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ORIGINAL ARTICLE

Growth of preterm infants during the first two years of life

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Abstract

Objective: To analyze the growth of premature children followed in a secondary referral service in their first two years. **Methods:** A cross-sectional study of preterm data less than 37 gestational weeks from September 2010 to December 2015. Postnatal growth was monitored throughout the first two years of corrected gestational age (CGI) using the Fenton 2013 curves up to the IGC of 50 weeks, and the 2006 World Health Organization (WHO) from this milestone. It built up a trend line by using a third-degree polynomial function to allow better visualization of anthropometric measurements according to the CGI. **Results:** 183 premature infants were included. The anthropometric measures of weight, height and body mass index (BMI) showed a predominance of adequacy throughout the analyzed period, with a tendency to increase the adequacy rates at the end of the observation period. High weight and BMI for age tended to increase, with a high BMI among the small for gestational age, while there was reduction in the rates of short stature for the age. **Conclusions:** The growth parameters of premature infants tend to be adequate during the first two years of CGI, with the most intense growth in the first six months. High BMI for age at the end of the second year signals the need for longer follow-up time and, especially among the small for gestational age, the understanding of their different rhythm of growth and follow-up. The monitoring of preterm birth and appropriate interventions may minimize the future development of chronic non-communicable diseases.

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INTRODUCTION

A correlation seems to exist between the likelihood of suffering from a noncommunicable disease and the conditions one is exposed to during intrauterine and early extrauterine life. Noncommunicable diseases such as coronary artery disease, hypertension, metabolic syndrome, and chronic kidney disease have been associated with preterm birth, low birth weight, small for gestational age neonates, and intrauterine/extrauterine growth restriction.[1–3]

Although premature infants showing greater weight gain present superior neurological development, greater weight gain in relation to height does not confer additional benefits and has been associated with obesity and future cardiovascular risk - factors that may be mitigated if the infant is provided proper nutritional guidance during the first years of life.[4–6]

The challenge for health care providers is, therefore, to monitor the growth of premature infants and minimize the future progression of noncommunicable diseases. Based on these assumptions, this study aimed to analyze the growth of premature infants seen at a referral secondary care center throughout the first two years of their lives.

METHODS

This cross-sectional study used data collected from the charts of premature infants seen at the State Special Care Center (CEAE; Brazilian acronym) in Viçosa, Minas Gerais, between September of 2010 and December of 2015. The semi-structured nature of the data collected by the CEAE allowed for reliable data extraction.

Population and study site

The São Sebastião Hospital (HSS; Brazilian acronym) is the center where all births in Viçosa and surrounding towns take place. It has been a referral center for high-risk pregnancies since 2009, and its facilities include a human milk bank started in 2005 and a neonatal intensive care unit opened in 2004.

The CEAE is the only referral center for premature infants in the Viçosa region, and covers 20 municipalities with a total of 227,203 inhabitants. The annual number of live births in Viçosa during the study ranged between 632 and 959, and the rate of preterm births varied from 8.8% to 9.9%. A multidisciplinary team comprising pediatricians, nurses, nutritionists, psychologists, physiotherapists, and social workers follows premature infants through an agreement signed with the Federal University of Viçosa (UFV; Brazilian acronym). Upon hospital discharge, all premature infants are referred to the CEAE to have their growth and development monitored. The CEAE was opened in September of 2010 and followed 190 premature infants until December of 2015, with annual entries ranging from 18 (in the period soon after it was opened) to 66 patients.

Inclusion and exclusion criteria

The study included premature infants born at less than 37 weeks' gestation regardless of birth weight at the HSS and followed at the CEAE. Individuals whose charts were not found, infants with severe malformations or diseases known to compromise nutrition and growth were excluded.

Study variables

Prematurity: neonates with gestational ages (GA) at birth of less than 37 weeks. Chronological age (ChA): age measured from birth. Corrected age (CA): infant's actual age in weeks minus the number of weeks the infant was preterm. The number of weeks the infant was preterm is calculated as 40 weeks minus the infant's GA at birth.[8,9]

Sociodemographic variables: maternal and paternal age; maternal and paternal education (up to or above ninth grade); and household income measured in Brazilian minimum wages (MW; < 2 MW or ≥ 2 MW)[10]. Prenatal and perinatal variables: type of delivery; sex; referral to neonatal intensive care unit (NICU); GA at birth (in weeks; < 32 weeks or ≥ 32 weeks), weight at birth (WB in grams; < 1500g or ≥ 1500g). The appropriateness of WB for GA at birth was analyzed based on the Fenton growth charts. The infants were categorized as small for gestational age (SGA; individuals below the 10th percentile) or non-SGA (above the 10th percentile).[8,11]

Infants in their first visit were categorized as being offered breastfeeding (BF; alone or with supplementation) or artificial feeding (AF).[12] The total duration of BF was recorded in months of CA. The term "cow's milk" was used to refer to raw cow's milk, not infant formula.

