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The Role of Maternal Factors, Postnatal Nutrition, Weight Gain, and Gender in Regulation of Serum IGF-I among Preterm Infants

EVA ENGSTRÖM, AIMON NIKLASSON, KERSTIN ALBERTSSON WIKLAND, UWE EWALD, AND ANN HELLSTRÖM

Göteborg Pediatric Growth Research Center [E.E., A.N., K.A.W., A.H.], Department of Pediatrics, Institute of the Health of Women and Children, Department of Clinical Neurosciences [A.H.], Section of Ophthalmology, The Sahlgrenska Academy at Göteborg University, S-416 85 Göteborg, Sweden, Department of Women's and Children's Health [U.E.], Uppsala University, S-751 85 Uppsala, Sweden

ABSTRACT

IGF-I is important for somatic growth and development of the human fetus and neonate. IGF-I also plays an important role in normal vascularization of human retina, as it has been suggested that insufficient IGF-I may be a factor in the development of retinopathy of prematurity. The principal regulator of the bioavailability of IGF-I in the circulation is IGF binding protein 3 (IGFBP-3). The aim of this study was to study factors associated with postnatal serum concentrations of IGF-I and of IGFBP-3 in preterm infants from birth to an age corresponding to 40 wk postmenstruation. We conducted a prospective, longitudinal study in which we measured serum IGF-I and IGFBP-3 concentrations in 76 preterm infants from birth (postmenstrual ages 23–32 wk) until discharge from hospital around 40 wk. Information regarding nutrition, weight gain, maternal factors, and treatment with corticosteroids were collected weekly. Variables found to be associated with postnatal change over time of serum IGF-I and IGFBP-3 were postmenstrual age ($p < 0.001$), weight gain (standard deviation score) ($p < 0.001$), and enteral intake of protein ($p < 0.001$). Male gender was associated with lower IGF-I levels ($p < 0.001$). The relationship between protein intake and IGF-I (and also between protein intake and IGFBP-3) was positive, as was the relationship between weight gain and IGF-I (and between weight gain and IGFBP-3). These results indicate that the degree of prematurity, low enteral protein intake, male gender, and slow weight gain are associated with a slower postnatal increase of IGF-I in preterm infants. **(*Pediatr Res* 57: 605–610, 2005)**

Abbreviations

AGA, appropriate for gestational age
BPD, bronchopulmonary dysplasia
CI, confidence interval of the mean (95%)
GA, gestational age in weeks
IGFBP-3, IGF binding protein 3
NEC, necrotizing enterocolitis
PMA, postmenstrual age in weeks
ROP, retinopathy of prematurity
SDS, standard deviation score
SGA, small for gestational age
ΔSDS, individual change in SDS during a predefined time period

IGF-I, which is important for somatic growth and development of the human fetus and neonate, is detectable in fetal tissues from 9 wk of gestation (1) and in the fetal circulation from 15 wk (2). Receptors for IGF-I are found in various tissues early in gestation (3), and fetal tissues seem to have enhanced sensitivity to IGF-I compared with later in life (4). Using cordocenteses, it has been possible to determine the "normal" range of IGF-I in fetal serum and to define a positive correlation between serum concentration of IGF-I and gestational age (5–10). IGF-I levels are similar in arterial and venous cord serum, suggesting a fetal origin (1). The bioavailability of IGF-I is regulated by IGFBP. As in children and adults, IGFBP-3 is the principal carrier of IGF-I during late intrauterine life (11,12). Preterm infants have lower serum levels of IGF-I than term infants, and size at birth is correlated with the level of IGF-I in cord serum (7,13,14). Therefore, infants born SGA have lower IGF-I values than infants born AGA (5,10,13,15–17). Nutritional status, *i.e.* intake of protein and of total energy, has been shown to regulate IGF-I (18), and measurements of IGF-I can be used to assess changes in the nutritional status of malnourished patients (19). Studies in both

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Correspondence: Eva Engström, M.D., Göteborg Pediatric Growth Research Centre, Department of Pediatrics, The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, S-416 85 Göteborg, Sweden; e-mail: eva.engstrom@vgregion.se
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children and adults have shown that serum IGF-I concentrations fall with fasting and rise with re-feeding (20–22).

