Diabetes and Obesity in the Offspring of Pima Indian Women With Diabetes During Pregnancy

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OBJECTIVE— To review the long-term effects of the diabetic pregnancy on the offspring among the Pima Indians of Arizona.

RESEARCH DESIGN AND METHODS— Studies published by the Phoenix Epidemiology and Clinical Research branch of the National Institute of Diabetes and Digestive and Kidney Diseases, since the inception of the longitudinal diabetes studies in 1965 were reviewed. In addition, pertinent studies from other centers, mentioned as references in these publications, were reviewed. As far as possible, all original articles and abstracts on this aspect of the Pima Indian studies were discussed.

RESULTS— The offspring of women who had diabetes during pregnancy, on average, were more obese and had higher glucose concentrations and more diabetes than the offspring of women who developed diabetes after pregnancy or who remained nondiabetic. Although no new analyses were attempted, several of the older publications were updated by repeating the analyses on later, expanded data sets.

CONCLUSIONS— The diabetic pregnancy, in addition to its effects on the newborn, has effects on the subsequent growth and glucose metabolism of the offspring. These effects are in addition to genetically determined traits.

Pima Indians who live in the Gila River Indian Community in southern Arizona have the world's highest reported incidence and prevalence of NIDDM (1). A characteristic of the disease in this population is its onset at a young age (2). The onset of diabetes in women before or during their childbearing years often complicates pregnancy. Diabetes in pregnancy produces a number of well-defined complications (3–6), including higher rates of cesarean sections and toxemia for the mothers, and high birth weights, prematurity, congenital anomalies, and perinatal mortality rates for the newborns. As shown in Fig. 1, diabetic women are more than three times as likely as nondiabetic women to have newborns with congenital anomalies (5). In addition, the anomalous infants of diabetic women are more likely to have multiple anomalies than those of nondiabetic and prediabetic women. Among Pima Indians, diabetes during pregnancy has been found to have long-term anthropomorphic and metabolic effects on the offspring (7–14). This paper reviews the data on the long-term effects of the diabetic pregnancy on the offspring in this population.

Residents of the Gila River Indian Community have participated in a longitudinal population study of chronic diseases since 1965 (15,16). For this study, all residents of the community who were ≥5 yr of age were asked to participate

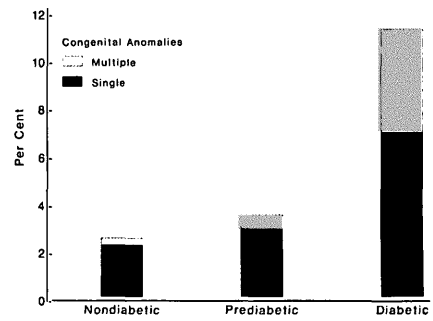

Figure 1—*Prevalence of single and multiple congenital anomalies according to maternal diabetes status. Nondiabetic, mothers who remained nondiabetic (n = 2013); prediabetic, mothers who developed diabetes at some time after delivery (n = 511); diabetic, mothers who had diabetes as a complication of pregnancy (n = 114). Adapted from Bennett et al. (5).*

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NIDDM, NON-INSULIN DEPENDENT DIABETES MELLITUS; CI, CONFIDENCE INTERVAL.

Table 1—*Number of subjects examined in each age-group according to maternal diabetes*

	Maternal diabetes during gestation			
	Nondiabetic	Prediabetic	Diabetic	Total
Age at examination (yr)				
5–9	273	89	37	399
10–14	481	356	55	862
15–19	343	355	44	742
20–24	201	283	18	502
25–29	145	145	5	295

Subjects are counted once in each age-group in which they were examined. A subject may be counted in more than one age-group.

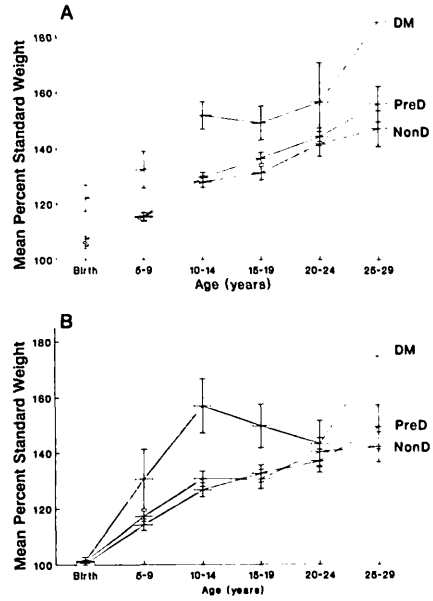

Figure 2—*Percentage of standard weight (average birth weight for gestational age or standard weight for height) according to age at examination and maternal diabetes status (A) for all subjects, and (B) for subjects with a normal birth weight (90–109% of weight for gestational age). Values are means ± 1 SE. (DM), offspring of diabetic women; (PreD), offspring of prediabetic women; (NonD), offspring of nondiabetic women. A: P < 0.001 for the effect of having a mother with diabetes during rather than only after pregnancy, adjusted for age, sex, and parental obesity. B: P < 0.005. Adapted from Pettitt et al. (7) and Pettitt et al. (10).*

every 2 yr in a standardized examination that includes an oral glucose tolerance test and measurements of height and weight.

