



ORIGINAL ARTICLE

Growth of preterm low birth weight infants until 24 months corrected age: effect of maternal hypertension[☆]



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KEYWORDS

Child;
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Abstract

Objective: To evaluate the growth pattern of low birth weight preterm infants born to hypertensive mothers, the occurrence of growth disorders, and risk factors for inadequate growth at 24 months of corrected age (CA).

Methods: Cohort study of preterm low birth weight infants followed until 24 months CA, in a university hospital between January 2009 and December 2010. Inclusion criteria: gestational age < 37 weeks and birth weight of 1,500–2,499 g. Exclusion criteria: multiple pregnancies, major congenital anomalies, and loss to follow up in the 2nd year of life. The following were evaluated: weight, length, and BMI. Outcomes: growth failure and risk of overweight at 0, 12, and 24 months CA. Student's t-test, Repeated measures ANOVA (RM-ANOVA), and multiple logistic regression were used.

Results: A total of 80 preterm low birth weight infants born to hypertensive mothers and 101 born to normotensive mothers were studied. There was a higher risk of overweight in children of hypertensive mothers at 24 months; however, maternal hypertension was not a risk factor for inadequate growth. Logistic regression showed that being born small for gestational age and inadequate growth in the first 12 months of life were associated with poorer growth at 24 months.

Conclusion: Preterm low birth weight born infants to hypertensive mothers have an increased risk of overweight at 24 months CA. Being born small for gestational age and inadequate growth in the 1st year of life are risk factors for growth disorders at 24 months CA.

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PALAVRAS-CHAVE

Criança;
Baixo peso ao nascer;
Prematuro;
Hipertensão materna;
Crescimento

Crescimento de prematuros de baixo peso até a idade de 24 meses corrigidos: efeito da hipertensão materna

Resumo

Objetivo: Avaliar o padrão de crescimento de prematuros de baixo peso nascidos de mães hipertensas, a ocorrência de distúrbios de crescimento e os fatores de risco para inadequado crescimento aos 24 meses de idade corrigida (IC).

Métodos: Estudo de coorte de prematuros de baixo peso acompanhados até 24 meses IC, em um Hospital Universitário, entre Janeiro 2009 e Dezembro 2010. Critérios de inclusão: idade gestacional < 37 semanas e peso de nascimento de 1500-2499 g. Excluídas: gestações múltiplas, anomalias congênitas maiores e perda de seguimento no segundo ano de vida. Foram avaliados: peso, comprimento e IMC. Desfechos: falha de crescimento e risco de sobrepeso com 0, 12 e 24 meses de IC. Teste t Student, X², ANOVA-RM e regressão logística múltipla foram usados.

Resultados: Foram estudados 80 prematuros de baixo peso nascidos de mães hipertensas e 101 de mães normotensas. Houve maior risco de sobrepeso em crianças de mães hipertensas aos 24 meses, entretanto a hipertensão materna não foi fator de risco para inadequado crescimento. A regressão logística mostrou que nascer pequeno para idade gestacional e ter inadequado crescimento nos primeiros 12 meses de vida associaram-se com pior crescimento aos 24 meses.

Conclusão: Prematuros de baixo peso nascidos de mães hipertensas têm risco aumentado de sobrepeso aos 24 meses de IC. Ser pequeno para idade gestacional e ter inadequado crescimento no primeiro ano são fatores de risco para distúrbios no crescimento aos 24 meses de IC.

