Secular Trends in Birth Weight, BMI, and Diabetes in the Offspring of Diabetic Mothers

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OBJECTIVE — The offspring of mothers who had diabetes during pregnancy experience increased risk later of diabetes and obesity later. We hypothesized that, in light of the historical improvements in the management of diabetes during pregnancy, these late consequences of the early environment might be diminishing with time.

RESEARCH DESIGN AND METHODS — Birth weight and information on BMI and glucose tolerance have been collected as part of the epidemiological survey of the Gila River Indian Community in Arizona. We examined birth weight, BMI, and diabetes in offspring of mothers with type 2 diabetes during pregnancy born in four 10-year time intervals since 1955 compared with offspring whose mothers either had not developed diabetes or were prediabetic (i.e., developed diabetes after the index pregnancy).

RESULTS — Offspring of diabetic mothers (ODM) were heavier at birth, had a higher BMI at all ages throughout childhood, and had an increased incidence rate of diabetes in childhood and early adulthood (7- to 20-fold, offspring of nondiabetic mothers [ONDM]; 3- to 5-fold, offspring of prediabetic mothers [OPDM]). Relative differences in birth weight and BMI between ODM and ONDM were greatest for those born before 1965. In those born after 1965, despite secular trends to higher BMI and diabetes incidence in the ONDM, differences in BMI and birth weight of ODM versus ONDM and OPDM appeared to have been maintained.

CONCLUSIONS — With the possible exception of individuals born before 1965, the increased risk of diabetes and obesity experienced by ODM does not seem to be diminishing with time.

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The offspring of mothers who had diabetes during pregnancy experience an unusually high rate of type 2 diabetes (1,2) and obesity (3,4) in later life, suggesting that influences in the intrauterine environment provided by a diabetic mother might act to program later risk of metabolic disease (5). The importance of early environmental rather than genetic influences is supported by similar effects occurring in animal models of diabetes during pregnancy (6), in offspring of mothers with type 1 diabetes (7), and in comparison of Pima Indian siblings born before and after onset of type 2 diabetes in their mothers (8). In populations with high rates of maternal diabetes during pregnancy, these effects are of great importance to the health of the next generation. Among Pima Indians, exposure to maternal diabetes in utero is associated with a 10-fold increase in the risk of diabetes in childhood and is the single strongest predictor of type 2 diabetes in Pima children (9). Little is known of whether this risk has changed with time or if these early environmental influences might be influenced to reduce the risk of diabetes in the next generation.

Information from the Pima community has been collected over the last 35 years, a period that has seen improvement in antenatal management of women with diabetes in pregnancy in the general population (10) and reductions in perinatal mortality in successive studies in the Pima population in particular (11,12). We hypothesized that such improved antenatal care might have resulted in a reduction in the difference between the offspring of diabetic mothers and their peers.

RESEARCH DESIGN AND METHODS

The subjects of this study are at least half Pima or Tohono O'odham or a mixture of these 2 closely related groups. Members of the community >5 years of age are invited to participate in biennial research examinations, including an oral glucose tolerance test (OGTT) after a 75-g glucose load. Diabetes is diagnosed if fasting blood glucose is ≥140 mg/dl, glucose is ≥200 mg/dl 2 h after the 75-g glucose load, or if diabetes has been diagnosed in a clinical setting. Data on glucose tolerance and BMI from research examinations were available for 4,577 individuals (9,841 examinations) with adequate maternal glucose tolerance information.

Birth weights and duration of gestation were derived either from the birth certificate or from review of hospital records at each biennial visit. Birth weight and presence of maternal diabetes during pregnancy were known for 3,638 children. When gestational age was available (2,096 children; 54% offspring of diabetic mothers [ODM], 62% offspring of prediabetic mothers [OPDM], and 57% offspring of nondiabetic mothers [ONDM]), birth weight was adjusted for sex and gestational age to allow for effects from variation in gestational age at the time of delivery. This adjusted birth weight was derived by linear regression of actual birth weight against sex and gestational age. The residual value was then added to the estimated mean birth weight at

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Abbreviations: ODM, offspring of diabetic mothers; OGTT, oral glucose tolerance test; ONDM, offspring of nondiabetic mothers; OPDM, offspring of prediabetic mothers.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Birth weights by year of birth and maternal diabetes*

