Original Paper

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr 2015;84:298–304
DOI: 10.1159/000439233

Received: May 13, 2015
Accepted: July 31, 2015
Published online: September 9, 2015

# Response to IGF-1 Generation Test in Short Prepubertal Children Born Very Preterm or at Term

Harriet L. Miles[a] José G.B. Derraik[a] Valentina Chiavaroli[a] Paul L. Hofman[a, b] Wayne S. Cutfield[a, b]

[a]Liggins Institute, University of Auckland, and [b]Gravida: National Centre for Growth and Development, Auckland, New Zealand

**Key Words**
Preterm children · Premature birth · Growth hormone sensitivity · Insulin-like growth factor-1

**Abstract**
***Aims:*** To investigate whether short children born very preterm (<32 weeks of gestation) exhibit features of growth hormone (GH) resistance compared to term peers. ***Methods:*** We studied 26 prepubertal children (aged 7.0 ± 2.0 years) with short stature (height adjusted for parents' heights <10th percentile), who were born appropriate for gestational age and either very preterm (n = 11) or at term (n = 15). Children underwent insulin-like growth factor-1 (IGF-1) generation test via a daily recombinant human GH (rhGH) dose (0.05 mg/kg/day) over 4 consecutive days. Hormone and binding proteins were measured at baseline and day 5. ***Results:*** At baseline, preterm children had lower IGF-binding protein 1 (IGFBP-1; –22%; p = 0.049) and IGFBP-3 (–24%; p = 0.013) concentrations than term children. Preterm children also had insulin concentrations that tended to be 39% higher (p = 0.059) than term peers. After stimulation, IGF-1 and IGFBP-3 concentrations increased similarly in term and preterm groups, while GH-binding protein (GHBP) concentrations decreased in both groups. Preterm children had higher GHBP (+50%; p = 0.049), insulin (+86%; p = 0.005), and leptin (+107%; p = 0.020) but lower IGFBP-1 (–47%; p = 0.006) concentrations than term children following rhGH stimulation. ***Conclusions:*** Preterm children who are short for genetic height potential show no evidence of GH resistance that would explain their short stature. However, there was indirect evidence of insulin resistance in the preterm children, as previously described in this group. 

## Introduction

More than 10% of all babies worldwide are born preterm (<37 weeks of gestation) [1], with 1–2% of babies being born very preterm (<32 weeks of gestation) [2]. Over the last decades, prognosis for low birth weight and preterm infants has continuously improved. In the UK, survival for infants born at 22–25 weeks at University College London Hospitals progressively increased from 32 to 71% over the period 1981–2000 [3].

It has been proposed that different adverse exposures in early postnatal life lead to programming effects in various systems/tissues with a common short stature phenotype [4]. The concept of a thrifty phenotype has emerged


1663–2818/15/0845–0298$39.50/0

E-Mail karger@karger.com
www.karger.com/hrp

Wayne S. Cutfield
Liggins Institute, University of Auckland
Private Bag 92019
Auckland 1142 (New Zealand)
E-Mail w.cutfield@auckland.ac.nz

whereby adverse exposures in fetal and early infant life result in compensatory responses to maximize chances of survival, with this programming persisting into adult life [5]. In children born preterm, the period equivalent to the third trimester occurs ex utero, and could result in inappropriate nutrition and increased physiological stress. Thus, preterm birth is likely associated with acute adaptive responses to maximize survival in a postnatal environment that is suboptimal in comparison to in utero conditions [6]. When there is a mismatch in the environment predicted between this sensitive period and that experienced in later life, these programmed responses can become maladaptive [7]. The findings of a persistent reduction in insulin sensitivity in preterm survivors are a good example of this [8].

Both insulin and the insulin-like growth factor (IGF) system are among the main modulators of human fetal growth [9], and different IGF isoforms are widely expressed in multiple fetal tissues from the first trimester of pregnancy [10]. Maternal nutritional status represents the most important regulator of fetal IGF-1, principally through glucose availability across the placenta [11], with the subsequent rise in insulin levels regulating secretion of fetal hepatic IGF-1. There is a progressive increase in circulating fetal IGF-1 levels throughout pregnancy [10], with a positive correlation between fetal cord serum IGF-1 and birth weight [9]. As modulators of IGF actions, IGF-binding proteins (IGFBPs) also play a significant role in the process of fetal growth, with fetal IGFBP-1 levels being inversely correlated with birth weight [9].

