Growth and development of term children born with low birth weight: Effects of genetic and environmental factors

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Objective: To evaluate the role of intrauterine growth retardation (IUGR) on childhood growth and development, controlling for environmental and genetic factors.

Methods: Women and infants enrolled in the National Collaborative Perinatal Project were analyzed. Weight, length, and IQ were assessed at birth and at 7 years in the entire National Collaborative Perinatal Project population in term infants born with and without IUGR ("population cohort"). To control for genetic and environmental factors, growth and development were also compared in 220 similar-sex term sibling pairs in which one sibling was born with IUGR and one was born without IUGR ("sibling cohort").

Results: At 7 years of age heights and weights of infants born with IUGR remained ~0.5 SD less than infants born without IUGR (weight-for-age: $p < 0.001$, height-for-age: $p < 0.001$). In the entire National Collaborative Perinatal Project population, IQ ($p < 0.001$) and Bender-Gestalt ($p < 0.001$) scores were significantly lower in infants born with IUGR compared with those in infants born without IUGR. There were no significant differences in IQ or Bender-Gestalt scores between siblings born with and without IUGR. However, siblings with IUGR and large deficits in head circumference demonstrated both decreased IQ ($p < 0.05$) and Bender-Gestalt ($p < 0.05$) scores.

Conclusion: Long-term growth deficits associated with IUGR appear largely independent of prenatal or postnatal environmental factors. IUGR had little impact on intelligence and motor development except when associated with large deficits in head circumference. (J Pediatr 1998;133:67-72)

Although many children born with intrauterine growth retardation demonstrate significant catch-up growth in early childhood,[1,2] substantial weight and height deficits remain in others.[3-7] In addition, children born with IUGR may demonstrate developmental deficits,[6-11] although other studies have not substantiated these findings.[5] Studies of growth of infants born with IUGR are difficult to interpret because they have rarely controlled for parental size. Because mothers of infants born with IUGR are often shorter and lighter than mothers of infants without IUGR,[12] many infants labeled as "IUGR" are probably genetically small. Genetic factors may therefore contribute to subsequent growth deficits. Similarly, studies of intelligence of infants born with IUGR have often involved small numbers of patients and have not adequately controlled for environmental, genetic, and socioeconomic factors that may influence the results of intelligence tests. Finally, studies of growth and development in identical twins with and without IUGR may not be generalizable, because the timing and cause of IUGR may differ in twins and nontwins.

HAZ	Height-for-age Z-score
IUGR	Intrauterine growth retardation
NCPP	National Collaborative Perinatal Project
WAZ	Weight-for-age Z-score

See editorial, p. 3.

To explore the long-term growth and developmental outcome of children with IUGR, we analyzed the data from the National Collaborative Perinatal Project, an eight-center collaborative study of perinatal risk factors and growth and development of infants. The large number of patients enrolled and the comprehensive follow-up allowed us to compare

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Table I. Demographic variables in the population and sibling cohorts

	Population cohort		Sibling cohort	
	Normal (*n* = 43,104)	IUGR (*n* = 2719)	Normal (*n* = 220)	IUGR (*n* = 220)
Maternal characteristics				
Income (% lowest quintile)	14	18*	16	14
% Smoke (≥1 cigarette/day)	44	60	59	59
Race (% nonwhite)	50	64*	51	51
Prenatal care (% registering before 3rd trimester)	73	69	74	74
Parity (% primaparous)	30	35*	21	20
Maternal prepregnancy weight (kg)	59.5 ± 11.6	55.5 ± 11.1*	56.8 ± 11.6	56.5 ± 11.0
Maternal height (cm)	161 ± 7	159 ± 7*	159 ± 7	159 ± 7
Weight gain during pregnancy (kg)	10.7 ± 4.7	8.5 ± 4.5*	9.6 ± 4.5	8.9 ± 4.3†
Toxemia (%)	6	7*	12	10
Chronic hypertension (%)	3	4*	3	3
Placenta weight (gm)	449 ± 91	336 ± 74*	416 ± 80	332 ± 71*
Newborn characteristics				
Sex (% female)	49	59*	61	61
Birth weight (gm)	3300 ± 430	2260 ± 280*	3000 ± 320	2260 ± 290*
Birth length (cm)	50.4 ± 2.3	46.3 ± 2.2*	49.3 ± 2.2	46.5 ± 2.4*
Head circumference (cm)	34.0 ± 1.3	31.7 ± 1.3*	33.2 ± 1.3	31.7 ± 1.2*
WAZ	0.13 ± 0.99	–2.17 ± 0.65*	–0.53 ± 0.67	–2.16 ± 0.74*
HAZ	0.21 ± 1.03	–1.72 ± 0.98*	–0.36 ± 0.98	–1.62 ± 1.07*
Birth depression (Apgar ≤6) (%)	3.0	6.9*	2.3	6.9†

