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GROWTH AND GROWTH HORMONE THERAPY IN SHORT CHILDREN BORN PRETERM

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ABSTRACT

Approximately 15 million babies are born preterm across the world every year, with less than 37 completed weeks of gestation. Survival rates increased during the last decades with the improvement of neonatal care. With premature birth, babies are deprived of the intense intrauterine growth phase and postnatal growth failure might occur. Some children born prematurely will remain short at later ages and adult life. The risk of short stature increases if the child is also born small for gestational age. In this review, the effects of being born preterm on childhood growth and adult height and the hormonal abnormalities possible associated with growth restriction are discussed, followed by a review of current information on growth hormone treatment for those who remain with short stature during infancy and childhood.

INTRODUCTION

Preterm birth is defined by the World Health Organization (WHO) as birth before 37 completed weeks of gestation, or fewer than 259 days since the first day of a woman's last menstrual period (1). Of the 135 million live births worldwide in 2010, WHO estimates that 14.9 million babies were born prematurely, representing an increasing burden with a preterm birth rate of 11.1% (2). The risk of preterm birth is high for both the poorest and the richest countries. Approximately 60% of all preterm births worldwide occurred in sub-Saharan Africa and South Asia. However, of the 1.2 million estimated to occur in high-income regions, more than 0.5 million (42%) occur in the United States (2). In England and Wales, it is estimated that 53,000 infants were born preterm in 2010 (3). The causes of prematurity differ among countries (3), with the increment in many high-income countries attributed to multiple gestation and assisted conceptions due to treatment for sub-fertility (4). The survival rate also varies among countries due to differences in basic care (5), with preterm birth considered one of the major causes of death before 5 years of age (2).

The measurement of gestational age (GA) indicates the length of gestation counted in days or weeks, from the first day of the last menstrual cycle, except for women undergoing assisted reproduction techniques. The term date, or 40 weeks (280 days), is calculated using the Naegele's rule, which adds seven days to the first day of the last menstrual period (LMP) and, to this date, sum nine months assuming a menstrual cycle of 28 days and ovulation in the 14th day (6). However, in many pregnancies, LMP is unknown or menstrual cycles are irregular. In these cases, measurements of the embryo or fetus obtained by ultrasonography performed up to 13 weeks and 6 days post-conception are accurate to determine or confirm the GA (7). In case of assisted reproduction, the expected date of birth is calculated from the day of technical implementation. In case of in vitro fertilization, from the day of embryo transfer to the uterus (7). After birth, GA can be estimated by physical examination and neurological maturity of the newborn (8).

Preterm birth can be subdivided on the basis of GA, with extremely preterm (EPT) occurring at less than 28 weeks of GA, very preterm (VPT) from 28 but less than 32 weeks and moderate preterm (MPT) occurring from 32 and less than 37 completed weeks of gestation. MPT can be subdivided, being late preterm those born between 34 to 36 weeks and 6 days (9). The majority of the infants born prematurely, about 84% or 12.5 million, are moderate premature (10). In addition to this definition, studies performed before antenatal ultrasound became a routine for evaluation of GA considered infants as extremely low birth weight (ELBW), if weight was lower than 1000 g, and very low birth weight (VLBW), if lower than 1500 g. The use of birth weight as a selection criterion had the disadvantage to include, in the same study group, more mature children born small for GA (SGA) and preterm infants born appropriate for GA (AGA) (11). Neonatal survival improves with an increase in GA and weight at birth (10). Lifelong morbidities among survivors include cerebral palsy, intellectual impairment, chronic lung disease and vision and hearing loss (3). Increased blood pressure, accelerated weight gain and growth failure are also among the comorbidities (2, 12, 13). In this review, we will highlight current information on growth in children born prematurely, mainly referring to publications with preterm classification based on GA; the hormonal abnormalities possible associated with lack of catch-up growth after the first months of life, and discuss potential treatment with recombinant human growth hormone (rhGH) for those who remain with short stature during infancy and childhood.

PRETERM GROWTH CHARTS

With the advances in neonatal care during the last decades, the perspectives of growth of children born prematurely changed. The growth charts used to monitor their growth also had to improve. Nowadays, different types of growth charts are available for formerly preterm infants. The *intrauterine growth charts* are based on measurements of infants with different GA, the *fetal growth charts* are constructed with fetal measurements obtained by ultrasound, and the *postnatal growth curves* are constructed with measurements of infants during the hospitalization period. Significant differences are observed between these reference charts for evaluation of postnatal growth, especially with regard to head circumference (HC) (14).

