Congenital Susceptibility to NIDDM

Role of Intrauterine Environment

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Non-insulin-dependent diabetes mellitus (NIDDM) during pregnancy in Pima Indian women results in offspring who have a higher prevalence of NIDDM (45%) at age 20–24 yr than in offspring of nondiabetic women (1.4%) or offspring of prediabetic women (8.6%), i.e., women who developed diabetes only after the pregnancy. These differences persist after taking into account paternal diabetes, age at onset of diabetes in the parents, and the offspring's weight relative to height. The findings suggest that the intrauterine environment is an important determinant of the development of diabetes and that its effect is in addition to effects of genetic factors. *Diabetes* 37:622–28, 1988

Diabetes during pregnancy has well-recognized immediate effects on the newborn, including high perinatal mortality and high frequencies of macrosomia, respiratory distress syndrome, congenital anomalies, and hypoglycemia (1,2). The long-term effects on the offspring of diabetes during pregnancy, particularly effects that may be attributable to the diabetic intrauterine environment, have received little attention. Whereas starvation during late pregnancy results in a lower frequency of obesity in the offspring (3,4), diabetes during pregnancy, a state of overnutrition for the fetus (5), results in offspring who are more obese as children, adolescents, and young adults (6). The possible effects of a diabetic environment in utero on the subsequent development of diabetes in the offspring are unknown. In this study the prevalence of diabetes has been examined in the offspring of women who had diabetes during the pregnancy and compared with the prevalence in offspring of women who developed diabetes only after the pregnancy as well as in the offspring of women who had not developed diabetes. Familial, presumably genetic, differences in diabetes frequency were accounted for by considering the father's diabetes status, the age at onset of diabetes in the parents, and the offspring's weight relative to height, which is closely associated with maternal diabetes in this population.

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SUBJECTS AND METHODS

The Pima Indians of Arizona have the highest reported incidence and prevalence of non-insulin-dependent diabetes mellitus (NIDDM) and have participated in a longitudinal study of diabetes since 1965 (7,8). This study has been conducted among the residents of the Gila River Indian Community, most of whom are Pima Indians but some of whom are Papago Indians, a closely related tribe that also has a high prevalence of NIDDM (9). Each community resident aged >5 yr is asked to have an examination every 2 yr that includes determination of the plasma glucose concentration 2 h after ingestion of 75 g carbohydrate (Dexcola, Custom Laboratories, Baltimore, MD; or Glucola, Ames, Elkhart, IN). Diabetes either in the parents or the offspring was diagnosed, according to World Health Organization (WHO) criteria (10), when the 2-h postload plasma glucose concentration was ≥200 mg/dl (11.1 mM) or if, during routine medical evaluation, a fasting or postprandial glucose concentration of ≥200 mg/dl was found (8). Impaired glucose tolerance was diagnosed on the basis of a 2-h postload glucose concentration of 140 (7.78 mM) to 199 mg/dl, and glucose tolerance was considered normal when the 2-h postload glucose concentration was <140 mg/dl.

Each individual was identified who lived in the Gila River Indian Community or a surrounding community, who had previously participated in the study, who had had at least one examination between the ages of 10 and 24 yr, inclusive, who was of at least half Pima and/or Papago heritage, and whose mother's diabetes status during the pregnancy was known. To avoid potential misclassification, offspring were

not included if the mother's diabetes status at the time of the pregnancy could not be certified. Therefore, we only included offspring whose mothers had been tested for diabetes with an oral glucose tolerance test at such a time as to make certain the diabetes status during the pregnancy. Because the mothers were tested during every pregnancy and the fathers were not, more fathers than mothers were considered not classifiable.

