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A Prospective Study of Serum Insulin-Like Growth Factor I (IGF-I) and IGF-Binding Protein-3 in 942 Healthy Infants: Associations with Birth Weight, Gender, Growth Velocity, and Breastfeeding

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Context: Many aspects of hormonal regulation and mechanisms of normal infancy growth are poorly understood.

Objective: The objective of this study was to establish the determinants of serum growth factor levels in infancy and their association with growth.

Design: A prospective, longitudinal, population-based birth cohort between 1997–2001 was studied.

Participants: Study participants were 942 healthy appropriate weight for gestational age (AGA) infants (538 boys and 404 girls) and 49 small for gestational age (SGA) children (29 boys and 20 girls).

Interventions: Interventions were anthropometrical measurements (0, 3, 18, and 36 months) and serum samples (3 months).

Main Outcome Measures: Height, weight, and serum IGF-I and IGF-binding protein-3 (IGFBP-3) were the main outcome measures.

Results: IGF-I levels showed no gender difference [boys, 92 ng/ml (confidence interval, 49, 162); girls, 91 ng/ml (47, 149); $P = 0.50$]. IGFBP-3 levels were significantly higher in females [2174 ng/ml (1295, 3330)] than in males [2103 ng/ml (1266, 3143); $P = 0.04$]. Infants receiving breast milk had lower IGF-I levels [90 ng/ml (48, 154)] than infants receiving formula [n = 62; 97 ng/ml (58, 165)] or both [n = 123; 94 ng/ml (48, 169); $P < 0.001$]. IGF-I and IGFBP-3 levels were positively associated with weight gain and height gain from birth to 3 months of age in AGA, but not in SGA, children. SGA children had significantly lower IGF-I [88.0 ng/ml (28, 145); $P = 0.05$] and IGFBP-3 [1835 ng/ml (1180, 2793); $P < 0.001$] levels than AGA children.

Conclusion: We found a significant, but weak, association between IGF-I and IGFBP-3 levels at 3 months and postnatal growth in AGA, but not SGA, children. Factors other than IGF-I must contribute to the regulation of normal postnatal growth, and these may differ between AGA and SGA children. IGFBP-3, but not IGF-I, showed a gender difference, which may reflect an influence of the postnatal activation of the pituitary-gonadal axis on binding protein levels. (***J Clin Endocrinol Metab*** **91: 820–826, 2006)**

OUR UNDERSTANDING OF the pathophysiology of being born after intrauterine growth restriction (IUGR) or small for gestational age (SGA) and the long-term consequences for health is increasing. However, very little is known about the regulation of normal fetal as well as early postnatal growth. IGF-I plays a major role in the regulation of postnatal human growth from late infancy onward (1). The liver is the principal source of circulating IGF-I, and postnatal hepatic production is regulated by pituitary GH as well as nutritional factors. High IGF-I levels are found in patients with acromegaly (2) and constitutionally tall stature (3), and low IGF-I levels are found in children with GH deficiency (4) and GH receptor dysfunction (5). Numerous studies have demonstrated that IGF-I levels in cord blood correlate to birth weight, with IUGR children having lower concentrations than normal children (6–9). There are also a few studies of normal IGF-I levels during infancy that demonstrate a relationship between the GH-IGF-I axis and the growth rate (9–13).

The aim of this study was to investigate determinants of serum growth factors [IGF-I and IGF-binding protein-3 (IGFBP-3)] at 3 months and their association with early postnatal growth in healthy infants and in children born SGA.

Subjects and Methods

Study design

A longitudinal prospective birth cohort study of pregnant mothers and their offspring from birth to 3 yr of age was performed at two university hospitals in the Copenhagen area (Rigshospitalet and Hvidovre). Pregnant women, geographically belonging to the hospital's primary obstetric referral area (not being referred because of expected complications in pregnancy), were consecutively recruited in the first trimester of pregnancy between 1997 and 2001.

The present study is part of a large ongoing baby cohort study investigating urogenital development and malformations (14) in newborns and establishing reference ranges for endogenous hormones (15). From this cohort, only those children in whom blood sampling at 3

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Abbreviations: AGA, Appropriate weight for gestational age; Δ, difference; IGFBP-3, IGF-binding protein-3; IUGR, intrauterine growth restriction; SDS, SD score; SGA, small for gestational age.

months of age had been successful were selected. This group comprised 942 children (538 boys and 404 girls) born with appropriate weight for gestational age (AGA) and at term (259–294 d gestation) and 49 children born SGA (29 boys and 20 girls). The SGA group comprised seven prematurely born children and four twins. AGA was defined as a birth weight deviation from the mean between −22% and 22%, which is equivalent to −2 and +2 SD (16, 17). SGA was defined as a weight for gestational age below −22%.

