less than 50	12	740	98.4	9	743	98.8	13	731	97.2	53	699	93.0
50 - 59	80	660	87.8	31	712	94.7	21	718	95.5	74	625	83.1
60 - 69	323	337	44.8	49	663	88.2	82	636	84.6	123	502	66.8
70 - 79	253	84	11.2	79	584	77.7	138	498	66.2	158	344	45.8
80 - 89	68	16	2.1	102	482	64.1	148	350	46.6	140	204	27.1
90 - 99	12	4	.5	93	389	51.7	122	228	30.3	93	111	14.8
100 - 109	1	3	.4	104	285	37.9	92	136	18.1	54	57	7.6
110 - 119	1	2	.3	90	195	25.9	53	83	11.0	29	28	3.7
120 - 129	0	2	.3	58	137	18.2	27	56	7.4	13	15	2.0
130 - 139	1	1	.1	53	84	11.2	30	26	3.6	10	5	.7
140 - 149	0	1	.1	23	61	8.1	11	15	2.0	2	3	.4
150 - 159	0	1	.1	30	31	4.1	8	7	.9	0	3	.4
160 - 169	0	1	.1	10	21	2.8	2	5	.7	1	2	.3
170 - 179	0	1	.1	12	9	1.2	0	5	.7	0	2	.3
180 and over	1	0	0	9	0	0	5	0	0	2	0	0
Total	752			752			752			752		

*Cumulative number or per cent at or exceeding the lower limit of the class interval.

tion having a blood glucose value higher than the stated range.

Glucose tolerance related to age, parity, and length of gestation

Glucose tolerance was correlated with age, parity, and length of gestation and each of the relationships studied was found to be statistically significant at the 5 per cent level (table 4). Age showed the closest relationship to the blood sugar level. The increase in this level per year of age ranged from 0.35 mg. to 1.55 mg. per 100 ml. This decreased tolerance for glucose is seen to be more pronounced per additional year of age at one and two hours following the carbohydrate load than at the fasting and three-hour interval.

TABLE 4

Change in milligrams per cent blood glucose per unit increase of specified factor (b), and strength of relationship (r)* by hour of test based on glucose tolerance tests in 752 unselected pregnancies

Factor and unit of change	Fasting		Hour of glucose tolerance test: One		Two		Three	
	b	r	b	r	b	r	b	r
Age in years	.35	.22	1.55	.33	1.24	.31	.60	.16
Parity	.51	.13	2.68	.23	2.43	.25	1.09	.12
Gestation in weeks	—.12	—.08	.64	.15	.32	.09	.29	.09

*Correlation coefficient calculated by the Pearsonian Method.

Positive increases in blood sugar level were found in relation to the number of previous pregnancies. When the associated influence of age was removed by partial correlation technics, very little correlation remained.

Although statistically significant, the week of gestation at which the glucose tolerance test was performed showed the smallest relationship to blood sugar level. It should be noted that this statistical conclusion could have resulted from the large sample size.

However, the foregoing data are of limited value since they concern different women, at different ages, at different times of gestation. These limitations and the occasional difference shown by longitudinal study data indicated that our findings should be subjected to further examination. Follow-up of measurements on the same persons at given points in time was required to obtain the longitudinal or cohort data for such examination.

Glucose tolerance related to trimester

Cohort data were provided by the 215 individuals who had glucose tolerance tests repeated in a subsequent trimester. These data were studied with relation to the effect of time of gestation on this test. Table 5

TABLE 5

Mean test values* and the mean differences of two glucose tolerance tests administred to 215 pregnant women

Hours	First test	Second test	Mean difference	Standard error of the mean difference
Fasting	69.4	69.8	.4	.8
One hour	94.9	111.5	16.6†	1.9
Two hours	85.3	93.3	8.0†	1.5
Three hours	73.9	82.5	8.6†	1.5

*Mg. per 100 ml.
†Significantly different from zero ($p = .001$).

records the mean values for the tests obtained in successive trimesters. With the exception of seven cases, the tests compared were performed during second and third trimesters. The difference between the first and second reading for each level was determined and the mean of the totaled differences obtained. It can be seen that there is no significant change in the fasting level. The difference of 16.6 mg. at one hour, 8.0 mg. at two hours, and 8.6 mg. at three hours is statistically significant ($p = .001$), and indicates a deterioration in glucose tolerance with progression of pregnancy. The range of plus and minus differences at each hourly interval, however, was great enough to make application of these results to any given individual unreliable. Figures including all three trimesters, while too small to analyze statistically, suggest that the trend existed from the first trimester.