	ONDM				OPDM				ODM			
	n	Birth weight (g)	Weight <2,500 g (%)	Weight >4,500 g (%)	*n*	Birth weight (g)	Weight <2,500 g (%)	Weight >4,500 g (%)	*n*	Birth weight (g)	Weight <2,500 g (%)	Weight >4,500 g (%)
1955–1964	587	3,399 ± 19	2.6	1.4	69	3,532 ± 57	4.3	2.9	16	3,996 ± 193*	2.4	25.0
1965–1974	1,080	3,372 ± 16	5.2	1.5	138	3,446 ± 49	5.1	2.9	63	3,658 ± 106*	4.8	9.5
1975–1984	593	3,416 ± 30	3.4	1.9	85	3,644 ± 158	7.1	9.4	50	3,679 ± 111	4 .0	16.0
1985–1994	756	3,462 ± 24	2.5	1.7	104	3,588 ± 50	1.0	3.9	97	3,767 ± 73*	5.1	12.0

Data for birth weight are means ± SEM. *Mean was significantly different from both ONDM and OPDM ($P < 0.05$) when analyzed within birth cohorts.

40 weeks to correct individual birth weights to 40 weeks of gestation and male sex.

For comparison of values of BMI (kg/m^2) and glucose between groups based on maternal diabetes, BMI and glucose values were adjusted for age and sex within age-groups. In brief, individual values were regressed against age (linear and quadratic terms) after stratification for age (5–9, 10–14, 15–19, and 20–29 years) and sex. Residual values were then used to create values adjusted for sex and to the midpoint of the age-groups (7.5, 12.5, 17.5, and 25 years).

Birth weight, adjusted birth weight, glucose, and BMI were examined in cohorts based on birth year and mother's diabetes. For birth-year cohorts, offspring were divided into 10-year groups ranging from offspring born 10 years before the start of the study and three 10-year intervals thereafter. The 4 groups comprised offspring born between 1 January 1955 and 31 December 1964, 1 January 1965 and 31 December 1974, 1 January 1975 and 31 December 1984, and 1 January 1985 and 31 December 1994. For estimation of BMI within groups, if offspring had been examined at >1 age within an age-group, then only the earliest examination was used.

A child was considered ODM if his or her mother had been diagnosed as having type 2 diabetes by World Health Organization criteria either before or during the index pregnancy. To control for both genetic and environmental factors in the later development of diabetes, 2 groups of offspring of mothers who did not have type 2 diabetes at the time of pregnancy were used for comparison. In both of these groups, all mothers had a nondiabetic oral glucose tolerance test (OGTT) at least once after the index pregnancy. To allow for differing potential length of follow-up in the various birth cohort groups, the offspring of mothers who were known to have developed diabetes within 10 years after the birth of their child were included as OPDM. All other offspring were included as ONDM, and these mothers had ≥1 nondiabetic examination after pregnancy and no record of diabetes onset within 10 years. It should be noted that because some of the offspring in the final birth cohort (born between 1985 and 1994) are not yet 10 years of age, the size of the OPDM group may be underestimated in this group.

Diabetes incidence was computed for all of those with known diabetes or ≥1 nondiabetic examination. Incidence rates (number of new cases divided by person-years at risk of diabetes) were calculated in 5-year age-groups from birth, after stratification for sex, birth cohort categories, and maternal diagnosis. Incident cases were defined as individuals diagnosed with diabetes at ages within the range of the age-group. Person-years at risk were counted *1*) from the opening age to the closing age of the age-group (where diabetes onset or a nondiabetic examination had occurred at an age older than the closing of the age-group), *2*) from the opening of the age-group to the age of onset of diabetes for incident cases, and *3*) from the opening of the age-group to a last nondiabetic examination for nonincident cases. Sex-adjusted incident rates were calculated as the average of rates for both sexes.

Incidence for age-groups 0–4 and 5–9 are not presented because of the low number of incident cases. For consistency with the presentation of data for BMI already described, incidence in ages 20–29 years is presented, calculated from the average of sex-adjusted incidence rates of age-groups 20–24 and 25–29. Sex- and birth cohort–adjusted incidence was calculated with equal weighting of the sexes and four 10-year birth cohorts from 1955 to 1994.