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Introduction

Among the causes of prematurity, hypertensive disorder of pregnancy is one of the most important, affecting 5% to 10% of pregnancies and demonstrating an increasing incidence in developing countries.^{1,2} This disease is an important cause of maternal and fetal mortality and morbidity, as well as one of the main medical indications of preterm birth, often associated with fetal growth restriction.^{1,3}

Preterm infants born small for gestational age (SGA) due to intrauterine growth restriction are at higher risk of neonatal morbimortality and growth and development disorders, when compared with those born with adequate weight for gestational age (AGA).^{4,5} Another point of concern regarding the consequences of prematurity or low birth weight in the long-term is that inadequate growth during the fetal period and in the early years of life increases the risk of chronic diseases such as hypertension, myocardial infarction, and diabetes in adulthood.⁶

There are scarce and contradictory studies on the prognosis of infants born to hypertensive mothers. There is evidence that exposure to oxidative stress in utero, triggered by maternal hypertensive disease, has implications in the pathogenesis of several diseases of preterm infants,³ and is associated with higher neonatal morbimortality, although it has not been established whether the worse prognosis of these preterm infants is due to maternal disease or degree of prematurity.^{3,7} However, some studies found no differences in the prognosis of preterm infants born to hypertensive mothers^{8,9} and others have suggested that stress in utero triggered by hypertension can accelerate the maturation of organs and improve the prognosis of these preterm infants.¹⁰ A recent study showed that most preterm infants born to

mothers with severe hypertension syndrome have intrauterine growth restriction and achieve complete "catch up" in the first 4 years, but at that age, these children are smaller and thinner compared to the population mean.¹¹

The scarcity and the lack of consensus of studies on the prognosis of premature infants born to mothers with gestational hypertension syndrome justify the need for surveillance of neonatal complications, and follow-up of these infants, for better understanding the impact of maternal disease on growth and development.

This study aimed to analyze the growth pattern of low birth-weight preterm infants born to hypertensive mothers, as well as to evaluate the occurrence of growth disorders and risk factors for inadequate growth at 24 months corrected age (CA).

Methods

This was a prospective cohort study of low birth weight preterm infants admitted to the Neonatal Care Unit and followed during the first 2 years of life at the Low Birth Weight Infant Outpatient Clinic of Faculdade de Medicina de Botucatu-UNESP, from January of 2009 to December of 2010.

The study was approved by the Research Ethics Committee of the institution. Maternal and neonatal data of interest were obtained from medical records at the first outpatient routine consultation, after obtaining the signed informed consent.

A convenience sample was studied, corresponding to the total number of patients who met the inclusion criteria during a two-year enrollment period, accepting a maximum loss of 20% of the cohort.

In the Low Birth Weight Infant Outpatient Clinic, starting in January of 2009, all preterm infants younger than 1 year were selected on the day of consultation and included in the study, when they met the following criteria: born in the Clinic's maternity ward, single gestation, gestational age < 37 weeks, birth weight between 1,500 and 2,499 g, without multiple congenital anomalies and no congenital infection, and who had at least three consultations in the 1st year of life. Lack of follow-up in the 2nd year of life was considered as a loss.

The study variables included: maternal data (age, level of schooling, height, and smoking status); pregnancy data (hypertensive disorder of pregnancy, regardless of the type and severity of the disease, diabetes mellitus; intrauterine growth restriction, preterm premature rupture of membranes, fetal distress, and type of delivery); neonatal data (gestational age according to the best obstetric estimate, birth weight and AGA according to Alexander et al.,¹² gender, Apgar score at 1 and 5 minutes after birth, neonatal morbidity, and length of hospital stay). After hospital discharge, the following variables were considered: breastfeeding in the 1st year of life; hospitalization in the first 2 years, anthropometric measurements (weight and length), and body mass index.

Anthropometric measurements were obtained at each visit by the previously trained medical and nursing staff of the service. Patients were weighed on a digital scale (Filizzola®, SP, Brazil) for children, with an accuracy of 5 g. Length was measured in the supine position, using a wooden stadiometer or in the standing position, using a ruler in millimeters.

CA was used for all preterm infants in the first 2 years of life, and anthropometric measurements were evaluated by calculating the Z-score to follow growth, as classically done in the literature. Growth assessment was performed by quarters in the 1st year and every six months in the 2nd year of life, considering the consultation that was closer to the expected date of assessment, namely: 40 weeks, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months CA.

