

# Gestational Glucose Tolerance and Risk of Type 2 Diabetes in Young Pima Indian Offspring

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The in utero environment is a powerful risk factor for type 2 diabetes in offspring, but little is known about the risk conveyed by nondiabetic gestational glucose levels. This issue was explored in 911 nondiabetic Pima Indian mothers and 1,436 of their children. Associations were assessed in multivariate models between maternal third trimester glucose tolerance and indexes of body composition and glycemic control in their children. At parturition, the mothers' ages ranged from 14 to 43 years. Offspring were studied at age 0–39 years. An SD (1.3 mmol/l) of maternal glucose was associated with 56 g higher birth weight ( $P = 0.0002$ ). This effect persisted when only offspring of normal glucose tolerant mothers were examined (57 g,  $P < 0.0001$ ). In Cox proportional hazards models, the adjusted hazard rate ratio for offspring risk of diabetes per SD maternal glucose was 1.6 (95% CI 1.3–2.0,  $P < 0.0001$ ). When only offspring of normal glucose tolerant mothers were examined, the risk was reduced but remained significant (1.3 [1.04–1.71],  $P = 0.026$ ). In conclusion, maternal glycemia during pregnancy is associated with increased birth weight and risk of diabetes in Pima Indian offspring, even when mothers are normal glucose tolerant during pregnancy. Thus, prevention of offspring type 2 diabetes may require strategies that focus on improving gestational glucose tolerance even within the normal range. *Diabetes* 55:460–465, 2006

The environment in which the fetus develops determines a considerable proportion of the risk of developing chronic metabolic disease during adulthood (1). Since in humans and other mammals the fetus is entirely dependent upon the supply of nutrients from the mother, maternal malnutrition or hyperglycemia can result in an in utero milieu that affects the growth and programming of fetal tissues and organs (2). In rodents, in utero hyperglycemia stimulates islet hyperplasia and  $\beta$ -cell hyperactivity within the fetal endocrine pancreas (2). These pancreatic adaptations augment uptake of glucose and amino acids, which manifests as fetal macrosomia. Because of this nutritional excess and the consequential hyperinsulinemia, hormonal growth factor

concentrations such as insulin-like growth factors increase (3), causing the offspring of diabetic mothers to be heavier for gestational age than the offspring of nondiabetic mothers (4). In addition, offspring of diabetic mothers incur a higher lifetime risk of type 2 diabetes and related complications (4–6).

Although a postchallenge glucose tolerance of 7.8–11.0 mmol/l (140–199 mg/dl) is conventionally used to determine impaired glucose tolerance, during pregnancy it is used to define gestational diabetes (7). Given the known effects of uncontrolled gestational diabetes on the growing fetus, treatment, usually in the form of dietary modification and/or insulin, is recommended above this threshold (8). However, the nature of the relationship between a nondiabetic mother's postchallenge glucose and the offspring's risk of type 2 diabetes has received little attention.

In the present study of American Indian mothers and their children, we explored the relationship between gestational postchallenge glucose tolerance and the risk of type 2 diabetes and related complications in the offspring. Previous studies have explored the relationship of third trimester glucose tolerance with quantitative traits and type 2 diabetes risk in this population (9), but the present analyses include more than a decade of additional follow-up, a wider range of age-groups, and more than twice the sample size. We also report data on the associations of third trimester glucose with birth weight in the offspring that have not previously been reported.

## RESEARCH DESIGN AND METHODS

Residents of the Gila River Indian Community in Arizona aged  $\geq 5$  years are invited to participate in a longitudinal study of type 2 diabetes. Participants for the present analyses consisted of 911 nondiabetic mothers and 1,436 of their offspring, the majority of whom are Pima or Tohono O'odham Indian (10,11). Ethnicity was assessed by asking the volunteer to describe whether each of their great grandparents was Pima or Tohono O'odham Indian. This variable was entered in the statistical models as a continuous covariate. The babies were born between 1965 and 1997, and the follow-up exams took place between 1970 and 2004.

