Gestational Diabetes: Infant and Maternal Complications of Pregnancy in Relation to Third-Trimester Glucose Tolerance in the Pima Indians

DAVID J. PETTITT, WILLIAM C. KNOWLER, H. ROBERT BAIRD, AND PETER H. BENNETT

A modified oral glucose tolerance test was done during the third trimester in 811 pregnancies in Pima Indian women over a 13-yr period, and maternal and fetal complications were documented. Diabetes was known to be present in 51 pregnancies. Among those who were not previously known to have diabetes, rates of perinatal mortality, macrosomia, toxemia, and cesarean section varied directly with glucose concentration, but congenital malformation and prematurity rates did not. Rates of all of these complications were higher in known diabetic women than in the remainder of the population. In addition to glucose concentrations, maternal weight and age were predictive of macrosomia and toxemia. Third-trimester glucosuria was found to be of very limited value as a screening procedure for gestational diabetes. In 233 women followed for 4–8 yr, the third-trimester glucose concentration was highly predictive of the subsequent incidence of diabetes. DIABETES CARE 3: 458–464, MAY–JUNE 1980.

Increased infant mortality and morbidity and excessive maternal morbidity are well-recognized complications of the diabetic pregnancy.[1–6] There is some evidence that gestational diabetes, i.e., glucose intolerance with its onset during pregnancy, is also associated with increased perinatal mortality and macrosomia.[7] Nevertheless, the level of glucose intolerance associated with increased morbidity and mortality, and hence what constitutes gestational diabetes, is at present poorly defined. Furthermore, the definition of gestational diabetes is complicated by the changes in glucose tolerance that occur during pregnancy.[8,9]

The Pima Indian population presents an unusual opportunity to investigate the effects of glucose intolerance in pregnancy. The incidence of non-insulin-dependent (type II) diabetes[10] in the Pima is 19 times that in the general U.S. population.[11] This, together with the relatively early age of onset of the disease and the continuing surveillance of the population for diabetes since 1965,[12] has provided the opportunity to assess the impact of impaired glucose tolerance in pregnancy. The present report examines the relationship of complications of pregnancy to glucose tolerance determined during the third trimester among women without previous evidence of diabetes.

METHODS

Subjects. Between October 1965 and January 1979, 2258 pregnancies were recorded among 1161 women. Women eligible for inclusion in the study were either residents of the Sacaton Service Unit area of the Gila River Indian Community or were Pima Indians who presented for prenatal care at the Sacaton Indian Health Service Hospital or the Phoenix Indian Medical Center. Seventy-two percent of these women were half- to full-blood Pima Indians, 18% were half- to full-blood Papago Indians (a closely related and geographically proximate tribe), and 9% were less than half Pima or Papago, or were of other Indian extraction. One percent were non-Indians.

In 811 pregnancies in 604 women a modified oral glucose tolerance test (GTT) was performed, usually at the first prenatal visit during the third trimester (mean ± SD = 34.2 ± 4.1 wk of gestation). Ninety-nine percent of the tests were performed at 25 wk of gestation or later. Diabetes, as defined below, was present before the onset of 51 of the pregnancies, but in the remaining pregnancies diabetes was not known to be present at conception. In 526 pregnancies a previous GTT had confirmed the absence of diabetes. The tests were administered without regard to age, pregnancy history, diabetes diagnosis, physical or laboratory findings, or treatment.

Test methods. A 75-g oral carbohydrate load [Dexcola (Custom Laboratories, Baltimore, Maryland) or Glucola (Ames Company, Elkhart, Indiana)] was administered in the morning, although subjects were not required to be fasting. Two hours later venous blood was drawn into a tube containing sodium fluoride and centrifuged. Plasma glucose concentration was determined on the Autoanalyzer.[13] The presence

of glucose was determined by Labstix (Ames Company, Elkhart, Indiana) in random urines during the third trimester. The height and weight of the mother, determined postpartum, were used to calculate percent desirable weight.[14] Gestational age at birth was assessed on the basis of all available information, often by the obstetrician or pediatrician.

A subset of 233 women was followed for 4–8 yr after parturition. These women were retested with an oral 75-g carbohydrate load and diabetes was diagnosed if the 2-h plasma glucose concentration was at least 200 mg/dl.

Definitions. For the purposes of the present analysis the following definitions were adopted.