Anthropometric measurements

Anthropometric measurements of the children were performed longitudinally. Examination dates were corrected for gestational age in seven prematurely born SGA children (<259 d gestation). All children were scheduled for examinations at 0, 3, 18, and 36 months. All SGA children were also seen at 6, 9, and 12 months of age. The total numbers of anthropometric examinations available were 916/48 (0 months), 940/49 (3 months), 0/35 (6 months), 0/36 (9 months), 0/35 (12 months), 819/43 (18 months), and 660/34 (36 months) for AGA/SGA children, respectively.

Birth data (weight, length, and gestational age) and obstetric history were obtained from medical records. Length was measured in the supine position with a portable infantometer (Kiddimeter, Raven Equipment Ltd., Essex, UK) to the nearest 0.1 cm; the mean of three measurements was calculated. At the age of 3 yr, an electronic stadiometer was used (Force Technology, Brøndby, Denmark). Weight was measured on a digital scale (baby scale model, Solotop Oy, Helsinki, Finland) to the nearest 0.005 kg, and the mean of three measurements was calculated. The intraobserver variation for anthropometric measurements was estimated from the averages of triple measurements of each child in the dataset of all normal children. These triplicate determinations reflect the variation between repetitive measures performed by one observer without repositioning the child, thus slightly underestimating the true intraobserver variation. The interobserver variation was determined in a subgroup of 72 children. Confidence intervals (95%) for intra- and interobserver variations were less than ±1.4 mm for height and less than ±25 g for weight. Head circumference was measured with a tape lasso (Child Growth Foundation, London, UK) to the nearest 0.01 cm, and the mean of three measurements was calculated.

Blood samples

A nonfasting peripheral venous blood sample was taken from an antecubital vein between midmorning and early afternoon at the age of 3 months. Only one attempt at venipuncture was made due to ethical considerations, and the overall success rate in the total baby cohort was approximately 70%. Samples were separated by centrifugation and stored at −20 C until analysis. All blood samples were taken after applying a topical anesthetic (xylocaine spray, 0.1%) and oral sucrose syrup.

Assays

IGF-I was measured in all subjects with an RIA originally described by Bang *et al.* (18) with some modifications. Serum was extracted by acid/ethanol and cryoprecipitated before analysis to remove interfering binding proteins and monoiodinated Tyr^{31}-[^{125}I]des-(1–3)IGF-I was used as radioligand. Inter- and intraassay variations were 8.7% and 3.9% (at a bound/free ratio of 0.4), respectively. The limit of detection was 21 ng/ml. IGFBP-3 was determined by RIA as described by Blum *et al.* (19). IGFBP-3 was measured on unprocessed serum using a polyclonal rabbit antiserum and a purified human IGFBP-3 fragment as standard and radioligand, respectively. Reagents for the analysis were obtained from Mediagnost GmbH (Tubingen, Germany). Inter and intraassay variations were 7.3% and 3.5%, respectively. The limit of detection was 300 ng/ml.

Statistics and calculations

SD scores (SDS) were calculated using the following equation: SDS = (measurement − mean)/SD. For this purpose, reference curves for weight and height were constructed by smoothing techniques using data from the 942 AGA children. The mean curve was estimated by local linear regression. Similarly, the variance function was estimated by local linear regression of the squared residuals (20). Means and corresponding SD for gender- and age-specific height and weight measurements were estimated from the curves for all data points with real measurements.

Reference curves for the distribution of IGF-I and IGFBP-3 levels as a function of age were estimated by a locally weighted regression quantile (21). The curves represent the 5th, 50th and 95th percentiles.

Changes in weight and height SDS over time were calculated by simple subtraction: (SDS at 3 months − SDS at birth), (SDS at 18 months − SDS at birth) in all children, and additionally (SDS at 6 months − SDS at 3 months) for SGA children. SDS changes were normally distributed and allowed the use of parametric tests.