Our analyses focused on third trimester maternal glucose tolerance as the exposure. For the main analyses, only women in whom 2-h postglucose challenge data were available, who had normal ( $< 7.8$  mmol/l [ $< 140$  mg/dl]) or impaired (7.8–11.0 mmol/l [140–199 mg/dl]) glucose tolerance during the third trimester of pregnancy, and in whom the necessary offspring data were available were included in the analyses. For comparison, we also included 199 offspring of diabetic mothers ( $n = 139$ ). These mothers were known to have type 2 diabetes (i.e., a 2-h postchallenge glucose  $\geq 11.1$  mmol/l [ $\geq 200$  mg/dl]) before pregnancy, as documented in medical records, but their third trimester glucose tolerance was not determined. The group of offspring of diabetic mothers were born within a similar calendar period, were of comparable ethnicity, and comprised similar proportions of males and females as the offspring of mothers in whom third trimester glucose was available. The selection of offspring of diabetic mothers has been described in detail previously (12,13). Seven women in whom third trimester glucose was  $\geq 11.1$

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TABLE 1  
Summary of sample sizes, follow-up duration, and incidence of diabetes for each third trimester glucose group

| Third trimester glucose group (mmol/l) | Mothers (n) | Offspring (n) | Offspring follow-up (person-years) | Cases of offspring diabetes (n) | Crude incidence of offspring diabetes (cases/1,000 person-years) |
|--|-------------|---------------|------------------------------------|---------------------------------|--|
| 3.3–4.4                                | 115         | 130           | 2,013                              | 2                               | 1.0  |
| 4.5–5.5                                | 364         | 429           | 7,218                              | 19                              | 2.6  |
| 5.6–6.6                                | 385         | 468           | 8,041                              | 28                              | 3.5  |
| 6.7–7.7                                | 231         | 259           | 4,406                              | 19                              | 4.3  |
| 7.8–11.0                               | 135         | 150           | 2,470                              | 19                              | 7.7  |
| Diabetes*                              | 139         | 199           | 3,231                              | 67                              | 20.7   |
| Total                                  | 1,369†      | 1,635         | 27,377                             | 154                             | 5.6  |

\*Diabetes in the mother diagnosed prior to pregnancy. †A total of 458 mothers appear more than once owing to >1 birth.

mmol/l ( $\geq 200$  mg/dl) were excluded from analyses because it was unknown whether diabetes existed before or first developed during pregnancy, and the characteristics of these women and their offspring may differ from women who developed type 2 diabetes before pregnancy and their offspring. All participants (or their parents or guardians) provided written informed assent/consent. The institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases approved the longitudinal study.

**Anthropometric and metabolic measurements.** Participants attended the clinic after a 12-h overnight fast. They underwent a 75-g oral glucose tolerance test for assessment of glucose tolerance according to World Health Organization diagnostic criteria (7). Type 2 diabetes was diagnosed if the 2-h plasma glucose concentration was  $\geq 11.1$  mmol/l ( $\geq 200$  mg/dl) or if a nonfasting glucose concentration  $\geq 11.1$  mmol/l ( $\geq 200$  mg/dl) was found in the course of routine medical care according to chart review. Diabetes in this population is thought to be entirely type 2 (14). Standard anthropometric data were collected by trained observers with participants in light clothing and no shoes. Height and weight were measured using a rigid stadiometer and a balance beam or calibrated scales, respectively. BMI was calculated as the ratio of weight (in kilograms) divided by the square of height (in meters). Obesity is expressed as either BMI  $>95$ th percentile for age and sex (5–19.9 years) or BMI  $>30$  kg/m<sup>2</sup> (20–24.9 years). The Centers for Disease Control and Prevention growth charts (15) were used as the reference population from which BMI percentiles were calculated. Waist circumference was measured at the umbilicus with the participant in the supine position. Glucose concentration was measured according to methods described in detail previously (10–12).