The offspring were divided into three groups based on the mother's diabetes status at the time of the pregnancy (6): offspring of nondiabetic mothers; offspring of prediabetic mothers, i.e., mothers who had normal glucose tolerance at the time of pregnancy but who developed diabetes sometime after the birth of the offspring; and offspring of diabetic mothers who were known to have had diabetes during the pregnancy. For inclusion in the study, nondiabetic and prediabetic mothers were required to have had a documented normal glucose tolerance ≥4 wk after delivery with 2-h glucose concentrations <140 mg/dl. We chose this interval to avoid testing in the immediate postpartum period, when glucose tolerance is often improved and an abnormality may be missed (11). Prediabetic women subsequently developed diabetes and were therefore identified in retrospect as being prediabetic at the time of pregnancy. Nondiabetic women did not develop diabetes as determined by glucose tolerance tests at follow-up examinations ≥5 yr later, although some eventually developed impaired glucose tolerance. Fathers of the offspring included in this study were also tested for diabetes and were similarly classified as nondiabetic, prediabetic, or diabetic. All nondiabetic fathers, like nondiabetic mothers, had normal glucose tolerance tests ≥5 yr after the offspring's birth. Prediabetic fathers developed diabetes with an onset after the offspring's birth and had at least one normal glucose tolerance test after the offspring's conception. All offspring and their parents were of at least half Pima and/or Papago heritage. Only 10- to 24-yr-old offspring were considered because diabetes occurred in very low frequencies in younger individuals.

Multiple logistic regression analysis (12), with either diabetes or abnormal glucose tolerance in the offspring as the binary dependent variable, was used to simultaneously control for mother's diabetes status, father's diabetes status, age at onset of mother's and father's diabetes, and offspring's age, sex, and relative weight (6). Parents' ages at onset and offspring's age and relative weight were entered into the models as continuous variables, and offspring's sex was entered as a binary variable. Because each parent's diabetes status was divided into three groups, two binary variables were used for each. One of these binary variables indicated whether the parent ever developed diabetes and

TABLE 1
Characteristics of subjects

	Father's diabetes status				
	Nondiabetic	Prediabetic	Diabetic	Unknown	Total
Offspring of nondiabetic mothers					
Subjects	260	101	13	239	613
Males	133	49	6	114	302
Females	127	52	7	125	311
Age (yr)*	17.4	17.9	16.4	17.0	17.3
Relative weight (%)*	123	126	113	125	124
Parents' ages (yr)†					
Mother	25.0	25.2	26.8	26.0	25.5
Father	30.2	28.7	34.0	30.0	30.0
Father at onset		43.1	29.3		
Offspring of prediabetic mothers					
Subjects	137	63	33	174	407
Males	70	28	15	81	194
Females	67	35	18	93	213
Age (yr)*	18.7	17.2	18.1	18.3	18.2
Relative weight (%)*	133	135	144	137	136
Parents' ages (yr)†					
Mother	25.8	25.1	30.6	25.9	26.1
Mother at onset	42.9	39.1	43.9	42.0	42.0
Father	29.1	30.8	32.5	30.2	30.1
Father at onset		41.3	29.3		
Offspring of diabetic mothers					
Subjects	13	3	10	18	44
Males	4	1	5	9	19
Females	9	2	5	9	25
Age (yr)*	17.4	14.7	14.8	17.8	16.8
Relative weight (%)*	144	147	133	143	141
Parents' ages (yr)†					
Mother	31.4	27.6	32.4	35.0	32.8
Mother at onset	27.0	23.5	30.3	31.5	29.4
Father	36.0	31.4	41.0	36.7	37.1
Father at onset		41.3	38.5		

*Data are means at latest examination.
†Data are means at delivery of offspring and at onset.

