The Potential Diabetic and Her Treatment in Pregnancy

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THE EVIDENCE that fetal wastage is greater in the pregnancies of women during the years preceding the diagnosis of diabetes mellitus is unquestioned.[5, 9, 10] Identification of these women during the preclinical phase of diabetes offers a challenge to preventive medicine. The characteristic medical history, such as diabetes in the family, the birth of large babies, or complications in pregnancy, has been helpful in predicting possible diabetes. However, the mainstay of early diagnosis has been the oral glucose-tolerance test. This test, when administered during pregnancy, is considered to have a predictive value[18] comparable to that of the steroid-modified test for nonpregnant persons.[3] Evidence has been presented associating an abnormal outcome of pregnancy with an abnormal response to glucose during pregnancy.[2, 6, 12] It has also been proposed that medical management with diet and insulin will lessen the pregnancy risks of such women.[6, 12]

Our own studies[21-23] have been interpreted as supporting this viewpoint,[12] but in more recent work, the very basis of these results is questioned. It has been argued that abnormal results in a glucose-tolerance test during pregnancy represent a normal physiologic change not necessarily related to the prediabetic state.[1, 11] Other studies indicate that fetal wastage in women shown to have abnormal glucose tolerance in the postpartum period is no higher than fetal wastage in women with normal test results.[20]

There is, therefore, a continuing need to study the relationship of maternal blood glucose to the outcome of pregnancy. This need is emphasized by the fact that such obstetric decisions as early termination of pregnancy are currently based on data that appear to be in conflict. In this presentation, the outcome of pregnancy in a group of patients who showed abnormal results in glucose-tolerance tests will be compared with the experience of normal controls. The latter were selected concurrently and at random from the same prenatal clinics. The effect of diet and insulin with otherwise unaltered ob-

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stetric care will also be investigated in a subgroup of those women with abnormal glucose tolerance.

MATERIALS AND METHODS

Selection of Patients

This study includes patients who attended the Prenatal Metabolic Clinic at Boston City Hospital between April 1954 and June 1960 and at Boston Lying-In Hospital for part of this time. All prenatal patients were screened. Those who met one or more of the following criteria were scheduled for a glucose-tolerance test: a venous blood sugar of 130 mg./100 ml. or more, 1 hr. after oral ingestion of 50 gm. of glucose; a history of having given birth to a baby weighing 4.1 kg. (9 lb.) or more; and a history of fetal death, neonatal death, congenital anomaly, prematurity (less than 5 lb., 6 oz. at birth), or toxemia (excessive weight gain, hypertension, or proteinuria) in 2 or more pregnancies. Women who met the screening criteria and who had normal glucose tolerance in one trimester received repeat tests in subsequent trimesters.

To select the potential diabetics, a 3-hr. oral 100-gm. glucose-tolerance test was administered. Analysis was by Somogyi-Nelson determinations on venous whole-blood samples. All patients were instructed to take 250 gm. of carbohydrate daily for 3 days before the test. For this study, women were considered potentially diabetic if any 2 or more blood-sugar readings met or exceeded the following levels: fasting, 110 mg.; at 1 hr., 170 mg.; at 2 hr., 120 mg.; and at 3 hr., 110 mg./100 ml. Persons classified as potential diabetics by this definition were randomly allocated into 2 groups: those receiving diet and insulin management, termed "positive treated," and those receiving routine prenatal care, termed "positive controls." A third group of patients, "negative controls," was selected randomly at regular intervals; only those with abnormal glucose tolerance were considered ineligible for this category.

Excluded from the study groups were all women with previously known diabetes; those with blood sugars exceeding 300 mg./100 ml.; those with classic diabetic symptoms; and potential diabetics who registered on or after the thirty-seventh week of pregnancy, since therapy of such short duration could not be properly evaluated.

Management of Patients

Positive controls and insulin-treated patients were given printed routine obstetric and dietary instructions by the obstetrician. Under the direction of an internist and a nutritionist, specific diets were given to the insulin-treated patients. These diets approximated 30 cal./kg. ideal body weight. The composition generally required 1.5–2 gm. of protein per kilogram, with 40% of the total calories derived from carbohydrates. The nutritionist evaluated the subsequent dietary intake. Initial insulin treatment, which consisted of 10 U. of NPH insulin, was given each morning. The majority of postprandial blood-sugar levels, for both treated and untreated potential diabetics, were within the normal range when judged by commonly accepted standards. Because these levels were unavailable on the morning of the patient's routine clinic visit, the increases of insulin dosage were arbitrarily determined by the fresh appearance of glycosuria, as determined by tests performed daily in the home or during attendance at the clinic.

