Original Contribution

Timing and Trajectories of Fetal Growth Related to Cognitive Development in Childhood

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Initially submitted January 13, 2009; accepted for publication August 17, 2009.

The authors investigated timing and trajectories of fetal growth in relation to childhood development in the National Institute of Child Health and Human Development–Scandinavian Study of Successive Small-for-Gestational Age Births (1986–1988) (n = 1,059). Fetal size was assessed by ultrasound at 17, 25, and 33 gestational weeks and at birth. Bayley Scales of Infant Development and the Wechsler Preschool and Primary Scale of Intelligence-Revised tests were conducted at ages 1 and 5 years, respectively, producing mental and psychomotor development indexes and verbal and performance intelligence quotients. Relative fetal size was calculated as a standard deviation score at each data point; growth trajectories were explored with longitudinal mixture models. Fetal size at 17, 25, and 33 weeks was positively associated with mental development index; larger size at 33 weeks and at birth was associated with higher verbal intelligence quotient scores (2.61, 95% confidence interval: 1.06, 4.15 and 1.90, 95% confidence interval: 0.67, 3.13 increase per 1 standard deviation score, respectively); findings were similar for performance intelligence quotient. Seven trajectories were identified; scores were lower for “small” and “medium-to-small” trajectories than for “medium” and “big” (representing normal size) trajectories: mental development index (P < 0.01), performance intelligence quotient (P < 0.001), and verbal intelligence quotient (P < 0.001). Overall, larger fetal size in the second and third trimesters was positively associated with childhood development. Fetal growth trajectories may matter beyond birth.

child development; cohort studies; fetal development; intelligence tests; ultrasonics

Prenatal development is increasingly recognized as a time period that may set the stage for lifelong development and disease status (1–4). The trajectory of optimal in utero growth is not linear and may be affected at different time points by time-varying maternal or environmental factors, resulting in adaptive growth responses by the fetus. The shape of the resulting growth trajectory and fetal size at different gestational weeks may relate differentially to outcomes later in life, as suggested by evidence from animal and human historical observational studies on outcomes such as obesity, diabetes, and cardiovascular diseases (5–7).

Prematurity and low birth weight have been associated with neurodevelopmental delays and cognitive deficits in childhood and later in life (8–12). However, the role of the fetal growth trajectory, and that of fetal size at different prenatal times, in childhood cognitive development remains not well understood. This issue may be related to the fact that earlier investigations of prenatal development in relation to cognitive outcomes later in childhood relied generally on fetal growth evaluation at birth, based on weight relative to gestational age, or on anthropometric indicators such as ponderal index or head size (8, 13) instead of using in utero assessments of fetal size at multiple gestational time points.

A few relatively small studies (n = 42–179) assessed restriction of fetal growth by using single third-trimester ultrasonography (14–16). Findings of these studies indicated that subjects who were growth restricted in late
population have been published previously. In brief, 1- or 2-parous pregnant women were recruited before 20 weeks of gestation at 3 Scandinavian study sites in 1986–1988. A total of 5,722 women were eligible to participate. At entry, 2 groups of women were selected for detailed follow-up during pregnancy: 1) a 10% random reference sample (n = 561) and 2) a “high-risk” group of 1,384 women, identified among the remaining women according to predefined risk factors for small-for-gestational-age births (previous birth of a low birth weight infant, smoking at conception, prepregnancy weight <50 kg, previous prenatal death, maternal chronic renal disease or hypertension). All term infants in the random group and all term small-for-gestational-age infants (<15 percentile of weight for gestational age) in the high-risk group were eligible for follow-up after birth (11, 12). All women were Caucasian and spoke one of the Scandinavian languages.

The study was funded by the National Institute of Child Health and Human Development and was approved by the local ethics committees for medical research. Written informed consent was obtained from the women.

### Pregnancy and follow-up samples

Serial prenatal ultrasound measurements were taken at 17, 25, 33, and 37 weeks of estimated gestational age; in this analysis, the 37-week measurement was excluded to achieve approximate equal distances of 8 weeks between the time points of ultrasound measurements and birth. Biparietal diameter, abdominal circumference, and femur length were measured.

