Early Growth in Offspring of Diabetic Mothers

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OBJECTIVE — By age 5 years, offspring of diabetic mothers (ODMs) are heavier and have altered glucose metabolism compared with offspring of mothers without diabetes (non-DMs). This study evaluates the growth pattern of ODMs before the age of 5 years.

RESEARCH DESIGN AND METHODS — Anthropometric measures (z scores) from birth, 1.5 years, and 7.7 years in Pima Indian children were compared by maternal diabetes status.

RESULTS — After adjustment for earlier gestational age at delivery (37.8 vs. 39.3 weeks, \( P < 0.01 \)), ODMs were heavier at birth (z score birth weight 0.49 vs. \(-0.04, P < 0.01\) than non-DMs. At age 1.5 years, ODMs were shorter than the non-DMs (z score = \(-0.24 \) vs. \(0.12, P < 0.01\) but their weight and relative weight (RW; weight adjusted for age, sex, and length or height) were similar. From birth to 1.5 years, ODMs showed significant “catch down” of weight compared with non-DMs (change in weight z score from birth to 1.5 years of ODMs and non-DMs was \(-0.56\) and \(0.12\), respectively, \( P < 0.01\)). By age 7.7 years, ODMs were heavier (weight z score 0.89 vs. \(-0.07, P < 0.01\)) but had similar height as non-DMs. Differences in glucose and insulin concentrations at age 7.7 years were dependent on RW.

CONCLUSIONS — ODMs had a dramatically different growth pattern from that of non-DMs. Gestational age–adjusted birth weight was higher. During the first 1.5 postnatal years, the change in weight z score and attained height were reduced. Subsequently, height caught up to that of non-DMs, while weight gain greatly exceeded that of non-DMs.

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There is an alarming increase in obesity and type 2 diabetes in children in the United States, particularly among high-risk populations such as Pima Indians (1). Because both of these disorders carry great morbidity and are so difficult to treat, understanding their pathogenesis in order to formulate treatment and prevention strategies is important.

A number of anthropometric and personal characteristics have been identified as risk factors for obesity and diabetes. These attributes are at times difficult to reconcile. In the Pima Indian population, maternal diabetes during pregnancy, usually associated with higher offspring birth weight, carries an increased risk of diabetes and obesity in their children (2,3). Lower birth weight, however, is also associated with increased risk of later type 2 diabetes in both the Pima (4) and other populations (5). Individuals who develop type 2 diabetes in adult life in Caucasian (6) and Asian (7) populations have been found to have low BMI in the first 2 years of life but accelerated weight gain thereafter. By contrast, “catch-up” growth (upward crossing of centiles) in this same postnatal period (birth to age 2 years) has been associated with increased adiposity in childhood (8), which in turn associated with early-onset diabetes (1). Breastfeeding, which does not alter the weight gain pattern of infants in the first 6 months of life (9), is associated with reduced risk of obesity and type 2 diabetes in some populations (10). In a randomized clinical trial of nutrition in babies born prematurely, however, nutritional supplementation–induced accelerated growth in the immediate postnatal period appeared to adversely program cardiovascular risk factors, including insulin resistance (11).

The purpose of this study is to explore the early growth pattern of Pima Indian children who are offspring of mothers with type 2 diabetes in order to determine the period of early life in which their growth is accelerated.

RESEARCH DESIGN AND METHODS — Subjects of this study were born between 1992 and 1998 and participated in a longitudinal epidemiological study conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in the Gila River Indian Community. Every 2 years beginning at the age of 5 years, community residents are invited to participate in biennial examinations. Informed consent from a parent and assent from the child are obtained. The study was approved by the Institutional Review Board of the NIDDK and the Tribal Council of the Gila River Indian Community.

Birth weight (BWT) and gestational age were obtained from medical records.
or birth certificates. Maternal diabetes was diagnosed by the World Health Organization criteria (75-g 2-h postload [2-h] glucose concentration ≥200 mg/dl) (12) before or during the pregnancy and their offspring were categorized as offspring of diabetic mothers (ODMs). Offspring of mothers without a preexisting diagnosis of diabetes and with a normal 2-h oral glucose tolerance test (OGTT) at their first exam after delivery were categorized as offspring of nondiabetic mothers (non-DMs). Children of mothers were not known to have diabetes but who did not undergo an OGTT after the delivery date were excluded. Because paternal diabetes does not influence the offspring via the in utero environment, offspring of fathers diagnosed before or after the pregnancy were considered offspring of diabetic fathers. The early childhood measurements were obtained from well-child examinations performed by the Department of Public Health Nursing. Early childhood weight (WT1.5) was obtained by electronic scale in subjects dressed only in undergarments or dry diapers. Supine length (HT1.5) was obtained by measuring board. When multiple examinations in the age range of 1–2 years were available, the measurement from the examination closest to 1.5 years was selected.