IGF-I plays an important role in neovascularization (23), and it has been suggested that lack of IGF-I in the early weeks of life, followed by a slow increase, is likely to increase the risk for development of ROP (24). It has also been observed that the greater the duration of low IGF-I, the more severe the ROP (25).

We performed a prospective study with the aim of determining the factors that may influence the longitudinal development of serum IGF-I and IGFBP-3 in a group of very preterm infants from birth to an age corresponding to 40 wk of gestation.

MATERIALS AND METHODS

Characteristics and selection of study group. Infants born at a PMA of <32 wk at The Queen Silvia Children's Hospital in Göteborg between December 1999 and April 2002 and at Uppsala University Hospital between February 2001 and April 2002 were recruited for the study. Exclusion criteria were inability to complete postnatal clinical follow-up until an age corresponding to 40 postmenstrual weeks, and any conspicuous congenital anomaly.

The parents of 70 children gave permission for participation at The Queen Silvia Children's Hospital. At Uppsala University Hospital, 15 infants were identified and recruited as potential participants. Seven infants in the combined group were excluded because of incomplete data, including missing blood samples during the first weeks. During data collection, two infants were moved to another hospital, leaving a total of 76 study subjects (34 male, 42 female), 64 from The Queen Silvia Children's Hospital and 12 from the Uppsala University Hospital. The median PMA at birth (based on fetal ultrasonography, performed at wk 16–18 postmenstruation) was 27.3 wk (range, 23.6–31.7 wk). Trained nurses at the neonatal intensive care unit measured weight at birth. Thereafter, weight was measured and recorded weekly until discharge from hospital.

Median birth weight was 1283 g (range, 530–1760 g) and −1.3 SDS (range, −5.0 to 1.9 SDS), (Table 1). During the first postnatal weeks, all infants lost weight. Twenty (26%) were born SGA with a birth weight below −2 SDS. In addition, 49 infants born AGA experienced postnatal growth retardation, such that 69/76 (90.8%) had a weight below −2 SDS during the neonatal period. Twenty-seven (27/76) of the infants were included in an earlier basic science study on the role of IGF-I in ROP (24) and the whole study group ($n = 76$) is presented in a clinical study on ROP (25).

The ethics committees of the medical faculties at Göteborg and Uppsala universities approved the study, and the parents of the infants gave informed consent.

Nutrition. All infants were hospitalized in neonatal intensive care units and nourished according to the routines for premature infants at the units. Enteral feeding with increasing amounts of breast milk was introduced early (2–48 h after birth). If full enteral feeding was not achieved, supplementary parenteral nutrition with glucose, amino acids, and fat was given. The breast milk given to infants with a birth weight <1500 g was fortified with 0.8 g protein/100 mL (gradually introduced over 1 wk) from 10 d of age until the infant weighed approximately 2 kg. If the amount of mother's milk was insufficient, unpooled donor milk was given until 35 wk of PMA. Thereafter, formula was introduced. The nutritional intake recorded in each infant's record was used to calculate the calories and protein taken during the period in which blood was sampled. At The Queen Silvia Children's Hospital, most of the mothers' and donors' breast milk was analyzed every second week for protein and calorie content (26), and results of these analyses were used to calculate nutrient intake. In cases where breast milk was not analyzed, the mean value of all analyses ($n = 272$) was used (0.7 kcal/mL and 1.7 g protein/100 mL before 33 wk PMA and 1.5 g protein/100 mL after 33 wk PMA). These values are similar to those obtained in other studies (27).

The nutritional goal was to follow the recommendations for infants with birth weight <1500 g, to achieve a daily intake of 3.5 g protein/kg and 120–130 kcal/kg (28,29).

Twenty-eight infants (28/76) were given only human breast milk and glucose infusion (10%), without any parenteral supplementation with fat or amino acids from the first days of life. The other infants (48/76) received breast milk plus parenteral fat and amino acids added to the glucose infusion. The parenteral nutrition was supplied for a mean of 7 d (0–155 d), including four infants with NEC who received infusions for an extended period of time (Table 2). All infants were fed human breast milk and, in most cases (65/76), the milk was fortified. None were formula fed before a PMA of 35 wk. In 22 infants, the nutrition (enteral and parenteral) was recorded daily, whereas in the remaining 54 infants, daily enteral nutrition data were summarized as mean per week.