*$p < 0.001$ compared with normal birth weight infants.
†$p < 0.05$ compared with normal birth weight infants.

childhood growth and development of infants born with IUGR with that of siblings who were born without growth retardation. The inclusion of siblings who share similar genetic and environmental backgrounds made it possible to examine the effects of IUGR on growth and development, controlling in part for genetic and environmental factors that may have confounded previous studies.

METHODS

Sample

The NCPP prospectively monitored 59,393 women enrolled during their pregnancy and their 55,760 children from 1959 to 1976. A total of 8411 women were enrolled for at least two different pregnancies. Pregnancy complications were elicited at the time of registration and throughout pregnancy. Gestational age was measured by dating the last menstrual period at the time of registration. Prepregnancy weight was determined by maternal recall at the time of registration. Infants were excluded if they had a gestational age <37 weeks, multiple gestation, neural tube defect, chromosomal anomaly, or other severe congenital diseases.

For all infants enrolled at birth (population cohort), weight and lengths were recorded at birth and at 7 years of age, and development was assessed at 7 years of age. Results were compared between infants with IUGR (defined as a birth weight ≤2500 gm) and those without IUGR. In addition, to control for genetic and environmental factors, the same growth and development assessments were compared in a subpopulation of the population cohort, which consisted of similar-sex sibling pairs in which one sibling was born with IUGR and one was born without IUGR (sibling cohort).

Measures

All infants were initially measured by trained study staff or staff clinicians at the time of admission to the nursery. Birth weight was measured to the nearest 10 gm, and birth length was measured with standard measuring tapes. Body proportionality was assessed with the ponderal index (gm/cm^3).[13,14] Head circumference was measured with a flexible measuring tape as the maximum circumference between the supraorbital ridge and occiput. Low head circumference was defined as <2 SD below the mean of the population cohort (≤31 cm). Children were reassessed at 7 years of age. Children were weighed undressed on a calibrated balance scale, and height was measured in the erect position on a standardized child measuring scale. Developmental assessment was done during a separate visit by trained staff blinded to birth weight with the Weschsler Intelligence Scale to assess intelligence and the Bender-Gestalt Test to assess visual-motor development. Growth and development was assessed in patients with and without birth depression (5-minute Apgar score ≤6[15]). In both

Table II. Growth and development at age 7 years of infants with and without IUGR

	Population cohort			Sibling cohort		
	Normal	IUGR	Difference	Normal	IUGR	Difference
WAZ	0.24 ± 1.1 (n = 31,391)	–0.38 ± 1.1 (n = 1,849)	0.62*	0.00 ± 1.0 (n = 146)	–0.53 ± 1.1 (n = 146)	0.53*
HAZ	0.03 ± 1.0 (n = 31,375)	–0.47 ± 1.1 (n = 1,846)	0.50*	–0.20 ± 1.0 (n = 145)	–0.61 ± 1.0 (n = 145)	0.41*
IQ	96.8 ± 14.8 (n = 32,365)	90.6 ± 14.8 (n = 1,921)	6.2*	92.4 ± 13.6 (n = 154)	91.0 ± 13 (n = 154)	1.3†
Bender-Gestalt	62.3 ± 13.8 (n = 31,837)	57.3 ± 13.9 (n = 1,871)	5.0*	60.3 ± 13.5 (n = 148)	58.9 ± 13.2 (n = 148)	1.4†

Differences in sample size are due to lack of follow-up data on all patients and separate follow-up for growth and developmental outcomes.
*$p < 0.001$.
†p = Not significant.