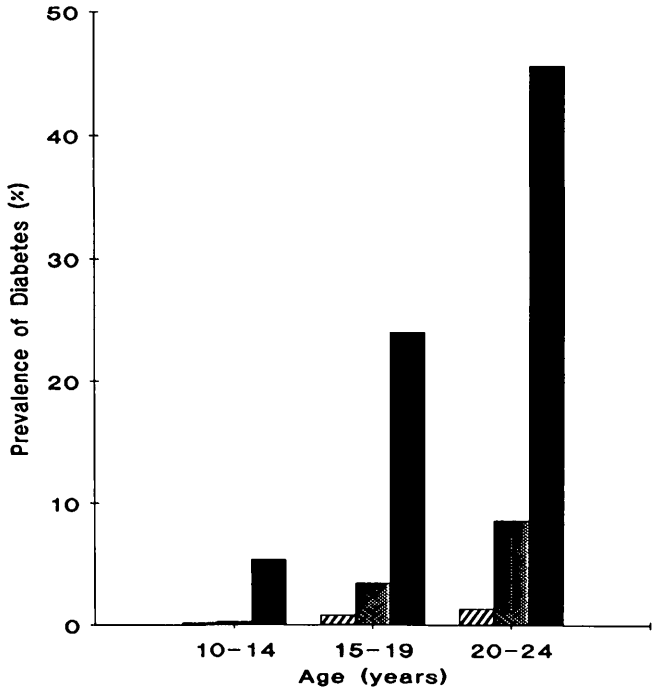

FIG. 1. Prevalence of diabetes (2-h postload plasma glucose concn ≥200 mg/dl) according to age at examination and mother's diabetes status. *Hatched bars*, nondiabetic; *crosshatched bars*, prediabetic; *solid bars*, diabetic.

was therefore an assessment of the effect of developing diabetes after the pregnancy compared with never having developed diabetes. The other binary variable indicated whether diabetes was present at the time of the pregnancy and thus was an assessment of the additional effect of having diabetes during pregnancy compared with having developed diabetes later. The overall effect of the mother's or father's diabetes status was calculated by evaluating the model both with and without the two diabetes status variables for that parent. Overall covariate-adjusted prevalence rates of diabetes for each of the nine combinations of parental values (3 maternal × 3 paternal groups) were calculated from the regression model by a method of covariance adjustment of rates described by Lee (13).

RESULTS

In all, 1064 offspring of 307 mothers and 323 fathers were studied (Table 1). Thirty-four of these offspring developed diabetes. There were 613 offspring of 183 nondiabetic women, 407 offspring of 99 prediabetic women, and 44 offspring of 28 diabetic women. (Three women were considered prediabetic at the time of their earlier pregnancies and diabetic for later pregnancies.) Because the fathers of these offspring were not routinely tested for diabetes at the time of the pregnancy, precise data on paternal diabetes status at the time of the pregnancy were unknown for 431 of these offspring. The data for unclassifiable fathers appeared to occur randomly, accounting for 39% of the offspring of nondiabetic women, 43% of the offspring of prediabetic women, and 41% of the offspring of diabetic women. Sixteen of the remaining 633 offspring, or 2.5%, developed diabetes by age 24 yr.

Figure 1 and Table 2 show the unadjusted prevalence of diabetes, according to age and mother's diabetes status, for all offspring whose mothers' statuses were known during pregnancy and whose fathers' diabetes statuses were known. Because of repeated examinations, offspring could contribute data to more than one age group; however, for subjects examined more than once in a given age range, only data from the examination closest to the midpoint of that range were used. Within each age group, offspring of diabetic women had higher rates of diabetes than did offspring of nondiabetic ($P < .05$ at 10–14 and $P < .001$ at 15–19 and 20–24 yr of age, Fisher's exact test) or prediabetic women ($P < .05$ at 10–14 yr and $P < .005$ in older groups). By 20–24 yr of age, 45% of the offspring of diabetic women had diabetes, compared to 1.4 and 8.6% for offspring of nondiabetic and prediabetic women, respectively. In the youngest age group, in which only 4 of 852 offspring had

TABLE 2
Prevalence of diabetes in offspring according to age at examination and each parent's diabetes status

Age at examination (yr)	Father's diabetes status	Mother's diabetes status: Nondiabetic Rate	Nondiabetic *n*	Prediabetic Rate	Prediabetic *n*	Diabetic Rate	Diabetic *n*	Total Rate	Total *n*
10–14	Nondiabetic	0	203	0	108	8.3	12	0.3	323
	Prediabetic	1.3	80	0	57	0	3	0.7	140
	Diabetic	0	12	0	32	11.1	9	1.9	53
	Unknown	0	183	0.7	140	0	13	0.3	336
	Total	0.2	478	0.3	337	5.4	37	0.5	852
15–19	Nondiabetic	0	151	1.1	94	25.0	8	1.2	253
	Prediabetic	0	66	2.4	42	0	2	0.9	110
	Diabetic	0	7	14.3	21	25.0	4	12.5	32
	Unknown	2.4	123	4.0	126	27.3	11	4.2	260
	Total	0.9	347	3.5	283	24.0	25	2.9	655
20–24	Nondiabetic	0	96	6.1	66	40.0	5	3.6	167
	Prediabetic	0	39	0	19		0	0	58
	Diabetic	0	3	40.0	15	100.0	1	36.8	19
	Unknown	3.8	80	6.7	75	40.0	5	6.3	160
	Total	1.4	218	8.6	175	45.5	11	5.7	404

