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ORIGINAL ARTICLE

Effect of predominant breastfeeding duration on infant growth: a prospective study using nonlinear mixed effect models

Maria Helena Constantino Spyrides,[1] Cláudio José Struchiner,[2] Maria Tereza Serrano Barbosa,[3] Gilberto Kac[4]

Abstract

Objective: The aim of this study is to assess the effect of predominant breastfeeding duration on infant growth by means of repeated measurements model.

Methods: This prospective study is comprised of four follow-up evaluations at approximately 0.5, 2, 6 and 9 months after birth, including structured interviews that simultaneously gathered information regarding infant growth and breastfeeding practices. The study took place in a healthcare center in Rio de Janeiro, Brazil, from 1999 to 2001. Four hundred seventy-nine postpartum women and their newborns were enrolled in the cohort. Body weight and length measurements taken at five different occasions (birth, 0.5, 2, 6, and 9 months) constituted the dependent variables. We expressed the growth process using nonlinear mixed models.

Results: Infants with longer predominant breastfeeding duration, although growing faster in the first months of life, reached an inferior equilibrium body weight and length compared to infants who received nonhuman milk earlier in life. The age at which the rate of weight gain of the formula-fed infants becomes greater than that of the breastfed infants is approximately 6.75 months for boys and 7 months for girls.

Conclusions: This study confirms the differences observed in infant growth according to different breastfeeding practices starting from the sixth month of life. Use of nonlinear models allowed for a greater precision of parameter estimates. We believe that this approach facilitates the analysis and interpretation of growth data at the individual and population levels.

J Pediatr (Rio J). 2008;84(3):237-243: Breastfeeding, infant growth, nonlinear mixed models, repeated measures.

Introduction

Infant growth patterns vary substantially as a function of several factors comprising determinants such as nutritional, cultural, environmental and social conditions, as well as biological and genetic factors. In the first 6 months of life, the most important source of nutrients is breast milk. As a consequence, it is important to know how breastfeeding duration influences the increase in body weight and length in infants.

The effect of breastfeeding on infant growth has been studied by several authors.[1-6] Several researchers have verified that breastfed infants show a higher growth rate early in

1. Doutora. Professora adjunta, Departamento de Estatística, Universidade Federal do Rio Grande do Norte (UFRN), Natal, RN, Brazil.
2. Doutor. Professor adjunto, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil. Pesquisador titular, Escola Nacional de Saúde Pública, Fundação Oswaldo Cruz (FIOCRUZ), Rio de Janeiro, RJ, Brazil.
3. Doutora. Professora adjunta, Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Rio de Janeiro, RJ, Brazil.
4. Doutor. Professor, Instituto de Nutrição Josué de Castro, Departamento de Nutrição Social Aplicada, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil.

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life when compared to formula-fed infants. Other studies[1,6,7] have reported that the rate of weight gain in formula-fed infants becomes greater than that of breastfed infants at some point during the first few months of growth. There is still an undergoing debate on the issue, especially after the release in 2006 of the World Health Organization (WHO) new standards to asses the growth and development of children under 5 years.[8,9]

The most common anthropometric measurements to assess infant growth are body weight and length. When these measurements are taken repeatedly on the same individual over time, it renders the analysis of the growth process more consistent. It is important to mention that it is difficult or even impossible to quantify the variability attributed to environmental factors in observational studies. As a result, the statistical analysis of these data sets requires models that account for other sources of variation to take into account the uncontrollable factors. In this regard, the use of nonlinear mixed-effects models is a novel approach.[10]

The aim of this study is to assess the effect of predominant breastfeeding duration on infant growth, using data gathered in a health center in Rio de Janeiro, Brazil. The approach of the present study improves on the methodology hitherto used to describe growth patterns among infants, since none of the studies cited previously has analyzed the breastfeeding effect on infant growth using nonlinear mixed models. This approach might facilitate the analysis and interpretation of growth data at both the individual and population levels.