Screening criteria and specified abnormal GTTSs

The first glucose tolerance tests on the 752 patients were divided into 705 (93.8 per cent) normal and 47 (6.2 per cent) abnormal by applying the criteria for abnormality defined in "Methods." At preliminary registration approximately half of the women were found to screen positive. The relationship of these screening results to the glucose tolerance test results and the ability of the former to select those with abnormal tolerances is shown in table 6. Their value is most accurately expressed by calculating both the ability of a positive screening test to identify an abnormal glucose tolerance test (sensitivity), and a negative screening test to identify correctly the person having a normal glucose tolerance test (specificity).[2] In this instance screening positive to at least one of the screening criteria used gave the highest sensitivity but the lowest specificity rating. It therefore produced the lowest number of false negatives and the highest number of false positives. A breakdown on the other items in the screening criteria used is similarly given.

TABLE 6

Evaluation of the screening devices used to select women likely to have abnormal tolerance for glucose during pregnancy, based on screening results and glucose tolerance tests in 752 unselected pregnancies

Screening criteria and results		Glucose tolerance test results: Total tests	Positive	Negative	Sensitivity rate per cent	Specificity rate per cent
All screenees		752	47	705	—	—
Blood sugar	Positive	109	21	88	—	—
	Negative	643	26	617	44.7	87.5
Large baby	Positive	89	12	77	—	—
	Negative	663	35	628	25.5	89.1
Other pregnancy history (see "Methods")	Positive	255	25	230	—	—
	Negative	497	22	475	53.2	67.4
Diabetes in family	Positive	73	8	65	—	—
	Negative	679	39	640	17.0	90.8
Positive to at least one criterion		381	40	341	85.1	51.6
Negative to all criteria		371	7	364	—	—

Specified abnormal glucose tolerances and related factors

It was thought that a retrospective look at the data for age, parity, and week of gestation with respect to the glucose tolerance test might reveal differences when the criterion for abnormality was preselected. Comparative tabulations are shown in table 1 that indicate that women with abnormal tolerances were generally older and had more pregnancies, a finding consistent with the previously described correlations. The distributions of the normal and abnormal groups by age and parity were significantly different from a statistical standpoint; however, our data do not allow consideration of their individual effects.

A final analysis was made of the first glucose tolerance tests and the relative ability of their hourly components considered separately to indicate an abnormal test as defined by our criteria. The fasting (110 mg. per 100 ml. or more), one-hour (170 mg. per 100 ml. or more), two-hour (120 mg. per 100 ml. or more) and three-hour (110 mg. per 100 ml. or more) values had sensitivity ratings of 6.4, 38.3, 95.8, and 74.5 per cent and specificity ratings of 100, 99.6, 94.6 and 96.9 per cent, respectively. Of all four values then, the one obtained two hours after ingestion of 100 gm. of glucose best reflected the abnormal tolerance test as a whole since it had a 95.8 per cent sensitivity and a 94.6 per cent specificity.

DISCUSSION

Because our subjects were entirely "unselected," examination of the glucose tolerance test during pregnancy without the restriction of preconceived criteria is of particular interest in this group. No detectable bias appeared to be introduced by the absence of data on 23 per cent of the registering women. The three previously known diabetics were rightly excluded. Although the clinic considered two of the 752 patients studied new diabetics, they were not excluded from any of the data analysis.