cohorts 70% of patients had developmental and anthropometric measurements at 7 years of age. More than 90% of patients with developmental assessments also had weights and heights determined at 7 years of age. Previous reports from the NCPP data have documented few differences between those patients who underwent follow-up and those who did not.[16,17]

Outcomes

Z-scores, which indicate the number of SD by which an infant's length and weight deviate from a reference population, were calculated with the Centers for Disease Control anthropometry software based on the FELS Research Institute (Wright State University, Yellow Springs, Ohio) longitudinal study and National Health and Nutrition Examination surveys.[18,19] We preferred the use of Z-scores to individualized weights and lengths, because Z-scores allow comparisons across sexes and minimize sample variation when measurements are not recorded at identical time intervals. "Catch-up growth" was defined as a child's height and weight within 1 SD of his or her sibling's height and weight at 7 years of age. Our use of the term "catch-up growth" is compatible with the general definition put forward by Tanner[20] and Ashworth and Millward,[21] who describe "catch-up growth" as the phase of recovery that occurs when a period of growth retardation ends and favorable conditions are restored.

Statistics

Data were analyzed with the SPSS-X program (SPSS Inc., Chicago, Ill.). Differences in proportions were compared by chi-squared analysis. Differences in continuous variables were determined by independent t test for population variables and paired t test for sibling data. Two-way analysis of variance was used to analyze the effects of IUGR and birth asphyxia on growth. The McNemar test was used to analyze paired dichotomous variables.

RESULTS

Maternal Characteristics (Table I)

In the population cohort mothers of infants born with IUGR were significantly lighter ($p < 0.001$) and shorter ($p < 0.001$) than mothers of infants with normal birth weight. In both cohorts significantly lower pregnancy weight gain occurred in mothers of infants with IUGR (population cohort: $p < 0.001$, sibling cohort: $p < 0.05$). Because mothers in the sibling cohort all had at least one child with IUGR, it is not surprising that they were also shorter and lighter than the general population studied. Mothers of infants with IUGR were also more likely to be nonwhite. Although statistically significant differences occurred in family income, prenatal care, toxemia, and maternal hypertension in the population cohort, these differences were small and were not replicated in the sibling cohort. Mothers with infants born with IUGR in the population cohort were more frequently smokers ($p < 0.001$). As expected, the percent of primagravida women was lower in the sibling cohort than in the population cohort. Placental weight was significantly lower in infants born with IUGR in both cohorts ($p < 0.001$). Maternal weight, maternal height, pregnancy weight gain, prenatal care, and pregnancy complications were similar in both cohorts of infants with IUGR.

Newborn Characteristics (Table I)

Between 5% and 6% of infants in the population cohort were born with IUGR. Females predominated among infants born with IUGR in the population cohort ($p < 0.001$). As expected, female infants were also overrepresented in the sibling cohort (chi-squared analysis <0.001). Although infants with IUGR had identical weights and lengths in both the population and sibling cohorts, siblings of infants born with IUGR were significantly shorter and lighter than the nongrowth-retarded infants in the population cohort. In both cohorts head circumference was significantly decreased in infants born with IUGR ($p < 0.001$). An increased prevalence of birth depression (Apgar ≤6) in infants with IUGR was seen in both cohorts ($p < 0.05$). Infants with IUGR in both the population and sibling cohort did not differ significantly at birth; they had similar mean weights, lengths, head circumferences, sex, placenta weights, and prevalence of birth depression.

Growth of Patients Born With IUGR (Table II)

At 7 years of age weights and heights were significantly lower in patients born with IUGR. In the NCPP population weights and heights of infants born with IUGR remained between –0.5 and –0.6 SD below those of patients born without IUGR (weight-for-age: $p < 0.001$, height-for-age: $p < 0.001$). A similar degree of growth stunting was observed when siblings born with IUGR were compared with their siblings without IUGR (WAZ Z-score: $p < 0.001$, HAZ Z-score: $p < 0.001$). Siblings born with IUGR were almost twice as likely to remain below the 10th percentile for weight at 7 years of age than their siblings without IUGR (22% vs 12%, $p < 0.001$). The presence or absence of birth depression, defined as an Apgar score of 6 or less, had no significant effects on growth in either cohort. Infants with birth weights more than 1 kg lower than their siblings had growth deficits at 7 years of age similar to those of infants with lesser weight deficits (ΔWAZ: –0.50 vs –0.54, $p = 0.9$; ΔHAZ: –0.43 vs –0.41, $p = 0.9$).