The weight (g), height (cm), and BMI of the infants were recorded until they reached two years of corrected age. Pediatricians or nutritionists took the anthropometric measures during regular visits with the aid of a digital scale and an anthropometer, and the findings were recorded in the patients' charts. Postnatal growth was monitored based on the 2013 Fenton growth charts until the patients reached 50 weeks of corrected age.[7] From this point on, they were monitored based on the 2006 WHO growth charts with z-scores based on their corrected ages.[8]

Occurrences of respiratory conditions and hospitalization during outpatient follow-up were recorded. Blood tests were performed as per the outpatient follow-up protocols in effect at the center. Patients were diagnosed with anemia when their Hb levels were below 11.0g/dL only after they reached corrected ages greater than six months to rule out possible interferences with anemia of prematurity.[9]

Statistical analysis

For purposes of descriptive analysis, the quantitative variables were presented as mean values and standard deviations or median values and their respective 25th and 75th percentiles. Qualitative variables were described through absolute values and proportions. The *Kolmogorov-Smirnov*

test was used to assess the normality of the distribution of the quantitative variables. Variables showing a parametric distribution were described in terms of mean values and standard deviations, whereas variables following a nonparametric distribution were presented based on median values and percentiles. Frequencies referred to the total number of valid responses. Missing data were not considered.

Growth analysis used the first two years of life corrected for gestational age. A polynomial trend line of the third degree was used to suppress minor data variations and enhance the visualization of the proportions of appropriate anthropometric measures versus corrected age.[10]

Microsoft Excel version 2010 and *SPSS* version 23.0 were used to store and treat the data during statistical analysis.

Ethics

This study was approved by the Ethics Committee for Human Research of the Federal University of Viçosa (CAAE 19676613.5.0000.5153) and is an integral element of project "Growth, development, and morbidity of preterm or low-weight-at-birth infants and preschoolers". The study complies with the Guidelines And Regulations For Research Involving Humans and Resolution 466 of December 12, 2012, issued by the National Health Council of the Ministry of Health, Brasília, DF. Patient data confidentiality was ensured throughout the study.

RESULTS

The data from 183 premature infants were included in the study (the charts of seven of the 190 infants seen at the Center were not found). Table 1 shows that the mean maternal and paternal ages were 26 and 29 years, respectively, and that 39.9% of the mothers and 52.6% of the fathers had completed ninth grade. More than half (53.4%) of the families had incomes below two Brazilian minimum wages. More than half (55.7%) of the premature infants were males, 72% were at 32 weeks' pregnancy or longer at birth, and 16.9% were deemed SGA.

The first visit took place when the infants were 41 weeks old, and 73.8% of them were being breastfed. The median duration of breastfeeding was five months, and 81.7% of the premature infants had cow's milk within their first year of life. Prevalence of anemia in the first and second years of life was 25.8% and 12.2%, respectively. During follow-up, 10.4% of the premature infants were hospitalized, mainly for respiratory conditions.

Figures 1, 2, and 3 show the two-year progression of the anthropometric parameters of the included infants. Predominantly appropriate weight, height, and BMI for age were observed, along with a trend toward proportional increases in anthropometric parameter appropriateness at the end of the observation period. Appropriate weight and height for age increased until six months of corrected age, but high weight levels for age grew slightly from 18 months of corrected age.

Table 1. Sociodemographic and perinatal characteristics during outpatient follow-up. Premature infants, Viçosa-MG, 2010-2015.w