Mean values at each hour of the initial glucose tolerance tests performed on patients were fasting, 69.3 mg. per 100 ml.; one hour, 103.6 mg. per 100 ml.; two hours, 91.7 mg. per 100 ml.; and three hours, 79.4 mg. per 100 ml. While this would appear to be a low curve, it must be remembered that a composite of means tends to be flatter than the curve in any one individual. The standard deviations and the distribution of the actual values are also given in order that specific criteria of abnormality may be judged against our results. The values for the fasting state are relatively less variable than for the other hours. This substantiates the opinion that there is less variability in blood glucose levels for persons who have reached an equilibrium state in their metabolic processes than is found after the ingestion of glucose when the blood sugar is affected by its rate of absorption and the ability of the various individuals to dispose of the glucose load.

Blood sugar behavior in successive trimesters shows a progressive rise in the postglucose values with advancing pregnancy when judged by the findings for the whole group studied, and also by the change seen on examining repeated glucose tolerance tests in 215 of the same women (cohort data). While this change was highly significant statistically, the observed individual values may show a rise or a fall thereby not permitting the application of this result with certainty to any given person. The fasting levels remain unchanged (cohort

and correlational values) with advancing pregnancy. Since most data were obtained in the last two trimesters, this period naturally played the greatest role in determining our results. It might be well to point out that these findings demonstrate behavior of the glucose tolerance test during pregnancy and not the total effect of pregnancy on the glucose tolerance test.

The effect of age on glucose tolerance is demonstrated, by a small but progressive deterioration in carbohydrate metabolism with advancing years. Our figures also demonstrate an apparent correlation between parity and rising blood sugar. Since the recurring stress of pregnancy is claimed to have an etiologic role in the development of diabetes mellitus,[3] an attempt was made to further assess this factor. Increasing parity must necessarily be accompanied by increasing age, and application of partial correlation technic to remove the effects of age from our data appeared to leave little correlation between blood sugar level and parity. More data would be required before this can be said with certainty.

It is of interest to observe that the increase in blood sugar levels noted to accompany advancing age, advancing age plus parity, and advancing pregnancy, as judged by correlation data, was in each case maximal at the one-hour period and diminished progressively through the two- and three-hour periods. This was more clearly shown by the cohort data where the percentage increase in blood sugar as the pregnancy progressed was greatest at one hour. Since such factors are considered by many to be related to the development of diabetes,[3,4] there is a suggestion that the blood sugar at this sixty-minute interval might prove the most sensitive for this condition. Blood sugar variability at this interval, although almost twice as great as that found with fasting levels, is approximately the same as that at the two- and three-hour periods, removing this as a consideration in judging between them. The one-hour period therefore, approached in value only by the results at two hours, stands as the one which best reflects the change produced by factors affecting the glucose tolerance test in pregnancy and, by interference, may be the period to examine in searching for early diabetes mellitus.

Our minimum criteria for abnormality of glucose tolerance test (GTT) and our screening criteria are those used to select prediabetics for a study of larger scope.[5] It is demonstrated here that of all our patients screening negative to such criteria, seven only had abnormal GTT's on their first test. The sensitivity/specificity ratings[2] reveal immediately that we lose 14.9 per cent of the positive GTT's sought (i.e., false negatives) and pick up 48.4 per cent of the unsought negative GTT's (i.e., false positives). In doing so we eliminate the necessity of doing glucose tolerance tests on 50 per cent of the population studied. In rounded figures it might be said that for every 100 patients screened, fifty screen positive and that by having a full glucose tolerance test five out of six abnormals will be found.

Comparing the results of the combined screening items with those affected individually indicates how surprisingly less favorable than anticipated are such well accepted devices as family history of diabetes, past history of large babies, and unfavorable pregnancy history. Since such items are judged in terms of our criteria for an abnormal glucose tolerance test, the clinical significance of the latter might be questioned. It must be acknowledged, however, that the levels reflect at least some degree of change, since there is a return below them in the postpartum period.[6,7] In addition it should be realized that our criteria are stricter than many in current use.[8-10] Also noteworthy is the fact that the statistically significant difference in the prevalence of large babies among those meeting these criteria can be corrected with insulin treatment.[5] Finally, our experience indicates that women whose blood sugars during gestation exceed such diagnostic standards have a cumulative incidence of diabetes over the next five or six years of approximately 20 to 67 per cent depending on the degree to which the criteria are exceeded.[6,7] On the other hand, the corresponding cumulative incidence in normal controls over the same period is 0.5 per cent.[7]

It might be concluded that a general reassessment of these screening criteria and their clinical application would be desirable. More data will be required to examine the many possible variables which might comprise these screening devices, in addition to measuring their worth against the glucose tolerance test by criteria currently recommended for their evaluation.