Morbidity. Twenty-two infants (22/76) were diagnosed with BPD, based on pathologic x-ray findings and need for oxygen supplementation at 36 wk PMA (30). Thirteen infants (13/76) had ROP stage 3 according to the International Classification (31). Four infants (4/76) had NEC with gut perforation and required surgery.

Mothers of seventeen infants (17/76) had preeclampsia and mothers of 14 infants had preterm rupture of the membranes (PROM, >24 h before delivery). A majority of the study group (56/76) received antenatal treatment with betamethasone (two doses, 12 mg i.v. given at 12-h interval). Postnatal treatment with dexamethasone (0.2–0.5 mg/kg/d, divided into two doses) was given for 3 d to 12 (12/76) infants in an attempt to shorten the time on the ventilator and to facilitate extubation, a regime used during the time of the present study. The dexamethasone was then tapered off over 4–5 d. If the infant could not be weaned off the ventilator, the treatment was repeated after approximately 1 wk.

IGF-I and IGFBP 3 analysis. Venous blood-samples (0.5 mL) were drawn weekly, and the serum was stored at −20°C to −80°C until assayed. All samples from an individual were analyzed in the same assay. IGF-I was measured in duplicate using an IGFBP-blocked RIA without extraction and in the presence of ~250-fold excess of IGF-II (32) (Mediagnost GmbH, Tübingen, Germany). The intra-assay coefficient of variation (CV) was 15.7% at 10.2 μg/L and 9.6% at 34.5 μg/L. The interassay CV was 23.9% at 10.2 μg/L and 12.1% at 34.5 μg/L.

IGFBP-3 was measured by RIA (Mediagnost GmbH) (32). The intra-assay CV was 6.9% at 900 μg/L, 6.9% at 1800 μg/L, and 7.4% at 3800 μg/L. The corresponding interassay CV was 15%, 14%, and 11%, respectively.

Statistical methods. A multiple regression analysis, allowing for repeated values within each individual, where IGF-I was assumed to be a function of the explanatory variables (PROC MIXED in SAS Release 8.12, SAS Institute, Cary, NC) was performed. With repeated measurements on the same individual, the values for different individuals are independent, whereas there is often a within-individual dependence. Therefore, the ordinary regression analysis is not suitable. Instead a random coefficient regression model can be estimated where the coefficients (a, b1, b2, etc.) are allowed to vary from one individual to the next. In our model, the intercept, a, is individual, allowing child 1 to have a different intercept than child 2, which means that the model of the development of serum IGF-I over time takes into account that each infant have its own starting level. In the random coefficient model, all values of all the study subjects were used.

As it has been reported that low IGF-I levels during wk 30–33 PMA are associated with morbidity (24), we also calculated the mean IGF-I value for

Table 1. *Gestational ages and birth weights in the study population ($n = 76$)*

	Gestational age (wk)				
	23–25 ($n = 20$)	26–27 ($n = 20$)	28–29 ($n = 23$)	30–31 ($n = 13$)	Total ($n = 76$)
Median birth weight (g)	760	858	1190	1385	1283
Range	530–950	685–1100	625–1540	710–1760	530–1760
Median birth weight (SDS)	−0.82	−1.28	−1.48	−1.37	−1.3
Range	−2.8 to 1.9	−3.5 to 0.8	−4.4 to 1.1	−5.0 to −0.6	−5.0 to 1.9
BW < −2 SD; boys (*n*)	2	5	1	1	9
BW < −2 SD; girls (*n*)	0	2	7	2	11

Table 2. *Number of infants exclusively enterally fed and those given parenteral nutrition in relation to median gestational age, median birth weight, and gender*

Nutrition	Enteral nutrition exclusively	Parenteral nutrition with fat and amino acids			
No. of days	0 (n = 28)	1–5 (n = 24)	6–10 (n = 13)	11–15 (n = 4)	>15* (n = 7)
Median gestational age (wk)	29.9	26.4	27.3	25.1	24.7
Range	24.9–31.7	24.7–29.6	25.0–30.1	24.4–25.3	23.6–26.6
Median birth weight (g)	1345	830	1195	700	700
Range	710–1760	530–1265	625–1475	640–950	530–950
Girls (n)	14	15	5	3	5
Boys (n)	14	9	8	1	2