Based on whether or not the cohort was exposed to gestational hypertension syndrome, the study groups were formed: preterm infants of hypertensive mothers and preterm infants of normotensive mothers. The outcomes of interest were: growth failure or risk of overweight at 12 and 24 months of age, according to the growth curve of the World Health Organization (WHO; 2006).¹³

Definitions used in the study:

- Gestational hypertensive syndrome: blood pressure 140/90 mmHg or higher, on two occasions, with an interval \geq 4 hours, according to the criteria of the Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.¹⁴ Hypertension diagnosed after the 20th week of gestation associated with proteinuria (> 300 mg in 24-hour urine) characterized pre-eclampsia.
- SGA: birth weight < 10th percentile, according to Alexander et al.¹²
- Growth failure: weight or length below the 3rd percentile on the WHO curve (2006).¹³

- Thinness: BMI \geq 0.1 percentile and < 3rd percentile on the WHO curve (2006).¹³
- Risk of overweight: BMI > 85th percentile and \leq 97th percentile according to the WHO curve (2006).¹³

Statistical analysis

Data were described by calculating the distribution of frequencies, means and standard deviations, medians, and percentiles. Associations between numerical variables were assessed by Student's *t*-test or the Mann-Whitney test when indicated, and the chi-squared test was used for categorical variables.

RM-ANOVA followed by Tukey's test was used for multiple comparisons between groups, and the chi-squared test for trend was used to assess change of proportions over time, with the sample stratified according to maternal hypertension and adequacy of birth weight for gestational age.

The outcomes of interest were analyzed by logistic regression for repeated measures. SAS software for Windows, release 9.2 (SAS Institute Inc, NC, USA), was used in the statistical analyses and the significance level was set at 5%.

Results

From January 2009 to December 2010, 241 premature infants eligible for the study were born in the Maternity Ward of Hospital das Clínicas da Faculdade de Medicina de Botucatu-UNESP. Among these, there were three in-hospital deaths and 238 were referred for follow-up at the Low Birth Weight Infant Outpatient Clinic, but in four cases the consultation was not scheduled (2%). Thus, 234 eligible preterm infants were enrolled in the study, but 40 of these preterm infants were twins, and 13 had malformations and were excluded. Therefore, the cohort consisted of 181 preterm infants, 101 born to normotensive mothers and 80 to hypertensive mothers, of whom 63 (80%) had pre-eclampsia.

At the end of the first year of life, 69 preterm infants of hypertensive mothers (86%) and 84 preterm infants of normotensive mothers (83%) were evaluated. At 24 months, 149 preterm infants were evaluated, with a loss of cohort of 15% in the hypertensive group and 20% in the normotensive group. There were no differences in the neonatal characteristics of preterm infants followed up to 24 months compared to those who were lost to follow-up, except for gestational age, which was lower in the lost cohort of the normotensive group (32 ± 2 weeks vs. 33 ± 2 weeks in the other groups, $p = 0.035$).

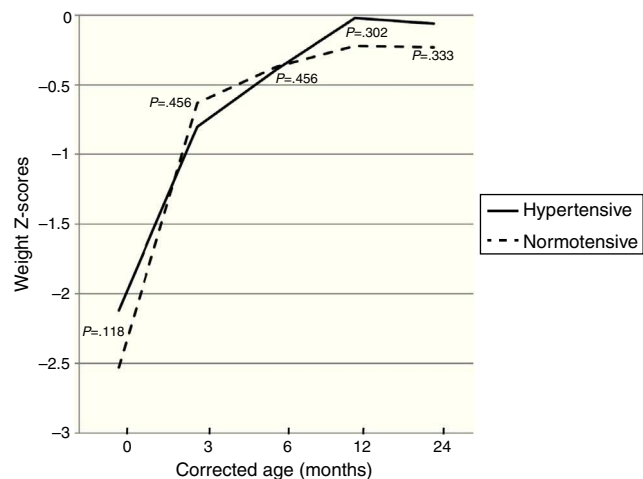
Mean maternal age was 25-26 years, mean height was 1.59 m, and 40% of the mothers had only elementary education, with no difference between groups. Premature rupture of membranes was more frequent in the normotensive group (41% vs. 2.5%, $p < 0.001$), whereas cesarean delivery predominated in the hypertensive group (82% vs. 40%, $p < 0.001$).