TABLE 3
Results of multiple logistic regression models

Dependent variable: abnormal glucose tolerance in offspring*					Dependent variable: diabetes in offspring†				
Variable	$\hat{\beta}$	SE of $\hat{\beta}$	χ^2	P	Variable	$\hat{\beta}$	SE of $\hat{\beta}$	χ^2	P
Prediabetic mother	0.8077	0.2749	20.64	<.001	Prediabetic mother	2.2188	1.0790	15.35	<.001
Diabetic mother	1.4215	0.4988			Diabetic mother	2.0340	0.8058		
Prediabetic father	0.2085	0.2966	0.52	.771	Prediabetic father	0.3236	0.8720	10.75	<.005
Diabetic father	−0.0811	0.4638			Diabetic father	1.7981	0.8740		
Age	0.1619	0.0375	18.64	<.001	Age	0.3195	0.1092	8.56	<.005
Sex	0.4168	0.2770	2.27	.132	Sex	−0.4214	0.6423	0.43	.512
Relative weight	0.0182	0.0040	20.84	<.001	Relative weight	0.0156	0.0087	3.20	.074
Intercept	−8.6353	0.9354			Intercept	−14.0028	2.6738		

When value of regression coefficient $\hat{\beta}$ is negative, the predictor variable is negatively associated with the dependent variables. The prediabetes indicator is the effect of developing diabetes after pregnancy; the diabetes indicator reflects the effect of having diabetes before the delivery.
*2-h postload plasma glucose ≥140 mg/dl.
†2-h postload plasma glucose ≥200 mg/dl.

developed diabetes, there was little difference in the prevalence of diabetes between the offspring of nondiabetic and prediabetic women, but by 20–24 yr of age, the offspring of prediabetic women had a significantly higher prevalence (8.6%) than did offspring of nondiabetic women (1.4%, $P < .005$, Fisher's exact test). These data could of course not be adjusted for the father's diabetes status because they included those of unknown fathers' statuses.

The variables included in the logistic models are shown in Table 3. For subjects examined more than once, only data from the last age range were used. Because the data for the unclassifiable fathers were distributed proportionately, their offspring were not included in the analysis, and no adjustments were made for the missing data. The father's diabetes status was not a significant predictor of abnormal glucose tolerance after adjustment for mother's diabetes status and for the age and relative weight of the offspring, but maternal diabetes status and age and relative weight of the offspring were all important predictors. On the other hand, the father's diabetes status as well as the mother's diabetes status and child's age, but not relative weight, were strong predictors of diabetes in the offspring.

Figure 2 shows the prevalences of both diabetes and impaired glucose tolerance adjusted for age at last examination, sex, and relative weight by multiple logistic regression. Offspring of women with diabetes during pregnancy had a higher prevalence of both diabetes and total abnormal glucose tolerance (defined as impaired glucose tolerance or diabetes) than did offspring of either prediabetic or nondiabetic women, regardless of the father's diabetes status. Because neither sex nor relative weight added significantly to the model as predictors of diabetes, they were not included in subsequent models in which diabetes in the offspring was the dependent variable.

As can be derived from Table 1, parents classified as diabetic at the time of the pregnancy had developed the disease at a younger age than those classified as prediabetic. The mean age at onset of diabetes (±1.96 SE) for diabetic parents (men and women combined) was 30.3 ± 1.5 yr and for prediabetic parents was 42.1 ± 0.7 yr. However, at every age, offspring of diabetic women had a higher prevalence of diabetes than did offspring of prediabetic women, regardless of the age at which the mother developed diabetes (Table 4).