Methods

Study design

The data set used in this analysis comes from a research project that evaluated body composition and maternal obesity, simultaneously gathering information about infant growth and breastfeeding practices. Criteria for recruitment and selection are available in other publications.[11-15] A prospective cohort of Brazilian women aged 15 to 45 years living in the city of Rio de Janeiro, Brazil, was followed for 9 months. Data collection lasted 24 months (15 months for recruitment plus 9 months for follow-up), from May 1999 to April 2001. Four hundred seventy-nine women and their newborns were enrolled in the cohort. This prospective study includes four follow-up evaluations at approximately 0.5, 2, 6 and 9 months after birth. In addition to these evaluations, weight and length at birth were also observed comprising five repeated measurements over time.

Inclusion and exclusion criteria

The eligibility criteria for inclusion in the cohort were: a) infants born alive from mothers ranging from 15 to 45 years of age; b) infants being less than 1 month old by the time of the first interview; c) mothers with no chronic illnesses, d) not being the mother of twins and e) living within the catchment area of Marcolino Candau Municipal Health Center in Rio de Janeiro, Brazil.

Infants whose anthropometric indexes lied outside the normal biological range as specified in the guideline of the WHO[16] were excluded. None of the children in this study scored outside of these bounds, but those who lacked information about breastfeeding duration or had too little information regarding body weight and length were excluded.

Study variables

Infants' body weight and length data were obtained in four follow-up evaluation sessions, as mother and child visited the healthcare center during the 9-month follow-up period. Body weight and length at birth were reported by mothers at the moment of the first interview. The anthropometric measures taken at five occasions (birth, 0.5, 2, 6, and 9 months) constituted the dependent variable of the model.

Body weight was measured with the infant positioned on the mother's lap by means of a digital scale (Model PL 150, Filizola S/A, São Paulo, Brazil), accurate to 0.1 kg. The mother was weighed first and then the weight of the infant was obtained by subtraction. Length was measured using the Kiddimetre infantometer (Child Growth Foundation, UK) accurate to 0.1 cm, with the infant lying down, and by following the recommendations of Lohman et al.[17]

Breastfeeding practices were determined following the Pan American Health Organization (OPAS)/WHO[18] guideline that defines as predominantly breastfed the infants receiving only breast milk and other liquids, such as water, tea or juices. For the analysis, predominant breastfeeding duration (in months) at each follow-up evaluation was treated as the main covariate. Note that this is a time-dependent variable, which means that at each point in time this variable might assume a different value. Otherwise, once the maximum value was reached we kept constant thereafter.

Other covariates studied included age, sex (boys, girls), gestational age (in weeks) and type of delivery (natural or by cesarean delivery). Gestational age was obtained through the information on the date of the last menstrual cycle. Newborns with a gestational age < 37 weeks at birth were considered as premature. Type of delivery was reported by the mother. Infant age, although measured in days from birth to the corresponding follow-up evaluation, was expressed in months.

Statistical modeling

Recently, the use of nonlinear mixed effects models has become increasingly common in scientific research. They are particularly useful when dealing with repeated measures with data not equally spaced in time, a data structure which is very common in public health, biology and other areas. Infant growth pattern follows a nonlinear trajectory in time. Nonlinear statistical models are, therefore, required to describe this behavior. There are many nonlinear functions that can be used. Based on the observed data, the behavior of these measurements (body weight or length) throughout the analyzed period had the shape of the asymptotic regression function. It means that in the earlier months the growth acceleration is greater, slowing down at the end of the observed period. So, the function that fits best with these prospective data of the infant growth in the first months of life is the asymptotic regression model described by Pinheiro & Bates.[10] That model has three parameters and their interpretation is as follows: $P_{asymp.}$ represents the equilibrium body weight or length, i.e., the equilibrium body weight or length at the end of the study period (9 months of age); P_0 represents the body weight or length at birth, and log_*rate* is the logarithm of the rate of body weight or length gain.