"Catch-up" Growth in Siblings Born With IUGR

In the NCPP population only 9% of term children with siblings were >1 SD lower in height and weight than their sibling at 7 years of age. In contrast, 22% of infants born with IUGR had heights and weights >1 SD lower than their siblings without IUGR at 7 years of age. We detected no significant difference in maternal weight, gestational weight gain, smoking, placenta size, toxemia, diabetes, or chronic hypertension between infants whose growth was or was not within 1 SD of their siblings at 7 years of age. Similarly, we found no significant differences in birth weight, length, head circumference, ponderal index, or sex in infants with IUGR with and without catch-up growth.

Mental and Motor Development of Patients Born With IUGR (Table II)

In the entire NCPP population IQ measurements at 7 years of age were six points lower for patients born with IUGR ($p < 0.001$). Visual-motor development was also lower in patients born with IUGR ($p < 0.001$). Similar results were obtained when patients with birth depression were excluded from the analysis. However, when patients born with IUGR were compared with their siblings without IUGR, there was no significant difference in IQ ($p = 0.18$). Similarly, there was no significant difference in visual-motor development in siblings born with or without IUGR ($p = 0.19$).

Effect of Head Circumference on Development of Siblings Born With IUGR

Children in the sibling cohort with both IUGR and low head circumferences (≤31 cm) had significantly lower IQ and Bender-Gestalt scores than infants with IUGR and normal head circumferences (IQ: 86.0 ± 13.2 vs 94.2 ± 12.8, $p < 0.001$, Bender-Gestalt: 53.3 ± 13.2, vs 63.0 ± 11.0, $p < 0.001$). Similarly, infants with IUGR and a head circumference ≥3 cm smaller than their siblings (>2.5 SD) had significant mental and motor deficits at 7 years of age compared with their siblings (IQ: 86.0 ± 15.7 vs 92.0 ± 14.4, $p < 0.02$, Bender-Gestalt: 54.4 ± 15.3 vs 60.0 ± 12.2, $p < 0.02$, $n = 32$). In contrast, infants born with IUGR with a head circumference within 3 cm of their siblings had comparable mental and motor development (IQ: 92.4 ± 11.8 vs 93.1 ± 13.3, $p = 0.6$, Bender-Gestalt: 60.7 ± 12.1 vs 60.5 ± 14.0, $p = 0.9$, $n = 115$). Birth weights of infants with IUGR were lower in those with smaller head circumferences than in those with normal head circumferences; however, these differences were relatively small (WAZ: –2.25 ± 0.60 vs –2.05 ± 0.60, $p < 0.05$).

DISCUSSION

Infants with birth weights <2500 gm remained significantly lighter and shorter compared with nongrowth-retarded infants. The mean WAZ and HAZ of infants with low birth weight at 7 years of age were approximately 0.5 SD less than those of infants with normal birth weight. These differences correspond to an average height deficit of 2 cm and a weight deficit of approximately 1.6 kg at 7 years of age. Because mothers of infants born with IUGR are both shorter and lighter than mothers who do not have infants born with IUGR, it is not surprising that the siblings with normal birth weight remain smaller than their population counterpart. However, siblings born with IUGR remained significantly lighter and shorter than their siblings without IUGR. The growth deficits associated with IUGR were independent of the severity of IUGR or other prenatal and postnatal factors including low Apgar scores.

Exposure of the fetus to either intrauterine starvation, overnutrition, hyperglycemia, tobacco, or alcohol as early as the first trimester of pregnancy can result in altered growth during childhood.[22] The mechanisms that account for the effects of the intrauterine environment on growth remain unclear. Winick and Noble[23] provided evidence that neonatal malnutrition permanently affected growth by reducing cell proliferation and size. In rats early postnatal malnutrition impedes cell division, resulting in a decreased numbers of cells throughout the organism and permanent growth stunting. Later malnutrition results in decreased cell size but not cell number, resulting in reversible growth deficits. Although we observed lower maternal weight gain in infants born with IUGR, we could not identify any differences in prenatal nutritional factors between those infants who demonstrated catch-up growth and those who did not. Therefore low maternal weight gain alone does not appear responsible for the persistent growth deficits in infants with IUGR. Furthermore birth weight, birth length, head circumference, ponderal index, maternal weight gain, maternal size, placental size, smoking, toxemia, and hypertension were similar in those infants who experienced "catch-up" growth and those who did not. These observations suggest that genetic factors rather than environmental factors account for the persistent effects of IUGR on growth. However, our data do not exclude the possibilities that intrauterine experience may contribute to the reductions in later growth.

