Comparison of intergrowth-21st and Fenton curves for evaluation of premature newborns

Lorena Oliveira Peixoto 1 https://orcid.org/0000-0002-7196-5868

Mônica Raquel Chaves Pinto² b https://orcid.org/0000-0003-2694-9671

Jéssica de Queiroz da Silva ³ b https://orcid.org/0000-0001-7933-3446 Ana Vaneska Passos Meireles ⁴ b https://orcid.org/0000-0003-0927-5281

Raquel Guimarães Nobre ⁵ D https://orcid.org/0000-0001-8469-7703

Julyanne Torres Frota ⁶ b https://orcid.org/0000-0002-3539-4674

^{1,2,5,6} Assis Chateaubriand Maternity School. Coronel Nunes de Melost., s.n. Rodolfo Teófilo. Fortaleza, CE, Brazil. CEP: 60.430-270. E-mail: lorena_lop@hotmail.com ³ Federal University of Ceará. Fortaleza, CE, Brazil

⁴ University of Fortaleza. Fortaleza, CE, Brazil

Abstract

Objectives: to compare the intrauterine and postnatal growth of preterm infants according to the Intergrowth-21st and Fenton curves.

Methods: study carried out in a maternity hospital, reference in high-risk pregnancy, with preterm infants born in 2018 who were hospitalized in the neonatal units of the institution. Preterm newborns weighed at least twice after birth were included in the sample and those that were syndromic, malformed or presented fluid retention were excluded. Proportions and means were compared using Pearson's chi-square and Student's t tests for paired samples, respectively. The McNemar test was used to compare categorical variables and the Kappa test to verify the degree of agreement between birth weight classifications obtained by the curves.

Results: one hundred and fifty three infants with a median gestational age of 34.4 weeks were included. The incidences of the categories of nutritional status at birth did not differ between the curves. There was perfect agreement between the curves, except when newborns born under 33 weeks of gestational age were evaluated, in which case the agreement was substantial. About 21% of the babies classified as small for gestational age (SGA) by Intergrowth-21st were adequate for gestational age (AGA) according to Fenton and, on average, 20% of cases that had postnatal growth restriction (PNGR) according to Fenton standards were categorized as adequate weight by Intergrowth-21st. Postnatal weight classifications obtained by the evaluated curves had perfect agreement.

Conclusions: the differences in the classifications found between the charts reveal the importance of choosing the growth curve for monitoring preterm infants since behaviors based on their diagnoses can impact the life of this population.

Key words Growth charts, Premature newborn, Nutritional status



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Introduction

Growth is an excellent indicator of a child's health, as it reflects a process resulting from intrinsic and extrinsic factors, including genetic, environmental, hormonal and nutritional factors.^{1,2} Birth-related characteristics such as weight or gestational age (GA) at birth, and especially small size for GA at birth, act directly on the individual's growth and development.¹

Several conditions place premature newborns (NB) at nutritional risk, among them the interruption of growth during the faster phase, low nutrient reserves at birth, and physiological immaturity and immaturity of the immune system.^{3,4} Thus, close monitoring of the growth of this population is necessaryin order to carry out early interventions aimed at stimulating optimal growth and reducing deficits associated with adverse long-term outcomes.⁵

One of the tools used for child health screening and pediatric clinical monitoring are growth charts. There are two types of charts available, namely, the reference and standard charts.⁶

In general, reference curves describe how a given population grows without considering the environmental, nutritional, socioeconomic and health conditions of this sample, not characterizing a normality pattern to be followed.⁷ They include the birth weight curves by GA, such as Fenton⁸ and Intergrowth-21^{st3} charts for the assessment of very premature NB.^{8,10} Standard curves, on the other hand, are prescriptive, representing the monitoring of healthy prospective longitudinal growth and are intended to indicate how children should be born and growwhen submitted to optimal conditions of nutrition and health care.^{10,11} As an example, there are the standard birth weight charts and postnatal growth resulting from the Intergrowth-21st project.^{9,12}