The analysis involved a 3-step process (Figure 1). First, we selected women who had a term pregnancy (>258 days) and reported knowing the date of their last menstrual period within 3 days. We further restricted the analysis to women whose estimated gestational age of the fetus was confirmed by ultrasonography within 14 days of the last menstrual period at 17 weeks to ensure accurate dating of gestational age and who had complete information on maternal prepregnancy body mass index and parity (n = 1,595). Pregnancies in the random reference group meeting these criteria were used to create an internal growth standard (n = 448). Second, to identify fetal growth trajectories, we further confined the analysis to those pregnancies for which information was complete on the 3 ultrasound measurements and birth weight (n = 1,059), comprising 322 pregnancies from the random group (322/561) and 737 from the high-risk group (737/1,384). Third, all children from this group (n = 1,059) for whom psychometric data were also available were included in the further analysis. From the random group, this process resulted in 285 children (88.5%) assessed at age 1 year and 258 children (80.1%) assessed at age 5 years. In the corresponding high-risk group, 132 infants were small-for-gestational-age births and thus were eligible for follow-up (11, 12); of those, 107 (81%) were assessed at birth at age 1 year and 100 (75.8%) at age 5 years. All children assessed at age 5 years also were assessed at age 1 year. Overall, the analysis comprised 392 children at age 1 year and 358 children at age 5 years (Figure 1, Table 1). Details on the follow-up studies to age 1 year (11, 19, 20) and age 5 years (12) have been published previously.

### Psychometric testing

The Bayley Scales of Infant Development test was conducted at children’s age 13 months, producing a mental development index (MDI) and a psychomotor development index (PDI) based on sets of standardized items assessing cognitive, language, personal/social, and motor development (21). In the 5-year follow-up group, IQ scores were assessed with the Norwegian version of the Wechsler Preschool and Primary Scale of Intelligence-Revised test (WPPSI-R). Verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) scores were calculated based on sets of subtests assessing verbal and nonverbal abilities (22). Norm values were used from the US version because no standardized Norwegian norms were available at the time of the assessment. In addition, information on
maternal smoking around the time of conception, education, height, and prepregnancy weight was ascertained with a self-administered questionnaire during pregnancy (11).

Statistical analysis

Univariate analyses of the sample characteristics at baseline were conducted and assessed by using chi-square or t statistics. An internal standard of fetal growth during pregnancy was established based on the pregnancies in the random sample, using a modified Hadlock et al. formula (23), adjusting for child’s gender, prepregnancy body mass index, and parity:

\[
\text{Estimated weight (g)} = \exp(a0 + a1 \times \text{gestational age(days)} + a2 \times (\text{gestational age(days)})^2 + a3 \times \text{gender} + a4 \times \text{body mass index} + a5 \times \text{parity}).
\]

Estimates for the parameters $a1$–$a5$ were obtained; they were significantly ($P < 0.01$) associated with fetal weight. The parameters were used to calculate individual standard deviation scores at each data point (corresponding to fetal size at 4 time points). The standard deviation scores were used on a logarithmic scale to achieve normal distribution. General linear models were applied to assess associations between the standard deviation scores at each data point as the independent variable and each psychometric variable (MDI, PDI, VIQ, PIQ) as the dependent variable; unadjusted and adjusted models including maternal age and education were assessed. Smoking was assessed and was not a confounder in this sample.