When children had attended multiple biennial examinations, the exam closest to the age of 7 years (range 5–11) was selected. Subjects were measured wearing light clothing and no shoes using an electronic scale for weight (WT7) and a stadiometer for height (HT7). Serum insulin and plasma glucose were measured after an overnight fast and 2 h after a 75-g oral glucose load. Serum insulin concentrations were determined by a chemiluminescent immunoassay (Beckman Access). Plasma glucose was measured by the hexokinase method (Ciba-Corning).

### Statistical analysis

Between the ages of 5 and 11 years, age correlated with weight z score derived from the Centers for Disease Control and Prevention (CDC) standards (13), making such scores unsuitable for the present analyses spanning this age range. Therefore, z scores were generated by linear regression in reference to the contemporary study population. Age and sex were covariates for weight and height, and height was included in the model for relative weight (RW). Gestational age and sex were the covariates for BWT. Each individual’s actual value of measurement minus the prediction from the regression equation is the residual value. The mean of all the residuals is, by definition, zero. Each residual divided by the root mean square error of the regression model (an estimate of the standard deviation of the residuals) equals the z score of the measurement. Thus, the z score has mean of zero and standard deviation of one. The difference between the WT1.5 z score and BWT z score of an individual describes the growth pattern (Δz0–1.5 z score). The variables were compared between the two groups using linear regression.

### RESULTS

There were 520 individuals born between 1992 and 1998 enrolled in the longitudinal study of health in Gila River Indian Community. Data from the 2nd year of life were available for 315 individuals, for whom maternal diabetes status was known in 267 (130 males and 137 females). There were no significant anthropometric differences in baseline measurements between the subjects of this report and the 253 children who were missing either the early exam or maternal diabetes status. The median Indian heritage expressed as fraction of great grandparents of full Indian descent was 8/8 (range 2/8 to 8/8), and 60% of the subjects were of full Indian heritage. The mean age of examination was 1.5 years for the early exam and 7.7 years for the later childhood exam in both the ODMs and non-DMs. There were 43 (20 males and 23 females) ODMs. Paternal information was available for a subgroup of 186 subjects, of whom 30% had a father diagnosed with diabetes. There were no statistically significant differences in BWT or childhood anthropometric measurements between the offspring of the diabetic and nondiabetic fathers (data not shown). BWT and gestational age were available for 249 subjects (39 ODMs and 210 non-DMs).

Table 1 shows the BWT and early weight-gain pattern of the subjects by maternal diabetes status. There was no difference in BWT between the ODMs and non-DMs. Gestational age was significantly lower, however, for the ODM group. Thus, BWT adjusted for gestational age was significantly higher in the ODM group (BWT z score = 0.49 vs. −0.01, P < 0.01). The growth pattern of the ODMs also differed from that of the non-DMs (Δz0–1.5 weight z score = −0.36 vs. 0.12, P < 0.01). This “catch-down” effect was not explained by differences in parental height.

The age- and sex-adjusted (z score) childhood data are shown in Table 2. While there were no differences in the WT1.5 z score or RW1.5 z score measurement, the HT1.5 z score of the ODMs was significantly less (−0.24 vs. 0.12, P < 0.01). By the age of 7.7 years, however, there was no longer any difference between the groups in height, but the weight and RW were dramatically greater in ODMs (WT7 z score 0.89 vs. −0.07, P < 0.01; RW7 z score 1.26 vs. 0.00, P < 0.01). The overall pattern of weight gain was markedly different between the two groups (Fig. 1). The early weight-gain pattern (Δz0–1.5 weight z score) of the ODMs was negative with dramatic acceleration occurring after age 1.5 years.

After excluding one ODM individual with diabetes, fasting insulin concentrations and 2-h glucose and insulin concentrations at age 7.7 years were higher in the ODMs (Table 3). However, these differences were not significant when adjusted for RW. There was no difference in fasting glucose concentration between the groups.