The standard curves of the Intergrowth-21^{st9,12} project were produced through a prospective longitudinal study of a cohort of precisely dated, uncomplicated pregnancies which took place in ideal environmental and nutritional conditions, with prenatal care started early and fetuses properly developed. The study included the population of eight developed and underdeveloped countries, including Brazil, in order to create a pattern of international growth. They allow the assessment of intrauterine growth from 33 gestational weeks and postnatal growth from 27 gestational weeks.^{9,12} However, this last study had an insignificant number of newborns born at less than 33 gestational weeks.¹²

Due to the fact that very premature births result from pregnancies with some risk factor for intrauterine growth restriction (IUGR), which makes it impracticable to make prescriptive standard graphs for this population, the Intergrowth-21^{st3} project built reference curves for monitoring preterm infants born before 33 weeks of gestation. In this case, the original sample was complemented with newborns followed in the same study, however born to mothers with some risk factors for IUGR, except smoking and severe obesity.³

Fenton's curves⁸ reflect intrauterine growth and were prepared based on a systematic review and metaanalysis of data from six large population studies carried out in developed countries, namely, Germany, the United States, Italy, Australia, Scotland and Canada. They allow the monitoring of premature growth from 22 weeks of gestation; however, these values are more robust after 24 weeks.⁸

Even though the Brazilian Ministry of Health and the Brazilian Society of Pediatrics recommend the use of curves from the Intergrowth-21st study to monitor the growth of preterm infants, Fenton charts are still widely used in Brazilian hospitals.

Considering that the two curves are used in the followup of Brazilian preterm infants and taking into account the scarcity of comparative studies on their use for this population, it is essential to know the differences and/ or similarities between the types of curves for a better understanding and analysis of their data. Because weight is the most sensitive parameter to nutritional problems, the present study aimed to compare intrauterine and postnatal weight increase of preterm infants according to the Intergrowth-21st and Fenton curves.

Methods

This is a retrospective observational study carried out at the Assis Chateaubriand Maternity School, a tertiary-level institution that is a reference for high-risk pregnancy in the city of Fortaleza, Ceará. Data collection was carried out between March and July 2019 and the study population consisted of premature NB born in the maternity and admitted to a neonatal unit of the institution during 2018.

Newborns with GA at birth equal to or greater than 27 weeks and less than 37 weeks and who had theirweight measured t least twice after birth were included in the study. Newborns with malformations, chromosomal alterations or pathologies that caused water retention were excluded.

Information on the newborn such as sex, GA at birth, birth weight, weekly weight measurements, length of stay in neonatal unit, and maternal age were collected from a secondary data source provided by the institution's Nutrition sector.

As this is a retrospective study, we chose to use the weight parameter as it is the first to reflect changes in nutritional status, as well as it is the only parameter routinely measured in the neonatal units of the maternity hospital.

A scale from the Filizolabrand, model BP15, was used to measure birth weight and a scale from the Balmak brand, model ELP 25BBA, was used for postnatal weight; both scales are produced in the national territory, in the state of São Paulo, and are submitted to periodicpreventive maintenance. The newborns were weighed naked, covered with a previously weighed cloth which wasdeducted from the total weight. The procedure was performed by professionals with a technical or higher nursing degrees or by physicians immediately after birth or daily at night.

Gestational age at birth was estimated by early prenatal ultrasound or, in the absence of this information, using the New Ballard method.

In order to characterize the sample, the newborns were classified according to gestational age at birth as proposed by the American Academy of Pediatrics (2017), the same categorization used in the maternity hospital: late preterm (34 weeks \leq GA \leq 36 weeks and 6 days), moderate preterm (32 weeks \leq GA \leq 33 weeks and 6 days), very preterm, (28 weeks \leq GA \leq 31 weeks and 6 days), extreme preterm (GA < 28 weeks).¹³

For classification of birth weight, the following criteria were used: extremely low weight (weight < 1000 g), very low weight (1000 g \leq weight < 1500 g), low weight (1500 g \leq weight < 2500 g), insufficient weight (2500 g \leq weight < 3000 g), adequate weight (3000 g \leq weight < 4000 g), and overweight (weight \geq 4000 g).^{14,15}

The adequacy of weight for gestational age at birth was assessed using the Fenton premature growth curve⁸ and reference or standard birth weight charts for preterms from the Intergrowth-21st project,^{3,9} depending on the NB' GA. For categorization of intrauterine growth, NB with birth weight between the 10th and 90th percentiles were considered adequate for gestational age (AGA), those below the 10th percentile were considered small for gestational age (SGA), and those above the 90th percentile of these curves were considered large for gestational age (LGA).¹⁶ Newborns were divided into three groups (total sample, born with less than 33 gestational weeks, and born at an age equal to or greater than 33 weeks of gestational age) for further analysis.

