Low-Birth-Weight Infants Show Earlier Onset of IDDM

NAZLIN KHAN, MD
JENNIFER J. COUPER, MD

OBJECTIVE — Pancreatic β-cell mass increases rapidly during gestation and early infancy. Infants who are small for gestational age, which is a marker for poor intrauterine nutrition, have reduced β-cell mass. We examined whether weight and length in early infancy, and in inference β-cell mass, is related to age at onset of insulin-dependent diabetes mellitus (IDDM).

RESEARCH DESIGN AND METHODS — Data from infant records of 232 patients with IDDM, including birth weight, birth length, gestational age, weight at 6 months of age, and feeding history during the first 6 months of life, were analyzed. Maternal recall was not used for data collection.

RESULTS — Low-birth-weight infants (<2.5 kg) showed a significantly earlier onset of diabetes (4.3 [3.2-6.0] years vs. 9.0 [5.3-11.8] years, median [25-75th percentile]; P < 0.0001). Infants small for gestational age also had earlier onset than those with birth weight above the 10th percentile after correction for gestational age (6.2 [3.6-10.5] vs. 9.2 [5.4-11.8] years; P < 0.0001). Infants with corrected birth weight: length ratio below the 10th percentile had earlier onset, as did infants with corrected 6-months weight below the 10th percentile (4.9 [2.8-6.0] years vs. 8.8 [5.2-11.8] years; P < 0.0001). Infants who were exclusively breast-fed for 6 months showed a slightly later onset of diabetes than those who were bottle- or mixed-fed, independent of weight (9.4 [5.0-11.3] years vs. 8.3 [4.2-11.7] years; P < 0.0001).

CONCLUSIONS — Weight and growth parameters in utero and early infancy may influence the age at onset of IDDM. β-cell mass is likely to be a significant factor.

Sensitive assays for islet cell antibodies suggest that the autoimmune process of insulin-dependent diabetes mellitus (IDDM) develops in early childhood (1). However, the clinical presentation of IDDM peaks around 5-7 years, and puberty (2), and may occur from infancy to adulthood. Several factors may influence the age at onset of IDDM: the rate of β-cell destruction, insulin requirements that increase during puberty, and β-cell mass.

Pancreatic β-cell mass increases rapidly during gestation and early infancy. In humans, it increases >130-fold between the 12th intrauterine week and the 5th postnatal month (3). Nutrition appears to be a major determinant of growth of the β-cells (4). Infants who are small for gestational age, a marker for poor intrauterine nutrition, have a reduced β-cell mass (5). Conversely, hyperglycemia during pregnancy leads to hyperplasia of β-cells in the neonate, and a positive correlation has been shown between β-cell mass and body weight (5). Recently, Hales and Barker et al. (6,7) have suggested that early infant nutrition may influence the development of glucose intolerance in adulthood by an effect on β-cell mass early in life.

With the knowledge that β-cell mass may be determined early in life, we aimed to examine whether weight and length in early infancy, and in inference β-cell mass, is related to age at onset of IDDM.

From the Department of Endocrinology and Diabetes, Adelaide Children's Hospital, South Australia.

Address correspondence and reprint requests to Jennifer J. Couper, MD, Department of Endocrinology and Diabetes, Adelaide Children's Hospital, South Australia 5006.

Received for publication 25 October 1993 and accepted in revised form 27 January 1994.

IDDM, insulin-dependent diabetes mellitus; CAFHS, Child, Adolescent, and Family Health Service; BMI, body mass index.
Low-birth-weight infants and IDDM

Table 1—Growth parameters versus age at onset

<table>
<thead>
<tr>
<th>Age at onset (years)</th>
<th>n</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.5 kg</td>
<td>4.3 (3.2–6.0)</td>
<td>14</td>
</tr>
<tr>
<td>&gt;2.5 kg</td>
<td>9.0 (5.3–11.8)</td>
<td>218</td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>6.4 (3.6–10.8)</td>
<td>50</td>
</tr>
<tr>
<td>&gt;10th percentile</td>
<td>9.2 (5.4–11.9)</td>
<td>182</td>
</tr>
<tr>
<td>Birth length</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>5.8 (2.8–10.9)</td>
<td>24</td>
</tr>
<tr>
<td>&gt;10th percentile</td>
<td>8.6 (5.0–11.7)</td>
<td>176</td>
</tr>
<tr>
<td>Birth weight/length</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>6.5 (3.8–10.8)</td>
<td>59</td>
</tr>
<tr>
<td>&gt;10th percentile</td>
<td>8.8 (5.2–11.6)</td>
<td>141</td>
</tr>
<tr>
<td>6-months weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>5.2 (3.2–6.3)</td>
<td>20</td>
</tr>
<tr>
<td>&gt;10th percentile</td>
<td>8.8 (5.1–11.9)</td>
<td>148</td>
</tr>
</tbody>
</table>

Data are median (25th–75th percentile).