Growth hormone (GH) secretion is influenced by many neuroendocrine, hormonal, and metabolic factors [12, 13], and at birth there is a switch from a relatively GH-resistant status in utero (characterized by high GH concentrations and reduced GH receptor density) to the complete activation of the GH/IGF-1 axis [14, 15]. However, this switch in preterm infants is still poorly understood. Elevated circulating GH levels in infancy and low IGF-1 and IGFBP-3 levels during the postnatal period and mid-childhood have been reported in those born preterm, suggesting that growth in these subjects may be constrained by partial GH resistance [15–17]. Therefore, it is conceivable that adaptations in preterm babies to their immediate postnatal environment may permanently alter the GH/IGF-1 axis.

A number of studies have shown that preterm birth is associated with adverse metabolic outcomes in childhood and adulthood [8, 18, 19]. There is growing evidence that children born preterm also have abnormalities of the GH axis, and it appears that preterm birth alters the endocrine regulation of postnatal growth in childhood and adolescence [6]. Although children born preterm can appear shorter than those born at term [6, 20, 21], the majority experience ongoing catch-up growth during childhood and adolescence, so that final height is usually appropriate for parental heights [22] and within the normal range [23, 24]. However, approximately 10% of children born very preterm will present an impairment of linear growth and will become short adults [4].

Marked prematurity seems to be associated with greater GH secretion in early infancy due to increased production rates with height burst amplitude [16, 17]. With increasing prematurity, a trend towards greater abnormalities of the GH/IGF-1 axis has been observed. Infants born <32 weeks of gestation have urinary GH levels that are 7- to 72-fold higher in early infancy in comparison to either term or preterm children born 34–37 weeks of gestation [25, 26]. In addition, it has been reported that prepubertal children born very preterm have low IGF-1 and IGFBP-3 concentrations despite elevated GH levels [27], which is consistent with the hypothesis that marked prematurity might be associated with GH resistance. However, formal assessment of GH secretion and action in mid-childhood has not yet been examined on subjects born very preterm.

Therefore, we aimed to investigate whether prepubertal children born very preterm with short stature exhibit features of GH resistance in comparison to term peers in response to recombinant human GH (rhGH) stimulation.

## Methods

*Ethics*

Ethics approval for this study was granted by the Auckland Ethics Committee (approval number AKY/03/06/135). Written informed consent was obtained from parents or guardians, as well as verbal or written consent from each child as was appropriate to their age.

*Participants*

The Endocrinology Service at Starship Children's Health (Auckland, New Zealand) provides specialist care for all children aged <15 years in the Auckland region (population approximately 1.5 million). Children born very preterm (<32 weeks of gestation) or at term (37–41 weeks of gestation) were identified from the clinic's database. All recruited children had short stature relative to their genetic potential, which was defined as height standard deviation score (SDS) adjusted for mid-parental height SDS (MPHSDS) below the 10th percentile (<–1.31 SDS) and a normal height velocity (defined as >25th percentile).

All recruited participants were aged 4–11 years, naturally conceived, from singleton pregnancies and born appropriate for gestational age (defined as birth weight >–2 SDS). Participants were prepubertal, otherwise healthy, and developmentally normal, with no specific endocrine abnormalities and no evidence of physical or psychological disease. Exclusion criteria included signs of puberty (Tanner stage 2 breast development in girls and testicular volume >3 ml in boys or evidence of adrenarche), genetic syndromes, GH deficiency, chronic illnesses or known medical syndromes, or receiving medication known to influence growth.

*Clinical Assessments*

All children were assessed at the Maurice and Agnes Paykel Clinical Research Unit (Liggins Institute, University of Auckland) after an overnight fast, with assessments carried out at baseline and at day 5. Birth weight data were recorded and transformed into SDS [28]. Children's heights were measured to the nearest millimetre using a Harpenden stadiometer. Weight was recorded to the nearest 0.1 kg using electronic scales in light clothing and no footwear. Height SDS were derived from Tanner/Whitehouse reference data [29], and body mass index (BMI) SDS according to British 1990 standards [30]. Maternal and paternal heights were recorded for all participants, and MPHSDS calculated using standard formulas [31].