Next, to identify clusters of fetal growth trajectories, we applied a longitudinal mixture model based on the standard deviation scores at each data point using the SAS procedure Proc Traj (24). Models with increasing numbers of clusters from 1 to 10 were computed and evaluated in a stepwise manner. The reduction in the Bayesian Information Criterion values of each model was assessed. We aimed to classify growth trajectories ensuring a minimum fraction of 2.5% in each subgroup and to select the simplest model that best described the data (24). The clusters of growth trajectories were named according to their relative location on the scale of standard deviation scores. Associations between the identified growth trajectories and the PDI, MDI, VIQ, and PIQ scores were evaluated by using general linear models, adjusting for maternal age at conception and education. Post hoc significance and trend tests were conducted also by using general linear models for a selected comparison of the lowest-relative-size groups to those considered normal size, and a trend analysis across relative fetal size groups was performed. All $P$ values presented in this paper are 2-sided. The analysis was carried out by using SAS statistical software, version 9 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The process of selecting the study groups is shown in Figure 1, and the basic sample characteristics of each subsample in the analysis are given in Table 1. Infants’ birth weight overall was within the normal range (mean = 3,504 g (SD, 508)). The average test scores were 114 (SD, 13) for the MDI and 107 (SD, 15) for the PDI at age 1 year and 104 (SD, 15) for the VIQ and 110 (SD, 15) for the PIQ at age 5 years. The proportion of small-for-gestational-age infants was 35.2% at age 1 year and 34.1% at age 5 years. No
The MDI was significantly associated with relative fetal size (assessed as standard deviation scores) at 17, 25, and 33 weeks of gestation, while fewer fetuses (28.6%) showed a period of either decelerated or accelerated growth. The majority of fetuses in the sample maintained the same relative position throughout gestation, with differences in size, we combined the constant “small” group (group 1) with those who declined in relative size from “medium to small” throughout gestation (group 6) and compared them with those considered normal of the smallest relative size with those considered normal fractions of 2.5% in the smallest subgroup, the model with 7 clusters was selected for further analysis. This classification resulted in 4 stable growth types (Figure 2A) and 3 types with periods of either decelerated or accelerated growth (Figure 2B).

When we considered the overall association of the growth trajectories with the psychometric outcomes, significant associations were observed for the MDI, VIQ, and PIQ ($P <$ 0.05) but not for the PDI (Figure 3). To compare the groups of the smallest relative size with those considered normal size, we combined the constant “small” group (group 1) with those who declined in relative size from “medium to small” throughout gestation (group 6) and compared them with the combined “medium” (group 2) and “big” (group 3) groups. Significant differences were found for the MDI, PIQ, and VIQ scores but not for the PDI score (post hoc test: combined groups 1 and 6 vs. groups 2 and 3 for the MDI: $P <$ 0.01; PDI $P = 0.30$; VIQ $P <$ 0.001; PIQ $P < 0.001$). For the VIQ and PIQ scores, the trend across “small,” “medium,” to “big” trajectories was significant ($P <$ 0.001).

**DISCUSSION**

To our knowledge, this study is the first to show associations of timing of relative fetal size and trajectories of fetal development with cognitive outcomes.
growth with mental development at age 1 year and with IQ at age 5 years. An increase in fetal size at 17, 25, and 33 weeks of gestation was positively associated with small, but significant increases in the MDI. Similarly, increases in size at 25 weeks (PIQ only), 33 weeks, and birth were positively associated with the VIQ and PIQ. No association with fetal