Venous blood samples were collected in sodium fluoride 2 h after ingestion of 75 g carbohydrate. Plasma was separated and stored at  $-20^{\circ}\text{C}$  until measurement by the alkaline potassium ferricyanide (Teckmin Autoanation) or the hexokinase method (Ciba-Corning, Palo Alto, CA). Postchallenge maternal glucose concentration during the third trimester was taken as an indication of exposure to in utero glycemia.

**Measurements in pregnancy.** Third trimester glucose tolerance tests were performed between 24 and 36 weeks gestation. Mothers were not required to be fasting. Impaired glucose tolerance in the mother was defined as a postchallenge glucose of  $\geq 7.8$  mmol/l but  $<11.1$  mmol/l. Mothers ( $n = 7$ ) with postchallenge third trimester glucose  $\geq 11.1$  mmol/l were excluded.

**Statistical analysis.** Analyses were performed using the Statistical Analysis System software (SAS Institute, Cary, NC). Participant characteristics are presented as the arithmetic mean  $\pm$  SD. Data were analyzed in their continuous form wherever possible. Analyses were conducted within 5-year age-groups, from age 5 to  $<25$  years. Because many of the offspring in this study attended more than one exam, the same individual may appear in different age strata. However, because we selected the first available exam within each age stratum, they can only appear once within a stratum. Linear regression models, adjusted for potential confounding factors such as ages of the mother and the offspring, sex, and birth date, were constructed to test the relationship between maternal glycemia and a number of metabolic traits in the offspring. A z-score was computed for the explanatory variable (third trimester glucose) in the complete dataset, and, for the purpose of comparison between models, this same SD value was used in all subanalyses. The regression models were fitted using generalized estimating equations (PROC GENMOD) to account for dependence among multiple offspring in a sibship. Proportional hazards models (PROC PHREG) were used to test the association between maternal glucose and risk of diabetes in the offspring. The cumulative incidence of type 2 diabetes was calculated by the product limit method. Follow-up time was determined as the time from birth until the event (i.e., diagnosis of type 2 diabetes) or the final examination attended if type 2 diabetes had not occurred. All individuals with third trimester glucose and follow-up data on type 2 diabetes were included in these models. Thus, in

contrast to the quantitative trait analyses, the date of diagnosis of type 2 diabetes or the last available exam for each individual was selected. In total, 1,436 offspring were included in this analysis, with 152 ( $\sim 10\%$ ) of the offspring having his/her last follow-up exam at age 25.0–39.4 years. All multivariate models included mother's and offspring's ages, offspring sex, birth date, and fraction of Indian heritage as covariates. The validity of the proportionality assumption was tested for each variable by including a time-dependent interaction term (16). None of these interaction terms was statistically significant at  $P < 0.05$ .

## RESULTS

Table 1 summarizes sample sizes, follow-up duration, and incidence of type 2 diabetes stratified by level of third trimester glucose or maternal type 2 diabetes before pregnancy. Table 2a shows characteristics of the 1,436 offspring of nondiabetic mothers who had attended at least one examination. Of these, 684 were male. On average, the offspring of nondiabetic mothers were overweight or obese and had normal glucose control at the time of their exam for the quantitative trait analyses. For analyses of type 2 diabetes risk, follow-up time ranged from 3.4 to 39.4 years (median 15.5 years; 90th percentile: 25.2 years). The lower half of Table 2 shows data in a second group of 139 mothers who had a date of diagnosis of type 2 diabetes before pregnancy and 199 of their offspring, who were included for comparison.