Figure 3 shows the age-adjusted prevalence of diabetes in the offspring, for which age at onset of parental diabetes has been controlled by the method of Lee (13). Because age at onset did not apply to nondiabetic parents, the effect of maternal age at onset could be assessed only in offspring of prediabetic and diabetic women. There were 259 offspring of prediabetic and diabetic women, and 15 of them had developed diabetes. Likewise, the effect of paternal age at onset could be assessed only in offspring of prediabetic and diabetic men. There were 223 of these offspring, and 10 of

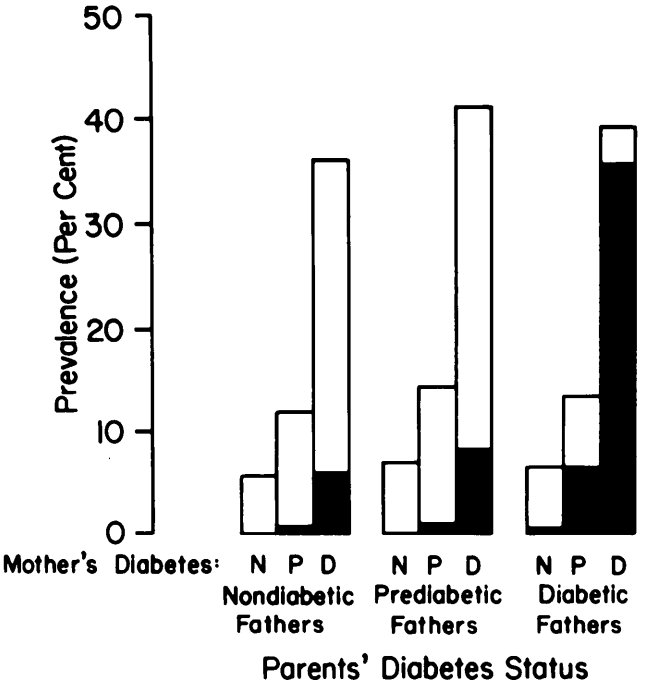

FIG. 2. Prevalence of diabetes and impaired glucose tolerance according to mother's and father's diabetes statuses and adjusted to mean age, sex, and relative weight of sample. *Solid bars*, diabetes (2-h postload plasma glucose concn ≥200 mg/dl); *open bars*, impaired glucose tolerance (2-h glucose concn 140–199 mg/dl). N, nondiabetic; P, prediabetic; D, diabetic women.

TABLE 4
Prevalence of diabetes in offspring of prediabetic and diabetic mothers

Mother's age at onset (yr)	Mother's status, with offspring 10–14 yr		Mother's status, with offspring 15–19 yr		Mother's status, with offspring 20–24 yr	
	Prediabetic	Diabetic	Prediabetic	Diabetic	Prediabetic	Diabetic
<30	4.3 (23)	0 (17)	10.5 (19)	18.2 (11)	20.0 (5)	40.0 (5)
30–34	0 (54)	8.3 (12)	3.2 (31)	33.3 (9)	6.7 (15)	50.0 (4)
35–39	0 (84)	12.5 (8)	5.1 (59)	20.0 (5)	5.0 (40)	50.0 (2)
≥40	0 (176)		2.3 (174)		9.6 (115)	

Data are percentages, with *n* sample sizes in parentheses.

them developed diabetes. Regardless of the father's diabetes status (Fig. 3*A*), offspring of diabetic mothers had a higher prevalence of diabetes than offspring of prediabetic women after controlling for the age at onset of the mother's diabetes. The odds ratio and its 95% confidence interval (CI) for diabetes in offspring of diabetic compared with prediabetic women, estimated from the coefficient of the mother's diabetes status (14), was 9.2 (CI 1.1–77).

On the other hand, after accounting for the father's age at onset of diabetes (Fig. 3*B*), the prevalence of diabetes, although higher in offspring of the diabetic mothers, was not significantly different in offspring of diabetic and prediabetic fathers (odds ratio 2.4, CI 0.3–19.1); this result is consistent with no additional effect of paternal diabetes occurring before pregnancy compared with paternal diabetes developing later.

Despite the reduced sample size in this analysis (n = 223), which may account for some loss of statistical power, the effect of the maternal diabetes variables, after controlling for sex, father's diabetes, and age at onset, remained significant (χ^2 = 6.45, df = 2, $P < .05$). A similar analysis with abnormal glucose tolerance as the end point and relative weight of the offspring as a variable showed that age and relative weight, but no other variables, were highly significant after adjustment for mother's age at onset.