Statistical analysis

Differences in birth weight or BMI between groups defined by maternal diabetes or birth cohort were analyzed using analysis of variance in a generalized linear model with post hoc testing by the Student-Newman-Keuls test.

RESULTS

Birth weight

ODM were significantly heavier than ONDM and OPDM (ODM 3,724 ± 52, OPDM 3,541 ± 41, ONDM 3,408 ± 11 g; $P < 0.05$). The difference between ODM and other groups appeared largely stable over the course of the study. When analyzed separately by birth cohort group (Table 1), ODM were significantly heavier than ONDM and OPDM in each cohort apart from between 1975 and 1984. In the whole group, unadjusted birth weight showed a small increase with time, with birth year (as a continuous variable) having a positive relationship with birth weight. Although significant ($P < 0.01$), the effect was small, accounting for <0.5% of the total variance of birth weight. This small positive effect of birth year was also present in the subgroup of ONDM (again representing <0.5% of the total variance; $P < 0.001$). By contrast, birth year was not a significant predictor of birth weight in either ODM or OPDM, the highest mean birth weights in the ODM group being in the 1955–1964 cohort. Despite this, when all data were modeled with birth year and maternal diabetes as predictor variables for birth weight, there was no significant interaction between the maternal diabetes group and birth year. This suggests that trends in birth weight with time in ODM, ONDM, and OPDM were not significantly different. Similar findings were obtained when the 1955–1964 cohort was omitted (data not shown).

Gestational age at birth was on average lower in the diabetic mothers (ONDM 39.8 ± 0.04, OPDM 39.6 ± 0.11, ODM 38.9 ± 0.18 weeks; $P < 0.05$). Birth weight adjusted for gestational age and sex followed the similar trends seen for the unadjusted birth weight. ODM were heavier than both OPDM and ONDM (ODM 3,936 ± 60, OPDM 3,623 ± 32, ONDM 3,483 ± 11 g; $P < 0.05$) over the whole group, and differences between ODM and other groups were statistically significant in all but 1 birth cohort (Fig. 1). For adjusted birth weight, effects of birth year were not significant ($P = 0.06$), and again there was no significant interaction between birth year and maternal diabetes group.

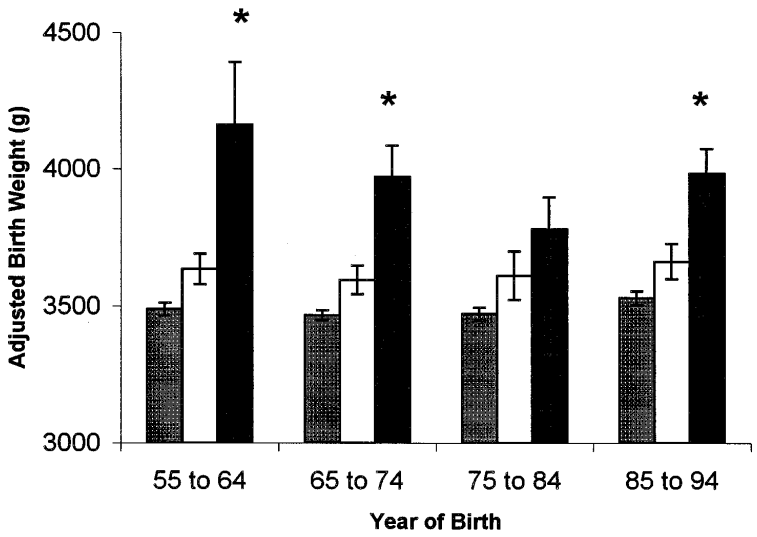

Figure 1—*Adjusted birth weight by birth cohort of ODM and control group. Gestational age and sex-adjusted birth weight (mean ± SEM) in ODM, OPDM, and ONDM. *Mean was significantly different from both ONDM and OPDM (*$P < 0.05$*) when analyzed within birth cohorts. ONDM,* ▦*; OPDM,* □*; ODM,* ■.