In this aspect, the nonlinear mixed model becomes an interesting alternative. While in the fixed effects model the same equation applies to each child, demanding therefore the use of a margin of error, in the random effects model parameters vary from child to child, increasing thus the precision of estimated parameters. The variations within and between infants are estimated separately: within-group variation comprises deviations in anthropometric measurements for one infant around his own growth behavior, while between-group variation describes how the coefficients vary from infant to infant.

Several correlation structures were tested, considering two components: one for the random effects and another for the correlation between repeated measurements. It is well known that repeated measurements are autocorrelated, which means that, for example, body weight at time 1 is correlated with body weight at time 2. For this reason it is necessary to include a correlation parameter. The restricted maximum likelihood estimation method (RMLE) was used to estimate the parameters in the model, using S-PLUS software (MathSoft, Inc, Cambridge, MA). Akaike information criterion (AIC) and likelihood ratio (LR), two procedures to test the model's goodness of fit, were used to help decide which model is best.

The main advantage of the use of nonlinear mixed-effects models is the possibility of employing a nonlinear function to represent the biological mechanism of the process being studied, allowing for parameters that offer a more natural interpretation of the infant's growth. Furthermore, it also allows the estimation of the individual variability from the mean response attributed to the group under study.

The study was approved by the appropriate research ethics committees (Universidade Federal do Rio de Janeiro and Universidade de São Paulo), and signed consent was obtained from each study participant.

Results

In this study, 479 children were followed. Of these, 63 were measured just once, 88 twice, 90 contributed three measurements, and 238 completed the four interviews. In total, 30% of the study participants were lost to follow-up. Losses of follow-up have been described as a function of explanatory variables elsewhere, and no selection bias was identified.

The sample of this study included 236 boys and 243 girls, a total of 479 infants in the first follow-up evaluation. Mean birth weight for boys was 3,254.3±507.2 g, and for girls, 3,115.0±478 g. Mean birth length was 49.3±2.4 cm and 48.6±2.4 for boys and girls, respectively. Mean gestational age was 38.6 weeks, varying from 30 to 42 weeks. The percentages of premature deliveries were 11.3 and 9.0% for boys and girls, respectively.

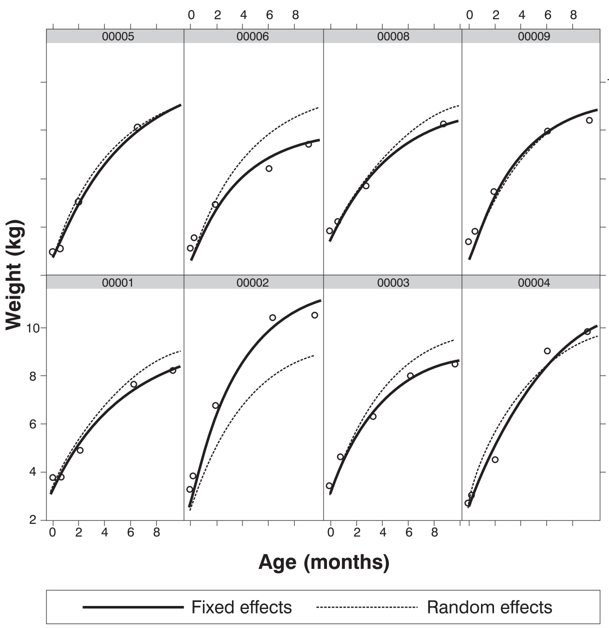
At the time of the first interview, 11.5% of the mothers declared they were predominantly breastfeeding. At 9 months postpartum, 40.0% of the infants received only formulas and 40.0% received a mix of breast milk and formulas. Median duration of predominant breastfeeding was 67 days, and 27% of the mothers' breastfed for 1 month or less. Median exclusive breastfeeding duration was 21 days for premature infants and 90 days for those born in term (results not shown).