It is possible that many infants born with IUGR are genetically small. Although the classic studies of Walton and Hammond,[24] Penrose,[25] and Morten[26] have demonstrated that genetic factors exert only minimal effects on birth size, these studies did not focus on the growth of infants with IUGR. Our data indicate that infants born with weights <2500 gm have limited growth potential compared with their siblings. The limited growth potential suggests that either genetic factors or some as yet unrecognized determinant of IUGR is likely responsible for both IUGR and decreased postnatal growth. The importance of a genetic contribution to IUGR is supported by the increased prevalence of IUGR within families[27] and the discovery of single gene mutations in some infants with IUGR.[28]

IUGR had little impact on long-term mental and motor development except when associated with large deficits in head circumference. In the population cohort infants with IUGR had significantly lower mental and motor scores, similar to those described in previous population studies.[6-11] However, population-based studies cannot adequately control for the multiple prenatal and postnatal variables associated with IUGR such as lower head circumference, lower socioeconomic status, lower rates of prenatal care, or genetic variability, all of which may also contribute to lower intelligence. We found that siblings born with IUGR had IQ and Bender-Gestalt scores similar to those of their non-IUGR siblings ($\alpha = 0.05$, $\beta = 0.20$, $n = 154$). However, the mental and motor development of siblings with IUGR was largely dependent on head size at birth. Growth-retarded infants with small to moderate reductions in head circumference are "head spared"; they exhibit motor and mental development similar to their siblings. In contrast, growth-retarded infants with very large deficits in their head size demonstrated significant developmental delays compared with their siblings. Our findings are similar to those of Berg,[29] who demonstrated that term infants with low birth weight and a decreased head size at birth had a significantly elevated risk of neurologic impairments in childhood. Finally, our study did not assess the prevalence of learning disabilities in children with IUGR. Children with normal intelligence and motor development may exhibit subtle deficits that would be undetected by the WISC or Bender-Gestalt tests.

We were unable to document any difference in body proportionality between those infants with IUGR who approached their sibling's growth and those who did not. Previous studies have suggested that term infants with asymmetric growth retardation demonstrated increased catch-up growth.[30-32] However, in those studies many infants were labeled "asymmetric" who had normal birth weights but low ponderal indexes. Other studies have demonstrated that heights and weights of "asymmetrically" growth-retarded infants remained low into mid-childhood.[33] Kramer et al.[34,35] also suggested that altered body proportionality in infants with IUGR may represent more severe growth retardation, not a distinct entity.

We chose to define IUGR as a birth weight <2500 gm, consistent with previous studies[36] largely based on the increased morbidity and mortality in infants born below this birth weight.[37-39] Other authors have defined IUGR as a birth weight <10th percentile for gestational age, <5th percentile for gestational age, <3rd percentile (2 SD) for gestational age, or <80% to 90% of average birth weight for gestational age. However, gestational age-based criteria are limited by the reference standard used, which varies greatly.[40] Fetal growth ratios are similarly dependent on the reference population selected. Gestational age-based criteria and fetal growth ratios are most useful in the assessment of IUGR in preterm infants when gestational age has been clinically confirmed, and infant growth is rapid. In term infants a simple weight cutoff is less likely to be affected by imprecise gestational dating or reference sample bias.

In summary, developmental deficits appear to occur only in the subset of infants with IUGR who demonstrate poor head growth in utero. There is little evidence that low birth weight by itself limits intelligence or motor development. In contrast, the growth effects of IUGR are independent of prenatal and postnatal environmental factors. Many infants labeled as "IUGR" may be genetically short. Therefore parents should be discouraged from trying to overfeed these children to normalize their growth, because there is no evidence that such an approach will lead to improved growth.

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