A diabetic pregnancy was a pregnancy in a woman who was known to have diabetes before the onset of pregnancy. The diagnosis of diabetes was based on a 2-h postload plasma glucose of at least 200 mg/dl or on prior use of hypoglycemic drugs.

Toxemia of pregnancy was diagnosed by the presence of any two of the following signs: proteinuria, hypertension, or edema. Convulsions were also diagnostic of toxemia of pregnancy.

Infants were considered large for gestational age (LGA) if they exceeded the 90th percentiles reported by Lubchenco et al.[15] Congenital anomalies were defined as previously specified.[16,17]

Statistical methods. The chi-square test was used to compare the differences in perinatal mortality rates between infants who were and were not LGA. Binary multiple regression was used to determine the relative contributions of glucose concentration, maternal weight, and maternal age to pregnancy outcome. A test for linear trend in proportions[18] was used in evaluating the changes in rates of pregnancy outcome and diabetes incidence over the range of glucose concentrations.

RESULTS

Frequency distributions. The frequency distributions of the third-trimester 2-h plasma glucose concentrations measured in 811 pregnancies are shown in Figure 1. The distributions were unimodal in women both below and above 25 yr of age. The mean plasma glucose concentration was 11 mg/dl higher in the older age group.

Pregnancy outcome. The complications of pregnancy as a function of third-trimester 2-h plasma glucose concentration are presented in Table 1. Among women not previously known to have diabetes, the perinatal mortality rate increased with an increase in plasma glucose from 5 deaths per 1000 live births in women with 2-h third-trimester glucose concentrations less than 120 mg/dl to 44 deaths/1000 in women with glucose concentrations between 160 and 199 mg/dl (Figure 2). There was one perinatal death among 8 women having glucose concentrations of at least 200 mg/dl. The rate in pregnancies of women with known diabetes was 59 deaths per 1000 live births.

Perinatal mortality was related to infant weight (Table 2). In term births, the overall perinatal mortality rate was 4.5 times greater and the stillbirth rate was 6 times greater in infants who were LGA than in infants who were not. The percent of pregnancies associated with LGA infants increased with increasing third-trimester glucose concentrations, from 25% in women with glucose concentrations less than 120 mg/dl to 80% in those with glucose concentrations of at least 200 mg/dl (Figure 3). Forty-three percent of the infants of diabetic women were LGA. The LGA rate also varied with

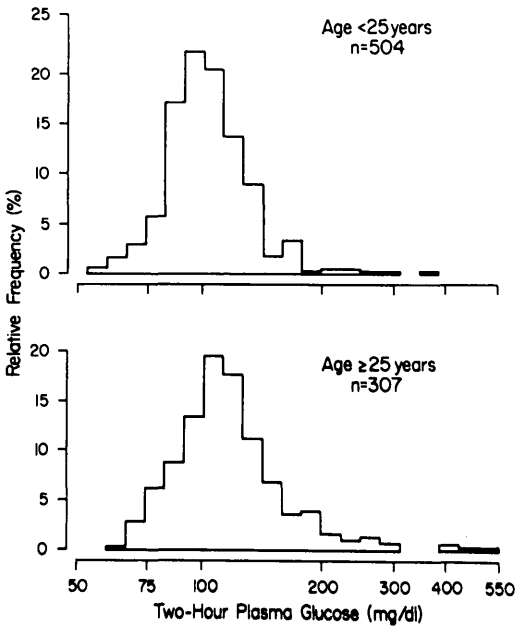

FIG. 1. Third-trimester 2-h plasma glucose frequency distributions for women aged less than 25 yr and those aged at least 25 yr. Glucose concentrations are plotted on a logarithmic scale. Note that glucose concentrations of known diabetic subjects are included.