| Table 2. Relative Fetal Size\(^a\) at 3 Prenatal Time Points and at Birth in Relation to the Bayley Scale of Infant Development Indices\(^b\) at Age 1 Year and to Verbal and Performance IQ\(^c\) at Age 5 Years at 3 Scandinavian Study Sites, 1986–1988 |
|---------------------------------|----------------|----------------|----------------|----------------|
|                                  | Mental Development Index (\(n = 390\)) | Psychomotor Development Index (\(n = 390\)) | Verbal IQ (\(n = 356\)) | Performance IQ (\(n = 356\)) |
|                                  | Score | 95% CI | Score | 95% CI | Score | 95% CI | Score | 95% CI |
| 17 weeks                         |       |       |       |       |       |       |       |       |
| Fetal size                       | 1.35* | 0.24, 2.46 | 0.87 | −0.46, 2.2 | 0.13 | −1.17, 1.43 | 1.08 | −0.32, 2.47 |
| Education\(^d\)                  | 1.75  | −0.67, 4.18 | −2.1 | −5.0, 0.81 | 8.86* | 5.95, 11.78 | 7.29* | 4.16, 10.4 |
| Maternal age\(^e\)               | −0.03 | −0.34, 0.28 | −0.08 | −0.46, 0.29 | 0.42* | 0.06, 0.78 | 0.60* | 0.21, 0.99 |
| 25 weeks                         |       |       |       |       |       |       |       |       |
| Fetal size                       | 1.93* | 0.73, 3.13 | 0.77 | −0.68, 2.23 | 0.63 | −0.77, 2.03 | 2.20* | 0.71, 3.69 |
| Education\(^d\)                  | 1.77  | −0.64, 4.19 | −2.09 | −5.01, 0.83 | 8.86* | 5.95, 11.8 | 7.28* | 4.17, 10.4 |
| Maternal age\(^e\)               | −0.06 | −0.37, 0.25 | −0.08 | −0.46, 0.23 | 0.39* | 0.02, 0.75 | 0.52* | 0.12, 0.91 |
| 33 weeks                         |       |       |       |       |       |       |       |       |
| Fetal size                       | 2.12* | 0.81, 3.42 | 0.82 | −0.77, 2.40 | 2.61* | 1.06, 4.15 | 3.70* | 2.06, 5.35 |
| Education\(^d\)                  | 1.56  | −0.85, 4.0 | −2.17 | −5.10, 0.75 | 8.55* | 5.68, 11.4 | 6.84* | 3.77, 9.90 |
| Maternal age\(^e\)               | −0.07 | −0.38, 0.25 | −0.08 | −0.46, 0.29 | 0.27 | −0.09, 0.64 | 0.43* | 0.05, 0.82 |
| Birth                            |       |       |       |       |       |       |       |       |
| Fetal size                       | 0.91  | −0.12, 1.94 | −0.84 | −2.08, 0.40 | 1.90* | 0.67, 3.13 | 2.74* | 1.43, 4.05 |
| Education\(^d\)                  | 1.44  | −1.02, 3.91 | −1.78 | −4.73, 1.17 | 8.15* | 5.24, 11.1 | 6.25* | 3.14, 9.36 |
| Maternal age\(^e\)               | 0.02  | −0.29, 0.32 | −0.04 | −0.41, 0.33 | 0.38* | 0.02, 0.73 | 0.58* | 0.20, 0.96 |

Abbreviation: CI, confidence interval.
*\(P < 0.05\).
\(^a\) Fetal size is expressed as a standard deviation score at each time point; 1 = 1 standard deviation.
\(^b\) Mental development index and psychomotor development index.
\(^c\) Wechsler Preschool and Primary Scale of Intelligence-Revised.
\(^d\) Education: 1 = \(≤11\) years (reference), 2 = \(>11\) years.
\(^e\) Maternal age: continuous by year.

Figure 2. Pattern and relative position of fetal growth trajectories at 3 Scandinavian study sites, 1986–1988 (\(n = 1,059\)) (shown are the fraction of each cluster, with bars indicating 95% confidence interval; 1 = 1 standard deviation). A) Stable trajectories, B) shifting trajectories (dashed line indicates “small-to-medium” trajectory for visual contrast).
size at any time point was found for the PDI. In line with these results, the overall associations between the trajectories and the test scores were significant for the MDI, VIQ, and PIQ but not for the PDI. Relatively small size, defined as constant small size ("small") or a restriction over the second and third trimesters ("medium to small"), was related to lower scores on the mental and cognitive tests compared with the scores for those considered to be at the normal level of fetal size ("medium" and "big" groups). In turn, our findings suggest that, in term pregnancies, increases in fetal size of the magnitude of 1 standard deviation during the second and third trimesters are positively associated with childhood mental and cognitive development.