**Association of third trimester 2-h glucose with risk of type 2 diabetes in offspring.** The median follow-up duration was 15.9 years, and at age 24 years, data on at least 10% of the original cohort were available within each third trimester glucose stratum. Therefore, Fig. 1 only includes data up to 24 years of age. The cumulative risk of type 2 diabetes in offspring of diabetic mothers was the highest of all gestational glucose tolerance groups; at age 20 years, it was  $\sim 35\%$ , rising to 51% at 24 years. The cumulative risk of type 2 diabetes in offspring of mothers who had impaired glucose tolerance during the third trimester was  $\sim 15\%$  at age 20 years, rising to  $\sim 30\%$  at age 24 years. In the 6.7- to 7.7-mmol/l (120–139 mg/dl) third trimester glucose category, the cumulative risk of type 2 diabetes at age 20 and 24 years was 5 and 19%, respectively, and in the 3.3- to 6.6-mmol/l (60–119 mg/dl) category the cumulative risk of type 2 diabetes was 4 and 8% at 20 and 24 years, respectively.

Cox proportional hazard models, adjusted for the mother's age at birth, offspring's birth date, fraction of Indian heritage, and sex, were used to test the association between third trimester glucose and risk of type 2 diabetes in the offspring. Of 1,436 offspring of nondiabetic mothers in whom follow-up data on type 2 diabetes were available, 87 developed type 2 diabetes (3.6 per 1,000 person-years

TABLE 2  
Characteristics of offspring by age-group

| Variable  | Age-group    |             |              |              |
|---|--------------|-------------|--------------|--------------|
|   | 5–9 years    | 10–14 years | 15–19 years  | 20–24 years  |
| Offspring of nondiabetic pregnancies (gestational glucose <11.0 mmol/l [ $<200$ mg/dl])             |              |             |              |              |
| <i>n</i>  | 631          | 998         | 684          | 330          |
| Age (years)   | 7.5 ± 1.4    | 12.0 ± 1.3  | 16.8 ± 1.3   | 21.7 ± 1.3   |
| Height (cm)   | 127.3 ± 10.7 | 154.3 ± 9.2 | 166.3 ± 8.3  | 166.3 ± 9.3  |
| Weight (kg)   | 32.4 ± 12.0  | 62.1 ± 20.2 | 85.2 ± 23.3  | 95.8 ± 24.7  |
| BMI (kg/m <sup>2</sup> )  | 19.5 ± 4.6   | 25.6 ± 6.6  | 31.0 ± 8.8   | 35.2 ± 10.3  |
| % obese   | 34.5         | 52.7        | 55.4         | 69.4         |
| Waist (cm)  | 62.4 ± 13.1  | 82.3 ± 15.8 | 95.6 ± 17.6  | 105.7 ± 19.0 |
| Fasting glucose (mmol/l)  | 4.7 ± 0.3    | 5.0 ± 0.8   | 5.1 ± 1.6    | 5.5 ± 2.1    |
| 2-h glucose (mmol/l)  | 5.3 ± 1.0    | 5.8 ± 1.9   | 5.8 ± 1.8    | 6.2 ± 2.7    |
| A1C (%)   | 4.9 ± 0.4    | 5.2 ± 0.7   | 5.3 ± 1.1    | 5.5 ± 1.5    |
| Offspring of diabetic pregnancies (2-h glucose prior to pregnancy ≥11.1 mmol/l [ $\geq 200$ mg/dl]) |              |             |              |              |
| <i>n</i>  | 96           | 52          | 84           | 47           |
| Age (years)   | 7.7 ± 1.4    | 11.9 ± 1.2  | 16.7 ± 1.3   | 21.5 ± 1.2   |
| Height (cm)   | 128.8 ± 10.7 | 154.6 ± 9.0 | 165.3 ± 8.3  | 164.7 ± 8.1  |
| Weight (kg)   | 38.6 ± 13.8  | 71.0 ± 18.6 | 94.3 ± 26.6  | 94.9 ± 25.6  |
| BMI (kg/m <sup>2</sup> )  | 22.6 ± 5.1   | 29.7 ± 5.8  | 34.3 ± 8.2   | 34.8 ± 8.1   |
| % obese   | 60.4         | 81.6        | 77.2         | 63.8         |
| Waist (cm)  | 73.6 ± 12.4  | 94.6 ± 12.6 | 110.4 ± 54.0 | 109.0 ± 20.0 |
| Fasting glucose (mmol/l)  | 4.9 ± 0.3    | 5.4 ± 1.5   | 5.8 ± 2.4    | 7.1 ± 3.7    |
| 2-h glucose (mmol/l)  | 5.8 ± 1.4    | 7.4 ± 3.6   | 8.4 ± 5.4    | 10.1 ± 7.0   |
| A1C (%)   | 5.0 ± 0.3    | 5.5 ± 0.9   | 5.3 ± 0.5    | 5.9 ± 1.6    |

