Obesity in Offspring of Diabetic Pima Indian Women Despite Normal Birth Weight

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The relationships of birth weight and maternal diabetes to the development of obesity were examined at 5–19 yr of age in the offspring of Pima Indian women. At each age, offspring of diabetic women, even those who were of normal birth weight, had a higher mean weight relative to height than offspring of nondiabetic and prediabetic women. Birth weight was predictive of relative weight in 5- to 9- and 10- to 14-yr-old offspring of nondiabetic women but not in the oldest group. In contrast, for offspring of prediabetic and diabetic women, birth weight was not predictive of subsequent obesity at any age studied. Offspring of diabetic women were heavier than offspring of nondiabetic and prediabetic women regardless of birth weight. Thus, maternal diabetes was important in predicting body size in the offspring even after accounting for the effects of the birth weight and maternal body size. *Diabetes Care* 10:76–80, 1987

Offspring of women who have diabetes during pregnancy are, on average, larger for gestational age at birth and more likely to be obese in childhood than offspring of women without diabetes (1–4). Because birth weight has a strong influence on later body weight up to at least 2 yr of age (5), one explanation for these observations might be that the diabetic pregnancy affects birth weight and that large birth weight is an important determinant of subsequent obesity regardless of the maternal diabetes status. Obesity and body weight in childhood, however, are also related to maternal obesity and are believed to be determined in part by hereditary factors (6). Because not all infants of diabetic women are large for gestational age at birth, whether normal-birth-weight infants of diabetic women subsequently develop obesity more frequently than do normal-birth-weight offspring of women without diabetes can be examined. We investigate the relative influences of birth weight and maternal diabetes on the development of obesity in the offspring of Pima Indian women.

MATERIALS AND METHODS

Subjects for this report were taken from the longitudinal study of diabetes that has been conducted among the residents of the Gila River Indian Community of Arizona since 1965 (7). Most of the study participants are Pima Indians or closely related Papago Indians. Residents of the community and surrounding areas who are ≥5 yr old are asked approximately every 2 yr to participate in an examination that includes measurement of height and weight and a modified glucose tolerance test, during which a venous plasma glucose determination is made 2 h after the ingestion of 75 g carbohydrate (Dexcola, Custom Laboratories, Baltimore, MD, or Glucola, Ames, Elkhart, IN). In addition, when possible during pregnancy, a glucose tolerance test is done after the 24th wk of gestation. After delivery, the medical records of the mother and the newborn infant are reviewed to assess outcome.

Offspring were included in our study if they were examined between 5 and 19 yr of age, their birth weights were known, their mothers' diabetes status during pregnancy and subsequently was known, and an adult (≥20 yr old) height and weight of the mother were known. All subjects were at least 50% Pima and/or Papago heritage. Study participants who met these criteria were included regardless of whether they lived in the Gila River Indian Community. Offspring were classified according to their relative birth weight (percentage of average birth weight for gestational age) (8) and according to mothers' diabetes status at the time of delivery. Their mothers were classified according to diabetes status during and after pregnancy, as previously described (4): *1*) nondiabetic mothers; *2*) prediabetic mothers, i.e., mothers with normal glucose tolerance at the time of the pregnancy who

TABLE 1
Number of subjects examined in each age range* according to percent of average birth weight and mother's diabetes status

Mother's diabetes status	Age at exam (yr)	Average birth weight (%)					
		<80	80–99	100–119	120–139	≥140	Total (N)
Nondiabetic	5–9	23	202	258	58	4	545
	10–14	26	205	258	62	4	555
	15–19	9	94	127	24	1	255
Prediabetic	5–9	13	76	101	39	11	240
	10–14	13	87	112	49	11	272
	15–19	14	67	79	35	8	203
Diabetic	5–9	1	5	19	6	6	37
	10–14	1	4	21	7	7	40
	15–19	0	2	12	5	7	26

*Some subjects were examined in more than one age group.

developed diabetes after the birth of the offspring; and 3) diabetic mothers, i.e., those who had developed diabetes before or during the pregnancy. Diabetes was defined as a 2-h postload plasma glucose concentration of ≥200 mg/dl. Both nondiabetic and prediabetic mothers had normal glucose tolerance tests with 2-h glucose concentrations below 140 mg/dl at least 4 wk after delivery; all previous glucose tolerance tests, if done, were also normal. Mothers who did not subsequently develop diabetes, as determined by glucose tolerance tests at follow-up examinations performed at least 5 yr later, were designated as nondiabetic. Women who subsequently developed diabetes ≥4 wk after delivery were identified, in retrospect, as prediabetic at the time of the pregnancy. This article deals with 747 offspring of 325 nondiabetic mothers, 313 offspring of 121 prediabetic mothers, and 52 offspring of 40 diabetic mothers. Many of the offspring were examined at more than one age, and the numbers of offspring examined in each age range are shown in Table 1.