IGF-1 generation tests were performed using rhGH at 0.05 mg/kg/day (Genotropin, Pfizer, N.Y., USA), administered in the home environment at 20:00 h over 4 consecutive evenings. The child's main carer was taught how to administer GH with a pen delivery device when they attended our centre on day 1; telephone advice was also available for the families throughout the study. Empty vials were collected to ensure compliance with GH administration.

Blood samples were taken at 08:00–10:00 on day 1 (baseline) and day 5 (rhGH stimulated) for assessment of growth factors and metabolic markers, which were likely to be influenced by rhGH administration. Thus, parameters measured included IGF-1, IGFBP-1, IGFBP-3, GH-binding protein (GHBP), insulin, leptin, and alkaline phosphatase. Blum's scoring system was used to assess GH sensitivity, where an increase in IGF-1 of <15 ng/dl and an increase in IGFBP-3 of <0.4 mg/l after a 4-day GH stimulation test indicates GH insensitivity [32].

*Assays*

Insulin was measured by enzyme immunoassay [IMX microparticle assay, Abbott Laboratories, Chicago, Ill., USA; inter-assay coefficient of variation (CV) <5%]. IGF-1 was measured using an Immulite analyser (Diagnostic Products Corporation, Los Angeles, Calif., USA; inter-assay CV = 9.3%). Commercially available enzyme-linked immunosorbent assays (Diagnostic Systems Laboratories, Webster, Tex., USA) were used to evaluate plasma IGFBP-1 (DSL-10-7800; intra-assay CV = 1.7%; inter-assay CV = 6.2%), IGFBP-3 (DSL-10-6600; intra-assay CV = 7.3%; inter-assay CV = 8.2%), and GHBP (DSL-10-48100; intra-assay CV = 4.8%; inter-assay CV = 5.1%). Alkaline phosphatase was measured in the laboratory at Auckland City Hospital. Due to the stable liver alkaline phosphatase levels in the age group studied, total alkaline phosphatase measurements were used rather than bone-specific alkaline phosphatase. IGF-1 values were transformed into SDS using reference range data from the Immulite assay manufacturer (Siemens).

**Table 1.** Demographic and anthropometric characteristics of children with short stature who were born at term or very preterm

| | Term | Preterm | p value |
|---|---|---|---|
| *Demography and birth parameters* | | | |
| Total children | 15 | 11 | |
| Age, years | 7.4±2.0 | 6.4±1.9 | 0.18 |
| Males, % | 67 | 55 | 0.69 |
| Gestational age, weeks | 39.3±0.8 | 27.0±2.4 | <0.0001 |
| Birth weight SDS | –0.58±0.97 | –0.44±1.17 | 0.75 |
| MPHSDS | –0.36±0.49 | 0.50±0.60 | <0.0001 |
| *Anthropometry* | | | |
| BMI SDS | –0.41±0.92 | –1.38±1.13 | 0.024 |
| Height SDS | –2.43±0.35 | –1.75±0.73 | 0.002 |
| Height SDS – MPHSDS | –2.05±0.63 | –2.22±0.67 | 0.53 |

Values are expressed as means ± SD unless otherwise indicated.

*Statistical Analyses*

Sex ratio and ethnic composition in both groups were compared with Fisher's exact tests, while demographic data were compared with one-way ANOVA (Minitab v.16, Pennsylvania State University, State College, Pa., USA). General linear regression models (SAS v.9.3, SAS Institute Inc., Cary, N.C., USA) were used to compare outcome responses between preterm and term children. Important confounding factors were adjusted for in the analyses, including sex, birth weight SDS, age, and BMI SDS. All statistical tests were two-tailed and maintained at a 5% significance level. Demographic data are presented as means ± standard deviation. Outcome data are presented as model-adjusted means (estimated marginal means adjusted for the confounding factors in the models), with associated 95% confidence intervals.

## Results

A total of 26 children aged 7.0 ± 2.0 years were recruited, including 11 born very preterm and 15 born at term. Participants were mostly boys (62%) and of New Zealand European ethnicity (88%). Based on Blums' scoring system, no participants had IGF-1 generation test results suggestive of GH insensitivity [32].