Data are means ± SD, unless otherwise indicated. Some offspring appear in more than one age stratum. The variable “% obese” represents the proportion of individuals whose BMI is either >95th percentile, based on Centers for Disease Control and Prevention 2000 U.S. population statistics (36) for age and sex (5–19.9 years) or BMI >30 kg/m<sup>2</sup> (20–24.9 years).

follow-up). In this group, third trimester glucose was strongly associated with risk of type 2 diabetes (hazard rate ratio per SD difference in maternal glucose [1.3 mmol/l]: 1.6 [95% CI 1.3–2.0],  $P < 0.0001$ ). When only offspring of mothers who had been normal glucose tolerant during pregnancy were included ( $n = 1,288$ ), the magnitude of the risk estimate was reduced (1.3 [1.04–1.71]) but remained statistically significant ( $P = 0.026$ ).

**Association of third trimester 2-h glucose with quantitative anthropometric and metabolic traits.** Associations were assessed by regression models adjusted for the mother’s age at birth, offspring’s age, birth date, fraction of Indian heritage, and sex among 1,436 adolescent offspring of nondiabetic pregnancies. The ODM were excluded from the analyses due to the lack of third trimester glucose data, although they are shown as a group in the figures.

An SD difference in third trimester postchallenge maternal glucose (1.3 mmol/l) was strongly associated with offspring birth weight (g) ( $\beta = 56$  g/SD maternal glucose;  $P = 0.0002$ ). When only offspring of mothers who were normal glucose tolerant during pregnancy were examined, the magnitude and statistical significance of this effect persisted ( $\beta = 57$  g/SD maternal glucose;  $P < 0.0001$ ) (Fig. 2).

In children aged 10–14 years, third trimester glucose was associated with waist circumference ( $\beta = 0.05$  SD/SD maternal glucose;  $P = 0.03$ ) and BMI ( $\beta = 0.06$  SD/SD maternal glucose;  $P = 0.06$ ) but not in offspring aged 5–9 and 15–25 years ( $P > 0.10$ ). No association was observed between third trimester glucose and fasting or 2-h glucose

in children aged 5–9 or 15–19 years, but associations were observed in 10- to 14-year-old children ( $\beta = 0.08$  SD/SD maternal glucose,  $P = 0.028$  and  $\beta = 0.11$  SD/SD maternal glucose,  $P = 0.0099$ , respectively) and 20- to 24-year-old offspring (fasting only:  $\beta = 0.15$  SD/SD maternal glucose;  $P = 0.03$ ). In 5- to 9- and 20- to 24-year-old subjects, no association was observed between third trimester glucose and HbA<sub>1c</sub> (A1C) ( $P = 0.97$  and  $P = 0.15$ , respectively). However, in 10- to 14-year-old subjects, a positive association was observed between these traits ( $\beta = 0.09$  SD/SD maternal glucose;  $P = 0.005$ ), and in 15- to 19-year-old subjects an association of borderline statistical significance was observed ( $\beta = 0.08$  SD/SD maternal glucose;  $P = 0.098$ ). For fasting and 2-h insulin, or homeostasis model assessment of insulin resistance, no statistically significant associations with third trimester glucose were evident at any age.

