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ORIGINAL ARTICLE

Preterm birth and the endocrine regulation of growth in childhood and adolescence

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Summary

Objective Poor growth during childhood is a common problem associated with preterm birth, but few studies have examined the associations between linear growth, weight and body composition with the postnatal hormonal milieu in preterm children. We aimed to define the IGF-IGFBP axis in preterm children and its association with growth.

Design and patients A cohort of healthy 2- to 20-year-old subjects who were born prematurely (<37 weeks gestation) and experienced normal neurological development were recruited. In total, 54 premature and 82 control subjects were included in this study.

Results Preterm subjects were relatively shorter ($P < 0{\cdot}001$) and leaner ($P < 0{\cdot}05$) than their parents in contrast to the term cohort. Preterm children also appeared to fail to reach their genetic height potential (prepuberty: $P < 0{\cdot}01$; puberty: $P < 0{\cdot}05$). Only IGFBP-2 differed between preterm and term cohorts, with higher levels observed in prepubertal preterm subjects ($P < 0{\cdot}01$). In the term group, height SDS was positively associated with IGF-I ($P < 0{\cdot}01$) and IGFBP-3 ($P < 0{\cdot}001$) concentrations, but no such associations were observed for preterm subjects.

Conclusion Preterm children are shorter and lighter than controls throughout childhood, remaining below their genetic height potential. Preterm birth appears to alter the endocrine regulation of postnatal growth in childhood and adolescence, so growth is no longer associated with its normal endocrine regulators.

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Introduction

Poor growth during childhood is a common problem associated with preterm birth, especially in those born at lower gestational ages.[1] Previous studies reported that preterm birth was associated with an increased risk of later short stature and a reduction in height potential relative to parental height,[2] but more recent data suggest that normal height is usually achieved.[1] Early catch-up growth occurs in the majority of these children, so 85% are in the normal range by 2 years of age.[3] In addition, children born preterm but appropriate for gestational age (AGA) seem to experience ongoing catch-up growth throughout childhood and into adolescence.[4] Studies in the Dutch premature cohort showed that preterm healthy AGA children reached normal height when correction was made for parental height.[1] Further, it was demonstrated that shorter final height generally only occurred in small for gestational age (SGA) preterm children.

Nonetheless, preterm birth leads to metabolic and growth alterations that are similar to those associated with being born SGA.[5–7] Both groups are exposed to early environmental stress involving variable nutritional restriction during a similar developmental period. However, while in SGA subjects this occurs *in utero*, this insult is primarily postnatal in preterm subjects. Despite these similarities, the pattern of growth in SGA children is different to that observed in preterm children.

Weight and body composition in preterm cohorts are not well characterized, but longitudinal data indicate that preterm birth is associated with increased weight and adiposity in early adulthood.[8] In addition, few studies have examined the associations between linear growth, weight and body composition with the postnatal hormonal milieu in preterm children. While IGF-I and IGFBP-3 are moderately well correlated with height in normal populations,[3,9] no data are available relating these growth factors to height and weight in preterm subjects during childhood. As the tempo of growth is altered in preterm subjects, we hypothesize that the endocrine regulation of growth is also altered. Thus, our study aimed to define the IGF-IGFBP axis in preterm children and its association with growth.

Methods

A cohort of healthy 2- to 20-year-old subjects who were born prematurely and experienced normal neurological development were recruited through a database of preterm survivors at the National Women's Hospital and the Auckland City Premature Play-Group

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(both in Auckland, New Zealand). Prematurity was defined as <37 weeks gestation, and all participants were from singleton pregnancies. Exclusion criteria included being born SGA (defined as a birth weight <-2 SDS), having chronic illness, chromosomal or syndromal diagnosis, or being administered medication known to affect growth. The control group included otherwise healthy children and adolescents born at term from singleton pregnancies.

All subjects were admitted to the Maurice and Nessie Paykel Clinical Research Unit (Liggins Institute, University of Auckland) on the morning of the test. Height and weight were measured on both the parents and the subject, with body mass index (BMI) subsequently calculated. All subjects had pubertal development assessed by an experienced paediatric endocrinologist (PLH). Growth data for both parents and subjects were converted to standard deviation scores (SDS) to correct for age and gender.[10,11] The parents' growth data were combined into a mid-parental height SDS and a mid-parental weight SDS.