The *intrauterine growth charts* are the most recommended for monitoring growth of preterm infants. At least 25 reference charts of this type are available (15). One of their disadvantages is the fact that the preterm infant usually is smaller than the healthy reference not exposed to the extrauterine environment (16-18). Furthermore, after preterm birth, weight gain and longitudinal growth are more intense close to term (37-40 weeks), whereas weight and length gain are already decreasing at the end of a normal full term gestation (19). In 2003, Fenton put together data of three different populations and developed an intrauterine growth chart starting at 22 weeks of gestation with scale of weight every 100 grams. The CDC-2000 growth data between 40th and 50th weeks post-conception were added resulting in a *fetal-neonatal growth chart*, which facilitates the adjustment of growth to prematurity, recommended up to 3 years of age (20). A new version was released in 2013 with data from six countries. It is now a gender-specific growth chart from 22 weeks gestation until 10 weeks after term and aligns with the WHO-2006 growth charts allowing a longer period of growth follow-up (19).

Fetal growth charts are constructed from fetal measurements obtained by ultrasonography. Theoretically, they reflect the expected growth for each gestational age without the effects of prematurity. Their disadvantage is the sensitivity of ultrasonography to assess fetal weight, especially during the first weeks of gestation (15, 21-23). The *postnatal growth charts* are longitudinal and constructed from sequential measurements of preterm infants, considering the delay of the early extrauterine growth (15). An example is the gender-specific curves from 24th week up to 2 years of corrected age from Sweden (24).

More recently, customised growth charts adjusted for physiological variables such as maternal weight and height, parity, ethnicity and smoking were created (25). The INTERGROWTH-21st Project, a prospective international multiethnic study, was launched to complement the WHO 2006 (26) by developing international standards for fetuses, newborn infants and postnatal growth of infants born prematurely (27). Data from pregnancies of low obstetric risk from Brazil, China, India, Italy, Kenya, Oman, United Kingdom and United States were included. The authors suggested that using multiple populations from several countries would enhance the diversity in the biological characteristics, such as parental size and maternal weight gain during pregnancy, as well as external factors influencing fetal growth (27). The resulting growth charts were recommended for preterm infants born after 33 weeks gestation to 6 months of corrected age for prematurity (28). Currently, no large randomized trials are available showing the benefits of customised growth charts (29).

EARLY GROWTH IN CHILDREN BORN PREMATURELY

Several factors might influence intrauterine growth, such as genetic, environmental and hormonal factors, placental development, supply of nutrients and maternal health (30). In uncomplicated pregnancies, the fetus has a high growth rate that will not be repeated in any other stage of life. With premature birth, babies are deprived of this intense intrauterine growth phase. In addition, preterm birth might disrupt the normal growth regulation of infancy.

The American Academy of Pediatrics recommends that infants born prematurely should grow similarly to the fetus with the same GA. This recommendation refers mainly to weight gain, although length and head circumference are also important, the latter associated with neurological outcome (31). Typically, weight loss is expected during the first days of life, similar to the initial weight loss observed in babies born at term. However, in preterm infants, the intensity of this loss is associated with GA, birth weight and time required to achieve full enteral nutrition (32). After this initial period, a transition phase should start, with stabilization of weight and a slight increase in length, followed by the catch-up period, when growth rate exceeds the expected for the fetus with the same GA. The last phase is characterized by growth rate comparable to that of children born at term (33-35). When growth restriction remains during early postnatal period with growth rates lower than expected, it is stated that the preterm infant is suffering extrauterine growth restriction (EUGR) (36, 37), more common among extremely and very preterm infants (38). There is no consensus on definition of EUGR. One definition considers a decrease of 2.0 SD or more in weight and/or length between birth and 36 weeks post-conception (39). Less strict definitions are also used by pediatricians (36, 37, 40). In addition to time of gestation, another factors were associated with increased risk of impairment of early growth, including male gender (37, 41), history of maternal hypertension (42), bronchopulmonary dysplasia (BPD) (37, 43, 44), necrotizing enterocolitis (37), postnatal use of corticosteroids (37, 45, 46), IUGR or SGA birth (47), high levels of total alkaline phosphatase during the neonatal period (42), EUGR (48, 49), and feeding difficulties (50, 51).