Table 1 shows the main neonatal characteristics. This table highlights the high percentage of infants born SGA in the two groups of preterm infants, and also the high frequency of breastfeeding at discharge, with exclusive breastfeeding more frequent in the normotensive group ($p = 0.033$).

Table 1 Neonatal characteristics of preterm low birth weight infants in hypertensive and normotensive mothers.

Neonatal variables	Hypertensive (n = 80)	Normotensive (n = 101)	p-value
Gestational age (weeks) \pm SD	33 \pm 1.9	33 \pm 2	0.437
Birth weight (g) \pm SD	1,754 \pm 303	1,839 \pm 301	0.061
Length (cm) \pm SD	41.5 \pm 2.4	42.2 \pm 2.4	0.087
Head circumference (cm) \pm SD	30.2 \pm 1.8	30.1 \pm 1.8	0.572
Small for gestational age	51%	40%	0.157
EBF at discharge	54%	69%	0.033
Mixed feeding at discharge	22.5%	21%	0.782
Days of hospitalization (md Q1-Q3)	15 (9.5-23)	13 (7-23)	0.769

SD, standard deviation; md, median; Q, quartile; EBF, exclusive breastfeeding.

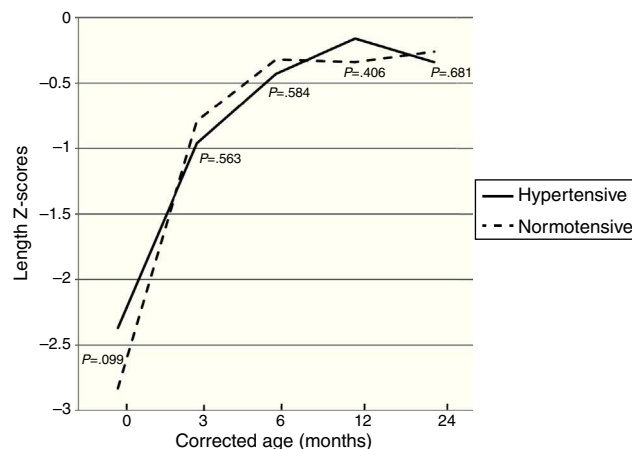
**Figure 1** Evolution of the weight Z-scores in preterm infants of normotensive and hypertensive mothers up to 24 months corrected age.

At the outpatient follow-up during the first 2 years of life, few preterm infants required hospitalization (2%) and the incidence of complications was low in both groups; the most common problem was anemia, diagnosed in 8% of patients, with no difference between groups. The feeding pattern of the preterm infants, monitored by the medical team with support from a nutritionist, was satisfactory in the 1st year of life, with high rates of exclusive or predominant breastfeeding (two-thirds of the sample in the two groups) in the first 6 months of life. The median duration of breastfeeding was 6.5 (3-12) months for preterm infants born to hypertensive mothers and 6 (3 to 11.5) months in the normotensive group.

In both groups of preterm infants, the curves of Z-scores for weight and length were superimposed in the first 2 years of life (Figs. 1 and 2).

Table 2 shows the mean values of Z scores for weight, height, and BMI, and the frequency of growth disorders at term, with 12 and 24 months CA. This table highlights the higher percentage of preterm infants born to hypertensive mothers with BMI > 85th percentile at 24 months CA (Table 2).

To determine whether gestational hypertension syndrome is a risk factor for growth disorders in low birth weight preterm infants, logistic regression models were constructed, controlled for gestational age and gender,

**Figure 2** Evolution of length Z-scores in preterm infants of normotensive and hypertensive mothers up to 24 months corrected age.

including maternal hypertension, adequacy of birth weight for gestational age, and effect of time on anthropometric measurements.