Postnatal growth was evaluated using the Fenton premature growth curve⁸ and the Intergrowth-21st preterm postnatal growth standard curve.¹² The weight obtained in the last weekly anthropometric assessment prior to hospital discharge or when the NB completed 40 weeks of corrected gestational age was used to investigate the existence of postnatal growth restriction (PNGR). Those whose weightwas in a percentile $\leq 10^{\text{th}}$ for the expected growth were considered to present PNGR.

Percentiles were calculated electronically using tools available from the above-cited growth charts (http://www. ucalgary.ca/fenton, https://intergrowth21.tghn.org).

Data normality was assessed using the Kolmogorov-Smirnov test. To compare the proportions and means between the methods of assessment of nutritional status, the Pearson's chi-square test and Student's t test were performed for paired samples, respectively. Categorical variables were compared using the McNemar test, as the groups were dependent. Data were presented as frequency and percentage or means and standard deviations. A p value less than 0.05 was considered statistically significant. The Kappa coefficient was calculated to verify the degree of agreement between birth weight classifications according to the different curves. Kappa values were interpreted to indicate: insignificant (Kappa = 0 to 0.20), intermediate (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0. 61 to 0.80), and perfect (0.81 to 1.00) agreement.¹⁸ The analyses were performed using the SPSS softwareversion 22.

This study was approved by the Research Ethics Committee of the Assis Chateaubriand Maternity School /MEAC/UFC, on July 31, 2020, and followed the Resolution number 466/12 of the National Health Council, being approved under Opinion 3.484.483 and CAEE 17811419.1.0000.5050.

Results

The study population consisted of 213 preterm infants, of which 60 were excluded due to genetic syndrome (8.3%), fetal malformation (11.7%), GA at birth lower than 27 weeks (10%), presence of edema (3.3%), microcephaly (5%), or because theirweight was measured only at birth (61.7%). The sample consisted of 153 NB, 77 (50.3%) male and 76 (49.7%) female.

The median maternal age was 26 years, with a minimum of 14 years and a maximum of 46 years (n=153). Most mothers (70%) were aged between 18 and 35 years, 13% were under 18 years and 17% were 35 years old or older.

At birth, the NB had a mean weight of $2148g (\pm 623g)$ and a median GA of 34.4 weeks, with 31.1 and 34.7 weeks being the median GA of those younger and older than 33 weeks, respectively. Most preterm infants were classified as having low birth weight, late prematurity, and adequate weight for gestational age (AGA) in the different growth curves used in the study (Table 1). The mean length of stay was 29 days, with a minimum of 7 days and a maximum of 178 days.

There was no significant difference (p < 0.05) in the distribution of birth weight/gestational age of NB according to the Fenton and Intergrowth-21st curves. The *Kappa* test revealed perfect agreement (*Kappa*=0.870

Table 1

lassification of newborns at birth. Fortaleza, 2018. Classification	Ν	%	p*	Kappa**
Birth weight			-	
Extreme low weight	4	2.6		
Very low weight	16	10.5		
Low weight	93	60.8		
Insufficient weight	31	20.3		
Adequate weight	8	5.2		
Overweight	1	0.7		
overweight	·	0.7		
Gestational age at birth			-	-
Extreme preterm	3	2.0		
Very preterm	19	12.4		
Moderate preterm	34	22.2		
Late preterm	97	63.4		
Weight for Gestational Age at Birth				
Total Sample (N=153)			-	0.870
SGA			0.36	-
Fenton	22	14.4		
Intergrowth-21 st	28	18.3		
AGA			0.29	-
Fenton	119	77.8		
Intergrowth-21st	111	72.55		
LGA			0.67	-
Fenton	12	7.8		
Intergrowth-21st	14	9.15		
Sample GA ≥ 33 weeks (N=119)			-	0.921
SGA			0.61	-
Fenton	21	17.6		
Intergrowth-21st	24	20.2		
AGA			0.56	-
Fenton	89	74.8		
Intergrowth-21st	85	71.4		
LGA			0.82	-
Fenton	9	7.6		
Intergrowth-21 st	10	8.4		
Sample GA<33 weeks (N=34)			-	0.622
SGA			0.16	-
Fenton	1	2.9		
Intergrowth-21st	4	11.8		
AGA			0.21	-
Fenton	30	88.2		
Intergrowth-21 st	26	76.5		
LGA			0.69	-
Fenton	3	8.8		
Intergrowth-21st	4	11.8		