RESULTS

The study groups were comprised of 328 negative controls, 307 positive-treated, and 308 positive-control patients. The 2 groups of potential diabetics were comparable with respect to age, parity, and body weight (Table 1). They were, however, older by more than 5 years and of a slightly higher parity than the negative controls. A further general characteristic of the potential diabetics was their greater tendency to be overweight (Table 2).

The number of large babies born to the positive controls (13.1%) was approximately 3 times the number born to either the negative controls (3.7%) or the positive-treated patients (4.3%). The latter 2 groups were not significantly different from each other (Table 3). Figure 1 depicts the full range of birth weights by study category. The differences between the groups became apparent at birth weights of 4.5–5 lb., and the positive-treated patients showed a significantly lower incidence for all birth weights above this level. Table 4 shows that treatment was as effective for the overweight mother as it was for one who was normal or underweight.

Further information on the outcome of the pregnancies is summarized in Table 3. Although there were significantly more viable losses among the potential diabetics than among the negative controls ($p<.01$), there was no corresponding difference between the positive controls and the treated group. These results remain unaltered even when the neonatal period is extended to 28 days, when

TABLE 1. AGE AND PARITY DISTRIBUTIONS FOR POTENTIAL DIABETICS AND NORMAL CONTROLS

	Positive treated		*Positive control*		*Negative control*	
Parity	*No.*	*Mean age (yr.)*	*No.*	*Mean age (yr.)*	*No.*	*Mean age (yr.)*
0	42	22.5	34	23.4	88	20.7
1	35	27.3	33	25.5	65	23.5
2	39	28.3	43	31.1	49	24.3
3	47	31.6	49	30.9	46	26.6
4	45	31.5	44	32.1	32	29.3
5	27	33.9	36	33.8	20	28.6
6	26	32.2	20	34.4	8	33.4
7	19	33.5	24	36.0	10	33.7
8	8	36.8	6	36.2	3	31.3
9	19	38.0	19	38.9	7	37.0
TOTAL	307	30.3	308	31.2	328	25.1
MEAN PARITY	3.6		3.7		2.2	

TABLE 2. USUAL WEIGHT STATUS OF STUDY PATIENTS

Weight status (%)	*Negative control*		*Positive control*		*Positive treated*	
	No.	*%*	*No.*	*%*	*No.*	*%*
≤−10	80	24.4	43	14.0	51	16.6
−09 to +9	162	49.4	121	39.3	122	39.7
10 to 19	48	14.6	50	16.2	49	16.0
≥20	38	11.6	94	30.5	85	27.7
TOTAL	328	100.0	308	100.0	307	100.0

TABLE 3. OUTCOME OF FIRST STUDY PREGNANCY BY STUDY CLASSIFICATION

	Negative control		*Positive treated*		*Positive control*	
Outcome	*No.*	*%*	*No.*	*%*	*No.*	*%*
Total viable deliveries	324	100.0	305*	100.0	306	100.0
No. of abnormal outcomes	76	23.5	74	24.3	100	32.7
Live: 9 lb. or more at birth	12	3.7	13	4.3	40	13.1
Live: congenital abnormality	44	13.6	40	13.1	49	16.0
Live: premature	25	7.7	26	8.5	24	7.8
Viable losses:	6	1.9	13	4.3†	15	4.9†
Death of viable fetus (>28 weeks)	4	1.2	8‡	2.6	8	2.6
Neonatal death (≤14 days)	2	0.6	5	1.6	7	2.3

* Twelve did not have insulin treatment.

† Losses among positives significantly were greater than among negative controls ($p<.01$). Significance remains ($p<.05$) if untreated patients are excluded. There is no statistical difference between positive-treated (with exclusion of untreated) and positive controls.

‡ Two occurred among persons untreated.