The difference in SDS (Δ value) between birth and 18 months was also grouped into quartiles for both the reference group of healthy infants and the SGA children. A change of more than ±0.67 SD was defined as catch up (0.67 is equivalent to the width of a percentile band in standard growth charts, *i.e.* the width between the 25th and 50th percentiles and between the 50th and 75th percentiles). Differences in growth factor levels between genders, growth velocity quartiles, between children with/without catch-up growth, and in relation to nutrition were tested by *t* test and ANOVA.

Feeding was categorized into three groups: 1, exclusively breast fed; 2, mixed diet with breast milk and formula; and 3, exclusively formula fed.

Correlations between IGF-I and IGFBP-3 and between growth factors and changes in height and weight SDS were calculated after adjusting for gender.

Multivariate regression models were used to assess the measurements of IGF-I levels at 3 months of age. Covariables entered into the model were identified by cross-correlations matrices, including maternal age, smoking, parity, placenta weight, gestational age, weight for gestational age, birth weight and height, infant gender, postnatal age at blood sampling, nutrition, as well as height and weight at 3 months of age. The final regression model included hereafter the following covariates (listed according to entry in the model): infant gender, nutrition, postnatal age at blood sampling, birth weight, gestational age, and weight and height at 3 months of age.

The inter- and intraobserver variations were estimated by means of random effect models, which included variance components for the variation between doctors, the variation between individuals, and the residual variation. The model was fitted by the restricted maximum likelihood method using PROC MIXED of SAS 6.12 (SAS Institute, Inc., Cary, NC). The statistical analyses were performed using SPSS version 11.0 (SPSS, Inc., Chicago, IL) and SAS 6.12 (SAS Institute, Inc.).

Ethical aspects

The study was performed according to the Helsinki II Declaration and was approved by the local ethics committee and the Danish Registry Agency. The parents gave written consent after oral and written information was provided to them.

Results

Characteristics of the reference population and infants born SGA are shown in Table 1. Figure 1 presents smoothed weight and height charts for the AGA and SGA infants from birth to 36 months of age. AGA male infants had significantly greater weight and length than females at all ages (all $P < 0.0001$). These differences were taken into account before all subsequent regression analyses. In the SGA group, boys had significantly greater weight and height than girls at 0 months ($P < 0.04$ and 0.03, respectively) and 3 months ($P < 0.01$ and 0.01, respectively). This gender difference was maintained for height, but not for weight, over the consecutive examinations at 6 months ($P < 0.03$), 9 months ($P < 0.10$), 12 months ($P < 0.02$), 18 months ($P < 0.06$), and 36 months ($P < 0.03$).

Thirty-five SGA infants completed the 6 months examination, and five of these children (14.3%) had not shown catch-up growth (defined as Δheight SDS >0.67) at 6 months

TABLE 1. Characteristics of the reference population (n = 942, term Danish infants born AGA) and SGA infants (n = 49)

	AGA infants				SGA infants			
	n	Males	n	Females	n	Males	n	Females
Total no.	538		404		29		20	
Smokers								
Yes	148		102		12		2	
No	379		276		17		17	
Parity								
1	331		239		27		15	
2	166		112		1		3	
≥3	40		30		1		2	
Delivery								
Vaginal	402		306		15		9	
Vacuum	60		40		1		1	
Elective cesarean	20		14		4		3	
Acute cesarean	54		40		9		7	
Mother's age (yr)	536	30.3 (18;44)	400	29.65 (18;42)	29	31.5 (23.6;42.4)	20	32.6 (24.7;40.5)
Gestational age (d)	538	283 (259;294)	404	281 (259;294)	29	281 (219;298)	20	269.5 (216;292)
Weight for gestational age (%)	538	−0.4 (−21.9;22.0)	404	0.5 (−21.9;21.9)	29	−25.7 (−42.5;−22.2)	20	−26.1 (−41.2;−22.1)
Birth length (cm)	538	53 (46;60)	401	52 (47;59)	29	49 (39;52)	19	52 (38;53)
Birth weight (kg)	538	3.65 (2.50;4.86)	404	3.520 (2.33;4.51)	29	2.65 (1.31;3.08)	20	2.35 (1.14;2.90)
Head circumference (cm)	522	35 (31;40)	395	35 (30;38)	29	34 (29;36)	19	33 (26;36)
Placental weight (g)	409	650 (250;1200)	295	658 (330;1046)	20	500 (265;1050)	10	480 (330;610)

Medians (ranges) are given for continuous data.

of age. Forty-three children were followed up to 18 months, and seven of these (16.3%) had not shown catch-up growth between birth and 18 months of age.