DISCUSSION

The much higher prevalence of diabetes in the offspring of women who had diabetes during pregnancy than in the offspring of prediabetic women suggests that the abnormal intrauterine environment of a diabetic pregnancy is largely responsible for the excess of diabetes that appears at an early age in the offspring. However, these findings must be considered in light of the fact that diabetes has a strong genetic component (15,16). Parents who developed diabetes at young ages, early in their child-bearing years, were more likely to be classified as diabetic than those who developed diabetes at older ages. Although in this relatively homogeneous population, all of the diabetes is believed to be NIDDM (17,18), age at onset is variable, and the propensity to develop diabetes at a given age is familial. Thus, a child whose parent developed diabetes at a young age is more likely to develop diabetes at a young age than a child whose parent did not develop the disease until later in life (19). This familial tendency appeared in the offspring of prediabetic women, as shown in Table 4, but was not apparent in the offspring of women who had diabetes during the pregnancy.

The effects of genes and of the intrauterine environment, both influencing the fetus from the time of conception, are so closely linked that it may not be possible to distinguish

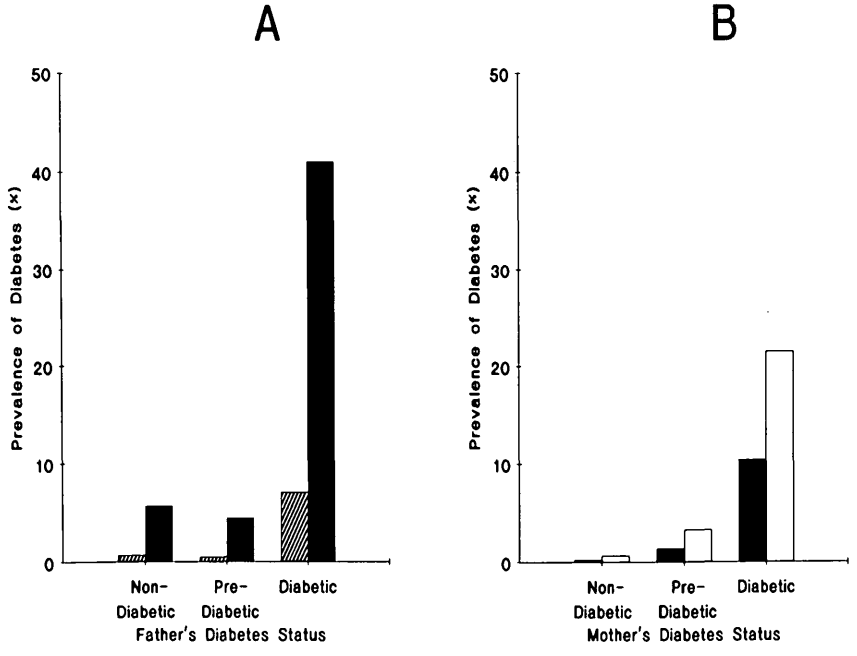

FIG. 3. *A*: prevalence of diabetes according to father's diabetes status in offspring of prediabetic (*hatched bars*) and diabetic (*solid bars*) mothers, controlling for age at onset of mother's diabetes by Lee's method (13). *B*: prevalence of diabetes according to mother's diabetes status in offspring of prediabetic (*solid bars*) and diabetic (*open bars*) fathers, controlling for age at onset of father's diabetes.

the separate effects with certainty until a complex segregation analysis is performed. A woman clearly cannot expose her fetus to a diabetic intrauterine environment unless she has developed diabetes before delivery, which in humans is unlikely to occur in the absence of specific gene action. However, if a genetically determined age at onset of diabetes, coupled with a genetically inherited susceptibility to diabetes, were sufficient to produce the results described in this study, the rates of diabetes in the offspring of women who developed diabetes at a given age would probably be just as high in those offspring born before the onset of the mother's disease as in those who were born after the onset. Such a result did not occur. In this population, after controlling for the age at onset, the rates of diabetes in the offspring of diabetic mothers were still higher (Fig. 3).