*Auxology*

There were no differences in age, sex ratio, and birth weight SDS between the two groups. Preterm children were 0.74 SDS taller than term children and had taller parents. However, when heights were adjusted for genetic potential (height SDS – MPHSDS), there were no significant differences in stature between the two groups, with both very preterm and term children being on aver-

**Table 2.** Concentrations of parameters measured in plasma at baseline and after rhGH stimulation in children of short stature born at term or very preterm

| | Baseline | | After rhGH stimulation | |
|---|---|---|---|---|
| | term | preterm | term | preterm |
| Total children | 15 | 11 | 15 | 11 |
| IGF-1, ng/ml | 76 (62 to 93) | 85 (67 to 107) | 169 (143 to 201)$^{††††}$ | 170 (140 to 207)$^{††††}$ |
| IGF-1 SDS | –1.34 (–1.84 to –0.84) | –1.10 (–1.67 to –0.52) | 0.50 (0.07 to 0.92)$^{††††}$ | 0.51 (0.02 to 1.00)$^{††††}$ |
| IGFBP-1, ng/ml | 107 (92 to 121) | 83 (66 to 100)* | 125 (101 to 150) | 66 (38 to 94)** |
| IGFBP-3, ng/ml | 4,092 (3,621 to 4,563) | 3,096 (2,556 to 3,636)* | 4,948 (4,365 to 5,532)$^{††}$ | 3,949 (3281 to 4618)*, $^{†††}$ |
| GHBP, pmol/l | 412 (297 to 572) | 573 (411 to 801) | 328 (246 to 436)$^{†††}$ | 491 (339 to 712)*, $^{†}$ |
| Alkaline phosphatase, U/l | 227 (181 to 274) | 222 (157 to 287) | 209 (173 to 245) | 233 (187 to 278) |
| Leptin, ng/ml | 4.76 (3.33 to 6.20) | 5.23 (3.45 to 7.01) | 2.87 (2.02 to 4.08) | 5.93 (3.85 to 9.15)* |
| Insulin, mU/l | 2.93 (2.01 to 3.85) | 4.06 (3.00 to 5.12) | 3.44 (2.62 to 4.52)$^{†}$ | 6.41 (4.66 to 8.83)**, $^{††}$ |

Values are expressed as means (95% confidence intervals) adjusted for confounding factors in the multivariate models. * $p < 0.05$ and ** $p < 0.01$ for comparisons between term and very preterm groups. $^{†}$ $p < 0.05$, $^{††}$ $p < 0.01$, $^{†††}$ $p < 0.001$, and $^{††††}$ $p < 0.0001$ for a change from baseline following rhGH stimulation.

age more than 2 SDS shorter than their parents. Preterm children also had BMI 0.97 SDS lower than that of term children, underpinning the importance of adjusting for BMI in the analyses conducted (table 1).

*Baseline*

At baseline, preterm children had lower IGFBP-1 (–22%; p = 0.049) and IGFBP-3 (–24%; p = 0.013) concentrations than term children, but there were no differences in IGF-1 or GHBP concentrations between the two groups. Preterm children also had insulin concentrations that tended to be 39% higher (p = 0.059), but baseline concentrations of leptin (p = 0.70) and alkaline phosphatase (p = 0.90) were not different. Note that term and preterm participants in our cohort had relatively low baseline IGF-1 SDS values, likely reflecting that these children were slim and short (factors known to be associated with lower IGF-1 levels; table 2).

*Response to rhGH Stimulation*

Both groups showed marked increases in IGF-1 concentrations with rhGH stimulation (table 2), with changes from baseline in term and preterm groups of 100 and 90 ng/ml, respectively (p = 0.59), and 134 and 105%, respectively (p = 0.24). Note that although the preterm group was not GH resistant, increasing severity of short stature was correlated with greater GH resistance (i.e. lower percent change in IGF-1 levels; r = 0.60; p = 0.037).

IGFBP-3 concentrations also increased, while GHBP concentrations decreased in both preterm and term groups. After stimulation, preterm children had higher GHBP concentrations (+50%; p = 0.049) but lower IGFBP-1 (–47%; p = 0.006) and IGFBP-3 (–20%; p = 0.040) concentrations than term children. Insulin concentrations increased by 18% in term children (p = 0.013) but by 58% in preterm children (p = 0.010). Thus, insulin levels were 86% higher in the preterm group (p = 0.005) following rhGH stimulation (table 2).