Variables	n (%)	Mean (+ SD)	Median (P25-P75)
Mother's place of birth			
Viçosa	80 (56,7)	-	-
Other municipality	61 (43,3)		
Mother's level of education			
< ninth grade	69 (39,9)	-	-
> ninth grade	104 (60,1)		
Father's level of education			
< ninth grade	81 (52,6)	-	-
> ninth grade	73 (47,4)		
Household income			
> 2 MW	69 (46,6)	-	-
< 2 MW	79 (53,4)		
Mother's age	-	26,4 (6,9)	-
Father's age	-	29,9 (8,5)	-
Sex			
Female	81 (44,3)	-	-
Male	102 (55,7)		
Type of delivery			
Vaginal	68 (37,2)	-	-
Cesarean section	115 (62,8)		
SGA			
Yes	31 (16,9)	-	-
No	152 (83,1)		
Hospitalization at NICU			
Yes	120 (65,6)	-	-
No	63 (34,4)		
Birth weight			
<1500g	54 (29,5)	-	-
>1500g	129 (70,5)		
Weeks' gestation at birth			
< 32 w	51 (28,0)	-	-
> 32 w	131 (72,0)		
CA on first visit (weeks)	-	-	41,3 (39,0-45,0)
Duration of BF (CA; months)	-	-	5,0 (2,6-7,0)
Type of feeding on first visit			
BF	135 (73,8)	-	-
AF	48 (26,2)		
Cow's milk given on 1st year of life			
Yes	76 (81,7)	-	-
No	17 (18,3)		
Hospitalization			
Yes	19 (10,4)	-	-
No	164 (89,6)		
Anemia on first year			
Yes	24 (25,8)	-	-
No	69 (74,2)		
Anemia on second year			
Yes	5 (12,2)	-	-
No	36 (87,8)		

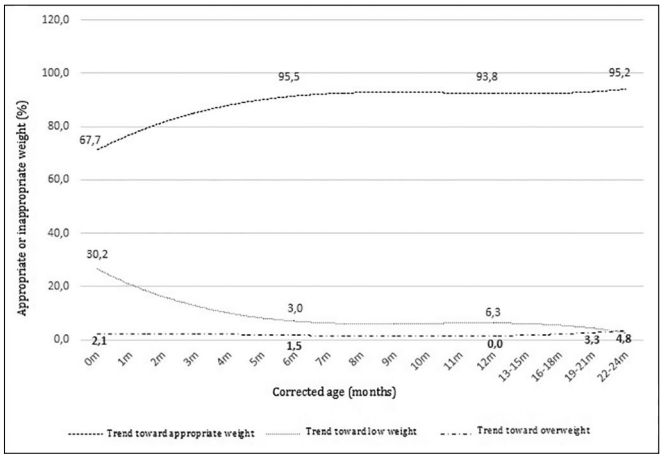

Figure 1. Proportions of individuals with appropriate and inappropriate weight within the first two years of life with ages corrected for prematurity and respective trend lines. Premature infants, Viçosa-MG, 2010-2015. Low weight includes individuals with low and very low weight for their ages.

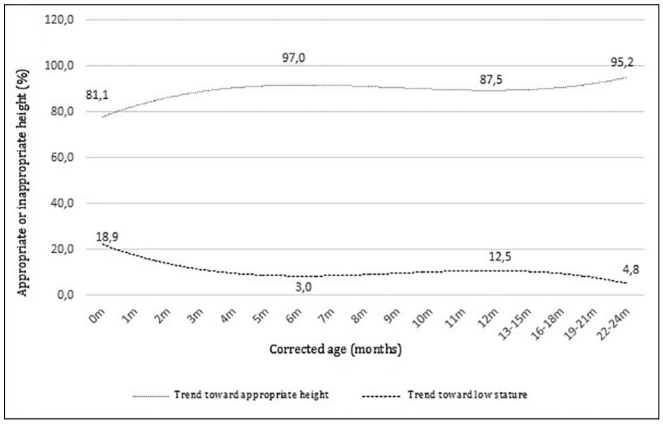

Figura 2. Proportions of individuals with appropriate and inappropriate height within the first two years of life with ages corrected for prematurity and respective trend lines. Premature infants, Viçosa-MG, 2010-2015. Short stature includes individuals with low and very short stature for their ages.

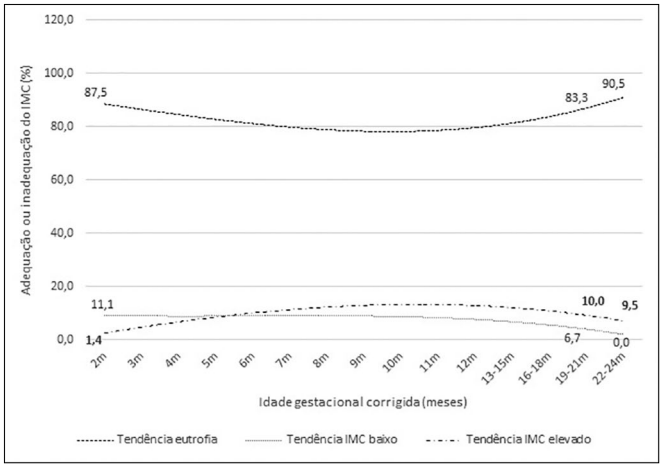

Figura 3. Proportions of individuals with appropriate and inappropriate body mass index (BMI) within the first two years of life with ages corrected for prematurity and respective trend lines. Premature infants, Viçosa-MG, 2010-2015. Low BMI includes underweight and extremely underweight individuals. High BMI includes individuals at risk of becoming overweight, overweight, and obese individuals. There is no BMI data before two months of age, since the Fenton growth charts were used in this period.