* p = Pearson's chi-square test; ** Kappa coefficient = 0.61 to 0.80: substantial; 0.81-1.00: perfect.

and standard error=0.063; *Kappa*=0.921 and standard error=0.039) between the two growth curves for the total sample and for NB born with GA greater than or equal to 33 weeks, respectively, and substantial agreement (*Kappa*=0.622 and standard error=0.165) for NB born with GA lower than 33 weeks. A higher incidence of SGA and LGA newborns was observed when evaluated using the Intergrowth-21st (Table 1).

After crossing the categories of birth weight by GA from the assessment of NB using the growth curves chosen in our research, 22 (14.4%), 111 (72.5%) and 12 (7.8%) NB were classified as SGA, AGA, and LGA, respectively, in both charts. However, 6 (21.4%) NB classified as SGA in the Intergrowth-21st growth tables were classified as AGA according to Fenton's chart (p < 0.03) (Table 2). The other changes in the classification of nutritional status perceived between the different charts, both for the total sample and for the smaller groups, were not significant.

When comparing the percentiles from the follow-up of postnatal growth, significant differences (p < 0.05) were found between almost all gestational ages observed (91%), except for weeks 47 and 49. Fenton curves were below the percentiles verified in the analysis by the intergrowth-21st for the same gestational age. The mean difference observed between the means of the percentiles was 9, with a minimum of 2 and a maximum of 22 (Figure 1).

The incidence of postnatal growth restriction (PNGR) was 46.4% and 37.3% as assessed by the Fenton and Intergrowth-21st curves, respectively; however the values did not show any statistical difference (p = 0.11). The *Kappa* test revealed perfect agreement between postnatal weight classifications (k=0.814 and standard error=0.047). About 20% of the newborns considered to have PNGR according to Fenton standards were categorized as having adequate weight when evaluated by Intergrowth-21st (p < 0.001) (Table 3).

Table 2

		%	p*
Total sample	SGA (IG21) to AGA (F2013)	21.4	0.031
		14.3	0.500
Sample	LGA (IG21) to AGA (F2013)	12.5	0.250
GA ≥ 33 weeks	SGA (IG21) to AGA (F2013)	10.0	>0.999
Sample	LGA (IG21) to AGA (F2013)	75.0	0.250
GA < 33 weeks	SGA (IG21) to AGA (F2013)	25.0	>0.999

SGA = Small for Gestational Age; AGA = Adequate for Gestational Age; LGA = Large for Gestational Age; F2013 = Fenton 2013; IG21= Intergrowth214; *p = McNemar Test.

Table 3

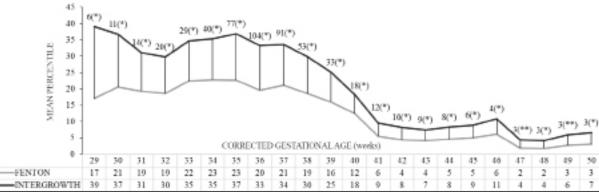
PNGR incidence rates according to Fenton and Intergrowth-21st. Fortaleza, 2018.

		Fenton	
	_	PNGR, % (n)	> 10 th percentile, % (n)
Intergrowth-21 st	PNGR, % (n)	80.3 (57)	0.0 (0)
	> 10 th percentile, % (n)	19.7 (14)	100.0 (82)
Total, % (n)		100.0 (71)	100.0 (82)

McNeman Test; p < 0.001; Kappa = 0.8136 and Standard error = 0.047; PNGR = Postnatal Growth Restriction.

Figure 1

Association between the means of percentiles verified in the Fenton and Intergrowth-21st curves. Fortaleza, 2018.