We also tested interaction between offspring age and third trimester glucose in the group of 5- to 24-year-old subjects. The purpose of these models was to ascertain whether the relationship between gestational glucose tolerance with body composition and glycemia in the offspring changes from childhood to young adulthood. There were interactions of third trimester glucose and offspring age for waist ( $P = 0.026$ ) and BMI ( $P = 0.078$ ), where the association with third trimester glucose was strongest at a younger age, and for fasting glucose ( $P = 0.05$ ), where the association with third trimester glucose was strongest at an older age. No interaction was observed for 2-h glucose, A1C, or fasting insulin.

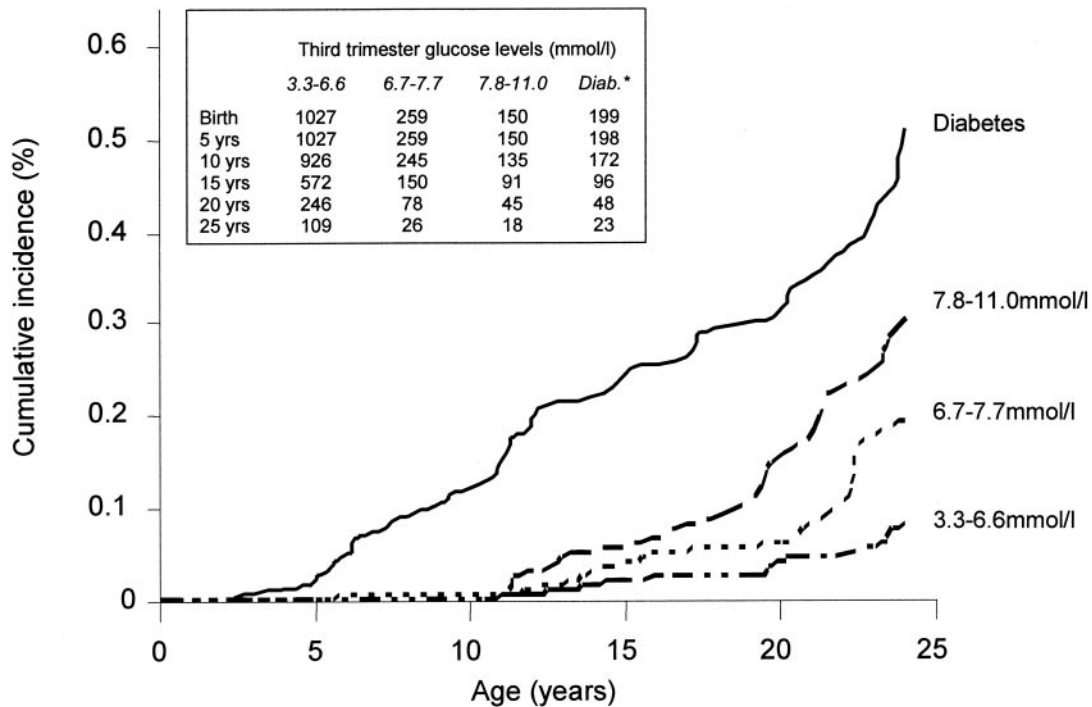


FIG. 1. Cumulative incidence of type 2 diabetes in offspring stratified by category of maternal third trimester 2-h glucose. Plots are curtailed where <10% of the original sample remains. *Insert* table shows the number of individuals at risk at 5-year intervals and within third trimester glucose strata. \*Type 2 diabetes in the mother diagnosed before pregnancy.

**DISCUSSION**

We explored the relationships between third trimester postchallenge glucose levels in nondiabetic Pima Indian mothers and type 2 diabetes risk, birth weight, and related metabolic phenotypes in their offspring. Third trimester glucose levels were positively related with offspring birth weight, even within the subgroup of children whose mothers' glucose tolerance was normal during pregnancy. Moreover, a strong association was observed between third trimester glucose levels and the offspring's risk of type 2 diabetes during young adulthood, which also remained statistically significant when only offspring of normal glucose tolerant mothers were examined. Third trimester glucose was also variably associated with measures of obesity and glucose control during childhood,

adolescence, and young adulthood, where associations with body composition tended to be more evident at a young age and more so with fasting glucose at an older age. These observations suggest that childhood obesity may precede the development of glucose intolerance in the offspring of hyperglycemic pregnancies. However, the statistical significance of these age interactions is marginal; therefore, the possibility that they are false-positive cannot be discounted.