### CONCLUSIONS

In discussions regarding growth in specific populations,
it is important to use measurements that are independent of important confounding variables such as age and sex. The growth pattern of Pima children markedly differs from U.S. references published by the CDC (14). Preliminary analysis of our data showed that age correlated with the CDC weight z score ($r = 0.2$, $P = 0.01$). Because we derived $z$ scores from regression models fit to the study population, these scores had the desirable properties of a mean of zero, a standard deviation of one, and being uncorrelated with age or sex.

There has been considerable interest in identifying patterns of early growth associated with later development of type 2 diabetes. This reflects the potential that specific environmental factors influencing growth, for example undernutrition in fetal and early postnatal life, might predispose to later development of diabetes.

In Pima Indians, maternal diabetes is associated with an increased risk of both type 2 diabetes and obesity (2,3). This relationship holds even among siblings discordant for maternal diabetes in pregnancy (i.e., one born before and one after the onset of maternal diabetes), indicating a role of the diabetic intrauterine environment in addition to transmission of genetic susceptibility (15). Silverman et al. (16) reported an increase in impaired glucose tolerance and obesity in offspring of a mixed population of mothers with type 1, type 2, and gestational diabetes. Offspring of mothers with type 1 diabetes have an increase in impaired glucose tolerance (17–19) and adiposity (18), as well as in insulin secretory defects (17). Notably, differences in adiposity have not been apparent in all studies of offspring of mothers with type 1 diabetes (17,20), although studies have been small (each study had <20 offspring of mothers with type 1 diabetes). The specific timing and nature of programming events in offspring of mothers with diabetes and in low BWT offspring are unknown.

We have shown that offspring of mothers with type 2 diabetes have a markedly different pattern of growth from their peers in early life. Gestational age–adjusted BWT is higher, but this is followed by a period of relatively poor growth with attendant catch down of growth. These data are in keeping with previous data of Silverman et al. (16), who also recorded catch down of growth in the first 2 years. This growth pattern persisted when the ODM group was further stratified into large for gestational age (LGA; BWT $z$ score $>1.28$) and appropriate for gestational age (AGA; $-1.28 < $BWT $\leq 1.28$) infants (data not shown).

Childhood linear growth has been separated into three phases: fetal, childhood, and adolescent (21). The initial

<table>
<thead>
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<th>Characteristic</th>
<th>non-DMs</th>
<th>ODMs</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>224</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>49</td>
<td>47</td>
<td>0.75*</td>
</tr>
<tr>
<td>Age at early exam (years)</td>
<td>$1.5 \pm 0.16$</td>
<td>$1.5 \pm 0.16$</td>
<td>0.82</td>
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<tr>
<td>WT$_{1.5}$ $z$ score</td>
<td>$0.06 \pm 0.68$</td>
<td>$-0.13 \pm 0.89$</td>
<td>0.10</td>
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<td>HT$_{1.5}$ $z$ score</td>
<td>$-0.12 \pm 0.71$</td>
<td>$-0.24 \pm 0.75$</td>
<td>&lt;0.01</td>
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<td>RW$_{1.5}$ $z$ score</td>
<td>$-0.03 \pm 0.72$</td>
<td>$0.05 \pm 0.99$</td>
<td>0.53</td>
</tr>
<tr>
<td>Age at later exam (years)</td>
<td>$7.7 \pm 1.4$</td>
<td>$7.8 \pm 1.6$</td>
<td>0.53</td>
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<tr>
<td>WT$_{7}$ $z$ score</td>
<td>$-0.07 \pm 1.56$</td>
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<td>&lt;0.01</td>
</tr>
<tr>
<td>HT$_{7}$ $z$ score</td>
<td>$-0.11 \pm 1.30$</td>
<td>$-0.03 \pm 1.56$</td>
<td>0.73</td>
</tr>
<tr>
<td>RW$_{7}$ $z$ score</td>
<td>$0.00 \pm 1.51$</td>
<td>$1.26 \pm 1.52$</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Father’s height (cm)$†$</td>
<td>$171.2 \pm 7.7$</td>
<td>$172.2 \pm 9.5$</td>
<td>0.56</td>
</tr>
<tr>
<td>Mother’s height (cm)</td>
<td>$161.0 \pm 5.2$</td>
<td>$160.4 \pm 5.5$</td>
<td>0.46</td>
</tr>
<tr>
<td>Midparental height (cm)$†$</td>
<td>$166.0 \pm 5.0$</td>
<td>$166.0 \pm 5.0$</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Data are means ± SD. Group comparisons made with t test. *Group comparison by $\chi^2$ test. weight, height, and RW $z$ scores at ages 1.5 and 7 years compared. $†n$ = 186 (161 non-DMs and 25 ODMs).