Concentrations of both leptin (–39%, p = 0.053) and alkaline phosphatase (–8%, p = 0.056) tended to decrease in term children, but these were unchanged in preterm children. As a result, after rhGH stimulation leptin concentrations were 107% higher in preterm children (p = 0.020; table 2).

## Discussion

This study showed that, within a cohort of prepubertal subjects with short stature, children born very preterm had a similar response to rhGH stimulation as short children born at term, with an appropriate increase in IGF-1 and no evidence of GH insensitivity. However, there was evidence of insulin resistance in preterm children, as reflected by higher baseline and stimulated insulin levels as well as lower IGFBP-1 concentrations than in those born at term.

The standard dynamic test of GH sensitivity, the IGF-1 generation test, is a component of clinical investigation in endocrine practice to assess GH receptor availability

and hepatic production of the IGF-1/IGFBP system [33]. Although this dynamic test has been used for approximately three decades in the investigation of short stature, it seems that no studies have previously examined the response to the IGF-1 generation test in those born very preterm. Following rhGH stimulation, we observed a similar increase in IGF-1 and IGFBP-3 levels in preterm and term children, showing no evidence of impairment of the GH/IGF-1 axis or hepatic resistance in our group of short children born very preterm.

The available evidence on the GH/IGF-1 axis on those born preterm is conflicting. We have previously reported lower IGF-1 and IGFBP-3 concentrations in children born very preterm compared to peers born at term [4], but we observed normal IGF-1 and IGFBP-3 levels in another cohort of preterm children and adolescents [6]. Conversely, others have observed higher IGF-1 levels in children born very preterm than in term controls [34, 35]. In the present study, we observed lower IGFBP-1 and IGFBP-3 concentrations in prepubertal children born very preterm, despite having similar IGF-1 levels. In addition, after stimulation preterm children had higher GHBP levels. These findings suggest adequate hepatic GH receptor density and IGF-1 secretion, but are suggestive of possible alterations in the IGF/IGFBP system and the peripheral IGF-1 receptor sensitivity.

Of note, we observed insulin concentrations that were considerably higher in preterm children than in term counterparts. These data are in accordance with previous studies showing abnormalities in glucose homeostasis in preterm infants in both neonatal and early infant period [36, 37]. Later in life, children and adults born preterm display reduced insulin sensitivity and increased insulin secretion [8, 18]. These alterations may influence the IGF/IGFBP system through insulin-stimulated changes. Insulin plays an integral role in hepatic IGF-1 release, with higher insulin levels being associated with higher IGF-1 levels [38, 39]. Insulin concentrations are also inversely associated with IGFBP-1 concentrations, an important regulator of IGF-1 bioavailability [40]. Thus, the increased insulin levels in preterm children may account for their reduced IGFBP-1 concentrations, which may result in larger IGF-1 availability in target tissues [34]. Therefore, it is conceivable that in preterm children there may be subtle IGF-1 resistance.

After rhGH stimulation, we found that leptin levels fell considerably in children born at term, but were relatively unchanged in those born preterm, so the concentrations were 2-fold higher in the latter group. While this is in contrast to the results of an IGF-1 stimulation test using one dose of rhGH [41], it is consistent with findings using longer courses of rhGH. Leptin concentrations were reduced by 20% after 10 days of GH therapy in short children [42], and by 60% after 3 months of rhGH treatment in children with Prader-Willi syndrome, independently of changes in body composition [43]. Higher circulating leptin concentrations have been found in preterm infants on day 1 of life compared to control infants, with a rapid decline after birth, suggesting a physiological advantage by limiting body energy expenditure for subsequent growth [44]. However, another study observed no differences in leptin levels between preterm and term children [34]. Leptin levels are stimulated by insulin, and it is therefore not surprising that leptin concentrations were higher in the preterm children who had higher insulin concentrations, particularly following the rhGH doses. Nonetheless, the complex relationship between the GH/IGF-1 axis and leptin is still unclear. GH decreases adiposity by increasing lipolysis and reducing lipogenesis, while leptin is one of the main factors involved in the central control of energy homeostasis. Thus, it has been suggested that GH treatment may induce a decrease in leptin levels, possibly through a reduction in adiposity. However, there are contradictory results in the literature. Some studies have reported a decrease in leptin levels in short children with [45, 46] and without [42] GH deficiency after 1 year of GH therapy. Conversely, Meazza et al. [47] have detected a significant increase in leptin levels after 1 year of GH treatment in children with GH deficiency.