BMI

BMI increased over the course of the study. From the 1955–1964 cohort to the last available cohort for each age-group (1985–1994 for offspring aged 5–9 and 10–14 years; 1975–1984 for offspring aged 15–19 and 20–30 years), there was an increase of 1.1 kg/m^2 for offspring aged 5–9 years, 3.6 for offspring aged 10–14, 3.3 for offspring aged 15–19, and 3.4 for offspring aged 20–30 (all $P < 0.05$). When analyzed by birth cohort, the BMI of ODM remained significantly higher up to the age of 20 years versus ONDM in all cohorts and was higher in those in the OPDM group in all but 2 cohort/age strata (Fig. 2). BMI was highest in absolute terms in ODM born in later cohorts. Compared with BMI of OPDM from the same birth cohort (to allow for secular trends in BMI), the increases in BMI of ODM were greatest in the earliest cohort (16% higher than OPDM aged 5–9 years, 27% higher than OPM aged 10–14, 19% higher than OPM aged 15–19) (Fig. 2*A–D*). In cohorts born after 1965, the differences between ODM and OPDM were maintained (5–13% higher for ages 5–9 years, 6–9% higher for ages 10–14, and 7–19% higher for ages 15–19) (Fig. 2*A–D*).

To assess secular effects, all data were modeled using birth year and maternal diabetes status (ODM vs. ONDM vs. OPDM) as predictors. BMI increased with later birth year in all age-groups ($P < 0.001$ in each). Maternal diabetes was a significant predictor of BMI in all but the oldest age-group ($P < 0.0001$ at ages 5–9, 10–14, and 15–19 years). There was no significant interaction between the effects of birth year and maternal diabetes status, suggesting that the same secular pattern was being observed in all groups.

Diabetes incidence

Over the whole study, the sex- and birth cohort–adjusted incidence of diabetes for Pima children in the ODM group was far higher than that of their peers. At ages 10–14 years, adjusted diabetes incidence was almost 5 times OPDM and >20 times ONDM (ODM 22.4/1,000, OPDM 4.8/1,000, ONDM 1.0/1,000 person-years). At ages 15–19 years, adjusted incidence of diabetes remained 2.4× OPDM and 7.7× ONDM (ODM 35.4/1,000, OPDM 14.6/1,000, ONDM 4.6/1,000 person-years), and between 20 and 30 years of age, it was 3.4× OPDM and 7.2× ONDM (ODM 111.6/1,000, OPDM 32.7/1,000, ONDM 15.5/1,000 person-years).

Diabetes incidence after adjustment for sex is displayed for the various birth cohort groups in Fig. 3. Diabetes incidence increased with age in all groups and also increased with later birth cohorts in OPDM and ONDM. Diabetes incidence had not risen as clearly in later birth cohorts in the ODM group but remained above that of offspring of both other groups in every age and birth cohort group.

The sex- and age-adjusted diabetes incidence rates for children aged 10–19 years in the 3 birth cohorts where data were available (1955–1964, 1965–1974, 1975–1984) doubled in the ONDM group from first to last birth cohort (1955–1964, 2.1/1,000 person-years; 1965–1974, 2.1/1,000 person-years; 1975–1984, 4.2/1,000 person-years) and increased even more in the OPDM group (birth cohort 1955–1964, 2.2/1,000 person-years; 1965–1974, 6.8/1,000; 1975–1984, 20.2/1,000). The incidence of diabetes in the ODM group remained higher at each age (birth cohort 1955–1964, 30.6/1,000 person-years; 1965–1974, 19.6/1,000; 1975–1984, 36.4/1,000).

CONCLUSIONS — Increases in birth weight and later obesity (3,4) and diabetes (1,2) in ODM have been well documented in this and other populations and appear to relate to influences in the intrauterine environment supplied by a diabetic mother in addition to genetic influences (8). Our hypothesis was that changes in the management of diabetic pregnancy might have led to improvements in long-term outcomes for children of diabetic mothers. Disappointingly, there is only limited evidence from our study to support this, and this mainly relates to those born before 1965. This group had the greatest difference in birth weight from ONDM and OPDM and had the largest proportion of infants born large for gestational age. In later life, the differences between these children and offspring in the OPDM and ONDM groups, born during the same years, were larger than in any other birth cohort for both BMI (at ages <30 years) and diabetes incidence (at ages <20 years).