![Figure 1](https://example.com/figure1.png)

Figure 1—Graph of weight $z$ scores from birth, early childhood (age 1–2 years, mean 1.5 years), and later childhood (age 5–11 years, mean 7.7 years) by maternal diabetes status. ODMs, $n = 39$; non-DMs, $n = 210$. 

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Table 3—Age- and sex-adjusted metabolic variables at the later childhood exam

<table>
<thead>
<tr>
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<th>Adjusted for age and sex only</th>
<th>Adjusted for age, sex, and RW</th>
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<tr>
<td></td>
<td>n</td>
<td>non-DMs</td>
</tr>
<tr>
<td>Fasting insulin (μIU/ml)*</td>
<td>173</td>
<td>4.7 (4.2–5.2)</td>
</tr>
<tr>
<td>2-h insulin (μIU/ml)*</td>
<td>117</td>
<td>30.9 (25.7–36.3)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)†</td>
<td>194</td>
<td>85 (84–85)</td>
</tr>
<tr>
<td>2-h glucose (mg/dl)†</td>
<td>132</td>
<td>92 (88–95)</td>
</tr>
</tbody>
</table>

Group comparisons are made with general linear regression modeling. *Data are age- and sex-adjusted geometric mean (95% CI), †data are age- and sex-adjusted arithmetic mean (95% CI).

References
10. Pettitt DJ, Knowler WC: Long-term effects of the intrauterine environment,

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growth of infants is very rapid and a continuation of the fetal growth pattern. The exact regulation of this growth phase is unknown but involves insulin and insulin-like growth factors with a lesser role of growth hormone (22,23). Growth hormone becomes the important regulator of growth in the 2nd year of life, and sex hormones have a role in the growth spurt of adolescence (21). The initial poor growth demonstrated in both individuals who go on to develop diabetes (6,7) and the ODMs of this study corresponds, in part, to the early period of growth that is independent of growth hormone and influenced by insulin (22).

BWT was early discovered as a marker of future growth and metabolic pathology, probably, in part, because of wide availability of such data. BWT has many determinants. The duration of gestation has a large impact (24) and can be manipulated. Maternal weight, weight gain during pregnancy, and glycemic control also have an impact on BWT (25–27). Low BWT is a risk factor for diabetes and cardiovascular disease in many ethnic groups (5,28,29). In the Pima population, however, the relationship with diabetes is U-shaped due to a significant presence of maternal diabetes. The majority of individuals, however, who develop diabetes are of normal BWT (2,500 g ≤ BWT ≤ 4,500 g) (4). Poor growth in the 1st year of life, in addition to low BWT, is a risk factor for the development of diabetes in adulthood, particularly if the subsequent growth (BMI) is excessive (6,7). That pattern of restricted growth, though not low BWT, followed by acceleration of weight gain, resembles the growth of the ODMs in this study.

Although gestational age was analyzed in this study, limitations of the study include the lack of birth length data and biochemical measurements before age 5 years. In addition, the mothers in this study were not specifically evaluated for type 1 diabetes, but diabetes in this population is probably entirely type 2 (30). It is also possible that offspring of mothers with gestational diabetes were included in the non-DM group. However, such a classification would likely serve to reduce the differences between the groups.

What strategies for preventing the long-term metabolic consequences for the child of the diabetic pregnancy are suggested by these findings? Although ODMs have high BWTs, on average, even those with normal BWTs suffer the long-term adverse effects of exposure to the diabetic intra-uterine environment (31). Thus, prenatal or obstetrical interventions aimed at normalizing BWT may not be effective in preventing the long-term consequences. Accelerating growth in the first weeks of life was studied in a randomized clinical trial of nutritional supplementation on preterm infants (11). There was a detrimental effect on insulin sensitivity in adolescence on the group that received the supplemented diet. To our knowledge, no interventional studies have been conducted during the 2nd through 7th years of life of ODMs, the period in which we found accelerated growth in height, weight, and RW. Undertaking a clinical trial of controlling weight gain in this period would be ambitious, but it might be necessary if this is the most critical period for increasing risk of obesity and type 2 diabetes in ODMs.