The proportion of appropriate BMI levels for age increased toward the end of the observation period, with trends becoming clearer from 12 months of corrected age. However, the number of cases of high BMI levels for age increased starting at 18 months of corrected age, as observed with weight, although accompanied by decreased proportions of individuals with appropriate height for their ages.

According to Figure 4, which shows the progression of anthropometric parameters for SGA infants, there was a trend toward the recovery of weight and height within the first two years of life. However, the high levels of BMI for age detected among SGA infants at five months of age were sustained until they reached a corrected age of two years.

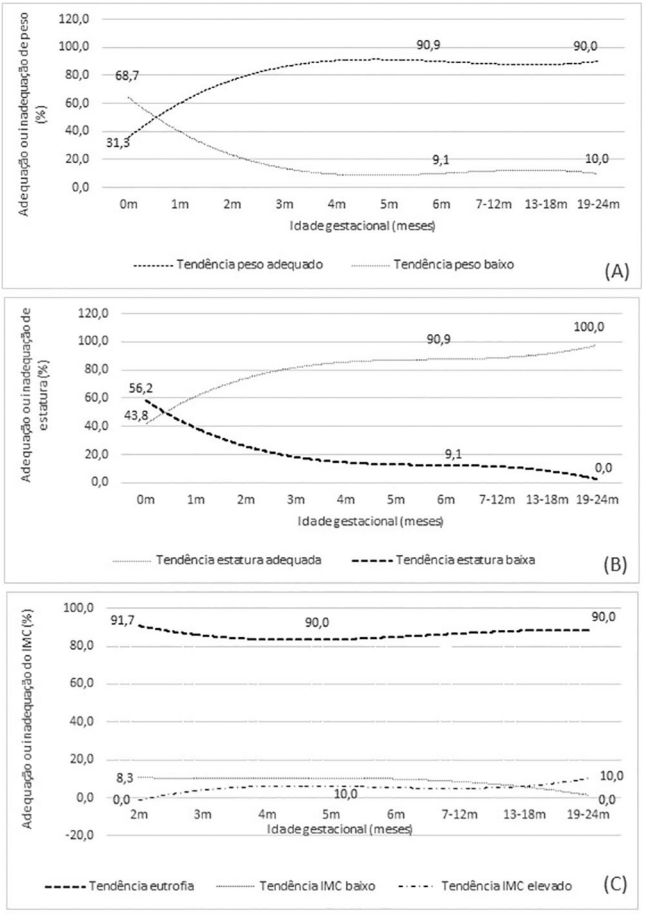

Figura 4. Percentuais de adequação e inadequação do peso (A), estatura (B) e índice de massa corporal-IMC (C) dos prematuros PIG nos dois primeiros anos de idade corrigida para a prematuridade e as respectivas linhas de tendência. Viçosa-MG, 2010-2015. Peso baixo: peso baixo e muito baixo para a idade; estatura baixa: estatura baixa e muito baixa para a idade; IMC baixo: magreza e magreza acentuada; IMC elevado: risco de sobrepeso, sobrepeso e obesidade. Não há dados de IMC antes dos 2 meses devido ao uso das curvas de Fenton nesse período.

DISCUSSION

Appropriate levels of weight, height, and BMI for age were observed throughout the period of the study, along with a trend toward increased anthropometric parameters at two

years of corrected age. A clear pattern of recovery of weight and height for age was seen within the first six months of life corrected for gestational age. However, the proportion of overweight individuals for age increased slightly from 18 months of corrected age, a finding that signals the need to follow this population for longer. Among premature infants, the larger increases in weight and BMI seen at two years of corrected age were associated with improved neurological development. Nonetheless, disproportionate increases in weight vis-à-vis height should be considered with caution, since they bring no additional benefit and may increase cardiovascular risk in the future.[4–6,11,12]

Growth is more intense within the first six months of life, as also observed in our study.[13] Initial weight gain is a predictor of catch-up growth.[14] C*atch-up* growth is defined as the increase in the growth rate of a child that allows it to recover after a period of slow or absent growth. It occurs in the following order: head circumference, length, and weight. Catch-up growth allows premature infants to achieve, within their first years of life, growth levels similar to full-term children.[13] Evidence suggests that preterm SGA infants present slower growth velocity in their first months of life when compared to non-SGA infants. Premature infants usually experience a peak in growth at 36 to 40 weeks of life, but extrauterine growth restriction in this period is a concern that is exacerbated in SGA infants, a condition observed in 16.9% of the premature infants included in our study.[15,16]