Logistic regression showed that maternal hypertension was not a risk factor for inadequate growth in weight (OR = 0.47, 95% CI: -0.10-1.05) and length (OR = 0.20, 95% CI: -0.29-0.69) at 24 months CA. Two risk factors for growth disorders were identified at 24 months CA: SGA and inadequate growth in the 1st year of life.

SGA increased the risk of inadequate weight by approximately two-fold (OR = 2.36, 95% CI: 1.34-4.14) and length (OR = 2.13, 95% CI: 1.30-3.50). Inadequate weight gain at 3 months (OR = 5.89, 95% CI: 3.07-11.30), at 6 months (OR = 2.95, 95% CI: 1.61-5.45), and at 12 months (OR = 2.45, 95% CI: 1.45-4.18) showed influence on weight at 24 months CA, whereas inadequate growth in length at 3 months (OR = 7.12, 95% CI: 3.80-13.35) and at 6 months (OR = 2.78, 95% CI: 1.45-5.35) was a risk factor for inadequate stature at 24 months CA.

Discussion

The main results of this study indicate a higher frequency of growth disorders in low birth weight preterm infants born to hypertensive mothers, but the effect of maternal disease

Table 2 Mean values of Z-scores for weight, length, and body mass index (BMI) and frequency of growth disorders at term, 12 months, and 24 months corrected age in the groups of hypertensive and normotensive mothers.

Corrected age	Variable	Preterm of hypertensive mother	Preterm of normotensive mother	p-value
At term (n = 153) H = 69; N = 84	Z weight	- 2.12 ± 1.61	- 2.53 ± 1.55	0.118
	Weight < p5	27%	34%	0.452
	Z length	- 2.37 ± 1.59	- 2.83 ± 1.65	0.099
	Length < p5	26%	28%	0.932
	Z BMI	- 1.10 ± 1.46	- 1.60 ± 1.45	0.046
At 12 months (n = 153) H = 69; N = 84	BMI > p85	22%	14%	0.237
	Z weight	- 0.02 ± 1.15	- 0.22 ± 1.23	0.302
	Weight < p5	7%	9.5%	0.833
	Z length	- 0.16 ± 1.30	- 0.34 ± 1.32	0.406
	Length < p5	13.5%	18%	0.607
At 24 months (n = 149) H = 68; N = 81	Z BMI	0.10 ± 1.02	- 0.03 ± 1.18	0.454
	BMI > p85	15%	15.5%	0.962
	Z weight	- 0.06 ± 1.03	- 0.23 ± 1.06	0.333
	Weight < p5	6%	4%	0.866
	Z length	- 0.34 ± 1.20	- 0.26 ± 1.10	0.681
	Length < p5	17.5%	12%	0.448
	Z BMI	0.23 ± 1.03	- 0.12 ± 1.02	0.044
	BMI > p85	27%	12%	0.029

H, hypertensive; N, normotensive.

was indirect, with inadequate fetal growth and growth failure in the first year of life representing the risk factors for the occurrence of growth disorders at 24 months CA.

In the present study, the growth profiles of preterm infants of normotensive and hypertensive mothers were similar in the first 2 years of life and found to be satisfactory according to the WHO standards. It must be considered that these preterm infants' birth weight was between 1,500 and 2,499 g, constituting a scarcely studied group whose prognosis for growth is not well established. An important fact that may have positively influenced the results was the high rate of breastfeeding at hospital discharge, with a mean duration of breastfeeding of 6 months in both groups. The literature highlights the importance of breastfeeding for preterm low birth weight infants, which results in a better pattern of growth and development for these children.¹⁵

The study sample was homogeneous regarding gestational age and birth weight, and may be considered of low neonatal risk, except for the high percentage of SGA preterm infants in both groups (51% and 40% in the hypertensive and normotensive groups, respectively). These figures are found in tertiary care services, with incidence reported in the literature of approximately 15-50% SGA newborns in pregnancies complicated by hypertension.^{1,16} Impaired fetal growth is expected especially in pre-eclampsia due to the physiopathology of the disease, which involves alterations in placental blood flow.² A study of pregnancies under 34 weeks complicated by hypertensive syndrome demonstrated that alteration in the umbilical artery Doppler velocimetry increases the incidence of SGA infants by 2.5-fold.¹⁷