Parameter estimates between the groups are similar, despite the fact that the model that considers the random effects presents a smaller standard error. This occurs because the fixed-effects model does not include the variability among groups, which is then absorbed in the residual standard error.

Residual analysis did not show any violation of the normality assumption, and the residuals show a symmetrical distribution around zero, with an approximately constant variance. This is a necessary step in checking the model's adequacy to the observed data. A final assessment of the model adequacy can be better visualized in Figure 1, by comparing observed and predicted values for both models (fixed and random). Observed data for infants numbered 5 and 9 overlap the population average predicted by the model. This pattern is not observed for other infants.

Both fixed and random effects were statistically significant in the final model (Table 1). Sex was significant in all three parameters: girls' body weights are significantly lower than boys' at birth (-0.0971), as well as their equilibrium body weight (-0.3639) and their tendency to have smaller rates of body weight gain (-0.0991) during the first months of life. Gestational age only affects birth weight (0.1338), that is, higher gestational age implies greater birth weight. Type of delivery has a significant effect (0.0766) on growth rate: infants born through the cesarean delivery method tend to have higher rates of body weight gain than infants born through normal delivery (Table 1).

The significant effect of breastfeeding duration on equilibrium body weight (-0.2813) and growth rate (0.0798) of



The information on the first eight children with complete follow-up data is shown.

Figure 1 - Adjusted models with fixed and random effects compared with the observed values of infant body weight (Rio de Janeiro, 1999-2001)

infants deserves special attention. Note that although growth rate is higher as predominant breastfeeding duration increases, equilibrium body weight is lower. This means that infants with longer predominant breastfeeding duration achieve a lower equilibrium weight at the end of the study period, although they are subject to a larger growth rate in the first few months of life (Table 1).

In Figure 2, the crossing point corresponds to the ages of 6.75 and 7 months, for boys and girls, respectively. From this time, infants predominantly breastfed for 6 months or more start to have a lower rate of body weight gain than infants breastfed for less than 6 months.

The growth rate is 16.4% per month, for boys, and 14.8%, for girls. This means that, on average, boys reached half of their equilibrium weight gain in 4.24 months, which is approximately 127 days, compared to 4.68 months (140 days) for girls.

Girls have a significantly lower length at birth (-0.6630) and smaller growth rate (-0.1218) when compared to boys. However, no significant difference for the equilibrium length was observed. Gestational age influences only length at birth (0.6088); the longer the gestational age, the greater length at birth (Table 2).

The breast-feeding duration has a greater effect on the rate of infant growth (0.0746) than on the equilibrium length (-1.5422). Similarly to what was observed for the response variable body weight, the equilibrium length for infants breastfed for a longer period of time is smaller, although this group experienced a higher growth rate in the first months of life (Table 2).

Discussion

This study shows the important effect of predominant breastfeeding duration on the growth rate of infants as well as on their equilibrium body weight and length. In it, it was observed that although the growth rate is higher in infants with longer predominant breastfeeding duration, their body weight at the end of the study is lower and their body length is smaller than their formula-fed counterparts. It was verified that this latter group grew heavier and bigger than the former, starting around 7 months of life. This occurrence in the third quarter of infants' growth period has been previously discussed in the literature.[1,6,7] The present study corroborates this hypothesis using a new class of models and it is in accordance with the results reported by the new WHO growth standards recently released[8,9] and with some other investigations comparing previous growth standards with the current WHO growth charts.[19,20]

Some authors have argued that the difference in growth rate observed between breastfed and formula-fed infants is due either to the excessive feeding of formula-fed infants[21] or to the high caloric intake of formulas.[22-24] Dewey et al.[1,25] observed that formula-fed infants consume more milk and gain body weight more rapidly than breastfed infants, behavior that is prone to a higher obesity risk. These authors stated that blood insulin levels can be affected by feeding practices through protein intake.[21] Other authors[26-28] have explained the same process as occurring in reverse causality, that is, deficits on infant growth lead to changes in feeding patterns, favoring complementation or earlier cessation of breastfeeding.