In this study, consecutive ultrasound measurements starting at 17 weeks of gestation, as well as psychometric testing conducted at 2 ages in childhood, were available for a population-based sample. Such data are still sparse. To our knowledge, only 2 earlier investigations used ultrasound assessments in the first half of pregnancy together with childhood cognitive assessments. Walker et al. (17) showed, in a study from Jamaica ($n = 186$), a 1.59-point reduction in the Raven’s Progressive Matrices test for children aged 6–8 years who had a 0.4 standard deviation smaller head circumference than the reference group at 14 weeks of gestation; no other association was reported regarding this or 2 other cognitive tests with any marker of fetal growth in the second or third trimester, which is in contrast to our results. However, the Jamaican sample differed notably from our Scandinavian sample, which was representative of a healthy, well-educated, affluent society (11), with regard to potentially modifying factors such as socioeconomic conditions and maternal and child nutrition, possibly explaining the differences in findings.

In one earlier United Kingdom study (25), infants ($n = 76$) below the 10th percentile of gestational age at birth and with growth restriction in the second trimester had in part further restrictions in the third trimester and in part no further restrictions. Similar neurologic impairments at age 1 year were found.

**Figure 3.** Fetal growth trajectories in relation to (A) mental development index (MDI) and (B) psychomotor development index (PDI) at age 1 year; and to (C) performance intelligence quotient (PIQ) and (D) verbal intelligence quotient (VIQ) at age 5 years at 3 Scandinavian study sites, 1986–1988 (shown are means, with bars indicating 95% confidence interval). $P < 0.05$ for MDI, VIQ, and PIQ, adjusted for maternal age and education in general linear models; designation of trajectories: 1 = small, 2 = medium, 3 = big, 4 = large, 5 = big to medium, 6 = medium to small, 7 = small to medium; fractions in %: age 1 year (MDI, PDI): 1 = 16.7, 2 = 27.6, 3 = 18.9, 4 = 2.6, 5 = 8.9, 6 = 14.0, 7 = 12.6; age 5 years (VIQ, PIQ): 1 = 17.9, 2 = 26.8, 3 = 18.2, 4 = 2.5, 5 = 9.5, 6 = 12.6, 7 = 12.
Several limitations apply to this investigation. The numbers in some groups of the fetal growth trajectories were small, producing overlapping confidence limits, thus limiting our ability to test differences between specific groups. The approach we developed to assess trajectories should therefore be considered explorative. A further limitation is the limited follow-up. Reported reasons for loss to follow-up between birth and childhood testing were mainly parental refusal and moving out of the region. Importantly, among those eligible, with complete fetal weight measurements, basic characteristics or the selection criteria did not differ between those assessed at ages 1 and 5 years and those lost to follow-up (data not shown). Moreover, no difference was found regarding basic characteristics or the selection criteria between those included in the identification of growth trajectories and those assessed in the follow-up at ages 1 and 5 years. Thus, while limited follow-up confined our ability to investigate differences between specific fetal size subgroups in relation to the developmental tests, it is highly unlikely that this factor biased the findings reported herein. Potential confounders were evaluated in this analysis; the regression models were adjusted for education and maternal age at conception. Other variables, including smoking, were not confounders in this sample. Although we cannot completely rule out uncontrolled confounding, it is highly unlikely to explain the reported findings.

Growth in utero involves complex interactions between individual sets of genetic and potentially time-varying environmental factors involving epigenetic changes, which may account for the processes of fetal growth adaptation. Maternal nutritional status, starting in early pregnancy or prepregnancy, appears to be such a factor that could set the trajectory of fetal growth, as shown, for example, in studies of sheep (32–34) or in relation to periods of famine in humans (35–37).

In conclusion, our findings suggest that larger fetal size during time periods of growth in fetal head circumference and height, but also later in pregnancy, when most growth is due to weight gain, is positively associated with cognitive development and that fetal trajectories can track with postnatal childhood development. These findings may have implications for identifying time-dependent prenatal impacts (e.g., environmental) on fetal and child development and for targeting subgroups of children potentially at risk of subtle developmental delays or impairments, especially among risk groups earlier in life.

ACKNOWLEDGMENTS

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Drs. von Ehrenstein and Mikolajczyk contributed equally to this work.
This work was supported in part by the Intramural Research Program at the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland.

Conflict of interest: none declared.

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