* Includes four infants (one boy and three girls with necrotizing enterocolitis leading to surgery in whom partial parenteral nutrition were given for 19, 36, 44 and >155 d, respectively. Median gestational age, 24.9 wk (range, 24.4–29.6 wk); median birth weight, 737.5 g (range, 535–780 g).

each infant during this time interval. A linear regression analysis was performed to analyze which explanatory variables that affected the mean IGF-I during wk 30–33 (using SPSS Release 11.0.0, SPSS Inc., Chicago, IL). An adjusted R^2, with a correction for degrees of freedom, was used as a measure of model fit, with a correction for degrees of freedom. Thirteen infants were >30 wk of gestation at birth and thus did not have measurements during the investigated time period (wk 30–33 PMA) and were, as a consequence, excluded, leaving 63 infants in the analysis of the mean values of IGF-I.

The following were considered possible explanatory variables: PMA, birth weight (SD), gender (male), weight development (SDS), enteral energy-intake (kcal/kg), enteral intake of protein (g/kg), preeclampsia, PROM >24 h before delivery, and antenatal and/or postnatal treatment with corticosteroids. When no information regarding weight, energy, and protein intake was available on the day in which the sample for IGF-I was drawn, the values were estimated by interpolation. For kilocalorie and protein variables, the interpolation for the missing value at time t was made using a linear regression based on the measurement made at the nearest time point before t and the measurement made at the nearest time point after t. The interpolation concerning weight development was modeled as a function of time (polynomial of degree 4) and the missing values were interpolated using this function. Of the values used in the analysis, 87% were actual measurements. All enteral intake variables are expressed as the amount per kilogram.

The variables PMA (adjusting to comparable biologic maturity) and weight expressed in SDS were used, instead of number of days from birth and weight in grams. This made it possible to consider a deviation from expected weight according to age (33) as well as comparing the results between infants irrespective of gestational age at birth.

In the analysis of which factors are associated with the mean serum IGF-I level, the repeated observations on enteral intake of energy as well as protein were summarized for each child, as the number of days to reach 120 kcal/kg and 3.5 g/kg, respectively. In a corresponding way, the weight change (measured in SDS) was summarized as the number of days to reach the lowest weight (SDS) as well as the magnitude of the maximal postnatal decline in weight (SDS). Analysis of IGFBP-3 was performed in the same fashion as the IGF-I analysis. p Values < 0.05 were considered significant.

RESULTS

IGF-I: Change over time. The following variables were found to be significantly associated with the change in serum IGF-I: PMA (weeks), gender, weight (SDS), and enteral intake of protein (g/kg).

Postmenstrual age had a positive but nonlinear relationship with IGF-I ($p < 0.001$). Analyzing the study group divided into subgroups (infants with different GA at birth analyzed separately), the results indicate that, independent of GA at birth, the rate of changes in IGF-I decreased over time, *i.e.* the rate was not constant, although positive (data not shown). This nonlinearity in IGF-I is accounted for in the model by including a quadratic term for biologic age. The relationship between enteral protein intake and IGF-I was positive, as was the relationship between weight development and IGF-I ($p < 0.001$). After having accounted for age, gender, and weight (SDS), enteral protein intake was still a significant modulator of IGF-I ($p < 0.001$). When analyzing the relationship between protein supplementation of the breast milk and IGF-I changes (data not shown), the results indicated that before an attained weight of 2 kg, the average increase in IGF-I was stronger than after a weight of 2 kg when the average increase was still positive but not as strong (Fig. 1). There was also a positive relationship between IGF-I and total enteral energy intake (kcal). However, when PMA was included in the model, the kilocalorie variable was no longer significant.

Male gender was associated with lower IGF-I levels ($p < 0.001$) at all PMA (Fig. 2).

IGF-I: Mean value wk 30–33 PMA. In the analysis of mean serum IGF-I values during wk 30–33 PMA, the variables gender, birth weight (SDS), difference between birth weight SDS and lowest weight SDS (ΔSDS), and days until reaching an enteral intake of 3.5 g protein/kg were found to be significant. The adjusted R^2 was 0.51.