CHILDHOOD OUTCOME

The first year of life is a critical period for children born prematurely. Hospital stay can be long and prone to morbidities as lung diseases, intraventricular hemorrhage, necrotizing enterocolitis, late onset-sepsis, among others (52). Weight and height gain is associated with the age of achievement of full enteral feedings and occurrence of EUGR (36, 37, 39). Those who survive to hospital discharge are shorter and lighter than full-term peers, despite the intense catch-up growth they may have had (53). Approximately 80% of formerly preterm children exhibit growth recovery during the first 2 years of life (33, 35, 54-57), with height percentile appropriated for genetic potential between 6 and 12 months of life. After 2-3 years of age, height gain correlates with parent's height (55, 58-62). At 3 years of age, approximately 80% reaches the normality for head circumference and 70% for weight. The lack of recovery is also associated with low socioeconomic status (63), long period of parenteral nutrition, neurological disorders, chronic respiratory diseases, EUGR and parental short stature (37, 41, 47, 64, 65). This review will focus on growth after 2 years of age, when a more stable healthy condition is expected with less hospital readmissions.

Infancy and childhood growth

Despite the majority of the preterm infants are MPT, much of the research to date on growth of infants born prematurely has focused on those born with less than 32 weeks of GA. More extreme the limit of viability, more the effects of preterm birth are confounded with those of intrauterine and extrauterine growth restrictions. In the extreme lower limit of weight at birth, Rieger-Fackeldey et al. (66) reported the follow-up of 19 children with a birth weight < 500 g who received immediate life support, all EPT, 18 born SGA. Seven of them caught up in length by 5 years of age, but all were below the 25^{th} percentile in height by this age. Another study, the EPICure cohort, evaluated 241 children born with GA ≤ 25 weeks (67). At

6 years of age, children born EPT were still leaner, shorter and have a smaller head circumference than their peers, with some catch-up growth observed from 30 months to 6 years of age. Birth weight for GA was strongly associated with growth outcome at 6 years. Follow-up to 11 years of age of 83 EPT children born in the 1990s was described by Farooqi et al. (54). Their mean GA was 24.6 weeks and mean birth weight was 765 g, six were born SGA and three were on GH treatment. A marked drop in weight SDS was observed to 3 months´ corrected age, when weight began to increase reaching the mean of the reference at approximately 11 years of age. Similar pattern was observed for height, with a significant increase in height SDS between the ages of 3 months of corrected age for prematurity and 3 years and between ages 7 and 11 years. At 11 years of age, EPT girls were 3.1 cm and the EPT boys 5.7 cm shorter than controls. Unfortunately, they did not have information on pubertal development; pubertal growth spurt could explain in part their later increase in height.

Among the VPT children, a French population-based study evaluated growth outcome to 5 years of age in 1597 children born in the late 1990s (68). At 5 years, 5.6% had short stature and 6 children received rhGH treatment between 2 and 5 years of age. Of the 118 children with short stature at 2 years, 55 (47%) remained with short stature at 5 years, whereas from the 276 with height between -1 and -2 SD at 2 years, 26 (9%) became ≤ -2 SD at 5 years. The highest incidence of short stature at 5 years was observed among preterm born AGA with EUGR, whereas the incidence among preterm born SGA did not change from 2 to 5 years, suggesting that catch-up growth in SGA children occurs mainly during the first 2 years of life, as previously reported (69). Knops et al. (58) demonstrated that VPT children born AGA had normal stature at 10 years of age, while those born VPT and SGA were lower even after correction for target height (AGA = 0.0 SDS; SGA < 32 weeks = -0.29 SDS; SGA ≥ 32 weeks = -0.13 SDS). Catch-up growth was especially seen in the children born SGA with a fast weight gain during the first three months of life. At a mean age of 8 years, Hack et al. (41) found height SDS of -2.6 for boys born with VLBW, significantly lower than the control group born full term. VLBW girls were leaner but did not differed significantly in height compared with the controls group. Ford et al. (64) observed an acceleration of growth between 8 and 14 years of age in teenagers born with BW < 1500g and GA < 30 weeks, suggesting a late catch-up growth. Most of them had weight and height higher than -2.0 SDS, but all were lower and lighter than the control group born at term and AGA. The risk of short stature increased with maternal height ≤ 160 cm, GA < 29 weeks, birth length < -2 SD and use of corticosteroids. The influence of being born SGA, maternal size and comorbidities on height of formerly preterm children at 5 years or older has been reported before (58-60, 62). Trebar et al. (59) evaluated 1320 children born with VLBW at 5-6 yrs of age, GA from 22 to 38 weeks, 730 born SGA and 590 born AGA. At age 6, 8.3% AGA and 13.4% SGA children were short (< -2 SDS). The most important predictors of height at 5/6 y of age were height at 1 year of age, the difference in height between ages 1 and 2 and midparental height SDS. Despite to have children born at term in their study, the majority was preterm with known GA. At 12 years of age, children born prematurely and SGA were shorter and leaner than children born full term and AGA, without increment in height after 8 years of age, whereas preterm born AGA with neonatal comorbidities still presented some gain in height after 8 years of age (70). These studies reinforce the influence of size at birth on catch-up growth among preterm children.