In addition to these biennial examinations, a glucose tolerance test is administered to women after the 24th wk of each pregnancy. Because family demographic data are maintained, the offspring from each pregnancy can be identified and followed in the longitudinal study, and the degree of glucose tolerance or intolerance experienced by the mother before, during, and after the pregnancy can be determined for each child.

Offspring are divided into three groups, as described previously (7,10,12), based on the presence of diabetes in the mother at the time of the pregnancy and at follow-up: *1*) the offspring of nondiabetic women are those whose mothers had normal glucose tolerance at the time of the pregnancy (no previous 2-h postload glucose concentration of ≥7.8 mM [140 mg/dl]) and did not develop diabetes during follow-up; 2) the offspring of prediabetic women are those whose mothers had normal glucose tolerance at the time of the pregnancy and at least 4 wk after delivery, but who subsequently developed diabetes; and *3*) the offspring of diabetic women are those whose mothers already had diabetes at the time of the pregnancy or developed it during the pregnancy. Offspring of nondiabetic women with <5 yr of follow-up, of women with a history of impaired glucose tolerance before pregnancy, and of women whose onset of diabetes could not be dated precisely relative to the pregnancy were excluded.

This study summarizes the long-term follow-up of half- to full-heritage Pima and/or Tohono O'odham (Papago) offspring. Table 1 shows, according to maternal diabetes status, the number of subjects seen at follow-up in each age-group.

Age- and sex-specific standard weights for height (17) were used to determine the standard weight for each child. For subjects who were ≥20 yr of age, the standard weight was taken from the National Research Council (18). The ratio of actual weight to standard weight was calculated for each subject and used as a measure of relative weight. Standard birth weight was taken from published data of the mean weight for gestational age (19).

Figure 2 shows the mean percentage of birth weight for gestational age and of weight for height for subjects in the three groups of offspring who were seen at birth and at least once at an older age (7,10). In Fig. 2*A*, all subjects, regardless of birth weight, are included. The offspring of diabetic women were, on average, heavier for gestational age at birth, and in each age-group were heavier for height than the offspring of nondiabetic and prediabetic women. The weights for height in these latter two groups were similar. Figure 2*B* shows the growth in that subset of subjects who were of normal birth weight, that is, who were 90–109% of mean weight for gestational age. The normal-birth-weight offspring of diabetic women were just as heavy by age 5–9 yr as the group as a whole, and much heavier than the normal-birth-weight offspring of nondiabetic and prediabetic women.

Figure 3 shows the prevalence of marked obesity (i.e., ≥140% of standard weight for height) in the three groups of

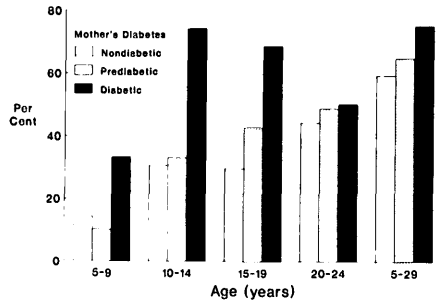

Figure 3—*Prevalence of obesity (≥140% of standard weight for height) according to age at examination and maternal diabetes during pregnancy. For maternal diabetes during pregnancy relative to occurring after pregnancy, P < 0.001 adjusted for age, sex, and parental obesity. Adapted from Pettitt et al. (7).*

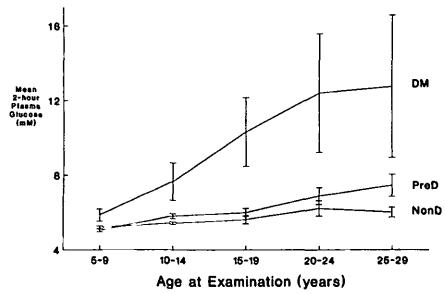

Figure 4—*Mean 2-h postload plasma glucose concentration according to age at examination and maternal diabetes during pregnancy. Values are means ± 1 SE. (DM), offspring of diabetic women; (PreD), offspring of prediabetic women; (NonD), offspring of nondiabetic women. P < 0.001 for the effect of having a mother with diabetes during rather than only after pregnancy, adjusted for age and sex.*

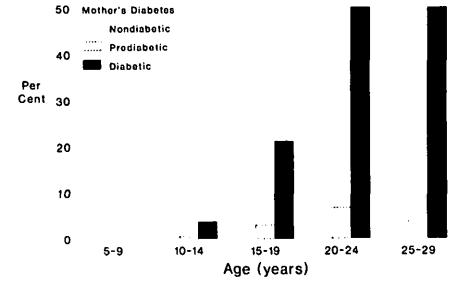

Figure 5—*Prevalence of diabetes (2-h postload plasma glucose concentration of ≥11.1 mM [200 mg/dl]) according to age at examination and maternal diabetes status. For maternal diabetes during pregnancy relative to occurring after pregnancy, P < 0.005, adjusted for age and sex. Adapted from Pettitt et al. (12).*

offspring (7). In each age-group, offspring of diabetic women had a higher prevalence of obesity than the offspring in each of the other two groups.