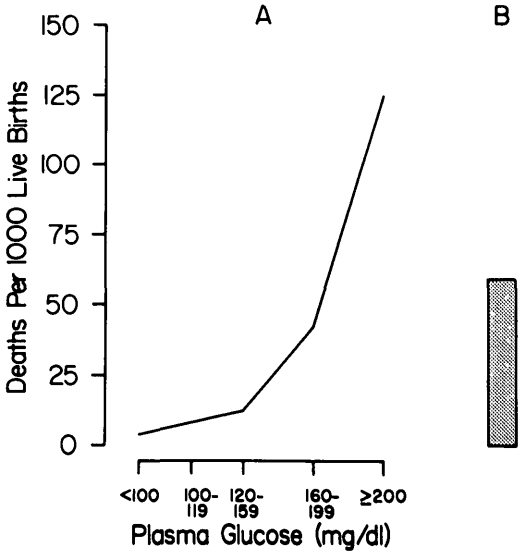

FIG. 2. Perinatal mortality rate by third-trimester 2-h plasma glucose concentration in pregnancies of women without known diabetes before this pregnancy (A) and in pregnancies of women with known diabetes (B).

TABLE 1
Complications of pregnancy as a function of third-trimester 2-h plasma glucose

	No previous diabetes											Previous diabetes	
	2-h third-trimester plasma glucose (mg/dl)												
	<100		100–119		120–159		160–199		≥200				
	Rate (%)	N	Rate (%)	N	Rate (%)	N	Rate (%)	N	Rate (%)	N	Association*	Rate (%)	N
Fetal and infant complications													
Perinatal mortality	0.3	(306)	0.8	(250)	1.2	(173)	4.3	(23)	12.5	(8)	P = 0.0010	5.9	(51)
LGA†	23.2	(233)	25.0	(184)	38.5	(122)	94.1	(17)	80.0	(5)	P < 0.0001	43.1	(51)
Prematurity	2.6	(233)	1.6	(184)	5.7	(122)	5.9	(17)	0.0	(6)	P > 0.05	26.0	(50)
Congenital malformation	1.6	(302)	0.4	(247)	1.8	(171)	2.5	(22)	0.0	(8)	P > 0.05	11.8	(51)
Any of above	29.0	(231)	27.9	(183)	43.8	(121)	50.0	(16)	80.0	(5)	P = 0.0001	64.6	(48)
Maternal complications													
Toxemia	9.2	(306)	8.0	(250)	19.7	(173)	13.0	(23)	62.5	(8)	P < 0.0001	21.6	(51)
Cesarean section	2.3	(302)	2.9	(246)	5.5	(165)	8.7	(23)	14.3	(7)	P = 0.0037	31.4	(51)

* Association with glucose concentration (P value from test for linear trend).
† LGA = large for gestational age.

maternal weight and maternal age (Table 3). Within strata of increasing maternal weight or age, LGA rates increased with the glucose concentration, except in the heaviest and oldest categories. The glucose concentration, maternal weight, and maternal age were all strongly related to each other, so it was difficult to determine which might be causally associated with macrosomia. After maternal age and weight were accounted for in a binary multiple regression analysis, third-trimester glucose concentration was no longer significantly associated with the LGA rate (P = 0.059).

The congenital malformation rate did not vary significantly with third-trimester glucose concentration among the offspring of those women without previously known diabetes (Figure 3). The overall rate of 1.6% was considerably lower than the rate of 11.8% in the diabetic pregnancies.

Toxemia of pregnancy was strongly associated with third-trimester plasma glucose concentration among women not previously known to have diabetes (Figure 4). Their overall rate of 11.8% was lower than the rate of 21.6% occurring in diabetic pregnancies. The rate of toxemia also varied with weight and age (Table 4). Binary multiple regression analysis showed that the effect of glucose persisted after accounting for age and weight (P < 0.005).

Women with diabetes were significantly more likely to have cesarean sections and premature infants than women without known diabetes. The cesarean section rate was 31% and prematurity rate was 26% in those women with diabetes compared with 3.5% and 3.0%, respectively, in those without previous diabetes. In this latter group the cesarean sec-

TABLE 2
Perinatal mortality by infant weight among term births

	LGA*		Not LGA		
	No.	Rate†	No.	Rate	Significance
Total births	466		955		
Stillbirths	11	23.6	4	4.2	P < 0.001
Neonatal deaths	2	4.3	2	2.1	NS
Perinatal deaths	13	27.9	6	6.3	P < 0.001

* LGA = large for gestational age (>90th percentile).
† Rate = deaths per 1000 live births.