Age at onset of diabetes was recorded using date of clinical diagnosis and uncorrected date of birth. Gestational age was calculated according to last menstrual period or an ultrasound assessment, if available. No patient had a congenital abnormality or intrauterine infection. Feeding during the first 6 months was classified as breast-fed if the baby was exclusively breast-fed; bottle-fed if cow’s milk–based commercial formulas were used; or mixed if a combination was used. Body mass index (BMI) was calculated as weight (kg) divided by surface area (m²).

Statistical analysis

Age at diagnosis was skewed distribution and was normalized by logarithmic transformation. Comparison between groups was performed using the paired Student’s t test. Linear regression analysis and analysis of variance was used to assess the relationship between age at onset and growth parameters. Birth weight and length were corrected for gestational age using the derived equations from the study cohort: corrected birth weight (kg) = −3.37 + 0.17 gestational age; corrected birth length (cm) = 23.89 + 0.69 gestational age.

RESULTS—The 232 patients showed the characteristic bimodal pattern of age at diagnosis, with peaks at 6 and 12 years. Male to female ratio was 1:1. Mean ± SD birth weight (3.4 ± 0.6 kg), birth length (49.5 ± 3.2 cm), and 6-months weight (7.9 ± 0.9 kg) did not differ significantly from the normal Australian population (8). Low-birth-weight infants, defined as those with a birth weight <2.5 kg, had a significantly earlier onset of diabetes (median [25–75th percentile] 4.3 [3.2–6.0] years vs. 9.0 [5.3–11.8] years; P < 0.0001). Infants below the 10th percentile for birth weight (2.95 kg), birth length (47.5 cm), or 6-months weight (6.5 kg) in normal Australian 40-week gestation infants (7) also had a significantly earlier onset of diabetes than did infants above or equal to the 10th percentile for these parameters (Table 1).

Of the 50 patients with birth weight below the 10th percentile, 10 were preterm (<37 weeks gestation) but appropriate for gestational age. The age of diagnosis was significantly earlier in the remaining 40 infants who were small for gestational age, i.e., birth weight below the 10th percentile after correction for gestational age, and in infants with corrected birth length and 6-months weight below the 10th percentile (Table 2). Infants who were small for gestational age had a mean BMI at diagnosis of IDDM that was at the 50th percentile for normal children of the same age (16.7 ± 3.8 kg/m²).

Linear regression analysis showed no relationship between corrected birth weight, birth length, or 6-months weight and age at onset (r = 0.13, 0.18, and 0.2, respectively). Patients with birth growth parameters above the 90th percentile did not show a later onset of IDDM.

During the first 6 months, 110 (48%) babies were exclusively breast-fed, 49 (21%) bottle-fed (all received cow’s milk–based commercial formulas), and 70 (31%) fed a combination. A similar percentage of small for gestational age in-

Table 2—Growth parameters (corrected for gestation) versus age at onset

<table>
<thead>
<tr>
<th>Age at onset (years)</th>
<th>n</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>6.2 (3.6–10.5)</td>
<td>40</td>
</tr>
<tr>
<td>&gt;10th percentile</td>
<td>9.2 (5.4–11.8)</td>
<td>192</td>
</tr>
<tr>
<td>Birth length</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>6.5 (2.0–10.4)</td>
<td>18</td>
</tr>
<tr>
<td>&gt;10th percentile</td>
<td>8.3 (4.9–11.6)</td>
<td>182</td>
</tr>
<tr>
<td>Birth weight/length</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>6.5 (3.8–10.6)</td>
<td>45</td>
</tr>
<tr>
<td>&gt;10th percentile</td>
<td>8.6 (5.2–11.7)</td>
<td>142</td>
</tr>
<tr>
<td>6-months weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>4.9 (2.8–6.0)</td>
<td>17</td>
</tr>
<tr>
<td>&gt;10th percentile</td>
<td>8.8 (5.2–11.8)</td>
<td>151</td>
</tr>
</tbody>
</table>

Data are median (25th–75th percentile).
fants were breast-(50%), bottle-(25%),
or mixed-fed (25%). Babies who were exclu-
sively breast-fed had a slightly later
onset of diabetes compared with babies
who were bottle- or mixed-fed, indepen-
dent of birth weight and weight at 6
months (9.4 [5.0–11.3] vs. 8.3 [4.2–
11.7] years, P < 0.0001 after log transfor-
mation). Information relating to the in-
troduction of solid foods was not
analyzed because an insufficient number
of patients had accurate written data in
their CAFHS records.