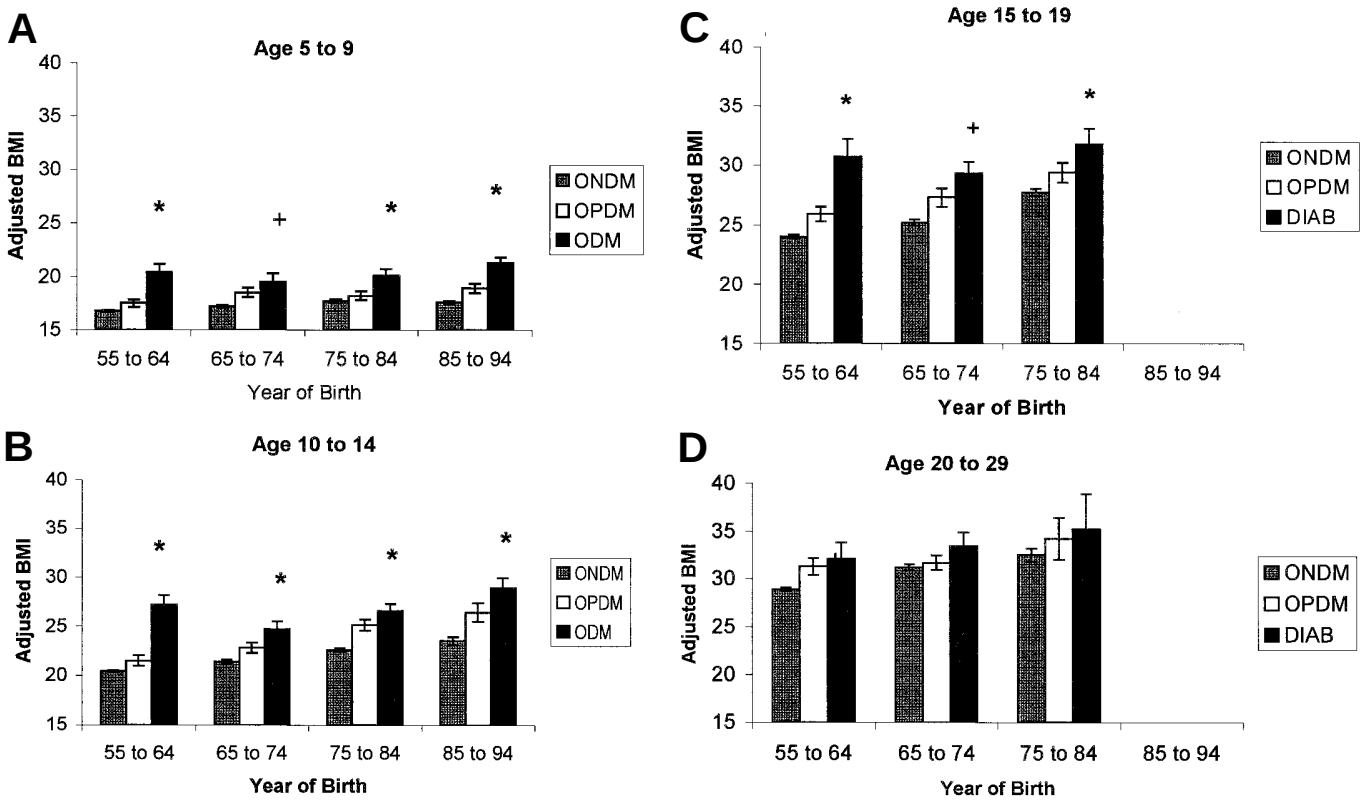

Figure 2—*Adjusted BMI by birth cohort of ODM and control group. BMI (mean ± SEM) in ODM, OPDM, and ONDM. Graphs for offspring aged 5–9 years* (A) *(ODM,* n = *170; OPDM,* n = *652; ONDM,* n = *2,251), 10–14 years* (B) *(ODM,* n = *164; OPDM,* n = *376; ONDM,* n = *2,748), 15–19 years* (C) *(ODM,* n = *97; OPDM,* n = *222; ONDM,* n = *1,818), and 20–29 years* (D) *(ODM,* n = *63; OPDM,* n = *159; ONDM,* n = *1,421). *BMI in ODM was significantly higher than that OPDM and ONDM; +significantly higher than ONDM alone (Student-Newman-Keuls test,* $P < 0.05$*).* ▦*, ONDM;* □*, OPDM;* ■*, ODM.*