When considering less premature infants, 1123 MPT children born between 2002-2003 in Netherlands were evaluated at the age of 4 years (71). Growth restraint was 2.5 times more prevalent in MPT than in term children; 32 boys (5.6%) and 18 girls (3.8%) were growth-restricted in height at this age. In a population-based study evolving 1414 late preterm infants (born between 34 to 36 weeks and 6 days) followed from birth to 3 years of age at the city of Kobe, Japan, the authors showed an incidence of 2.9% of short stature in the late preterm group, significantly higher than the 1.4% found in the term group. The risk for short stature was 4.5-fold higher if the late preterm were born SGA (13). Figure 1 illustrates growth trajectories that could occur in children born preterm based on the previous publications.

Regarding height at onset of puberty, data from adolescents born during the 1970s in Sweden showed that those born SGA were shorter at puberty onset with earlier menarche than the reference group, but neither age at puberty onset nor menarche was influenced by prematurity (72). In low birth weight children, including ELBW, despite they were shorter and lighter than those born at term at start of puberty, previous reports did not find difference in sexual maturity (61, 64, 73). Sullivan et al. (70), using self-assessment evaluation, found that 60% of the boys and 50% of the girls in a group of 194 adolescents born prematurely were Tanner stage 0 at 12 years of age. Few had completed puberty at this age. More recently, data of VLBW children born between 1978 and 1985 were evaluated to adult height and compared with data from full term born group (74). The study included VLBW born SGA (GA 29 – 35.6 weeks; birth weight 700 – 1499 g) and VLBW born AGA (GA 24.7 – 31.7 weeks; 600 – 1490 g). They all were shorter than controls during prepubertal years, as reported before. However, age at acceleration of growth velocity during puberty onset was earlier in both groups of VLBW, ten months earlier in VLBW AGA and 11 months earlier in VLBW SGA. Higher body mass index during prepubertal years was associated with an early growth spurt. Age at attaining adult height was also significantly lower. Age of puberty onset was in the normal range and no difference was observed in age of menarche or voice change (74), reinforcing the need of carefully follow all growth period of formerly preterm children, from birth to maturity, in order to detect any acceleration of growth velocity that could suggest an early growth spurt. Brandt et al. (75) found a significant difference in age at menarche among SGA girls born preterm without catch-up growth and girls born full term

(12.2 vs. 13.4 years, $p < 0.01$). Difference was also significant when compared with preterm girls born SGA with postnatal catch-up growth (12.2 vs. 13.6 years, $p < 0.01$), suggesting the importance of catch-up growth in age of menarche. Age of menarche was also associated with lower GA (74).

Although puberty begins at a normal age, children born prematurely are more prone to an earlier onset of pubertal development, faster progression of puberty and earlier menarche relative to full-term and AGA children (74). A modest bone age delay at the onset of puberty and more rapid bone maturation during puberty has been reported, similar to SGA children (76, 77). Peak height velocity is reached at an earlier pubertal stage and lasts for a shorter period in children born prematurely (74, 76), increasing the risk of a shorter adult height. Rapid weight gain early in childhood might be associated with unfavorable growth outcome (76, 77). Table 1 summarizes the risk factors for short stature in subjects born prematurely.

ADULT OUTCOME

Few studies are available on adult height in those born preterm (Table 2) (41, 57, 74, 75, 78-83). Some are cohort studies with strict inclusion criteria and subjects followed from birth to adult height, but with the disadvantages of long-term studies, such as loss of follow-up. There are also cross-sectional population-linkage studies, with data from birth linked to data in adult life, with the possibility of much larger samples (80).

In a nationwide population-linkage study in Norway, birth records and adult height of 348,706 young boys were evaluated, 15,454 of them (4.5%) born with GA from 26 to 36 weeks. Birth length was the best predictor of adult height. However, when stratified by GA, the relatively long infants born preterm became shorter adults compared with same-length infants born at term (12). In a cohort study in Germany (75) with evaluation of 108 VLBW infants born from 1967 to 1978, almost 50% had complete catch-up by adult age. The authors concluded that growth at earlier ages did not predict adult height due to a great intraindividual variability in growth patterns from birth to 6 years of age and to adulthood. GA ranged from approximately 28 to 35 weeks and could explain in part the variability in postnatal growth patterns. In Australia (84), a total of 42 ELBW subjects born after 1977 were followed from birth to 20 years of age. Catch-up growth was observed only at 14 years of age, during puberty. Two of the subjects received synthetic growth hormone (GH), and by early adulthood, all had attained height consistent with their parents' height. The same group followed 225 consecutive EPT survivors born during 1991–1992 to 18 years of age (83). For this evaluation, selection criterion was based on GA. EPT children were shorter than controls at all ages from 2 to 18 years. At 18 years, 9% of the EPT were < - 2 SD in height, against only one subject (0.7%) born at term with short stature. Height at 2 years explained 50% of the variability in final height. The control group born at term was significantly higher than their median parental height, whereas the EPT subjects were slightly lower than their parents.