Venous blood samples were collected and the serum frozen at −80 °C for later analysis. Assays for insulin-like growth factor I (IGF-I), IGF-II, IGF binding protein 1 (IGFBP-1), IGFBP-2, IGFBP-3 and growth hormone binding protein (GHBP) were performed following completion of subject recruitment. Hormones were measured using commercially available kits. Serum IGF-I (Immulite 2000 IGF-I; Siemens, Los Angeles, CA, USA) with an intra-assay coefficient of variation of 8·7%. Intra-assay and interassay coefficients of variation were, respectively, 3·1% and 6·4% for IGF-II (ELISA DSL-10-9100; Diagnostic Systems Laboratories, Inc., Webster, TX, USA), 2·9% and 6·9% for IGFBP-1 (ELISA DSL-10-7800; Diagnostic Systems Laboratories, Inc.), 2·0% and 3·9% for IGFBP-2 (ELISA DSL-10-7100; Diagnostic Systems Laboratories, Inc.), and 8·8% and 10·0% for IGFBP-3 (ELISA DSL-10-6600; Diagnostic Systems Laboratories, Inc.). GHBP (ELISA DSL-10-48100; Diagnostic Systems Laboratories, Inc.) was measured by radioimmunoassay, with intra-assay and interassay coefficients of variation of 4·5% and 6·6%, respectively.

Approval for the study was provided by the Northern X Ethics Committee. Informed written consent was obtained from all parents or guardians and older subjects. In younger subjects, oral consent was also obtained.

General linear regression models (GLMs) were used to investigate the differences in baseline characteristics and auxology. Hormone secretion is extensively affected by puberty, so prepubertal and pubertal populations were analysed separately. Plasma hormone concentrations were compared between groups using GLMs, with sex included as a factor, and age and BMI SDS as covariates. GLMs were also used to investigate the hormonal associations with auxological measurements. For the latter analyses, all data were combined, and GLMs were run with group (preterm *vs* term), pubertal status and sex as factors, and age and BMI SDS as covariates. All analyses were carried out in Minitab (Minitab v.15, Pennsylvania State University, USA). When necessary, data were normalized using the Johnson transformation. Significance was defined as $P < 0{\cdot}05$. All data are expressed as means ± standard error of the mean (SEM).

Results

Auxology

Fifty-four premature and 82 control AGA subjects were recruited, and their characteristics are shown in Table 1. SGA subjects were excluded, so birth weight SDS was similar in term and preterm groups (Table 1). Groups were of similar age, and approximately one-third of each group were in puberty (Table 1). Children in the preterm group were born of parents with lower mean parental height SDS ($P < 0{\cdot}05$; Table 1).

Among prepubertal subjects, despite adjusting for significant differences in mid-parental height, preterm children were shorter ($P < 0{\cdot}001$), lighter ($P < 0{\cdot}001$) and leaner ($P < 0{\cdot}01$) than those born at term (Table 2). Prepubertal subjects born prematurely were also relatively shorter than their parents in contrast to the term cohort ($P < 0{\cdot}01$; Table 2), even when parental anthropometry were accounted for. Height SDS across all subjects was positively associated with gestational age ($r^2 = 0{\cdot}15$, $P < 0{\cdot}001$; Fig. 1).

Differences in height and weight between the two groups persisted into puberty, but preterm children were no longer leaner than controls displaying similar BMI SDS (Table 2). Nonetheless, pubertal preterm children were still below their genetic height potential ($P < 0{\cdot}05$; Table 2).

Hormones

Of the hormones assessed, only IGFBP-2 differed between preterm and term cohorts with higher levels observed in prepubertal preterm subjects (641 ± 30 *vs* 536 ± 26 ng/ml, $P < 0{\cdot}01$). However, this association was no longer significant during puberty despite the suggestion of higher concentrations among preterms (389 ± 31 vs 478 ± 42 ng/ml, $P = 0.23$).

In the term cohort, height SDS was positively associated with IGF-I ($P < 0{\cdot}01$) and IGFBP-3 ($P < 0{\cdot}001$) concentrations (Fig. 2). However, no such associations were seen in the preterm cohort (Fig. 2).