The limitations of our study relate to the use of the IGF-1 generation test in children and our relatively small study population. There are many variants of the IGF-1 generation tests used, and these have not been standardized, yielding different IGF-1 responses. In addition, the test results are specific to the IGF-1 assay used, and there are many such assays currently available. Thus, IGF-1 generation test results cannot be easily applied across centres. There is also considerable variability in the IGF-1 response during the generation test, as we and others have observed [33]. Our relatively small population meant that this study was powered to detect differences in IGF-1 change from baseline between groups of 25 ng/ml or 30% (with $\alpha = 0.05$ and 80% power; based on data from Cotterill et al. [48]). However, the statistical power of our study was increased by adjustment for important confounders, and differences between groups of clinical significance would likely have been detected.

In conclusion, children born very preterm who are short for genetic height potential show no evidence of GH resistance. However, baseline and post-stimulation differences in binding protein levels and hormone concentrations suggest that preterm birth is associated with alterations of the IGF/IGFBP system. Further studies are needed to clarify the underlying endocrine and hormonal pathways involved in the impaired linear growth in those born very preterm.


## Acknowledgements

We thank the Paykel Trust for long-term support of the Maurice and Agnes Paykel Clinical Research Unit at the Liggins Institute, University of Auckland. This study was funded by grants from the Health Research Council of New Zealand and Pfizer.


## Disclosure Statement

The authors have no financial or non-financial conflicts of interest to disclose that may be relevant to this work. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## References