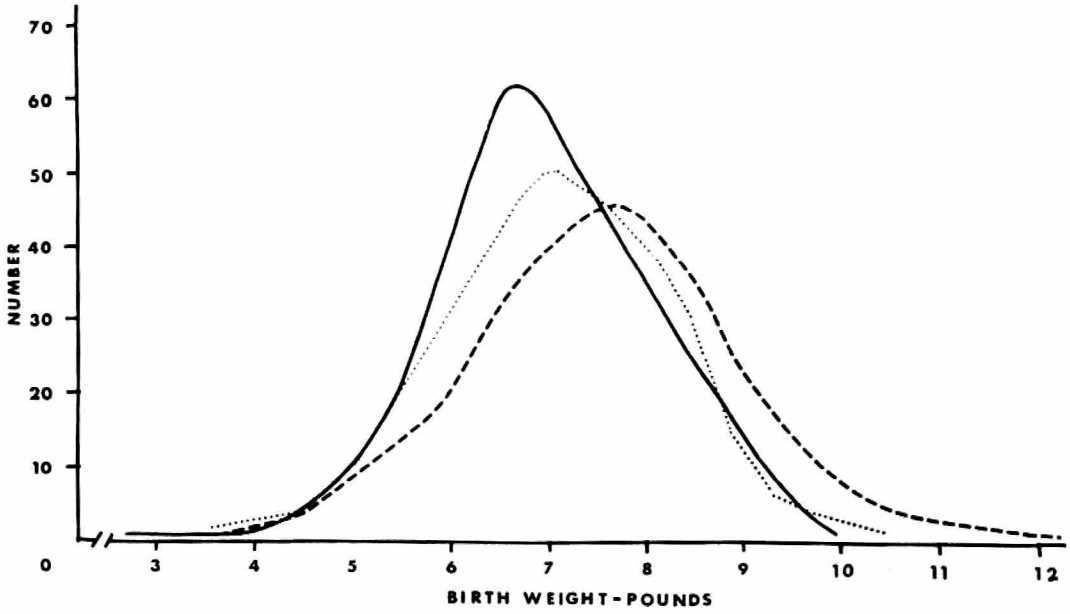

Fig. 1. Range of birth weights by study category. Solid line, negative controls; dotted line, positive-treated patients; dashed line, positive controls.

data for 6 pregnancies resulting in twins are excluded, and when women who did not take their insulin treatment are separated from the treated group. There was no significant difference between the study groups with respect to premature births or to the presence of congenital anomalies in the offspring.

Character of Treatment

A broad outline of the insulin treatment can be conveyed by the following analysis of the first 229 patients who were selected. The median values indicated that the insulin dosage was 658 U. and that it was taken over a period of 8 weeks, commencing at the thirty-second week of gestation. Possible dietary differences were sought by sample evaluation of 53 positive-treated and 33 positive-control patients. This revealed a statistically significant mean difference in daily carbohydrate intake; the positive controls ate 21 gm. more than the positive-treated patients. However, the average weight gain for the period of observation was only 2 lb. greater for the positive controls, which is not statistically significant.

TABLE 4. EFFECTIVENESS OF TREATMENT IN MOTHERS WHO WERE OVERWEIGHT, NORMAL, OR UNDERWEIGHT

Maternal weight status (%)	*% with large babies*		
	Positive treated	*Positive control*	*Negative control*
≤ 9	2.3	10.0	2.5
≥10	7.6	16.4	7.0

Effectiveness of Treatment

The effect of insulin and dietary management on carbohydrate metabolism was gauged in 2 ways. The number of postprandial blood sugars rated as abnormal when plotted on an arbitrary scale was obtained. This scale was comprised of milligrams per hundred milliliters against the time interval from the previous meal. The arbitrary norms for this graph were 100 mg./100 ml. at fasting levels and at 2 hr. or more, and 150 mg./100 ml. at 1 hr. Although the insulin-

TABLE 5. MEAN OF 2701 POSTPRANDIAL BLOOD SUGARS IN 432 PATIENTS, BY STUDY CATEGORY

Postprandial time (hr.)	Positive treated			Positive control			Negative control		
	No.	Mean	S.D.*	No.	Mean	S.D.	No.	Mean	S.D.
½<1†	76	93.3	20.7	59	99.8	24.8	54	81.6	16.4
1<2‡	427	88.8	23.1	412	92.6	23.2	323	74.3	15.2
2<3†	295	80.1	23.0	233	83.0	21.2	166	68.6	12.6
3<4†	65	71.6	18.4	58	73.9	16.2	54	67.3	12.5
>4 or fasting§	71	69.1	16.9	102	74.3	15.4	77	65.5	9.3

* Standard deviation.

† Insulin treatment did not reduce blood sugar significantly.

‡ Insulin treatment reduced blood sugar ($p < .01$).

§ Insulin treatment reduced blood sugar ($p < .05$).

treated and positive-control patients had significantly more abnormal blood sugars than the negative controls, they were not significantly different from each other. The second evaluative approach (Table 5) tested the mean postprandial blood sugars of each group. The negative controls had significantly lower mean blood-sugar levels for each postprandial time period. The mean peak blood-sugar levels that followed a meal occurred at the ½- to 1-hr. interval. These mean levels were no different in the positive-treated patients from those in the positive-control patients. The large sample size probably contributed to the significant difference seen at the 1- to 2-hr. interval, since the mean blood sugars at the 2- to 3-hr. and the 3- to 4-hr. intervals remained unaltered following treatment. On the other hand, the fasting blood-sugar level showed a significant lowering with treatment. Judging the effect of treatment, therefore, by both forms of analysis, it appears that the postabsorptive state was significantly affected, whereas changes in carbohydrate metabolism following the stress of a meal remained unaltered.