The relationship between the SDS for birth weight and mean IGF-I level was positive (the higher birth weight SDS, the higher the mean serum IGF-I level; $p < 0.001$), whereas male gender was associated with lower mean IGF- I levels ($p =$

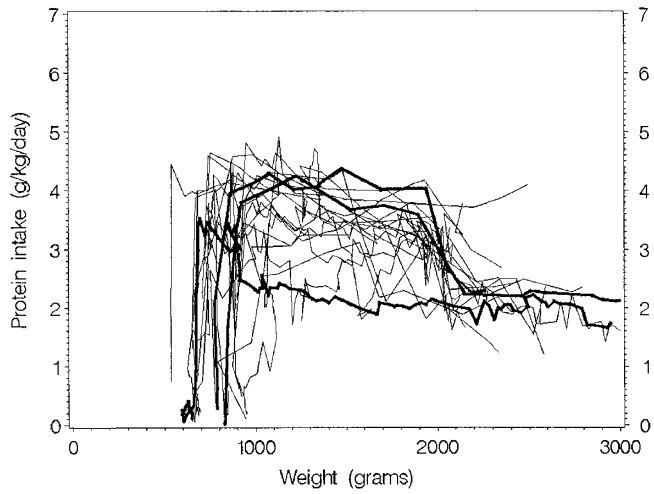

Figure 1. Daily protein intake (g/kg) in a subgroup of infants with gestational age >24 wk and <28 wk and birth weight <1000 g (n = 19) without any major clinical complications. *Heavy lines* exemplify three different infants. Tolerance to protein supplementation and termination because of direct breast feeding or attained size at approximately 2 kg influence the courses.

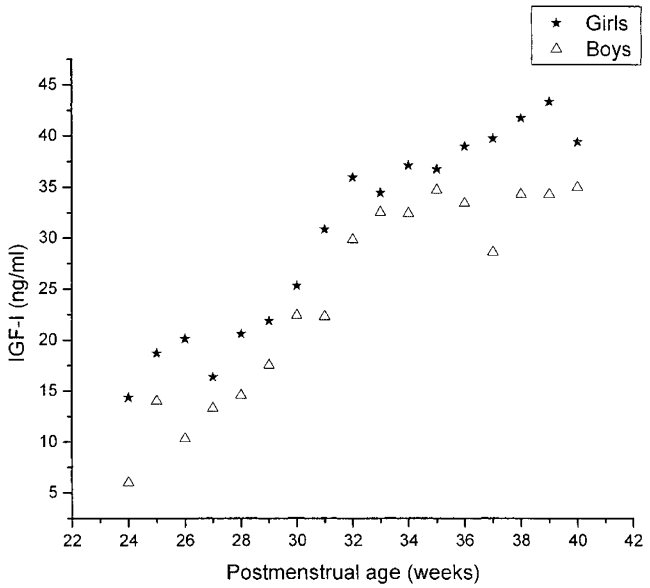

Figure 2. Mean values, in each gestational week, for all IGF-I samples drawn in girls and boys, respectively. Girls ($n = 42$) are depicted as *stars* and boys ($n = 34$) as *triangles*.

0.001). The children who had a poor weight gain also had lower mean serum IGF-I during wk 30–33 PMA ($p < 0.001$; Fig. 3). In addition, a longer time to reach a daily enteral intake of 3.5 g protein/kg was associated with a lower mean IGF-I level at wk 30 –33 PMA ($p = 0.006$). No association was observed between the mean IGF-I at wk 30–33 and the number of days to reach a daily oral energy intake of 120 kcal/kg.

For 54 infants, daily nutritional data were summarized as mean per week before calculation. This method was compared with a calculation from daily data for 22 infants. The two methods showed no differences in result.

Excluding the infants with morbidity from the analysis, the estimate of the model increased for enteral protein intake and weight (SDS) although the degree of significance was the same. The maternal factors—preeclampsia, PROM >24 h before delivery, or antenatal or postnatal with corticosteroids—did not have significant effect on postnatal serum IGF-I levels.

IGFBP-3: Change over time. In the random coefficient model (using PROC MIXED), the following variables were found to be significantly associated ($p < 0.001$) with the development of IGFBP-3: PMA (weeks), weight gain (SDS), and enteral intake of protein (g/kg).

There was no association between gender and longitudinal development of IGFBP-3 over time. Also, for IGFBP-3, a quadratic term for PMA was tried but was not significant, indicating a linear relationship with PMA and IGFBP-3. In the analysis of the change in IGFBP-3, neither infant morbidity, preeclampsia, nor antenatal treatment with corticosteroids was significant. However, PROM (>24 h before delivery) was followed by a more rapid rise in the IGFBP-3 values (data not shown).