1 Howson CP, Kinney M, Lawn J (eds): Born Too Soon: The Global Action Report on Preterm Birth. Geneva, World Health Organization, 2012.
2 Tucker J, McGuire W: Epidemiology of preterm birth. BMJ 2004;329:675–678.
3 Riley K, Roth S, Sellwood M, Wyatt JS: Survival and neurodevelopmental morbidity at 1 year of age following extremely preterm delivery over a 20-year period: a single centre cohort study. Acta Pædiatr 2008;97:159–165.
4 Cutfield WS, Regan FA, Jackson WE, Jefferies CA, Robinson EM, Harris M, Hofman PL: The endocrine consequences for very low birth weight premature infants. Growth Horm IGF Res 2004;14:S130–S135.
5 Hales CN, Barker DJ: The thrifty phenotype hypothesis. Br Med Bull 2001;60:5–20.
6 Rowe DL, Derraik JGB, Robinson E, Cutfield WS, Hofman PL: Preterm birth and the endocrine regulation of growth in childhood and adolescence. Clin Endocrinol (Oxf) 2011;75:661–665.
7 Hofman PL, Regan F, Cutfield WS: Prematurity – another example of perinatal metabolic programming? Horm Res 2006;66:33–39.
8 Mathai S, Cutfield WS, Derraik JGB, Dalziel SR, Harding JE, Robinson E, Biggs J, Jefferies C, Hofman PL: Insulin sensitivity and β-cell function in adults born preterm and their children. Diabetes 2012;61:2479–2483.
9 Giudice LC, de Zegher F, Gargosky SE, Dsupin BA, de las Fuentes L, Crystal RA, Hintz RL, Rosenfeld RG: Insulin-like growth factors and their binding proteins in the term and preterm human fetus and neonate with normal and extremes of intrauterine growth. J Clin Endocrinol Metab 1995;80:1548–1555.
10 Holt RI: Fetal programming of the growth hormone-insulin-like growth factor axis. Trends Endocrinol Metab 2002;13:392–397.
11 Gluckman PD, Pinal CS: Regulation of fetal growth by the somatotrophic axis. J Nutr 2003;133:1741S–1746S.
12 Bertherat J, Bluet-Pajot MT, Epelbaum J: Neuroendocrine regulation of growth hormone. Eur J Endocrinol 1995;132:12–24.
13 Goldenberg N, Barkan A: Factors regulating growth hormone secretion in humans. Endocrinol Metab Clin North Am 2007;36:37–55.
14 Gluckman PD, Sizonenko SV, Bassett NS: The transition from fetus to neonate – an endocrine perspective. Acta Paediatr Suppl 1999;88:7–11.
15 Kajantie E: Insulin-like growth factor (IGF)-I, IGF binding protein (IGFBP)-3, phosphoisoforms of IGFBP-1 and postnatal growth in very-low-birth-weight infants. Horm Res 2003;60:124–130.
16 Miller JD, Wright NM, Esparza A, Jansons R, Yang HC, Hahn H, Mosier HD Jr: Spontaneous pulsatile growth hormone release in male and female premature infants. J Clin Endocrinol Metab 1992;75:1508–1513.
17 Wright NM, Northington FJ, Miller JD, Veldhuis JD, Rogol AD: Elevated growth hormone secretory rate in premature infants: deconvolution analysis of pulsatile growth hormone secretion in the neonate. Pediatr Res 1992;32:286–290.
18 Hofman PL, Regan F, Jackson WE, Jefferies C, Knight DB, Robinson EM, Cutfield WS: Premature birth and later insulin resistance. N Engl J Med 2004;351:2179–2186.
19 Mathai S, Derraik JGB, Cutfield WS, Dalziel SR, Harding JE, Biggs J, Jefferies C, Hofman PL: Increased adiposity in adults born preterm and their children. PLoS One 2013;8:e81840.
20 Hack M, Schluchter M, Cartar L, Rahman M, Cuttler L, Borawski E: Growth of very low birth weight infants to age 20 years. Pediatrics 2003;112:e30–e38.
21 Sung IK, Vohr B, Oh W: Growth and neurodevelopmental outcome of very low birth weight infants with intrauterine growth retardation: comparison with control subjects matched by birth weight and gestational age. J Pediatr 1993;123:618–624.
22 Knops N, Sneeuw K, Brand R, Hille E, den Ouden AL, Wit J-M, Verloove-Vanhorick SP: Catch-up growth up to ten years of age in children born very preterm or with very low birth weight. BMC Pediatr 2005;5:26.
23 Elliman A, Bryan E, Walker J, Harvey D: The growth of low-birth-weight children. Acta Paediatr 1992;81:311–314.
24 Sann L, Darre E, Lasne Y, Bourgeois J, Bethenod M: Effects of prematurity and dysmaturity on growth at age 5 years. J Pediatr 1986;109:681–686.
25 Fuse Y, Nemoto Y, Wakae E, Tada H, Miyachi Y, Irie M: Maturational changes of urinary growth hormone excretion in the premature infant. J Clin Endocrinol Metab 1993;76:1511–1515.
26 Quattrin T, Albini CH, Mills BJ, MacGillivray MH: Comparison of urinary growth hormone and IGF-I excretion in small- and appropriate-for-gestational-age infants and healthy children. Pediatr Res 1990;28:209–212.
27 Cutfield WS, Hofman PL, Vickers M, Breier B, Blum WF, Robinson EM: IGFs and binding proteins in short children with intrauterine growth retardation. J Clin Endocrinol Metab 2002;87:235–239.
28 Niklasson A, Ericson A, Fryer J, Karlberg J, Lawrence C, Karlberg P: An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977–1981). Acta Paediatr 1991;80:756–762.
29 Tanner JM, Whitehouse RH: Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 1976;51:170–179.
30 Cole TJ, Freeman JV, Preece MA: Body mass index reference curves for the UK, 1990. Arch Dis Child 1995;73:25–29.
31 Tanner J, Goldstein H, Whitehouse R: Standards for children's height at ages 2–9 years allowing for height of parents. Arch Dis Child 1970;45:755–762.