The height and weight of the offspring measured at the periodic examination were used to calculate the relative weight by dividing the observed weight by a standard weight and expressing the result as a percentage. Standard weight was taken from the sex-specific tables of weight for height and age (at nearest birthday) for children aged 6–19 yr published by Jelliffe (9) and extrapolated to include ages 5 and 20 yr. The maximum body mass index (BMI, wt/ht^2 in kg/m^2) was calculated for mothers and, when available, for fathers from height and weight measured after age 20 yr. The BMI was calculated for the fathers of 768 (69%) of the offspring. Multiple linear regression analysis was used to test the significance of maternal diabetes status on weight in the offspring and to simultaneously control for confounding variables (10).

RESULTS

The means of relative weight for the groups of offspring at ages 5–9, 10–14, and 15–19 yr according to their relative birth weight and mothers' diabetes status are shown in Fig. 1. Offspring of diabetic women in each of the three age groups had a higher mean relative weight than offspring of prediabetic women ($P < .001$ at each age, adjusting for birth weight, sex, offspring's age, mother's age, and BMI within each age group). Offspring of diabetic women also had a higher mean relative weight than offspring of nondiabetic women ($P < .002$ for each age). The means of relative weight for offspring of nondiabetic and prediabetic women were not significantly different at any age ($P > .2$ at each age). Among offspring of nondiabetic women at 5–9 and 10–14 yr of age, the relative weight increased with percent of average birth weight ($P < .01$ for each age group, controlling for maternal BMI), but there was no association between birth weight and subsequent relative weight among offspring of diabetic or prediabetic women in any age group.

The combined effect of mother's diabetes status and obesity on the relative weight in the offspring is shown in Table 2. Maternal obesity influences relative weight in offspring of

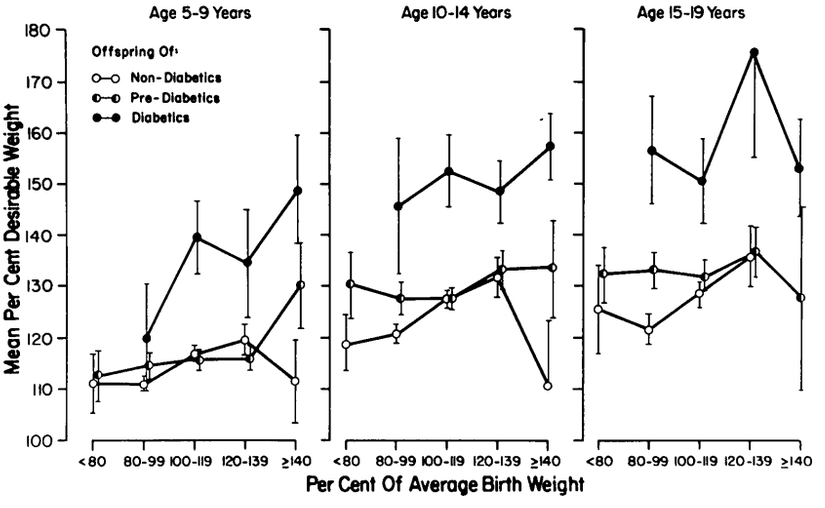

FIG. 1. Mean relative weight (±1 SE) at age 5–9 yr (*left panel*), 10–14 yr (*center panel*), and 15–19 yr (*right panel*). Subjects are classified according to percent of average birth weight and mother's diabetes status at time of delivery. *Points* represented by only 1 subject are not shown.