DISCUSSION

Over 97% of the women in the insulin-treated and positive-control categories were found to have nondiabetic glucose-tolerance tests within 6 months following delivery. The significant number of women who subsequently developed diabetes affirms the importance of abnormalities in results of the glucose-tolerance test in pregnancy,[18] despite the expressed doubts.[1] The designation "potential diabetes" is consequently valid; the patients' nonpregnant tests are normal, but they are still considered a high risk group for future diabetes.[14, 18] Since we have no documented evidence that all these persons will later develop diabetes, to consider that the patients have reached a later phase of the disease is either to disregard the widespread disagreement on diagnostic criteria or to err on the side of overdiagnosis. Therefore, the study of this early phase of diabetes has limitations. Since we are dealing with a group of potential rather than certain candidates for diabetes mellitus, the terms "potential diabetes" and "prediabetes" must be qualified on each occasion, to indicate the defined limitations. Groups of potential diabetics can be selected, for example, on a genetic basis which allows *group* identification, even at the intrauterine stage of life. They can also be chosen by specific subdiagnostic levels for glucose tolerance which will identify the risk group while it is closer to clinical diabetes.

This prospective study indicates that patients defined by a chemical abnormality, without evidence of clinical disease, have an increased viable fetal wastage. The obvious importance of this result, with respect to the routine screening of prenatal populations,

need not be belabored. It should be recognized, however, that data claiming to deny this conclusion have been retrospective; the glucose-tolerance test was performed *after* delivery, and the criteria were set considerably lower than ours, when allowances are made for methodologic differences.[20] The findings that bear on the management of this abnormality are of considerable practical importance and merit careful consideration. The low incidence of fetal wastage reported here reflects the high quality of routine obstetric care in the hospitals involved. The generally favorable figures, however, fail to mask the significance of this higher-risk group. The greater number of losses reported in similar patients who did not take advantage of routine prenatal care[2] indicates a magnification of the detrimental effects when conditions are less than ideal.

The insulin and dietary management employed did not reduce the number of viable losses. It must be recognized, however, that such management does not produce the same degree of chemical control that operates in the normal person. Consequently, Hoet's original work, which showed the beneficial effects of management,[6] should be re-examined. The most striking difference is that Hoet recommends insulin to tolerance. He hospitalizes women whose dosage exceeds 30 U./day in order to avoid unattended hypoglycemia, although such patients constitute a small group.[7] This approach has not been attempted with our patients. The further results of Hoet's studies are awaited with interest, particularly since the adequacy of his controls remains to be substantiated.[8]

Although Omers also ascribes beneficial effects to insulin treatment, comparisons are made difficult by the problems of defining the patients for study and determining what constitutes a fetal loss. Omers cites our study in support of the beneficial effect of insulin treatment, since total "abnormal outcomes" are significantly less in the positive-treated group. It should be recognized, however, that this conclusion is based entirely upon the altered birth weight pattern that is produced by treatment.

The significant reduction in the number of large babies—the traditional characteristic of prediabetes—is very striking. A higher blood-glucose level is generally accepted as the initiating factor that is responsible for the increased fat deposition in these babies.[4, 13, 19] The diminished birth weight for the babies of the treated patients reported here was not confined to those babies who were considered large, but was seen at lower birth-weight levels as well.

Our initial work, which implied a relationship between birth weight and blood sugar,[16] was later found to apply only to subgroups within the normal population. These subgroups consisted of overweight mothers, women with large babies, and those with blood-sugar levels in the upper 5% of the population.[15, 17] The potential diabetics whom we have discussed might be considered to be in the last category. Therefore, a change in blood sugar might logically have accounted for the reduction in birth weights. Evaluation of the data we have presented here shows that they support these conclusions. While the untreated prediabetics have significantly heavier infants, treatment effective enough to alter the postabsorptive, though not the postprandial state produces a significant reduction in birth weight. Because treatment does result in demonstrable changes in the birth weight of babies of potentially diabetic mothers, it is important to maintain observation of this group with respect to the possible delay or prevention of diabetes mellitus in the mother or the child.

SUMMARY

1. A total of 615 women shown to have abnormal glucose tolerance in pregnancy were randomly assigned to 1 of 2 categories: the positive treated, who received diet and insulin management; and the positive con-

trols, who received routine obstetrical care. Negative controls, 328 patients who were also receiving routine obstetrical care, were selected at random from the same clinics. Tests indicated that these negative controls had normal glucose tolerance. The evidence that designated the positive groups as potential diabetics is discussed.

2. The outcome of pregnancies revealed a significantly increased number of viable fetal losses in the women who had abnormal glucose tolerance. The lack of significant improvement in the number of viable losses following insulin and diet treatment is discussed in relation to the intensity of this treatment and its failure to effect a meaningful reduction in postprandial blood sugar levels.

3. Among the potential diabetics in the treated group, the number of higher birth weights approximated the normal range. The mechanism effecting this reduction is considered to be related to the significant lowering of postabsorptive blood-sugar levels.

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