IGF-I and IGFBP-3 in 3-month-old infants born AGA

Medians and 5th and 95th percentiles for IGF-I and IGFBP-3 levels in relation to age at blood sampling and gender are shown in Fig. 2. IGF-I and IGFBP-3 levels were detectable in all infants. No significant gender difference in IGF-I levels was seen [boys, 92 ng/ml (confidence interval, 49, 162); girls, 91 ng/ml (47, 149); $P = 0.50$]. IGFBP-3 levels were significantly higher in female [median, 2174 ng/ml (2.5th and 97.5th percentiles, 1295, 3330)] than in male infants [2103 ng/ml (1266; 3143); $P = 0.04$].

IGF-I and IGFBP-3 in 3-month-old infants born SGA

IGF-I and IGFBP-3 levels were significantly lower in SGA children compared with the reference population [88.0 (28, 145) *vs.* 92 ng/ml (48, 156); $P = 0.05$] and [1835 (1180, 2792) *vs.* 2134 ng/ml (1279, 3224); $P < 0.001$]. Similar findings were obtained if data were analyzed for each gender separately (data not shown). There was no significant gender difference for IGF-I [boys, 85 ng/ml (49, 156); girls, 106 ng/ml (48, 171)] or for IGFBP-3 [boys, 1976 ng/ml (1361, 3095); girls, 2274 ng/ml (1219, 4004); $P = 0.21$ and 0.25, respectively].

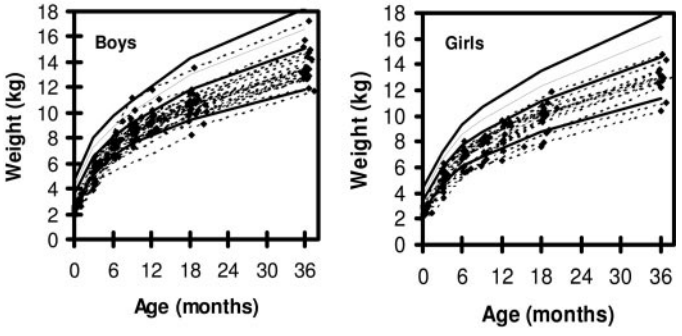

FIG. 1. Spontaneous growth in 49 infants born SGA (birth weight, <−22% for gestational age; ♦) in relation to normal references (*solid lines*) in boys and girls. The reference lines are based on smoothed weight measurements from a prospective, longitudinal Danish study of 942 healthy term AGA infants. *Lines* represent the mean ± 2 SD.

Determinants of IGF-I levels at 3 months of age in AGA children

Infants receiving only breast milk at 3 months of age (n = 607) had significantly lower IGF-I levels [90 ng/ml (48, 154)] than infants receiving formula [n = 62; 97 ng/ml (58, 165)] or both [n = 123; 94 ng/ml (48, 169); $P < 0.001$]. Similar findings were obtained when analyzing data for each gender separately (data not shown). IGFBP-3 levels were not significantly different between feeding groups ($P = 0.34$). Levels were 2130 ng/ml (1276, 3229) in breast-fed children, 2189 ng/ml (1288, 3317) in formula-fed children, and 2138 ng/ml (1235, 3091) in infants fed both. There was no gender difference for nutrition categories ($P = 0.50$).

At 3 months of age, IGF-I and IGFBP-3 levels were positively correlated to each other (r = 0.69; $P < 0.0001$). In a multivariate regression model, IGF-I was positively associated with weight at 3 months (r = 0.45; $P < 0.0001$), gender (higher values in girls; r = 0.14; $P < 0.0001$), and nutrition (higher values in formula feeding; r = 0.13; $P < 0.0001$) and negatively with birth weight (r = −0.24; $P < 0.0001$) and age at blood sampling (r = −0.18; $P < 0.0001$). In a similar model, IGFBP-3 was significantly dependent on weight at 3 months (r = 0.307; $P < 0.0001$), gender (higher values in girls; r = 0.19; $P < 0.0001$), and birth weight (r = −0.07; $P = 0.044$). If height at 3 months was removed from the model, the results did not change. If weight at 3 months was removed from the analysis, results were unchanged for IGF-I, but birth weight was no longer significant for IGFBP-3.