TABLE 2
Mean relative weight according to mother's maximum adult body mass index (BMI)*

Age of offspring (yr)	BMI of mother	Diabetes status of mother (N)		
		Nondiabetic	Prediabetic	Diabetic
5–9	<30	110 (117)	112 (20)	146 (3)
	30–34	115 (163)	112 (81)	130 (18)
	≥35	117 (265)	119 (139)	142 (16)
10–14	<30	119 (128)	122 (23)	153 (6)
	30–34	123 (159)	123 (90)	146 (19)
	≥35	129 (268)	133 (159)	156 (15)
15–19	<30	120 (52)	128 (15)	143 (5)
	30–34	120 (72)	126 (67)	158 (12)
	≥35	133 (131)	138 (121)	162 (9)

*The effect of maternal BMI on relative weight, after controlling for birth weight, was significant at the $P < .05$ level in offspring of nondiabetic women at all ages, in offspring of prediabetic women at 10–14 and 15–19 yr, but not in offspring of diabetic women.

nondiabetic women at all ages ($P < .05$ at each age, controlling for birth weight) and after age 10 yr in offspring of prediabetic women ($P < .005$ at 10–14 and 15–19 yr of age). However, among offspring of diabetic women, maternal obesity had no effect on relative weight ($P > .2$ at each age). The effect of adjusting for birth weight, sex, age, mother's diabetes status, mother's age at delivery, and mother's and father's BMI with multiple linear regression is shown in Table 3. Parental obesity, as measured by the BMI, was a very significant predictor of offspring's relative weight in all three age groups. However, even after adjusting for parental obesity, maternal diabetes status during pregnancy exerted a significant effect on relative weight in the offspring in all three age groups ($P = .002$ at 5–9 and 10–14, and $P = .044$ at 15–19 yr of age).

TABLE 3
Multiple linear regression model

Age (yr)	Variable	β	SE (β)	P value
5–9	Mother prediabetic	0.00	1.84	.002*
	Mother diabetic	13.98	4.08	
	Mother's BMI	0.30	0.13	<.017
	Father's BMI	0.76	0.13	<.001
	Mother's age	0.04	0.14	.755
	Age of offspring	3.11	0.75	<.001
	Average birth weight (%)	0.20	0.06	<.001
	Sex	1.78	1.68	.291
	Intercept	29.41	11.31	
10–14	Mother prediabetic	1.79	2.37	.002*
	Mother diabetic	18.95	5.38	
	Mother's BMI	0.63	0.18	<.001
	Father's BMI	0.88	0.19	<.001
	Mother's age	0.08	0.18	.656
	Age of offspring	−2.08	1.14	.038
	Average birth weight (%)	0.23	0.07	.001
	Sex	0.66	2.18	.763
	Intercept	75.90	18.80	
15–19	Mother prediabetic	1.40	3.00	.044*
	Mother diabetic	18.14	7.22	
	Mother's BMI	0.81	0.21	<.001
	Father's BMI	1.31	0.26	<.001
	Mother's age	0.45	0.24	.062
	Age of offspring	0.88	1.32	.503
	Average birth weight (%)	0.15	0.09	.114
	Sex	5.24	2.87	.069
	Intercept	−0.98	28.65	

*P value for overall effect of maternal diabetes status.

The means of relative weight at 5–9, 10–14, and 15–19 yr of age for offspring who were of normal birth weight (90–109% of average weight for gestational age) are shown in Fig. 2. Despite similar birth weights, by 5–9 yr of age, the offspring of diabetic women had a higher mean relative weight than offspring of nondiabetic and prediabetic women, and this difference persisted in later years. Table 4 shows the means of relative weight adjusted for offspring's age and sex and mother's age and BMI. At 5–9 and 10–14 yr of age, maternal diabetes status had a significant effect on relative weight in the offspring ($P = .004$ at age 5–9 yr, $P = .010$ at age 10–14 yr). At 15–19 yr of age, this effect was not statistically significant ($P = .2$), but the sample size was small and included only six offspring of diabetic women.

DISCUSSION

The excessive birth size of infants of diabetic women is generally believed to be a result of maternal hyperglycemia and other nutrient abnormalities during the third trimester that induce hyperinsulinemia that in turn leads to excessive growth and adipose tissue accumulation in the fetus during the last part of gestation (11,12). The development of obesity in such infants might represent a continuation of the same process such that the infant who is overweight at birth may be predisposed to develop excessive obesity in childhood and adolescence.

Birth weight is predictive of weight during the first 2 yr after birth (13), and as shown by this study, an effect of birth weight in offspring of nondiabetic women persists until 10–14 yr of age. The degree of maternal obesity also influences the development of obesity in the offspring, and indeed such an effect was found among the Pima offspring of the nondiabetic and prediabetic women. However, among the offspring of diabetic mothers, such an effect was not apparent, although the offspring of the diabetic pregnancies were heavier than those of the nondiabetic or prediabetic women regardless of the extent of maternal obesity. Thus, the presence of diabetes during pregnancy appeared to exert an influence on the development of obesity in the offspring that was stronger than that related to either birth weight or maternal obesity.