Whether this relates to less well-controlled diabetes in pregnancy is impossible to know. It is important to note that regular screening for diabetes had not been instituted before 1965. This may have affected the case ascertainment in these years, resulting in underdiagnosis of diabetes both before and during pregnancy. Mothers diagnosed before 1965 may therefore have had more clinically obvious and less well-controlled diabetes.

For offspring born after 1965, it is more difficult to ascertain improvements in these outcomes. Birth weight remains higher in ODM. Against a background of a marked rise in diabetes and BMI in the population in general, the differences in BMI between ODM and other groups also appeared to increase in offspring born after 1965, being greater in absolute terms for children <15 years of age for those in the 1985–1994 cohort than those born 20 years earlier (1965–1974). Diabetes incidence also rose dramatically overall, being higher in the 1975–1984 cohort than in the 1965–1974 cohort in each group dependent on maternal diabetes status (ONDM, OPDM, and ODM) and in both age-groups available (10–14 and 15–19 years). The only evidence of potentially improved outcome in the ODM group is that, although diabetes incidence has increased in ODM, the rises in the other groups (OPDM and ONDM) appear to have been greater with time.

There is a dramatic increase in childhood obesity and diabetes in this population. Part of this increase is accounted for by increased numbers of offspring born to mothers with type 2 diabetes during pregnancy. ODM comprised 2.6% of the 1955–1964 cohort (for birth weight) in this study and 11.4% of the 1985–1994 cohort. If the risk attributable to the effects of diabetes during pregnancy cannot be modified, we may predict further increases in childhood obesity and diabetes as the numbers of offspring of diabetic mothers increase. It is equally important to note that type 2 diabetes and obesity have increased in ONDM and OPDM. There are clearly other environmental factors acting that are increasing the risk of these diseases in all groups.

In attempting to discern genetic from environmental effects, we have divided our comparator groups into offspring of mothers who developed diabetes within 10 years after the birth of their child and those who had not developed diabetes in this time. This method may be imperfect for 2 reasons. First, it does not entirely correct for genetic differences between groups. Where we observe differences between the ODM and OPDM groups, it is tempting to ascribe this to effects of the early environment. This may not be entirely the case, because mothers in the ODM group are likely to have diabetes of earlier onset than those in the OPDM group and therefore might have passed on a greater genetic propensity to diabetes. Conversely, a second effect may tend to underestimate early environmental influences. Mothers in the OPDM group are likely to have a higher blood glucose than mothers in the ONDM