Evidence in our data suggests that the specified one-hour blood sugar eventually may prove most indicative of abnormality. Since the two-hour level would appear best if judged solely in terms of our preselected criteria, possible deficiencies are suggested in the criteria themselves. In the absence of ideal whole population studies, all such currently accepted diagnostic standards are necessarily somewhat arbitrary. This artificiality in no way diminishes their previously noted clinical usefulness, although our study on an unselected group of women indicates the advisability of seeking modifications of these criteria in the future.

SUMMARY

1. Seven hundred and fifty-two or 76.3 per cent of the 986 registering prenatal patients at Boston City Hospital completed one or more glucose tolerance tests (GTT's) during pregnancy.

2. Their mean blood sugar values, and the change in blood sugar levels obtained on 215 of the women in successive trimesters were examined. No change was apparent in fasting values. Postglucose values showed a definite rise with the progression of pregnancy, but this was not necessarily true for any given individual.

3. The correlation shown between increasing age and parity with increasing blood sugar levels is discussed.

4. Suggested evidence that the one-hour value eventually may prove the most useful for determining abnormalities is discussed in relation to the observation that the two-hour value best reflects the abnormal glucose tolerance test by defined criteria. The advisability of exploring possible further improvements in the diagnostic criteria for the oral glucose tolerance test in pregnancy is indicated.

5. Using a specific criterion of abnormality for the glucose tolerance test, the sensitivity and specificity ratings for each of the following are given: family history of diabetes, large baby, other pregnancy history items, and a venous blood sugar of 130 mg. per 100 ml. one hour after 50 gm. of glucose. Our data suggest that further study is required in order to place such screening criteria for prediabetes in their proper perspective.

SUMMARIO IN INTERLINGUA

Un Studio del Tolerantia pro Glucosa e Criterios Usate in Tests de Cribrage in 752 Non-Seligite Gravidas

1. Septe centos cinquanta-duo del total de 986 registrantes pre-parturitive al Hospital Municipal Boston (76,3 pro cento) completava un o plure tests de tolerantia pro glucosa durante le curso de lor pregnantia.

2. Le valores medie pro sucro sanguinee e le alterationes in ille valores in successive trimestres del pregnantia esseva obtenite ab 215 del feminas. Le comparation del datos de iste examines monstrava nulle alteration in le apparente valores in stato jejun. Le valores post le repasto experimental de glucosa monstrava un definite ascendita con le progresso del pregnantia, sed iste constatation non valeva necessarimente in omne caso individual.

3. Es discutite le correlation inter le avantiamento del etate e le numero del completate pregnantias de un latere e le augmento del nivellos de sucro sanguinee del altere latere.

4. Le suggestion que le existente datos indica que possibilemente le valores post un hora va esser recognoscite in le curso del tempore como le plus utile in determinar anormalitates es discutite in relation al facto que le valores post duo horas reflecte le melio un anormal test de tolerantia pro glucosa secundo le hic-definite criterios. Es signalate le desirabilitate de explorar possibile meliorationes additional in le criterios diagnostic pro le test del tolerantia pro glucosa in gravidas.

5. Con le uso de un criterio specific pro anormalitate in le test de tolerantia pro glucosa, le grado de sensibilitate e specificitate pro le sequente parametros es presentate: Antecedentes familial de diabete; grande peso del infante; altere aspectos del curso del pregnantia; e un nivello de sucro in le sanguine venose de 130 mg per 100 ml un hora post le ingestion de 50 g de glucosa. Nostre datos indica que studios additional es requirite pro placiar tal criterios de prediabete in un correcte perspectiva.

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