The earlier age at onset of diabetes in diabetic fathers compared with prediabetic fathers, however, did account for the higher prevalence of diabetes in the offspring of diabetic fathers, even though in the same sample the effect of maternal diabetes remained statistically significant. This adds evidence to the idea that age at onset of NIDDM may be familial; however, in this population the effect was not strong enough to account for the large differences in diabetes prevalence seen between offspring of diabetic and prediabetic women (20).

Obesity has been shown in this population to be strongly associated with the incidence of new cases of diabetes (21), and the diabetic pregnancy has been shown to be associated with more obese offspring (6). It is therefore not surprising that the relative weight was associated with glucose tolerance, with the heavier offspring being more likely to have abnormal glucose tolerance. However, relative weight was not significantly associated with diabetes in the offspring and did not confound the association between parental diabetes status and diabetes in the offspring.

As expected, the offspring of prediabetic Pima Indian women eventually had a higher prevalence of diabetes than the offspring of nondiabetic women, as seen in the 20- to 24-yr-old offspring in this study, presumably because of their genetic susceptibility to the disease. However, even at this age, diabetes was much more prevalent in the offspring of diabetic than of prediabetic women. These findings seem most compatible with the hypothesis that the diabetic intrauterine environment leads to an earlier age at onset of diabetes in genetically predisposed subjects, but whether the diabetes prevalence in the offspring of prediabetic women will eventually be as high as that of offspring of diabetic women can be answered only by longer follow-up.

An influence of the intrauterine environment on glucose tolerance in the offspring, greater than what can be attributed to genetic factors, has also been reported in animals. Aerts and Van Assche (22) found that when the female offspring of rats with streptozocin-induced diabetes became pregnant, their blood glucose concentrations during late pregnancy were higher than those of control pregnant animals. Because the mothers of these rats had chemically induced diabetes, it seems likely that the exposure of those offspring to an abnormal intrauterine environment had influenced their propensity to develop glucose intolerance later. Third-generation fetuses also demonstrated morphologic abnormalities that were attributed to the glucose abnormalities of late pregnancy in their mothers and in turn were attributed to the diabetes induced in the previous generation.

The mechanisms by which the diabetic intrauterine environment leads to an earlier and more frequent appearance of diabetes in the offspring are unknown. A possible genetic explanation (for which no direct evidence exists) would need to postulate that women who develop diabetes before pregnancy give their offspring more, or more penetrant, diabetes-susceptibility genes or a combination of genes that determine both diabetes susceptibility and age at onset than do women who develop diabetes at the same age but after the pregnancy and that fathers who develop diabetes before the birth of the offspring do not. It appears unlikely that there is a sudden change in the home environment when a woman develops diabetes that could cause her subsequently born offspring to become more susceptible postnatally to diabetes than they would have been had they been born before the onset of the mother's disease.

Freinkel (5) hypothesized that excessive nutrition may be teratogenic. He argued that the presentation to the developing fetus of abnormal concentrations of fuels might cause permanent changes in endocrine or neuroendocrine metabolism. Factors associated with the diabetic environment in utero, e.g., exposure to elevated concentrations of glucose, amino acids, lipids, ketones, and possibly altered concentrations of other nutrients, may have a direct effect on the fetus, increasing insulin secretion and perhaps leading to the development of resistance to insulin-mediated glucose disposal in the child. Insulin resistance is an abnormality characteristic of adult Pima Indians (23), is a factor that predicts the development of NIDDM (24), and is presumably present to some degree in Pima Indian children (25). It seems reasonable to speculate that the diabetic intrauterine environment may lead to earlier or more severe insulin resistance in the offspring.

Whatever the mechanisms, the offspring of women who had NIDDM during pregnancy are at very high risk for the development of diabetes at an early age. The early appearance of diabetes in female offspring would in turn be expected to lead to an increase in the proportion of diabetic pregnancies and the even earlier appearance and higher frequency of diabetes and obesity in the subsequent generation. It is unknown whether this cycle can be broken with strict control of diabetes and impaired glucose tolerance during pregnancy, a practice that is being attempted in this population (26).

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