Fetal growth is governed by the nutritional status of the mother. Thus, maternal glucose tolerance during gestation is an important risk factor for type 2 diabetes in the progeny (5). Exposure to adverse environmental factors including malnutrition in utero and during early life directly affects the development and maturation of organs

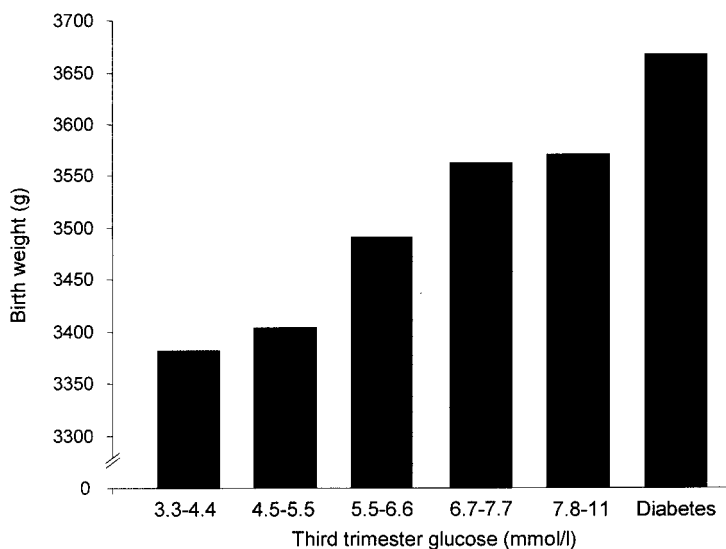


FIG. 2. Association between maternal third trimester 2-h glucose and offspring's birth weight. Data are unadjusted means stratified by age-group. \*Type 2 diabetes in the mother diagnosed before pregnancy.

and tissues, particularly the endocrine pancreas and  $\beta$ -cells (17).

Pancreatic organogenesis is regulated by extracellular signals emanating from neighboring cells which, via changes in gene expression, control the specification, differentiation, proliferation, and apoptosis of pancreatic cells (18). These signals are transmitted by both soluble and membrane-bound molecules. The high levels of glucose, and the fetal hormones stimulated during the diabetic pregnancy such as insulin and insulin-like growth factors, interact with these signaling molecules and affect the flow of maternal nutrients (19), directly influencing pancreatic morphology. Furthermore, as shown in experimental murine models (20), it is plausible that the human fetal pancreas is overstimulated during the diabetic pregnancy causing subsequent deterioration in  $\beta$ -cell function and the development of diabetes in early life. Because fetal growth in this scenario is accelerated, birth weight is frequently used as a marker of exposure to chronic hyperglycemia in utero. The tendency of mothers with diabetes to have children with higher birth weight is well recognized (21,22), but the present study demonstrates a statistically significant and apparently linear relationship between gestational glucose and the child's weight at birth, even in nondiabetic pregnancies.

The programming that tissues and organs undergo in utero determines the risk trajectories for a wide range of disorders later in life (23). These may include type 2 diabetes (24), obesity (25), hypertension (26), heart disease (27), dyslipidemia (28), depression (29), and some cancers (30). In Pimas, as in other populations, diabetes in pregnancy corresponds with increased risk of perinatal mortality, excessive birth weight, and cesarean section (31). Pimas exposed to diabetes in utero are also at elevated risk of later life obesity and type 2 diabetes (6,9,12,13,24,25,32–36). However, most of our previous studies have compared outcomes in offspring exposed to a diabetic pregnancy versus those not exposed to a diabetic pregnancy. Several studies in non-American Indian populations have reported an inverse association between birth weight and type 2 diabetes risk (15,37–39). In the present study, we did not directly test this relationship, but we did observe positive relationships between gestational glucose levels and offspring birth weight and risk of diabetes. This indicates that higher–birth weight babies are at increased risk of diabetes by comparison with normal–birth weight babies in this cohort. This apparent paradox may well be due to the small numbers of very-low–birth weight babies in our cohort and supports previous observations in Pima Indians (21) that across the full spectrum of birth weights, the relationship between birth weight and type 2 diabetes is U shaped.