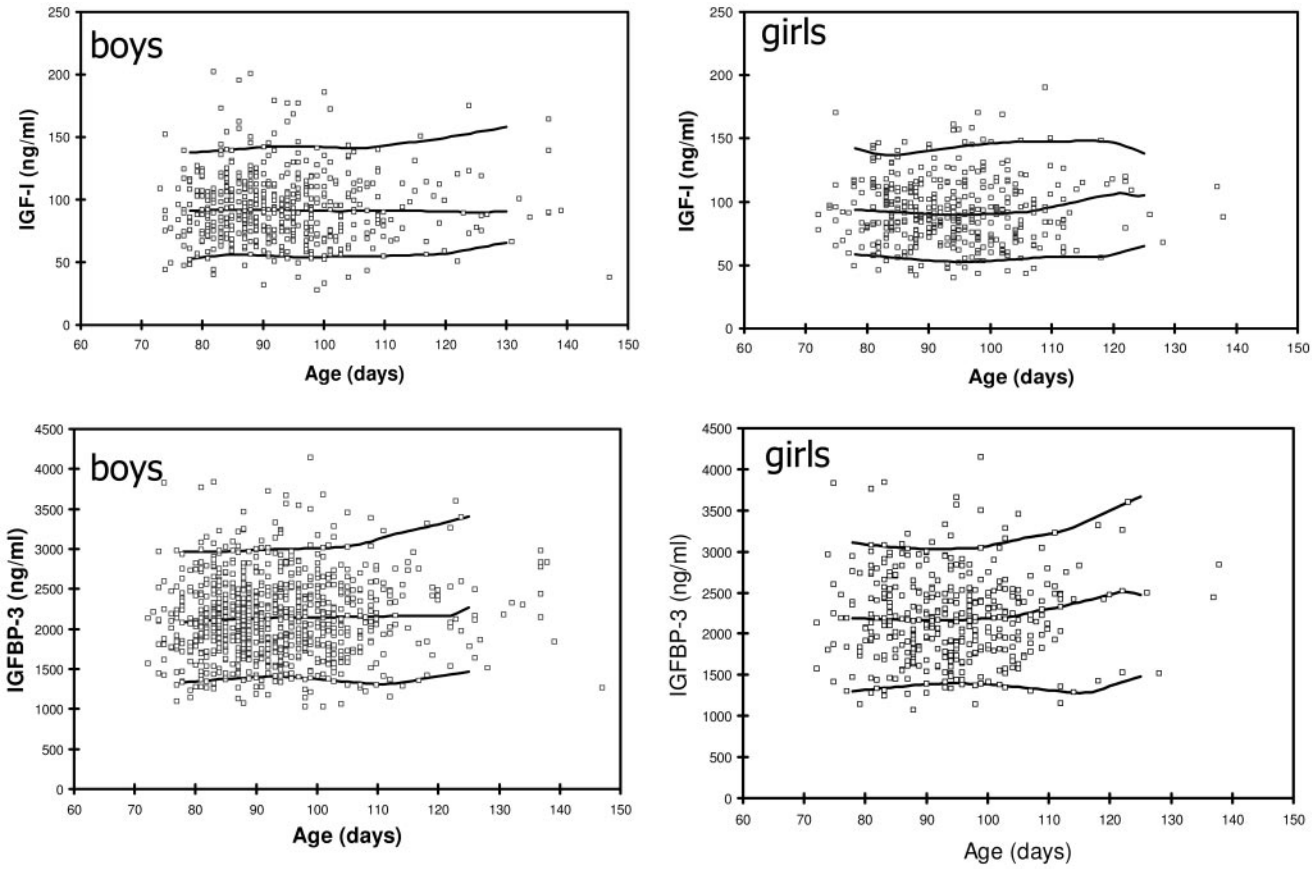

FIG. 2. IGF-I and IGFBP-3 serum levels in 942 healthy term AGA infants according to chronological age and gender. *Lines* represent 5th, 50th and 95th percentiles.

IGF-I levels and weight and height gain in AGA children

Changes in weight and height SDS between birth and 3 months of age were positively correlated to IGF-I ($r = 0.28$; $P < 0.0001$ and $r = 0.12$; $P < 0.0001$, respectively) and IGFBP-3 ($r = 0.21$; $P < 0.0001$ and $r = 0.099$; $P < 0.003$, respectively). Changes in weight and height SDS between birth and 18 months of age were positively correlated to serum IGF-I ($r = 0.10$; $P < 0.004$ and $r = 0.16$; $P < 0.0001$, respectively), but not with IGFBP-3. Changes in weight SDS, but not height SDS, between 3 and 18 months were negatively correlated to IGF-I ($r = -0.19$; $P < 0.0001$) and IGFBP-3 ($r = -0.236$; $P < 0.0001$).