Among the offspring of women with diabetes during pregnancy, there was a subset with normal birth weight. By 5–9 yr of age, however, this group of infants was also more obese than the normal-birth-weight offspring of either the prediabetic or nondiabetic women. This finding suggests that the excessive obesity characteristic of the offspring of diabetic

TABLE 4
Adjusted mean relative weight* in normal-birth-weight offspring

	Mother's diabetes status (*N*)			
Age (yr)	Nondiabetic	Prediabetic	Diabetic	Effect
5–9	115.7 (300)	113.7 (116)	135.8 (12)	*P* = .004
10–14	127.1 (290)	126.9 (131)	152.4 (13)	*P* = .010
15–19	127.0 (144)	130.6 (96)	147.1 (6)	*P* = .203

*Adjusted by least-squares means for sex, age within each age group, and maternal age and body mass index (10).

women is not the direct result of the excessive growth that often occurs in utero and leads to excessive birth weight in infants of diabetic mothers. Rather, the findings suggest that the determinants of obesity in childhood and adolescence among offspring of diabetic pregnancies are at least somewhat different from those that determine birth weight in these infants. Thus, among offspring of diabetic women, neonatal macrosomia and later obesity may be manifestations of different metabolic disturbances associated with the diabetic pregnancy.

Neonatal macrosomia appears to be preventable (14,15), and it has been postulated that prevention of macrosomia at birth may also prevent the development of obesity (3). The results of our study cast doubt on this hypothesis, because normal-birth-weight offspring of diabetic women are more likely to be obese during childhoood than are normal-birth-weight offspring of nondiabetic and prediabetic women.

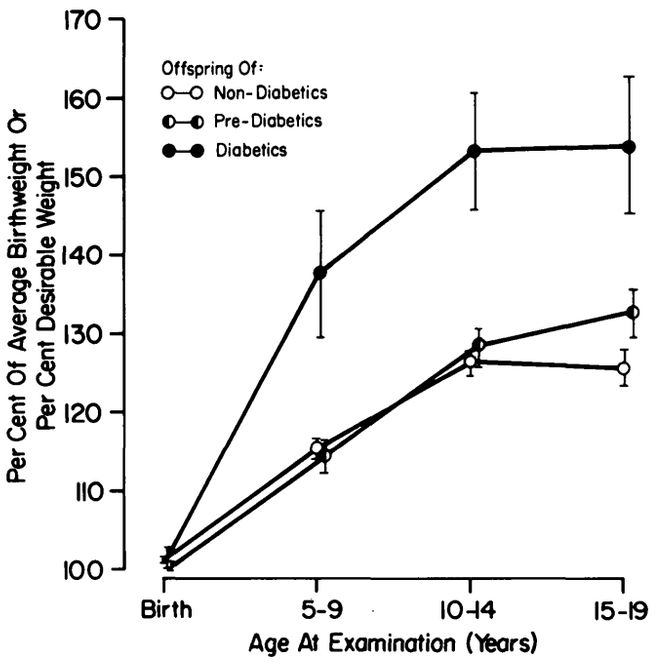

FIG. 2. Mean relative weight (± 1 SE) at ages 5–9, 10–14, and 15–19 yr for subjects who were 90–109% of average birth weight.

Whereas diabetes control and weight gain during pregnancy are related to infant birth weight (16,17), and birth weight in most children is related to obesity during the first 24 mo of life (13), the factors leading to the subsequent development of obesity in infants of diabetic mothers remain obscure. Mild degrees of hyperinsulinemia and large fat cells, characteristics of young Pima children (18), may be important determinants of obesity in the offspring of women with diabetes during pregnancy, leading to excessive obesity in these children. In the oldest group, the effect on obesity of the mother's diabetes status at the time of the pregnancy was less significant and, although in the same direction, was not significant in the offspring who were of normal birth weight. This may be a reflection of sample size, which at 15–19 yr of age is little more than half of that at each of the two younger ages, or may reflect that hereditary obesity is more likely to be manifest in the older child. The diabetic pregnancy may cause the expression of "genetic obesity" at a younger age. Metabolic disturbances insufficient to cause macrosomia at birth may still cause alterations in metabolism, leading over years to the development of obesity. Although good control of maternal hyperglycemia during pregnancy is associated with improved outcome in the neonate (19,20) and has been shown to reduce birth size, it remains to be seen whether control of diabetes in pregnancy will also prevent the obesity that develops in childhood. Our study indicates that excessive obesity may still develop in the offspring of diabetic women despite normal birth weight.

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