Another way to evaluate outcome in infants born prematurely is to consider neonatal growth and the occurrence of EUGR in addition to GA. Finken et al. (57) evaluated 380 adolescents born VPT (<32 weeks GA), 21% of them born AGA and with EUGR, confirmed with measurements at 3 months of age. Their height near 19 years of age was compared with height of VPT AGA without EUGR and with height of VPT born SGA. The AGA group with EUGR was characterized by a low GA, a high prevalence of respiratory distress, intracranial hemorrhage and glucocorticoid therapy. The prevalence of short stature at 5 years of age was close to 20% in both VPT SGA and VPT AGA with EUGR. In addition, height <-2 SD at the age of 5 years in these two groups points to a high risk (≈90%) of short stature in adulthood. Their growth was compared with that described previously for SGA children born at term, suggesting that they could benefit from GH treatment. Hack et al. (41) evaluated 195 VLBW young adults at 20 years of age. Compared with control group, boys were leaner (-0.35 ± 1.25 *vs* 0.53 ± 1.06 SDS) and shorter (-0.44± 1.10 *vs* 0.03± 0.95 SDS), 7% with height < -2.0 SDS. Short stature at 20 years of age was associated with lower maternal education, lower maternal height and lower birth weight.

HORMONAL ABNORMALITIES

It has been proposed that adverse exposures during fetal and early postnatal life lead to unfavorable programming effects (85-87). In infants born prematurely, the period equivalent to the third trimester of gestation occurs extra utero, with higher risk of alterations of the GH and insulin-like growth factor (IGF) system (88). Few and conflicting data are available on GH axis in formerly preterm children with short stature during infancy and childhood. Elevated circulating GH levels during neonatal period with low IGF-1 and low GH binding protein (GHBP) concentrations were reported, suggesting immaturity of the GH receptor with less inhibitory feedback on hypothalamopituitary axis (89, 90). Association of IGF-1 levels with growth restriction and catch-up growth in the immediate postnatal period (91), low IGF-1 and IGF-binding protein 3 (IGFBP-3) concentrations (88, 92) with high IGF-2 during mid-childhood (88), normal IGF-1, IGF-2, IGFBP-1 and GH binding protein (GHBP) with high IGFBP-2 (93), and lower prolactin and higher IGF-1 levels than control at start of puberty (94) were also reported. Normal response to IGF-1 generation test (95) were reported in short children at mean age of 7 yr.-old, with no clear evidence of GH or IGF insensitivity, but with some suggestion of alterations of the IGF/IGFBP system. During the immediate postnatal period to 6 months postterm, IGF-1 levels were not associated with nutrient intake (91, 96). A highly significant influence of the genomic deletion of exon 3 of the GH receptor, d3-GHR isoform, on the postnatal growth pattern was also reported, with higher probability of postnatal catch-up growth in those who carry at least one GHRd3 allele. Children heterozygous or homozygous for GHRd3 also had higher serum levels of IGF-1 and IGFBP-3 (97). Recently, Guasti et al. evaluated fibroblast growth factor 21 (FGF21) serum concentrations during the first 5 weeks of life in VPT infants. They found an inverse association with linear growth but not with weight gain (98). High FGF21 level impairs linear growth by a mechanism involving direct inhibition of GH action on chondrocyts at the growth plate. This could be an explication for the GH resistance secondary to prematurity (98).

These results might reflect the heterogeneity of preterm birth, with possibilities of intra and extrauterine growth retardation and an immature fetal state of the GH/IGF-1 axis during the early postnatal period with relatively low GHR expression. During mid-childhood and puberty, with more mature GH/IGF-I axis, alterations of the IGF/IGFBP system might occur.