IGF-I, but not IGFBP-3, levels were also significantly and positively associated with Δweight SDS between birth and 18 months of age ($P = 0.027$; Fig. 3A) and Δheight SDS between birth and 18 months of age ($P < 0.001$; Fig. 3B).

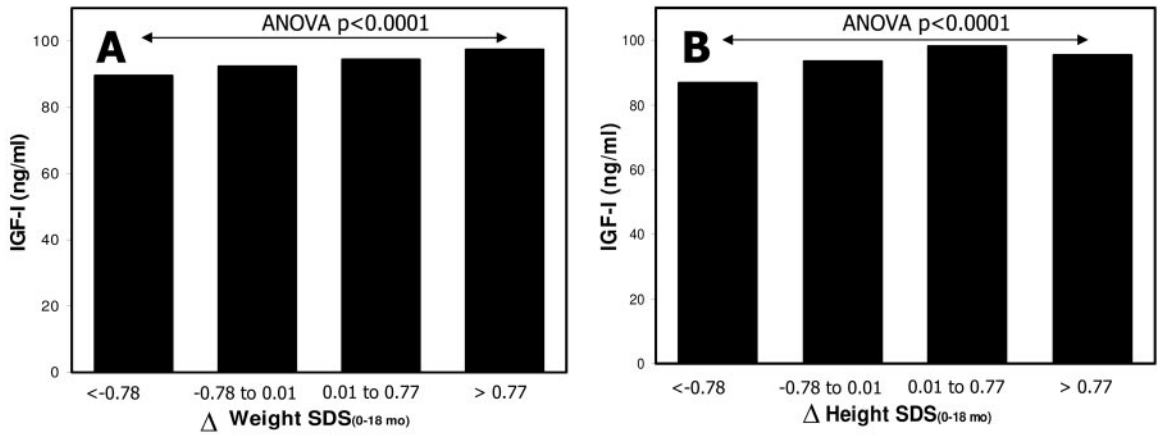

FIG. 3. Mean IGF-I levels at 3 months of age in term AGA children in relation to growth velocity quartiles for weight (A; $P < 0.027$) and height SDS (B; $P < 0.001$). Growth velocity is grouped in quartiles according to changes in SDS between birth and 18 months of age.

IGF-I levels and weight and height gain in SGA children

Although median levels of IGF-I were lower in SGA children with no catch-up growth between birth and 18 months of age [64 ng/ml (953, 109)] compared with SGA children with catch-up growth [88 ng/ml (24, 146)], these differences were not statistically significant. In addition, IGF-I and IGFBP-3 levels at 3 months were not significantly associated with changes in weight or height SDS between birth and 3 months, between 3 and 6 months, or between birth and 18 months of age.

Discussion

This large longitudinal cohort study not only provides reference ranges for IGF-I and IGFBP-3 levels at 3 months of age, it also showed an interesting association among serum growth factors, nutrition, and postnatal growth in AGA infants. IGF-I and IGFBP-3 were measurable in all blood samples, with large interindividual variations. We found IGF-I levels at 3 months of age to be positively related to current weight and inversely correlated to birth weight. Children who showed rapid weight or height gain in the first 18 months of life had the highest levels of serum IGF-I at 3 months of age. In addition, we found lower serum IGF-I levels at 3 months of age in SGA infants compared with infants born AGA, but IGF-I did not correlate with catch-up growth in this group of children.