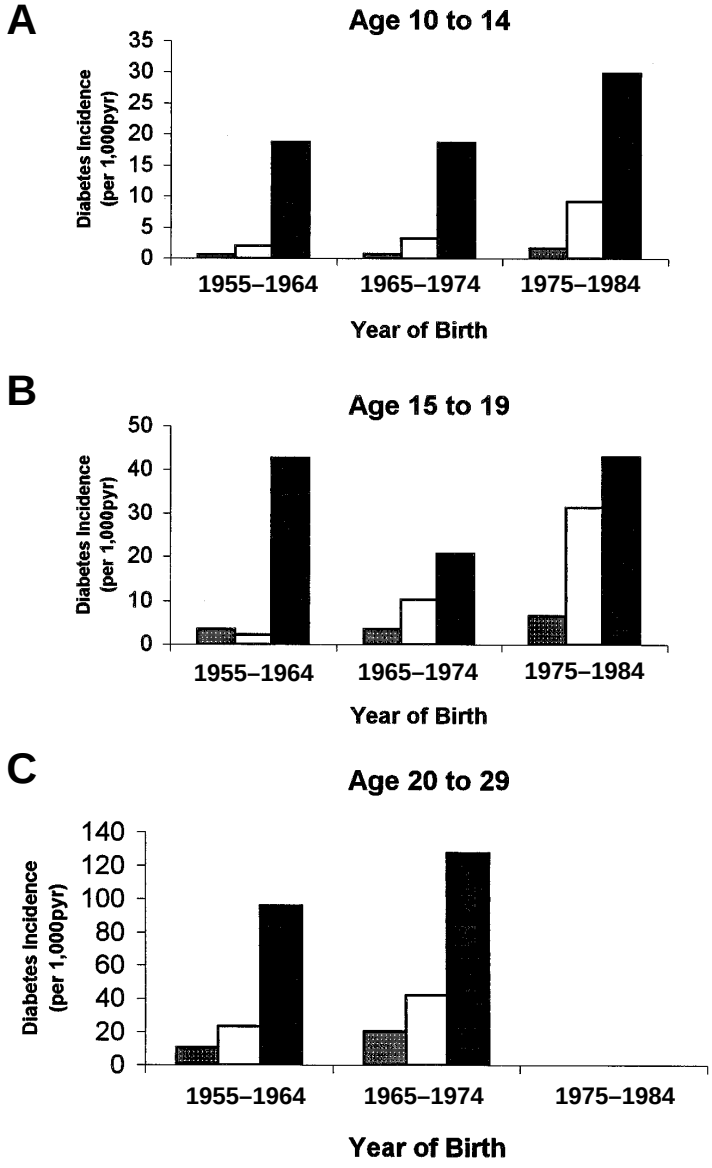

Figure 3—*Diabetes incidence by birth cohort of ODM and control group. Sex-adjusted diabetes incidence (per 1,000 person-years [pyr]) in ODM, OPDM, and ONDM. Graphs for birth cohorts born before 1965 (*A*), 1965–1974 (*B*), and 1975–1984 (*C*) are shown. Note that the scales on the* y*-axes differ.* ▦*, ONDM;* □*, OPDM;* ■*, ODM.*

group at later times in pregnancy, and, therefore, some of the increase in diabetes, obesity, and birth weight in the OPDM group might potentially be ascribed to early environmental effects. Overall, however, our classification will delineate groups of offspring with different in utero exposure to maternal diabetes.

In hypothesizing that differences in birth weight, obesity, and diabetes between ODM and other groups might have diminished with time, we relied on 2 assumptions: first, that metabolic control during pregnancy had improved, and second, that such improvements would have resulted in a reduction in long-term sequelae of maternal diabetes. Although we lack a systematic clinical measure of glycemic control during pregnancy in these cases, born over a span of ~40 years, this period was marked by major changes in the management of diabetes during pregnancy and dramatic reductions in maternal and fetal mortality (10). Changes in mortality have also occurred in the Pima population. In a cohort born up to 1966, 26% of 47 offspring born to Pima mothers with known diabetes died perinatally (11). A later study records a perinatal mortality rate of 59/1,000 live births in offspring born between 1966 and 1979 to mothers with diabetes (12). It seems likely then that management has improved. Long-term data are as yet sparse to support the second part of our hypothesis: Do changes in maternal glycemic control result in improvements in metabolic outcomes for offspring? In the follow-up studies at Northwestern University, amniotic fluid insulin levels, which in turn can be related to maternal metabolic control, predicted long-term outcomes (diabetes and obesity) (2,4). In the Pima population, previous studies have demonstrated a graded relationship between third trimester glucose values for the mother during pregnancy and later outcomes for the child (12). Our knowledge of the specific factors in diabetic pregnancy that lead to programming events in the offspring is limited, making it difficult to predict how management of diabetes during pregnancy might then affect metabolic outcomes for the child.

This study confirms previous findings regarding the striking increase in obesity and diabetes experienced by the offspring of mothers who had diabetes during pregnancy. The appearance of type 2 diabetes and obesity in these numbers at such young ages in the population is a relatively new phenomenon but carries the same risk of complications and morbidity as disease in older age-groups. Although it is clear that maternal diabetes acts as the major risk factor for type 2 diabetes in childhood in this population (9), we understand little of why the risk of diabetes and obesity might be increased in these children and, therefore, how this risk might be modified. Our study suggests that although changes in clinical practice between 1955 and 1994 have already been shown to have improved important perinatal outcomes, their impact on metabolic risk may be more limited.

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