GROWTH HORMONE TREATMENT

GH treatment was given to seven preterm infants born SGA from postnatal day 7 until a body weight of 2000 g was reached at postnatal week 7-8 in an attempt to improve nutrition. No significant effects were observed on growth, body composition, net protein gain and glucose metabolism (99). Recently, VPT infants received recombinant human GH (0.03 mg/kg/day) after birth. At 6 months of treatment, growth velocity, body weight, length and HC were significantly higher compared with the control group. Time to reach adequate oral feeding and time to restore birth weight were shorter and less EUGR was observed (100). IGF-1 and IGFBP-3 levels were not different at birth, with significantly higher concentrations at 3 and 6 months in the treatment group. The authors suggested that GH treatment regulates the preterm endocrine and metabolic state without severe adverse effects (100). No further studies with GH treatment at this early age were available at present time.

Studies on the effects of GH for treatment of short stature of different etiologies usually included children born prematurely, especially those involving children born SGA (101, 102). GH treatment was approved by the US Food and Drugs Administration in 2001 for children born SGA who fail to manifest catch-up growth by the age of 2 years. Approved GH dose was 0.070 mg/kg.d. In Europe, treatment was approved by the European Agency for the Evaluation of Medical Products in 2003 with the dose of 0.035 mg/kg.d for children older than 4 years of age. The consensus statement from the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society proposed that children born SGA with height below -2.5 SDS at the age of 2 years or with height below -2.0 SDS at the age of 4 years should be eligible for GH treatment (103). In the SGA studies, the preterm ones were often younger and shorter than the term ones, with height velocity SDS below zero which reinforces that they were not presenting spontaneous catch-up growth (104, 105). de Kort et al. (104) evaluated a cohort of 392 short SGA children treated during 3 years with GH. The response to GH treatment was similar for both preterm and term short SGA groups. After 4 years of treatment, the effects of GH on metabolic and cardiovascular risk factors were similar between preterm and term SGA children, with no significant changes in glucose homeostasis and a decrease in blood pressure and fat mass in the preterm ones (104). Among very young short children born SGA (chronological age at start of GH treatment from 2 to 4 years), those born prematurely received a higher GH dose and presented higher growth velocity during the first year of therapy (105).

Few studies in which only formerly preterm children were included are available to date. The first year growth response to GH treatment in short children born preterm (26 to 37 uncompleted weeks of GA) was demonstrated using information from a large international database of children treated with rhGH, including 1928 preterm AGA, 629 VPT AGA, 519 preterm SGA and 139 VPT SGA, all prepubertal and with different GH secretion status (106).

Age at started ranged from 3 to 12 years and all four groups presented a significant increase in height velocity and weight gain during the first year of GH treatment. Age at GH start, bone age, and adjusted parental height were inversely associated with the first year growth response, whereas GH dose had a positive association. Gestational age and birth weight SDS had a weak correlation with the growth response only for the preterm born AGA. One year rhGH treatment of short children born with VLBW both AGA and SGA, showed similar increase in height velocity, height, weight and muscle strength in both groups, with increment of IGF-1 concentrations (107). Growth response and adult height could be predicted using prediction models independent of GH secretion status and size at birth (108, 109). Garcia et al. (110) evaluated the growth response with a relatively high GH dose (0.066 mg/kg/day) in very young SGA children born prematurely. They reported an increment of 1.3 SD after the first year with a subsequent gain of 2.1 SD for the 17 children who completed 2 years of GH treatment. These studies suggest that, when growth failure occurs and persists during infancy and childhood, children born prematurely might benefit from GH treatment.

CONCLUSION

Growth pattern of children born prematurely has unique characteristics. Weight loss is expected during the first days of life, followed by stabilization of weight and a slight increase in length. A catch-up period is further expected with growth rates comparable to that of children born at term. Approximately70 to 80% of children born preterm will have adequate height, weight and head circumference by 3 years of age. However, when growth restriction remains during infancy and childhood, children born prematurely are of increased risk of short stature. Growth failure may be compounded in the presence of intrauterine or extrauterine growth restrictions, extreme prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis or metabolic bone disease of prematurity. Those who are short at 2 years of age are unlikely to reach normal height during childhood. A careful follow-up is recommended. If further catch-up growth is not observed, they might be candidates to GH treatment.

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LEGEND TO FIGURE 1

Growth from birth to 10 years in children born preterm. Five possibilities of growth trajectories are presented:

AGA: Initial growth deceleration similar to babies born at term followed by a catch-up period and stabilization of growth.
AGA - EUGR: More intense initial growth restriction followed by a catch-up growth that occurs before 3 years of corrected age.
AGA - EUGR no catch-up: No catch-up growth after the intense initial growth restriction. Growth resembles growth pattern of SGA children without catch-up growth.
SGA - no catch-up: Preterm SGA children without catch-up growth.
SGA - catch-up: Preterm SGA with late catch-up growth, up to adolescence, but keeping lower height compared to peers born at term.