In one previous report from our group including a subsample of the participants described in the current article (9), glucose tolerance in adolescent offspring was compared with the mothers' levels of third trimester glucose tolerance. In this report, maternal glucose tolerance during pregnancy was directly associated with glucose tolerance in the offspring during adolescence. In the original publication, 552 offspring were included in the analyses. In the present analysis, no further data were available in 93 of these individuals. Data are extended in the remaining 459 by approximately a decade, and an additional 1,066 subjects are included. These additional data allowed us to test the association of third trimester glucose tolerance with birth weight and risk of type 2

diabetes in offspring, the former of which was not a feature of the previous study.

The associations in the present study were adjusted for a number of possible confounding factors, but data were unavailable for factors such as maternal smoking, physical activity level, and use of medication. However, the prevalence of smoking among Pima Indians is lower than in other U.S. populations. Indeed, <1% of adult Pima Indians smoke one pack of cigarettes per day (40,41), and thus smoking is unlikely to be a major confounding factor. An additional limitation of our data are that gestational age was known in only a small subsample of the cohort, but adjusting for gestational age in the subsample of the children in whom this variable was available did not materially alter the magnitude of the association between third trimester glucose and birth weight. A further consideration, when determining the reliability of the data on third trimester and diabetes risk, is that after 20 years of follow-up, the number of cases in some glucose strata are few, as shown in Fig. 1. Finally, from the present data it is not possible to determine whether the observed relationships result from a causal effect of exposure to a hyperglycemic in utero environment. Alternative explanations for the associations we report include genetic and ex utero factors, such as the shared familial environment, which could explain some of the associations we report. However, data from animal studies, in which in utero hyperglycemia is experimentally induced, show independent effects on fetal growth and development of cardiovascular disease (2). Moreover, studies of Pima sibships (24) have demonstrated that although some of the in utero transmission of type 2 diabetes is likely to be genetic, exposure to diabetes in utero further increases type 2 diabetes risk in the offspring.

The results of the present study further quantify the risks of type 2 diabetes and its complications in offspring of mothers with impaired glucose tolerance during pregnancy. They also raise the question of whether clinical interventions to improve maternal glycemia are warranted at levels below the current diagnostic threshold for gestational diabetes, which includes impaired glucose tolerance (7). However, the adverse effects of gestational hypoglycemia should also be considered when weighing the risks, costs, and benefits of treatment. The importance of recognizing and treating impaired glucose tolerance in pregnancy was shown in a recent randomized clinical trial (42). In this study, rates of serious perinatal complications were substantially reduced, birth weight was lower, and macrosomia was less frequent in the invasive treatment group by comparison with the group in which mothers received normal care. Intervention studies that explore the effect of treating women with gestational glucose levels <7.8 mmol/l (140 mg/dl), possibly through intensive dietary advice, will be necessary to define an evidence base for optimal care at this level of glycemia.

In summary, the relationship between third trimester glucose tolerance and metabolic disturbances in the offspring is strong and statistically significant even among mothers whose 2-h glucose values are in the normal range. However, the relationship between gestational glucose and obesity is strongest at early ages and becomes weaker from late adolescence through early adulthood, which supports earlier observations (9). In contrast, the relationship between gestational glucose tolerance and glucose regulation in the offspring is weak during childhood and becomes strong during adolescence and early adulthood.

These observations suggest that the development of obesity may precede deteriorations in glucose control following exposure to elevated glucose levels in utero.

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