IGFBP-3: Mean value wk 30–33 PMA. The analysis of the mean IGFBP-3 during wk 30–33 PMA revealed a significant relationship with birth weight (SDS; low birth weight SDS was associated with low mean IGFBP-3; $p < 0.001$), gender (lower mean IGFBP-3 for boys; $p = 0.027$; Fig. 4), and change in weight (large decrease in weight SDS was associated with low mean IGFBP-3; $p < 0.001$). We found no association between the enteral intake of protein and the mean value of IGFBP-3. In addition, the explanatory power of the model for IGFBP-3 was less than for IGF-I ($R^2 = 0.37$ *versus* $R^2 = 0.51$ for IGF-I).

Postnatal treatment with corticosteroids was not significant.

DISCUSSION

In this study, we found that enteral protein intake (g/kg), weight (SDS), gender, and PMA were associated with postnatal change in serum IGF-I levels in very preterm infants. The lower serum IGF-I levels among the most preterm infants at birth had no association with the attained mean value of serum

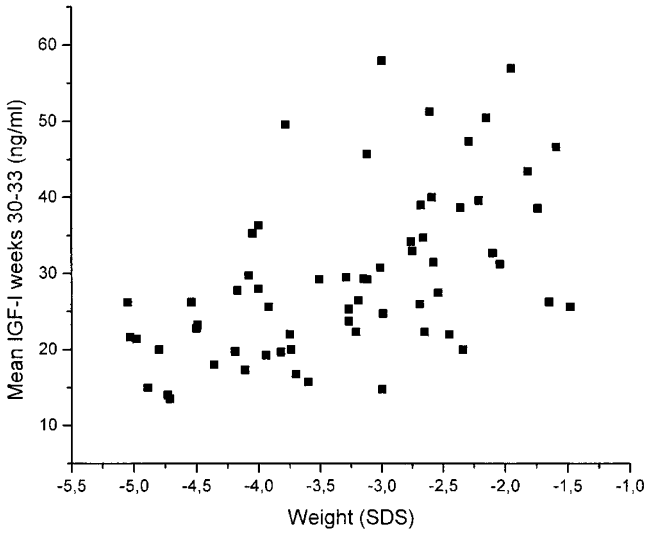

Figure 3. Scatterplot in 63 infants (PMA <30 wk) demonstrating an association between lowest weight (SDS) during the neonatal period and the mean IGF-I level in wk 30–33 ($R = 0.5$, $p = <0.001$).

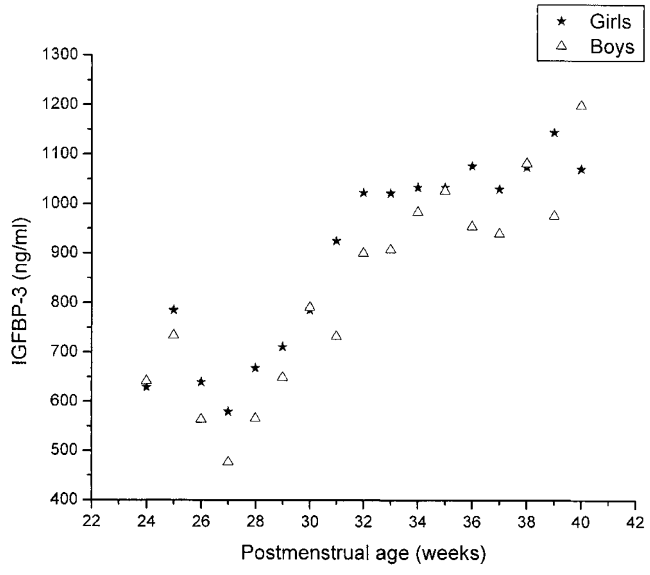

Figure 4. Mean values, in each gestational week, for all IGFBP-3 samples drawn in girls and boys, respectively. Girls ($n = 42$) are depicted as *stars* and boys ($n = 34$) as *triangles*.

IGF-I at wk 30–33 PMA. However, there was a significant association with PMA and IGF-I, reflecting the physiologic development over time (7,13,14).