AGA (appropriate for gestational age); SGA (small for gestational age); EUGR (extrauterine growth restriction)

Table 1 – Risk factors for growth failure in children born preterm

PERIOD	RISK FACTORS
Perinatal	Intrauterine growth retardation
	Pregnancy-induced hypertension
	Male sex
Neonatal	Gestational age < 32 weeks (specially < 28 weeks)
	Birth weigh < 1500 g
	Birth length < -2 SD
	Small for gestational age
	Extrauterine growth restriction
	Bronchopulmonary dysplasia
	Metabolic bone disease of prematurity
	Necrotizing enterocolitis
	Post-natal corticosteroids use
	Long time in total parenteral nutrition
	Feeding difficulties
Infancy	Chronic respiratory diseases
	Cerebral palsy
	Neurodevelopment delay
	Feeding difficulties
	Lack or delay of catch-up growth
	Low target height
	Low socioeconomic status
Adolescence	Young age at onset of pubertal growth spurt and fast progression of puberty
	Lack or delay of catch-up growth
	Low target height
	Maternal short stature (specially < 160 cm)
	Low maternal education
	Low socioeconomic status

Note: For details, see references 37,41-51, 63-65 and 74.

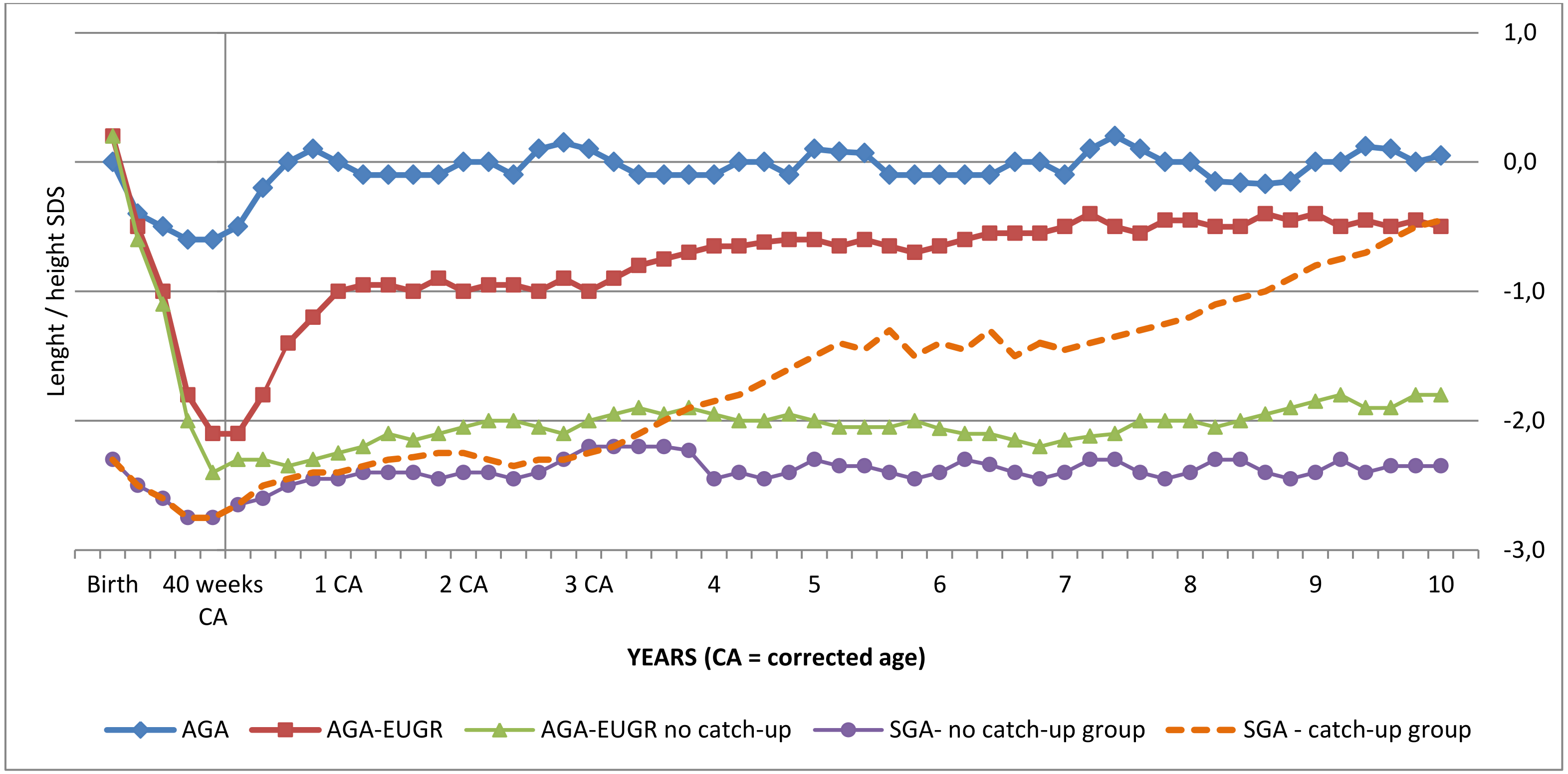
TABLE 2 – Studies of adult height of preterm subjects measured in early adulthood