Other important variables were also analyzed. Gestational age affects body weight and length at birth, and does not show a significant effect on the equilibrium body weight and length on the growth rate. With regard to sex, boys tend to weigh more than girls, and to have larger birth weight and a higher rate of body weight gain. Infants who were born through cesarean delivery presented higher weight gain than those born via natural delivery. Although several studies[29,30] have discussed the relationship between delivery type and breastfeeding duration, none of them has dealt with the influence of delivery type on the evolution of infant growth in the first few months of life.

Previous works published in the literature have addressed the effect of predominant breastfeeding duration on infant growth. However, the statistical procedures used are based on linear models or in logistic regression. These models, although useful and easy to interpret, do not consider the behavior of the underlying mechanism producing the

Table 1 - Parameters of nonlinear mixed effect model for body weight (kg) of children aged less than 1 year old (Rio de Janeiro, 1999-2001)

Fixed effects	Estimates	Standard error	p
$P_{asymp.}$ (intercept)	11.2074	0.1858	< 0.0001
$P_{asymp.}$ sex	- 0.3639	0.1887	0.0541
$P_{asymp.}$ $AMPRED_i$ (mo)	- 0.2813	0.0390	< 0.0001
P_0 (intercept)	3.0985	0.0362	< 0.0001
P_0 sex	- 0.0971	0.0254	0.0431
P_0 gestational age	0.1338	0.0133	< 0.0001
Log_*rate* (intercept)	-1.8104	0.0385	< 0.0001
Log_*rate* sex	- 0.0991	0.0357	0.0056
Log_*rate* $AMPRED_i$ (mo)	0.0798	0.0110	< 0.0001
Log_*rate* delivery type	0.0766	0.0289	0.0083
-2 log-likelihood	2069.3		
AIC	2103.3		

Random effects	Estimate (95%CI)
$\sigma_{asymp. (intercept)}$	1.2512 (1.4170 to 1.6048)
$\sigma_{P0 (intercept)}$	0.3391 (0.3766 to 0.4183)
$\sigma_{log\_rate (intercept)}$	0.1312 (0.1722 to 0.2260)
Cor [Asymp., P_0]	- 0.1148 (0.0520 to 0.2159)
Cor [Asymp., log_*rate*]	- 0.5666 (- 0.3882 to - 0.1750)
Cor [P_0, log_*rate*]	0.0393 (0.3376 to 0.5806)
$\sigma_{residual}$	0.2514 (0.2669 to 0.2834)

95%CI = 95% confidence interval; AIC = Akaike information criterion; $AMPRED_i$ = predominant breast-feeding duration; fixed effect = reflect the overall average profile; log_*rate* = logarithm of the rate of body weight gain or length gain; $P_{asymp.}$ = equilibrium body weight or length at the end of the study period; P_0 = body weight or length at birth; random effect = reflect how subject-specific profiles deviate from the overall average profile; *residual* = unexplained variation.

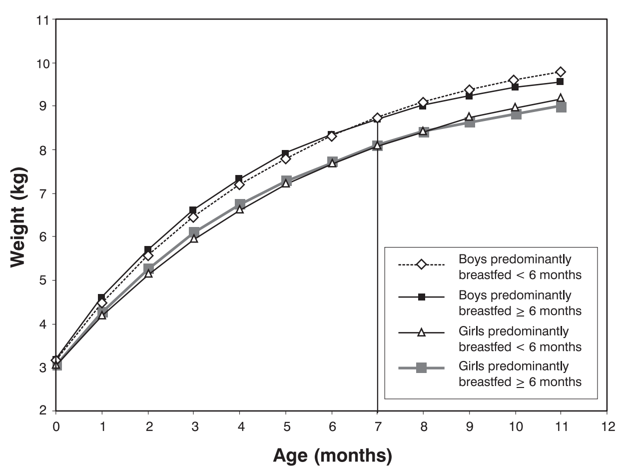


Figure 2 - Body weight (kg) as a function of predominantly breast-fed groups stratified by sex (Rio de Janeiro, 1999-2001)

response variable, which in this case refers to the body weight and length of infants in the first months of life. In the great majority of studies regarding growth models, the interest lies on fitting individual curves. In this context, random effect models are especially attractive given their model components. This procedure increases the precision of estimated parameters.