32 Blum WF, Cotterill AM, Postel-Vinay MC, Ranke MB, Savage MO, Wilton P: Improvement of diagnostic criteria in growth hormone insensitivity syndrome: solutions and pitfalls. Acta Paediatr 1994;83:117–124.
33 Buckway CK, Guevara-Aguirre J, Pratt KL, Burren CP, Rosenfeld RG: The IGF-I generation test revisited: a marker of GH sensitivity. J Clin Endocrinol Metab 2001;86:5176–5183.
34 Kistner A, Vanpee M, Hall K: Leptin may enhance hepatic insulin sensitivity in children and women born small for gestational age. Endocr Connect 2013;2:38–49.
35 Kistner A, Deschmann E, Legnevall L, Vanpee M: Preterm born 9-year-olds have elevated IGF-1 and low prolactin, but levels vary with behavioural and eating disorders. Acta Paediatr 2014;103:1198–1205.
36 Jackson L, Burchell A, McGeechan A, Hume R: An inadequate glycaemic response to glucagon is linked to insulin resistance in preterm infants? Arch Dis Child Fetal Neonatal Ed 2003;88:F62–F66.
37 Mitanchez-Mokhtari D, Lahlou N, Kieffer F, Magny JF, Roger M, Voyer M: Both relative insulin resistance and defective islet beta-cell processing of proinsulin are responsible for transient hyperglycemia in extremely preterm infants. Pediatrics 2004;113:537–541.
38 Boni-Schnetzler M, Schmid C, Meier PJ, Froesch ER: Insulin regulates insulin-like growth factor I mRNA in rat hepatocytes. Am J Physiol 1991;260:E846–E851.
39 O'Brien RM, Granner DK: Regulation of gene expression by insulin. Physiol Rev 1996;76:1109–1161.
40 Schreiner F, Gohlke B, Stutte S, Bartmann P, Woelfle J: Growth hormone receptor D3-variant, insulin-like growth factor binding protein-1 -575G/A polymorphism and postnatal catch-up growth: association with parameters of glucose homeostasis in former extremely low birth weight preterm infants. Growth Horm IGF Res 2010;20:201–204.
41 Coutant R, Boux de Casson F, Rouleau S, Douay O, Mathieu E, Audran M, Limal JM: Body composition, fasting leptin, and sex steroid administration determine GH sensitivity in peripubertal short children. J Clin Endocrinol Metab 2001;86:5805–5812.
42 Matsuoka H, Fors H, Bosaeus I, Rosberg S, Albertsson-Wikland K, Bjarnason R: Changes in body composition and leptin levels during growth hormone (GH) treatment in short children with various GH secretory capacities. Eur J Endocrinol 1999;140:35–42.
43 Elimam A, Lindgren AC, Norgren S, Kamel A, Skwirut C, Bang P, Marcus C: Growth hormone treatment downregulates serum leptin levels in children independent of changes in body mass index. Horm Res 1999;52:66–72.
44 Ng PC, Lam CW, Lee CH, Wong GW, Fok TF, Chan IH, Ma KC, Wong E: Leptin and metabolic hormones in preterm newborns. Arch Dis Child Fetal Neonatal Ed 2000;83:F198–F202.
45 Lopez-Siguero JP, Lopez-Canti LF, Espino R, Caro E, Fernandez-Garcia JM, Gutierrez-Macias A, Rial JM, Lechuga JL, Macias F, Martinez-Aedo MJ, Rico S, Rodriguez I, Guillen J, Arroyo FJ, Bernal S, Espigares R, Nunez M, Escribano A, Barrionuevo JL, Gentil J, Barrios V, Fernandez-Nistal A, Martos-Moreno GA, Martinez V, Argente J: Effect of recombinant growth hormone on leptin, adiponectin, resistin, interleukin-6, tumor necrosis factor-alpha and ghrelin levels in growth hormone-deficient children. J Endocrinol Invest 2011;34:300–306.
46 Ciresi A, Amato MC, Criscimanna A, Mattina A, Vetro C, Galluzzo A, D'Acquisto G, Giordano C: Metabolic parameters and adipokine profile during GH replacement therapy in children with GH deficiency. Eur J Endocrinol 2007;156:353–360.
47 Meazza C, Elsedfy HH, Pagani S, Bozzola E, El Kholy M, Bozzola M: Metabolic parameters and adipokine profile in growth hormone deficient (GHD) children before and after 12-month GH treatment. Horm Metab Res 2014;46:219–223.
48 Cotterill AM, Camacho-Hubner C, Duquesnoy P, Savage MO: Changes in serum IGF-I and IGFBP-3 concentrations during the IGF-I generation test performed prospectively in children with short stature. Clin Endocrinol (Oxf) 1998;48:719–724.