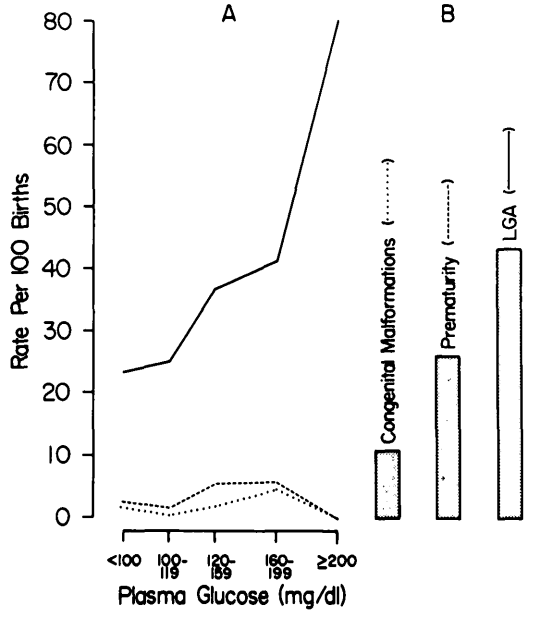

FIG. 3. Rates of large for gestational age infants (LGA), prematurity, and congenital malformations by third-trimester 2-h plasma glucose concentration in pregnancies of women without known diabetes before this pregnancy (A) and in pregnancies of women with known diabetes (B).

TABLE 3
Percent of infants who are LGA by maternal weight and age

2-h plasma glucose (mg/dl)	Maternal percent desirable weight <115% Percent LGA	N	115–149% Percent LGA	N	≥150% Percent LGA	N
<100	4	(28)	23	(99)	42	(53)
100–119	0	(19)	31	(72)	29	(52)
120–159	29	(7)	33	(58)	52	(29)
160–199	50	(2)	46	(13)	55	(11)
≥200	50	(2)	100	(6)	33	(6)

2-h plasma glucose (mg/dl)	Maternal age (yr) <20 Percent LGA	N	20–29 Percent LGA	N	≥30 Percent LGA	N
<100	23	(78)	25	(138)	50	(20)
100–119	12	(49)	25	(104)	42	(33)
120–159	36	(25)	35	(75)	36	(33)
160–199	50	(2)	46	(22)	46	(11)
≥200	—	(0)	70	(10)	50	(12)

TABLE 4
Percent of pregnancies with toxemia by maternal weight and age

2-h plasma glucose (mg/dl)	Maternal percent desirable weight <115% Toxemia (%)	N	115–149% Toxemia (%)	N	≥150% Toxemia (%)	N
<100	7	(43)	7	(129)	13	(70)
100–119	9	(23)	3	(102)	14	(59)
120–159	8	(13)	26	(78)	22	(36)
160–199	50	(2)	13	(15)	15	(13)
≥200	0	(2)	17	(6)	50	(6)

2-h plasma glucose (mg/dl)	Maternal age (yr) <20 Toxemia (%)	N	20–29 Toxemia (%)	N	≥30 Toxemia (%)	N
<100	6	(97)	9	(175)	19	(37)
100–119	10	(63)	5	(147)	19	(42)
120–159	19	(36)	20	(104)	25	(44)
160–199	50	(2)	12	(25)	14	(14)
≥200	—	(0)	30	(10)	36	(14)

tion rate increased with increasing third-trimester glucose concentration, but the prematurity rate did not (Figures 3 and 4).

Urine screening. Random third-trimester urine specimens were evaluated as a possible screening technique for gestational diabetes. Glucosuria varied directly with plasma glucose, from 2% in women whose third-trimester glucose was less than 100 mg/dl to 74% in those whose concentration was 200 mg/dl or greater (Figure 5).

Subsequent diabetes. Third-trimester 2-h postload glucose was evaluated as a predictor of subsequent diabetes in 233 women without known diabetes. The percent who developed diabetes within 4–8 yr increased with the glucose concentration measured during the third trimester, from 4.5% in those with glucose concentrations of less than 100 mg/dl to 45.5% in those with glucose concentrations between 160 and 179 mg/dl (Table 5).