Figure 4 shows the mean glucose concentration measured during the oral glucose tolerance test 2 h after the glucose load, according to age, in the three groups. The offspring of diabetic women had a higher glucose concentration than offspring in either of the other two groups.

Figure 5 shows the prevalence of diabetes in the three groups according to age (12). Offspring of diabetic women had a higher prevalence than offspring in the other two groups. Although age of onset of diabetes might be a familial trait, the prevalence rates of diabetes in offspring of prediabetic and diabetic women were compared, stratified by the age of onset of the mother's diabetes. Regardless of the age of onset in the mother, the offspring of women who had developed diabetes before delivery had higher rates of diabetes. Controlled for age, father's diabetes status, and age of onset of mother's diabetes, the offspring of diabetic women had a significantly higher rate of diabetes than the offspring of prediabetic women (odds ratio = 9.2, 95% CI 1.1–77) (12).

In the studies reviewed herein, effects attributable to the intrauterine environment can be separated from those attributable to heredity. The comparison of glucose concentrations and rates of obesity and diabetes between the offspring of prediabetic and those of nondiabetic women contrasts children who may have inherited the diabetic gene or genes from their mothers and those who probably did not. There is, of course, some misclassification in that some of the women classified as nondiabetic will eventually develop diabetes, and their status at the time of pregnancy will need to be reclassified at that time. However, the group of nondiabetic women includes all the women who lack the propensity to develop diabetes, whereas the group of prediabetic women includes only women with this propensity. Therefore, from a population standpoint, the two groups of offspring are, on average, genetically different, but their intrauterine experiences were similar, because all the mothers had normal glucose tolerance at the time of the pregnancy.

On the other hand, the comparison between the offspring of prediabetic and those of diabetic women contrasts children who could have inherited the propensity to develop diabetes from their mothers, but who had different intrauterine experiences. Offspring of diabetic women experienced a hyperglycemic intrauterine environment, whereas the offspring of prediabetic women did not. Because diabetes has already developed in all the mothers of these two groups, these classifications cannot be changed by future events.

The diabetic intrauterine environment appears to have lasting effects on the anthropomorphic and metabolic development of the offspring. This phenomenon was predicted by Freinkel (3) and is presumably a result of the fetal adaptation to an excess of fuels or nutrients supplied during gestation. Other investigators have recognized the prenatal and early postnatal period as a critical time for the development of fat cells (20–23).

The diabetic intrauterine environment results in offspring who are more obese, and who, by the time they reach childbearing age, are at a high risk of already having diabetes. The offspring of diabetic women are, on average, large for gestational age at birth and heavier for height at every age at which they were subsequently examined. As shown in Fig. 2, however, high birth weight is not

a prerequisite for the later development of obesity in the offspring of diabetic women.

The mean glucose concentration of the offspring of prediabetic women was only slightly higher than that of the offspring of nondiabetic women. This difference is presumably the result of the genetic differences between these two groups, whereas the difference between the offspring of the diabetic and prediabetic women presumably reflects the effect of the intrauterine environment superimposed on the genetic differences. As seen in Fig. 5, by age 20–24 yr, at a time when they are having their own children, ~50% of the offspring of diabetic women already have diabetes. This was true regardless of the age of onset of the mother's diabetes (12). The children of these women will, in turn, be the offspring of diabetic women, and will share with their mothers the high risk of having diabetes at a young age. As the incidence of diabetes in this population increases (24), the prevalence of diabetic pregnancies can be expected to increase.

These findings, based on data collected almost exclusively in Pima Indians of Arizona, also can be expected to be relevant to other populations. The difference between diabetic pregnancies in the Pima Indians and in other populations is probably only a matter of frequency. Because diabetes often has an onset before or during the child-bearing years in the Pima population, a high proportion of the children result from pregnancies complicated by diabetes. Other North American Indian tribes also have high and increasing rates of obesity, diabetes (25–30), and diabetic pregnancies (31–33), all manifest at relatively young ages. The same phenomena associated with diabetic pregnancies in Pima Indians may occur in these other peoples and in non-Indian populations that have high rates of obesity and diabetes (34–39). A woman with NIDDM or gestational diabetes will produce offspring who not only have the hereditary potential for developing diabetes, but also have had prenatal exposure to the diabetic intrauterine environment and will be at a particularly high risk of disease at a young age. If the deleterious effects of the intrauterine environment could be eliminated, the long-lasting benefits to the offspring would carry over into subsequent generations, with fewer women developing diabetes early enough in life for it to affect their pregnancies and their offspring.

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