Some limitations of the present study must be addressed. Although prospective data analysis is sensitive to follow-up losses, fortunately this was not the case in the present study. Statistical analyses indicated that follow-up losses were random according to several variables of interest, such as age category, skin color, schooling and others.[15] Another possible limitation originates from the use of weight and length at birth as reported by the mother. However, they were captured in the first interview and did not show inconsistencies with the other observed measures, which is an indication of the quality of reported data.

In conclusion, the present study confirms the differences observed in infant growth based on different feeding practices between the sixth and the seventh month of life and it is consistent with the results observed by WHO new growth standards. We believe that the merit of the current paper is its potential contribution to the dissemination of a new

Table 2 - Parameter estimates for the nonlinear mixed effects model for length (cm) for infants aged less than 1 year old (Rio de Janeiro, 1999-2001)

Fixed effects	Estimate	Standard error	p
Asymp. (intercept)	86.0871	1.0226	< 0.0001
Asymp. $AMPRED_i$ (mo)	-1.5422	0.2208	< 0.0001
P_0 (intercept)	49.1013	0.2961	< 0.0001
P_0 sex	-0.6630	0.1847	0.0431
P_0 gestational age	0.6088	0.0481	< 0.0001
log_*rate* (intercept)	-2.1667	0.0514	< 0.0001
log_*rate* sex	-0.1218	0.0173	0.0056
log_*rate* $AMPRED_i$ (mo)	0.0746	0.0119	< 0.0001
-2 log-likelihood	6619.2		
AIC	6649.2		
Random effects		**Estimate (95%CI)**	
$\sigma_{asymp. (intercept)}$		0.9952 (1.6151 to 2.6210)	
$\sigma_{P0 (intercept)}$		1.5260 (1.6654 to 1.8176)	
$\sigma_{log\_rate (intercept)}$		0.0832 (0.1111 to 0.1483)	
Cor [Asymp., P_0]		0.1334 (0.4566 to 0.6920)	
Cor [Asymp., log_*rate*]		-0.1008 (0.0038 to 0.1085)	
Cor [P_0, log_*rate*]		-0.1033 (0.0053 to 0.1138)	
$\sigma_{residual}$		1.1116 (1.1691 to 1.2186)	

95%CI = 95% confidence interval; AIC = Akaike Information Criterion; $AMPRED_i$ = predominant breast-feeding duration; fixed effect = reflect the overall average profile; log_*rate* = logarithm of the rate of body weight or length gain; $P_{asymp.}$ = equilibrium body weight or length at the end of the study period; P_0 = body weight or length at birth; random effect = reflect how subject-specific profiles deviate from the overall average profile; *residual* = unexplained variation.

approach which might facilitate the analysis and interpretation of growth data for both individuals and populations.

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MHCS participated in the statistical analysis and in the writing of the manuscript. GK participated in all phases of the study, including its conception, drawing, follow-up, data interpretation and writing of the manuscript. CJS participated in several phases of the study, including data interpretation and writing of the manuscript. MTSB participated in data interpretation and writing of the manuscript. There are no conflicts of interest by the authors of this work.

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Correspondence:
Gilberto Kac
Universidade Federal do Rio de Janeiro
Instituto de Nutrição Josué de Castro
Departamento de Nutrição Social e Aplicada
Av. Brigadeiro Trompowsky s/nº, bloco J, 2º andar
CEP 21941-590 – Rio de Janeiro, RJ – Brazil
E-mail: kacetal@gmail.com, gkac@nutricao.ufrj.br