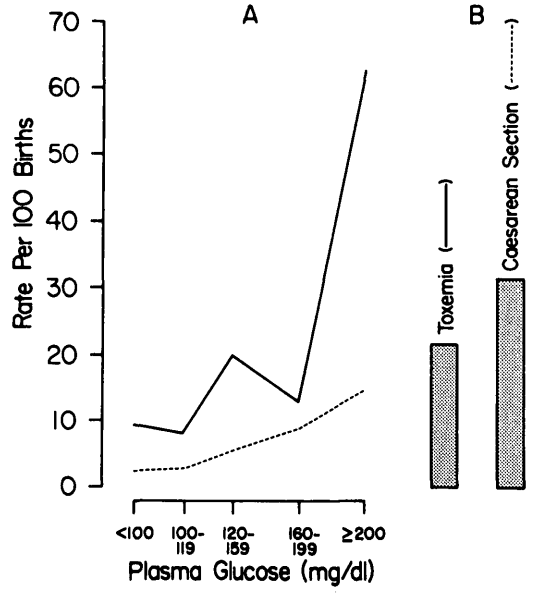

FIG. 4. Rates of toxemia and cesarean section by third-trimester 2-h plasma glucose concentration in pregnancies of women without known diabetes before this pregnancy (A) and in pregnancies of women with known diabetes (B).

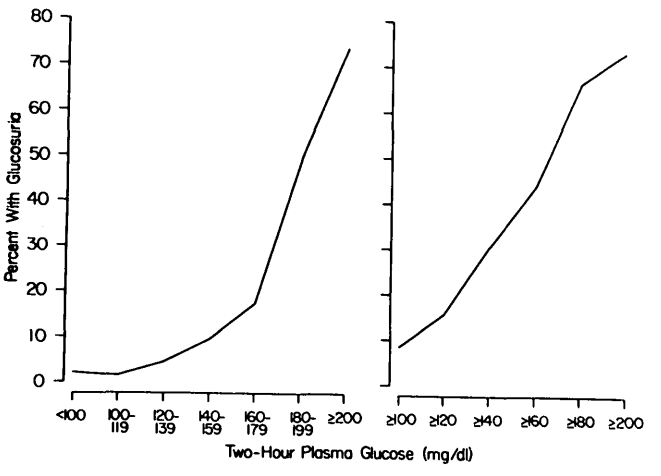

FIG. 5. Third-trimester glucosuria by 2-h plasma glucose concentration. Left, percent with glucosuria within each plasma glucose group, and right, percent with glucosuria at or above each plasma glucose concentration.

TABLE 5
Diabetes incidence in women 4–8 yr after the first pregnancy in which a third-trimester 2-h plasma glucose was measured

Third-trimester glucose (mg/dl)	Percent with follow-up glucose (≥200 mg/dl)	N
<100	4.5	89
100–119	5.3	75
120–139	20.0	40
140–159	16.7	18
160–179	45.5	11
		233

The increase in incidence rates with increasing glucose concentration was significant ($P < 0.0001$) by a test for linear trend in proportions.

DISCUSSION

Most data relating to the effects of diabetes in pregnancy pertain primarily to women with insulin-dependent (type I) diabetes. However, before the diagnosis of diabetes, women who are subsequently recognized to have diabetes have an excess of stillbirth, neonatal death, prematurity, macrosomia, congenital anomaly, maternal obesity, toxemia, and family history of diabetes.[19–24] In many of these studies, however, the presence of glucose intolerance, especially in the later stages of pregnancy, was not systematically excluded.

In women aged 25 yr and over, O'Sullivan et al. demonstrated an increased rate of large babies (9 lb and over)[25] and an increased perinatal mortality rate[26] associated with gestational diabetes determined by GTT during pregnancy. An increased rate of subsequent overt diabetes in these women was also demonstrated.[27] Excessive perinatal mortality associated with third-trimester hyperglycemia was confirmed by Abell and Beischer[28] in 2000 Australian women, but an increased frequency of macrosomia was not found. Evidence of an excess of congenital anomalies in the offspring of women with gestational diabetes is lacking.

The present study presents data from a population in which diabetes during pregnancy, despite stringent criteria for diagnosis, occurred 40 times more frequently than reported by O'Sullivan[27] and 10 times more frequently than reported by Gyves et al.[29] These high rates reflect the Pima Indians' extraordinarily high prevalence of diabetes, which is associated with the occurrence of both the specific and nonspecific vascular complications of diabetes and with the typical complications of diabetes in pregnancy.

Bimodality in the frequency distributions of the 2-h plasma glucose concentrations has been demonstrated previously in nonpregnant Pima women aged at least 25 yr, with the hyperglycemic component of the frequency distributions containing subjects who clearly have diabetes by conventional standards.[30] No bimodality, however, was apparent in the frequency distributions of the third-trimester glucose concentrations, even in women over 25 yr of age. Thus, the frequency distribution gave no indication of a glucose level that could be regarded as diagnostic of gestational diabetes.