Study	Preterm (n)	Control group (n)	Age (years)	Adult Height	
				Preterm	Control
Weiler et al. (2002) (79)	25 (6 SGA) BW < 1500 g GA < 37 weeks	25	17.2 ± 1.2	164.8 (6.4) cm 0.3 (1.0) SDS	172.1 (9.7) cm[a] 1.2 (1.5) SDS[a]
Hack et al. (2003) (41)	195 (39 SGA) BW < 1500 g GA 29.8 weeks	208	20.0	M: 173.7 (7.9) cm F: 161.7 (7.3) cm 5 SGA < - 2 SDS	M: 177.0 (6.8) cm[a] F: 163.0 (7.0) cm
Doyle et al. (2004) (80)	42 (7 SGA) BW: 500 to 999 g GA < 32 weeks	37	20.3 ± 1.0	all: -0.52 (1.18) SDS M: 172.3 (7.7) cm F: 161.0 (7.4) cm All SGA: < -2 SDS	M: 178.0 (3.9) cm[a] F: 165.5 (7.5) cm
Brandt et al. (2005) (75)	108 (46 SGA) GA < 37 weeks AGA BW: 1350 ± 150 g		22.8 (17 to 28)	SGA no catch-up (n = 25): -1.89 (0.86) SDS SGA catch-up (n = 21): 0.03 (0.99) SDS	
Saigal et al. (2006) (81)	147 (36 SGA) BW: 501 to 1000 g GA: 27.1 ± 2.3 weeks	131	M: 23.5 ± 1.4) F: 23.2 ± 1.1	M: 170.6 (9.5) cm F: 158.3 (6.8) cm	M: 177.8 (7.7) cm[a] F: 164.5 (6.7) cm[a]
Finken et al. (2006) (57)	27 SGA/ 79 AGA PGR* / 274 AGA no-PGR BW < 1500 g GA < 32 weeks		19.0	SGA: -1.2 SDS AGA PGR: -1.1 SDS AGA no-PGR: -0.4 SDS[b]	
Hovi et al. (2009) (82)	144 (49 SGA) BW < 1500g GA < 32 weeks	139	22.6 ± 2.2	M: -0.45 (1.06) SDS F: -0.49 (1.31) SDS	M: 0.30 (0.92) SDS[a] F: 0.35 (1.14) SDS[a]
Odberg et al. (2010) (78)	134 (75 SGA) BW < 2000 g GA: 32.2 ± 3.3	135	19.0	168.1 (8.2) cm	174.1 (10.4) cm[a]
Wehkalampi et al. (2011) (74)	113 (35 SGA) BW < 1500 g GA < 32 weeks	146	SGA: 22.6 AGA: 22.4	SGA M: 175.8 (8.0) cm F: 160.3 (5.8) cm AGA M: 174.8 (7.2) cm F: 164.5 (8.6) cm	M: 180.2 (6.2) cm[a] F: 167.9 (6.4) cm[a]
Roberts et al. (2013) (83)	166 BW < 1000 g GA < 28 weeks	152	18.0	-0.47 (1.14) SDS	0.26 (0.98) SDS[a]

BW (birth weight), GA (gestational age), SGA (small for gestational age), AGA (appropriate for gestational age), PGR (preterm growth restraint).

*PGR defined as length and/or weight <-2 SDS at 3 months postterm.

[a] Difference statistically significant between preterm and control group. [b] Difference statistically significant between AGA PGR and AGA non-PGR.



1,0
0,0
-1,0
-2,0
-3,0
Lenght / height SDS
Birth
40 weeks CA
1 CA
2 CA
3 CA
4
5
6
7
8
9
10
YEARS (CA = corrected age)
AGA
AGA-EUGR
AGA-EUGR no catch-up
SGA- no catch-up group
SGA - catch-up group