The growth prognosis for preterm infants born to hypertensive mothers has been poorly studied and the results are controversial. Silveira et al.¹⁸ evaluated 40 very low

birth weight preterm infants born to mothers with pre-eclampsia and 46 born to normotensive mothers, and showed that at 12 and 18 months CA, the preterm infants of mothers with pre-eclampsia showed no catch-up weight, whereas growth in height and head circumference did not differ between groups. The authors attributed the failure to thrive to the high percentage of SGA preterm infants in the pre-eclampsia group (62% vs. 39% in the normotensive group). A recent study assessed the growth of preterm infants born to mothers with hypertensive syndrome who had fetal growth restriction and showed good prognosis for growth in stature, with catch-up in 94% of children, although the children became thinner during the first 5 years of life.¹¹

Postnatal growth restriction is a very frequent event in very low birth weight preterm infants and those admitted at the neonatal ICU, who mostly demonstrate retarded growth, with decreased Z-scores for weight and length between birth and 40 weeks CA.^{19,20} Consistent with this expectation, in this study more than one-quarter of the sample had weight below the 5th percentile when they reached term, but at the end of the 1st year of life, weight was higher than the 5th percentile in more than 90% of preterm infants in the two groups. Similar developments occurred in height growth. These results are in agreement with literature data showing that most preterm infants experience catch-up growth, reaching their percentis between the limits of normality on reference curves by 2-3 years of age.²¹

By analyzing the evolution of BMI, an important aspect was demonstrated at 24 months; there was an increased risk of overweight in preterm infants of hypertensive mothers. There is no data in the literature to justify this result; therefore, the authors' hypothesis is that this finding could reflect excessive catch-up, which may be associated with

future complications, including obesity in childhood, adolescence, and adulthood, as well as increased risk of metabolic syndrome.^{22,23} It is suggested that maternal hypertension may have an impact on growth in premature infants, which occurs in the medium or long term, and warns of the need for prolonged follow-up of these children. More studies are needed to confirm these findings.

As there was a higher risk of overweight in the hypertensive group, maternal hypertension was investigated as a risk factor for growth disorders at 24 months of CA by logistic regression. However, in this analysis, maternal hypertension was not an independent risk factor for growth disorders in both weight and height. The identified risk factors were SGA and inadequate growth in the first year, especially in the first semester of life.

This study has some limitations, as the severity of maternal hypertensive disease was not assessed and the follow-up time was limited to the first 2 years of life. However, the study sample was homogeneous, the loss of the cohort was acceptable ($\leq 20\%$), and the results brought new knowledge on the growth of preterm infants with birth weight between 1,500-2,499 g.

The lack of effect of maternal hypertension on the preterm infant growth can be partly attributed to the fact that maternal disease severity was not evaluated. Nonetheless, this study reinforces two issues that have been highlighted in the literature: the direct influence of fetal growth on postnatal growth and the importance of the early years of life, a critical period for the occurrence of catch-up growth in preterm infants.²¹

Kelleher et al.²⁴ documented an incidence of 20% of growth failure in low birth weight preterm infants followed until age 3 years and identified SGA as an independent risk factor for growth failure.

The most important results of this study are related to the lack of differences in the growth of preterm infants of normotensive and hypertensive mothers in the first 2 years of life; however, at 24 months, the preterm infants of hypertensive mothers showed higher frequency of overweight, which can translate as a late-manifestation effect of maternal disease. These data indicate the importance of follow-up of preterm infants of hypertensive mothers in the long term, as excess adiposity in early life can later develop into metabolic syndrome, with negative effects on adult health.^{22,25}

In conclusion, preterm low birth weight infants born to hypertensive mothers have an increased risk of overweight at 24 months of CA. SGA and inadequate growth in the first year are risk factors for growth disorders at 24 months of CA.

Conflicts of interest

The authors declare no conflicts of interest.

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