Eighty percent of premature infants reach normal height and head circumference by the time they are three years old, and 70% achieve normal weight. Lack of recovery has been associated with low socioeconomic status and occurrence of disease. Other factors that may affect catch-up growth and growth within the first years of life include inadequate nutrition during hospitalization and after discharge, bronchopulmonary dysplasia, and intrauterine growth restriction.[13,14,16] The growth velocity of premature infants after birth speaks of the relevance of providing nutritional advice, since evidence indicates that adequate nutrition may positively affect growth.[17,18]

In our study, 4.8% of the premature infants had short stature at two years of corrected age despite the trend toward decreased proportions of individuals of short stature for age at this point. Interestingly, a separate analysis of SGA infants revealed they had appropriate height at two years of corrected age. Children subject to extrauterine growth restriction have lower weight and height at the age of eight years when compared to individuals not suffering from extrauterine growth restriction, which indicates the relevance of monitoring this factor during the follow-up of infants born prematurely.[19] Although a significant proportion of premature infants achieve normal height by the age of three years, short stature after two years of age should be investigated and properly addressed.[20] Similarly to children suffering from extrauterine growth restriction, SGA infants have trouble achieving their potential stature. Growth hormone therapy should be considered for SGA infants.[20,21]

Appropriate BMI for age showed a trend toward increased proportions at two years of corrected age with clearer increases starting at 12 months of corrected age. However, a trend toward increased BMI for age was observed from 18 months of corrected age, evincing a direct correlation with excessive weight for age and an inverse correlation with short stature for age. Ten percent of the SGA infants had a high BMI for their ages from the end of the first semester to two years of corrected age. High BMI for age is a finding that indicates the need to follow premature infants for longer, since weight gain and increased BMI within the first two years of life corrected for gestational age has been linked to overweightness and obesity in school-age children.[22] Additionally, prematurity, low birth weight, SGA, and intrauterine/extrauterine growth restriction have been associated with noncommunicable diseases such as coronary artery disease, hypertension, metabolic syndrome, and chronic kidney disease.[22,23,2,24,3,25] This is shown in the higher blood pressure levels and changes in lipid profiles of adolescents and young adults born prematurely[26,27], in the combination between prematurity and intrauterine growth restriction and their associations with glucose metabolism disorders and metabolic syndrome[11], and in the combination between prematurity and extrauterine growth restriction and their associations with metabolic and blood pressure disorders during puberty.[19]

Considering that the growth of premature infants may be affected by biological, socioeconomic, and cultural factors, our study found the following concerns: short duration of breastfeeding; high proportions of premature infants being fed cow's milk in the first year of life; high prevalence of anemia; parents with low levels of education; and low household income. Children given only human milk for the first six months of life are more protected against becoming overweight at school age, and appropriate nutrition within the first years of life may foster phenotypic reprogramming and decreased risk of obesity.[18,22] However, children raised in low income households weaned precociously and exposed do diets rich in sugar, starchy foods, and cow's milk tend to experience rapid weight and height recovery, and a growth rate that may increase the risk of cardiac and metabolic conditions.[18,28–30]

The weaknesses of our study include its descriptive nature, which does not allow the analysis of associations, and the losses inherent to a study based on secondary data, an issue minimized by the semi-structured patient chart system in use at the healthcare center. Its strengths include the continuing follow-up of premature infants at the referral center for the municipality and region, which will allow us to better understand their longer-term growth patterns, study associated factors, contribute with scientific knowledge on the subject, and improve care practices for premature infants.

Our findings are in line with the literature, in that the growth parameters - weight, height, and BMI - of premature infants tended to reach appropriate levels within the first two years of life corrected for gestational age. During the study we also observed a perceptible decrease in the proportion

of individuals with short stature for their ages. However, the presence of high BMI for age, particularly among SGA infants, is worthy of consideration and signals the need to follow them up more closely, since they gain weight and grow in stature more slowly within the first few months of life, a fact potentially misinterpreted as need for higher calorie intake. Our results showed that all children gained weight and grew in stature in the studied period to reach levels close to those of their full-term counterparts. Therefore, healthcare teams are faced with the challenge of monitoring the growth of premature infants in order to mitigate the future onset of noncommunicable diseases.

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