The complications of pregnancy associated with diabetes, which have been described in other populations, also occurred in this population and were more common in those having diabetes at the onset of pregnancy than in those without previously known diabetes. Furthermore, in women without previously known diabetes, the severity of the glucose intolerance was predictive of the rates of perinatal mortality, LGA infants, toxemia, and cesarean section but not of prematurity or congenital malformations. In the present study, the rates of complications increased with increasing plasma glucose throughout the range of glucose concentrations that were studied, with no obvious inflection point upon which to base a separation of nondiabetic women from those with gestational diabetes.

The present data confirmed the increased frequency of congenital malformations in diabetic pregnancies.[16,17] The malformation rate in those with diabetes was over seven times as great as in those without known diabetes. Glucose concentration, however, did not affect the risk of congenital malformation in the infants of women who were not previously known to have diabetes. This is perhaps not surprising in that if elevated glucose causes malformations, we would expect them to occur only in women who already had diabetes very early in pregnancy when organogenesis occurs.[31]

Cesarean section and prematurity rates were studied, although it is recognized that both these parameters depend largely on current individual medical practice. Thus, prematurity defined by gestational age may not be a complication but a result of medical care. Similarly, cesarean section may be the optimal method of delivery in a potentially large infant with a high risk of death late in gestation. While prematurity was not found to be associated with the third-trimester glucose level, the higher rates of cesarean section presumably reflect, to some extent, the increased frequency of fetal macrosomia associated with higher third-trimester glucose levels.

The importance of screening for and recognizing impaired glucose tolerance in pregnancy is emphasized by the present findings. In the past, glucosuria, past pregnancy history, a family history of diabetes, and maternal age have been considered indications of possible impaired glucose tolerance, although O'Sullivan has demonstrated the unreliability of pregnancy history and family history for identifying those with gestational diabetes.[32] The presence of glucosuria also appears to be an inadequate method of screening for gestational diabetes.

Since urine is tested for glucose as a routine part of prenatal visits, the results of this simple test are readily available throughout the pregnancy. In the present study, however, only 74% of women with a glucose concentration of 200 mg/dl or greater in the third trimester would have been detected if glucosuria alone had been used as a screening technique. If the target population were expanded to include those with lower glucose concentrations, the yield would be even lower. For example, only 44% of women with a third-trimester glucose of 160 mg/dl or greater had glucosuria.

Thus, glucosuria cannot be relied upon to identify those with impaired glucose tolerance of a degree clearly associated with increased morbidity and mortality.

Glucose tolerance during pregnancy is useful in predicting the subsequent development of diabetes in the mother, as well as in predicting complications of the current pregnancy. O'Sullivan has previously demonstrated a high incidence of subsequent overt diabetes in women with glucose intolerance during pregnancy,[27] and this finding was confirmed in the present study. The incidence of diabetes during a 4–8-yr period following delivery increased with increasing third-trimester glucose concentration. Women with a glucose concentration between 160 and 179 mg/dl had over 10 times the incidence of diabetes as women with a concentration of less than 100 mg/dl.

In conclusion, the association of glucose tolerance during pregnancy with the rate of complications and the subsequent incidence of diabetes in the mother was continuous throughout the range of glucose concentrations studied. Rates of all complications were high in known diabetic subjects, but among those who were not previously known to have diabetes, rates of perinatal mortality, macrosomia, toxemia, and cesarean section varied directly with glucose concentration while rates of congenital malformation and prematurity did not. The distribution of third-trimester glucose levels was unimodal and continuous. These results indicate that it is not possible to identify a specific level of glucose intolerance that can be designated as gestational diabetes. Nevertheless, the present observations suggest that amelioration of hyperglycemia during the third trimester of pregnancy may result in reduced morbidity and mortality. Safe and effective methods of reducing hyperglycemia should be determined and evaluated by randomized controlled clinical trials.

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From the Southwestern Field Studies Section, Epidemiology and Field Studies Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, Phoenix, Arizona.

Address reprint requests to David J. Pettitt, NIAMDD, 1440 East Indian School Road, Phoenix, Arizona 85014.

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