It may be speculated that the introduction and withdrawal of protein-fortified breast milk is a determinant of the observed nonlinear relationship between PMA and the change in IGF-I over time, with a stronger positive relationship at a lower PMA than higher. In addition, the sooner the daily enteral intake of protein reached a level of 3.5 g /kg, the higher the mean IGF-I during wk 30–33. Furthermore, the protein content in breast milk is known to decline over time (34). These above-mentioned factors often coincide with weaning from tube-feeding and step-wise introduction of direct breast-feeding.

A positive influence of calorie intake upon IGF-I levels has been described (18,35,36). We also observed a relationship between IGF-I and calorie intake. However, when PMA was included in the model, the calorie variable was no longer significant. An explanation of the difficulties in estimating the effect of energy intake could be that this variable is highly correlated with protein intake and protein intake is more important than the energy intake in very preterm infants. Smith *et al.* (35) reported that increasing protein intake produced a quadratic increase in the IGF-I levels, whereas the relationship between calorie-intake and IGF-I was linear, which supports this possibility.

It has been suggested that the level of IGF-I may be an indicator of nutritional status, *i.e.* the uptake of nutrients in sick preterm infants (37). This study was an observational study and, based on estimated enteral intake, the causality cannot be proven. Interestingly, in the four infants requiring surgery for NEC, and thereafter experiences by periods of poor enteral nutrition, low levels of serum IGF-I were demonstrated (although not significantly different from the rest of the study group). The small number of observations or compensation by parenteral infused protein may explain this.

Preterm infants with AGA birth weight had higher serum IGF-I levels than infants born SGA or with a prolonged negative postnatal weight development. The analyses also indicated that poor weight gain, leading to postnatal growth retardation, resulted in lower levels of serum IGF-I. This is in line with reports stating that size at birth is correlated with the cord blood IGF-I concentrations (5,10,13,15–17).

AGA infants who are born preterm have increasing serum IGF-I and reach the same values at an age corresponding to term as infants born AGA at term (38). Thus, it seems that weight appropriate for age is as important at birth as during the neonatal period for increasing the serum IGF-I to the levels in AGA infants, and that postnatal growth retardation might be as harmful as intrauterine growth retardation.

We observed a gender difference in which boys had lower serum IGF-I and IGFBP-3 than girls, more pronounced for IGF-I, as has been described in older children (39,40). Results from measurements of IGF-I in serum of fetuses and preterm or term newborn infants have been more variable, as some groups find no difference in serum IGF-I concentrations between the male and female gender (6,10,13,15) and others report higher IGF-I in girls than boys (41,42). Reasons for this gender difference are not clear, but it has been suggested that differences in sex steroids could influence the secretion of IGF-I *in utero* (43).

None of our analyses revealed a strong relationship between maternal factors and postnatal serum IGF-I or IGFBP-3, although preeclampsia has been reported to be associated with an increased IGF-I concentration in the cord blood and an elevation of binding proteins in the wall of the umbilical artery (44). PROM is associated with intra-amniotic microbial invasion and inflammation (45). Inflammatory reactions have been reported to reduce serum IGF-I (46). In our limited study group, however, we found no association between PROM and serum IGF-I levels. There was, however, a significant elevation of the serum IGFBP-3.

Neither antenatal nor postnatal treatment with corticosteroids appeared to alter serum IGF-I significantly. An explanation for this may be that we used moderate doses of dexamethasone for short periods to facilitate extubation. A single dose of dexamethasone has been reported not to affect the GH–IGF-I axis in pregnant women (47), and Kajantie *et al.* (41) and Bloomfield *et al.* (42) have indicated that the influence of corticosteroids on IGF-I and IGFBP-3 might be dose dependent.

Low serum levels of IGF-I in preterm infants have been shown to be associated with increased morbidity. It has been suggested that an early lack of IGF-I followed by a slow increase could predispose to the development of ROP (23,24). It has also been shown that the greater the duration of low IGF-I, the more severe the ROP (25).

In conclusion, our results indicate that the degree of prematurity, a low enteral protein intake, male gender, and slow weight gain or weight loss are associated with a slower longitudinal postnatal increase of serum IGF-I in preterm infants.

Future studies may reveal whether enhanced nutrition or other interventions, such as supplementation of IGF-I, will affect the postnatal serum IGF-I levels, or whether restoring serum IGF-I levels to intrauterine levels is of benefit in preterm infants.

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