As preterm birth did not affect most hormone levels, potential associations were examined with both cohorts combined (with term *vs* preterm as a factor in the model). Age was positively

Table 1. Characteristics of children born prematurely (Prem) or at term (Control)

Characteristics	Control	Prem
N	82	54
Age (years)	9·8 ± 0·4	8·7 ± 0·5
Males (%)	51	42
Gestational age (weeks)	39·6 ± 0·2	30·3 ± 0·5***
Range (weeks)	37–42	23–36
Birth weight (g)	3477 ± 48	1540 ± 97***
Birth weight SDS	0·11 ± 0·1	0·00 ± 0·15
Pubertal (%)	33	31
Mid-parental height SDS	0·26 ± 0·09	−0·07 ± 0·11*

Data are mean ± SEM. *$P < 0{\cdot}05$, ***$P < 0{\cdot}001$ *vs* Control.

Table 2. Characteristics of prepubertal and pubertal children born prematurely (Prem) or at term (Control)

	Prepubertal		Pubertal	
Characteristics	Control	Prem	Control	Prem
N	55	37	27	17
Age (years)	7·8 ± 0·2	7·0 ± 0·4*	13·9 ± 0·5	12·6 ± 0·4
Males (%)	55	46	44	29
Height SDS†	0·51 ± 0·13	−0·47 ± 0·18***	0·75 ± 0·22	−0·28 ± 0·25**
Weight SDS†	0·45 ± 0·13	−0·57 ± 0·20***	0·85 ± 0·20	−0·03 ± 0·30*
BMI SDS†	0·22 ± 0·15	−0·44 ± 0·19**	0·55 ± 0·21	0·22 ± 0·38
(Height SDS) − (MP height SDS)†	0·23 ± 0·14	−0·43 ± 0·21**	0·52 ± 0·18	−0·15 ± 0·25*

MP, mid-parental. Data are mean ± SEM. *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$ *vs* Control. †Significant differences remained after adjustment for parental variables.

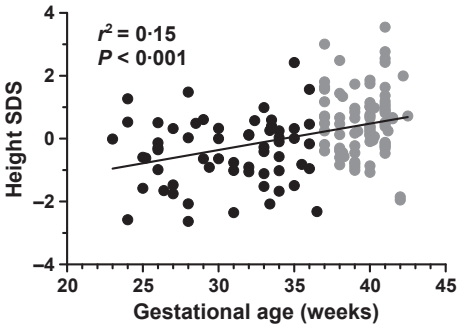

Fig. 1 The association between gestational age and height SDS. Black circles represent premature subjects, and grey circles those born at term.

associated with IGF-I ($P < 0·001$), IGF-II ($P < 0·01$), IGFBP-3 ($P < 0·001$) and GHBP ($P < 0·01$). BMI SDS was also positively associated with IGF-I ($P < 0·001$), IGFPB-3 ($P < 0·05$) and GHBP ($P < 0·001$). However, both age and BMI SDS were negatively associated with IGFBP-1 and IGFBP-2 (all $P < 0·001$). In addition, female subjects had higher concentrations of plasma IGFBP-3 ($P < 0·05$) and GHBP ($P < 0·01$), but lower IGFBP-2 ($P < 0·05$) than male subjects.

Discussion

This study showed that preterm subjects are shorter and lighter than controls throughout childhood. Although preterm children were leaner prior to the onset of puberty, these differences were no longer observed among pubertal subjects. This reduced leanness in pubertal preterm subjects may reflect growing adiposity during childhood and adolescence.[8,12,13] Longitudinal follow-up into later adulthood will be important to determine whether this group continues to have accelerated fat mass accumulation, a situation already reported in adults born SGA.