CONCLUSIONS—The age at onset of
the clinical diagnosis of IDDM is clearly
multifactorial. The recent knowledge that
the autoimmune process begins early in
life (1) might indicate that the rate of de-
struction of β-cells is the major remaining
determinant, with a contribution from
prevailing insulin requirements, which
change during puberty and intercurrent
illness. However, we have shown that
growth and weight parameters in early in-
fancy, which may correlate with β-cell
mass, are also important. Some of the
sample sizes in the analysis were small;
therefore, despite the statistical signifi-
cance and consistency of the findings,
they need to be interpreted with caution.
However, we believe this is the first time
the effect of early growth parameters on
the age at onset of IDDM has been ad-
dressed.

Low-birth-weight infants, includ-
ing both those who are small and those
who are appropriate for gestational age,
showed a significantly earlier onset.
The effect was also seen after analysis of
length and weight/length parameters. The
latter correlates best with skinfold thickness,
which is an indicator of nutrition in the
newborn (9). After correction for gesta-
tional age, small for gestational age babies
showed younger age at onset, confirming
that intraterine nutrition is an important
factor. It is still possible that these babies
have some factor other than β-cell mass
explaining their earlier onset. However,
with our current knowledge, it is not pos-
sible to control for the rate of β-cell de-
struction, and because the children had
an appropriate BMI for age at diagnosis,
increased insulin requirements seem an
unlikely factor. Small for gestational age
infants may have altered cell-mediated
immunity that confers an increased risk
of infection (10), but an effect on autoim-
nunity has not been observed. We were
not able to analyze another autoimmune
disease as a control.

The research focus relating early
nutrition and IDDM has concentrated on
whether breast-feeding may play a pro-
tective role, particularly in high-risk hu-
man leukocyte antigen genotypes (11). It
has been hypothesized that there may be
molecular mimicry between islet antigen
P69 and bovine serum albumin in cow's
milk (12). Infant formulas contain bovine
serum albumin, casein, and β-lactoglob-
ulin. Approximately half of our patients
were exclusively breast-fed for 6 months;
this figure compares closely with the
prevalence of breast-feeding in the nor-
mal Australian population in the 1980s
(13). Breast-fed babies had a slightly later
onset of IDDM than did the bottle- and
mixed-feeding group; the effect was inde-
dendent of weight. We believe this has
not previously been documented and
could be explained by later exposure to
an environmental trigger during early
life. Because we used only recorded data
and not that based on maternal recall, we
did not have sufficient information on the
introduction of solids in the infants’ diets
to control for this factor. Introduction of sol-
ids normally begins at 4–6 months of age
in Australia.

An inverse relationship between
birth weight and impaired glucose tol-
erance in adults has been noted by Hales
and Barker et al. (6). They hypothesized
that poor nutrition early in life leads to a
smaller β-cell mass and thereby contrib-
utes to inadequate insulin production
later in life, particularly in overweight
adults (7). We were not attempting to ex-
amine any contribution of early nutrition
to the incidence of IDDM. The mean
growth parameters of our patients with
diabetes did not differ significantly from
the normal Australian population. Al-
though ~20% of the children were below
the normal 10th percentile for birth
weight and length, one would require a
considerably larger sample size to assess
distribution of early growth parameters in
the IDDM population.

Our findings that both low-birth-
weight and small for gestational age in-
fants have earlier onset of IDDM have two
relevant implications. First, β-cell mass
may be a significant factor in determining
the onset of diabetes, in addition to the
rate of β-cell destruction and insulin re-
quirements. Second and more import-
antly, these first events in the child’s life
may affect how early future interventional
therapies must begin to be effective. Some
of the current therapies being tested in
clinical trials may only postpone IDDM
rather than prevent the disease (14,15).
Early growth parameters therefore may
need to be considered in the analysis of
the intervention under trial.

Acknowledgments—This study was sup-
ported by a Channel 7 Research Foundation
South Australia Grant. We thank Jill Lyon-Green for assistance
with data collection, Alan Staples for statistical
advice, Drs. Karen Simmer and Richard
Couper for review of the manuscript, and Julie
Temby for secretarial assistance.

References
1. Pilcher CC, Dickens K, Elliot RB: ICA
only develop in early childhood: Proceed-
ings of the 11th International Immunol-
ogy Diabetes Workshop. Diabetes Res Clin
Pract 14 (Suppl. 1):S82, 1991
2. Sperling MA: Diabetes mellitus. In Nel-
sen’s Textbook of Paediatrics. 14th ed. Behr-
man RE, Ed. Philadelphia, PA, Saunders,
1992, p. 391
3. Hellerstrom C, Swenne I, Anderson A:
Islet cell replication and diabetes. In The
Pathology of the Endocrine Pancreas in Dia-
betes. Lefebre PJ, Pipeleers DG, Eds. Hei-
delberg, Germany, Springer Verlag, 1988,
p. 141–170
4. Swenne I, Bone AJ, Howell SL, Heller-
Low-birth-weight infants and IDDM