In accordance with other studies, we found a positive correlation between IGF-I levels and IGFBP-3. We did not detect an influence of gender on IGF-I levels at 3 months of age in a univariate analysis. Such a gender effect has previously been suggested by others (22, 23). Girls had higher IGF-I levels compared with boys in those studies. A gender effect was only found in our material if other determinants of serum IGF-I, such as birth weight, gestational age, nutrition, and size at 3 months, were taken into account in a multivariate model. Because we found strong correlations between growth factors and growth parameters, such as weight and height velocity, which, in turn, was gender specific, our results point toward an intricate interaction between gender-specific growth patters and the IGF-I axis. Our study design did not permit us to determine the causal relationship between growth velocity and growth factors. However, the direction of the association between growth velocity and growth factors changed from being positive from birth to 3 months of age and negative from 3 to 18 months postnatally. Thus, IGF-I may be one of the factors involved in the physiological growth pattern of regression toward the mean within normal growth percentiles in the postnatal period. We found that infant girls had significantly higher IGFBP-3 levels compared with male infants. This resembles findings in children at the onset of puberty (1), when girls also show higher levels of IGFBP-3 than boys. Because our blood samples were taken at the time of postnatal activation of the pituitary-gonadal axis, this gender difference may be related to the influence of gonadal hormones. Our study of IGF-I levels in 3-month-old infants confirms the negative association found between birth weight and IGF-I levels in cord blood or even later in childhood (22, 24, 25) and young adulthood (26), which could suggest that fetal growth restraint may reprogram the IGF-I axis.

As a novel finding, we report that IGF-I levels were lower in breast-fed infants *vs.* infants receiving formula or both independently of weight at 3 months. This finding is in line with recent data relating IGF-I levels to the degree of protein intake and suggesting that higher protein intake stimulates IGF-I secretion (27). Likewise, others have found that formula-fed children have higher insulin levels compared with breast-fed children (28). Thus, hypothetically, both changes in IGF-I and insulin could in part explain the higher postnatal growth rate in formula-fed children compared with breast-fed infants (29).

Epidemiological studies have pointed out a link between being born SGA/IUGR and later risk of development of hypertension, noninsulin-dependent diabetes mellitus, obesity, and other endocrine and cardiovascular disorders (30, 31). Recently, not only has low birth weight (as a proxy of intrauterine growth) been related to risk of certain adult diseases, but also (and more importantly) rapid weight gain or large size early in postnatal life was associated with increased risk of adult obesity (32, 33), cardiovascular disease (34), noninsulin-dependent diabetes mellitus (35), and some forms of cancer (32). The linkage between these associations could be due to alterations in the programming of insulin, IGF-I, and IGF-II, because mutations in the insulin variable number of tandem repeat, IGF-I, and IGF-II genes are associated with poor intrauterine and postnatal growth as well as with insulin resistance in later life (36–38). In humans, mutations in the IGF-I gene causes IUGR and postnatal growth failure associated with insulin resistance (39), and certain frequent IGF-I gene polymorphisms occur more often in children born SGA compared with controls (40). Furthermore, mutations in the IGF-I receptor gene that lead to abnormalities in the function or number of IGF-I receptors may also retard intrauterine and subsequent postnatal growth in humans (41).

Our findings of low IGF-I levels in SGA children compared with normal controls (although only moderately decreased) are in accordance with the results of several other studies (42, 43), suggesting an altered programming of the IGF-I axis in fetal life. However, we did not find a difference in IGF-I levels among the SGA infants with catch-up and those without catch-up growth in the first 18 months of life. This may be explained by the small sample size and the large variation in the timing and magnitude of the individual catch-up growth, taking into consideration the wide variability of IGF-I levels at 3 months of age. However, it could also indicate that the regulation of postnatal growth in SGA infants is different from that in AGA children and does not follow the normal pattern.

In our reference population of 942 children, we found that the changes in weight and height between birth and 18 months of age were positively related to IGF-I levels at 3 months of age, which was also true after adjustment for confounders (29). Importantly, we found that IGF-I levels at 3 months of age explained less than 1% of the variation in growth rates seen from birth to 18 months of age, suggesting that in addition to IGF-I, other factors, *e.g.* the degree of

insulin resistance (44), must play additional roles in determining early childhood growth rates.

In conclusion, the present longitudinal study demonstrated that IGF-I levels at 3 months of age were positively related to current weight and inversely correlated to birth weight. Our study has also provided normative charts for IGF-I and IGFBP-3 at 3 months of age. Children receiving breast milk at 3 months of age had lower IGF-I levels compared with children receiving formula or both. Mature AGA children who showed rapid weight or height gain the first 18 months of life had the highest levels of serum IGF-I at 3 months of age. However, IGF-I explained only a minor part of the variation in growth during infancy in our 942 healthy AGA children, and IGF-I did not correlate to catch-up growth in the group of SGA children. Thus, other factors must contribute to the regulation of early postnatal growth in infants.

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