We also observed that preterm subjects in our study were shorter than their genetic height potential. Height during childhood in preterm subjects is consistently reported as lower than expected, both

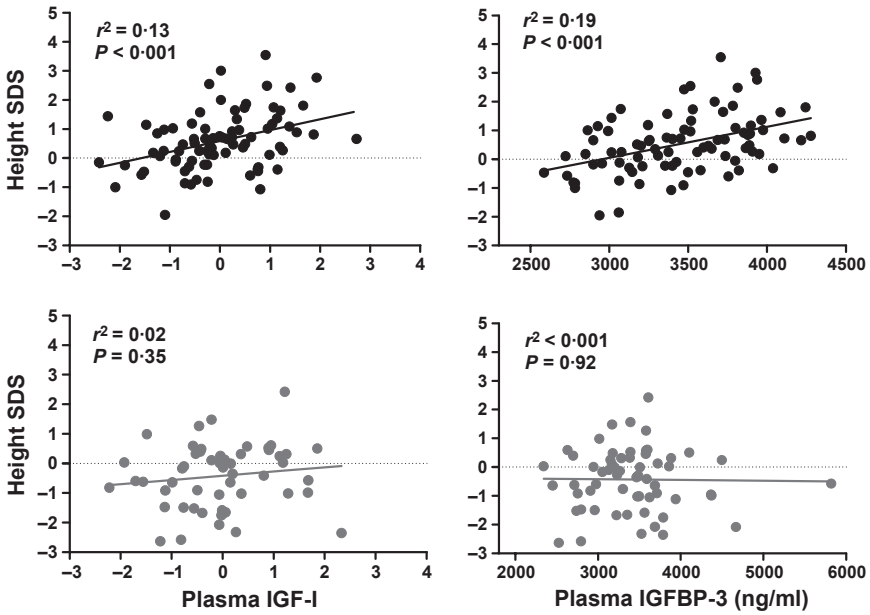

Fig. 2 The association between height SDS and plasma IGF-I and IGFBP-3 concentrations in term (black) and preterm (grey) groups. Note that plasma IGF-I data have been normalized (using Johnson transformation).

compared with healthy term controls and with genetic potential.[14] However, recent data suggest final height in healthy preterm AGA children is not compromised, but the tempo of growth is altered, so ongoing catch-up growth in height and weight are observed up to and including pubertal years.[15,16] This may explain why our preterm subjects have not yet reached their genetic height potential, especially as the mean age in the pubertal group was 12·6 year.

While growth restriction has been noted at gestations <32 weeks and/or birth weight <1500 g, the effect at 32–36 weeks gestation are less clear.[8,17] This study demonstrates that the effect of gestation on height is continuous, with reduction in height during childhood observed even among those born 32–37 weeks gestation.

Interestingly, preterm birth appears to have altered the associations between height and plasma IGF-I and IGFBP-3 concentrations, known endocrine regulators of growth. Hormonal regulation (via growth hormone secretion) results in direct effects in the growth plate, as well as indirect effects primarily via the induction of hepatic IGF-I and IGFBP-3. There is a modest correlation between height and IGF-I and IGFBP-3 concentrations in humans,[18,19] as observed in our term controls. In contrast, no correlation was observed in the preterm cohort. This was not attributed to reduced systemic IGF-I or IGFBP-3 concentrations, as their relative amounts were unchanged (data not shown), which indicates normal hepatic production and secretion.

IGFBP-2 was the only growth factor that differed between premature and term subjects. Nutrition is one of the main regulators of IGFBP-2, and increased levels are observed in association with anorexia nervosa and prolonged fasting.[20] In particular, protein restriction increases IGFBP-2 concentrations, which return to normal levels only with a high-protein diet.[21] IGFBP-2 is widely expressed during foetal development and (along with IGFBP-1) is a major binding protein in utero.[22] Preterm birth is associated with elevated IGFBP-2 levels that decrease postnatally with age and increasing dietary protein consumption.[23] We speculate that this early nutritional insult leads to persistent alterations in IGFBP-2 regulation, which results in a later increase in IGFBP-2, possibly related to alterations in protein intake in later childhood.

In summary, this study showed that preterm subjects are shorter and lighter than controls throughout childhood. Preterm children remain below their genetic height potential even into early adolescence. Importantly, preterm birth appears to alter the endocrine regulation of postnatal growth in childhood and adolescence, so growth is no longer associated with the normal hepatic regulators of growth. Further, plasma IGFBP-2 concentrations were higher in preterm children, which may reflect nutrition abnormalities in the perinatal period.

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Disclosure

The authors have no conflicting interests and have nothing to disclose.

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