N(p); *p < 0.05; **p > 0.05.

Discussion

The results of the present study did not show a significant difference in the incidence of SGA, AGA and LGA NB at birth assessed by the Fenton⁸ and Intergrowth-21^{st3,9} reference growth charts. The agreement between the two curves was considered perfect.

In a study with 221 late preterm infants, Barreto *et al.*¹⁹ found significant differences when comparing the nutritional status at birth assessed with the same charts used in the present study. However, their research showed a greater diagnosis of SGA NB according to Fenton⁸ chart and of LGA NB according toIntergrowth-21st chart.⁹ This was also seen by Marques *et al.*²⁰ in an assessment of 617 NB with a median GA of 35 weeks. Barreto *et al.*¹⁹ found substantial agreement between the curves in their study, however the authors considered only preterm infants classified as SGA.

However, in an evaluation of 248 preterm infants born with GA less than 32 weeks, Tuzun *et al.*²¹ noticed a significantly greater difference in SGA NB using the Intergrowth-21^{st3} curve than using Fenton's curve,⁸ and the same was found by Marques *et al.*²⁰ when analyzing 240 preterm infants born with GA of 24 to 33 weeks. Marques *et al.*²⁰ believe that this finding may be related to the age of the sample, as in studies where most of the sample is composed of moderate or late preterm infants, the result is different.

In the present study, only 14.4% of the sample was represented by extremely premature or very premature NB. The participation of these NB in the total sample may be the reason why we found different result from those of the studies by Barreto *et al.*¹⁹ and Marques *et al.*,²⁰ in the assessment of predominantly late preterm NB, where we found a greater number of SGA NB according to Intergrowth-21^{st.3,9}. When the *Kappa* test wasapplied only between the curves for monitoring NB born with less than 33 weeks, it revealed a lower agreement, although the weight to GA ratio at birth did not show significant differences.

Furthermore, six NB classified as SGA by Intergrowth-21^{st3,9} were considered to have AGA according to Fenton's curve.⁸ This may have occurred because the sample in the present study did not meet the same selection criteria of the Intergrowth-21st research,^{3,9} which sought a population without risk for IUGR or, at the very least, with limited risk factors, in the case of NB under 33 weeks at birth. On the other hand, Fenton⁸ only excluded babies already diagnosed with growth restriction in routine ultrasound evaluation.

In the follow-up of postnatal growth, significantly lower percentile values were found for NB when evaluated by the Fenton⁸ charts than by Intergrowth-21st charts.¹² Regarding the PNGR rates, there was a trend towards reduction when analyzed according to Intergrowth-21st,¹² but without statistical difference. However, the result of this change in the classification was significant, in which 20% of the NB considered to have PNGR by Fenton⁸ were above the 10th percentile by Intergrowth-21st.¹² Similar data were observed by Tuzun *et al.*²¹ who evaluated the rates of PNGR during hospital discharge or the 36th week of corrected GA and verified that 22% of NB with PNGR according to Fenton⁸ did not present growth restriction when analyzed by the Intergrowth-21st curve.¹²

The fact that Fenton⁸ used birth weight data demonstrates that the physiological water loss that occurs after birth was not taken into account for the construction of thechart.²² However, the same did not occur in the construction of the Intergrowth-21st curves,¹² as weights were collected prospectively and longitudinally.

Another distinct point among the charts used in the research is related to the diet of the selected sample. The Intergrowth- 21^{st12} project included in its sample only NB fed with the gold standard, human milk, while in the research by Fenton,⁸ this was not an exclusion criterion adopted. However, Ziegler *et al.*²³ state that babies fed exclusively with breast milk gain less weight in the first year of life than those fed with artificial milk.

These questions may be related to the lowest percentiles observed according to Fenton⁸ in comparison to Intergrowth-21^{st,12} since the nutritional diagnosis of NB varies according to the curve selected for evaluation and according to the adequacy criteria adopted. It is noted that the differences between the Fenton⁸ and Intergrowth-21^{st12} curves are due to the different methodologies used in the construction of these curves.

The choice of curve used for this follow-up will influence the nutritional care offered to these individuals, where NB with growth restriction will receive hypercaloric nutrition in order to compensate for this deviation.²⁴ In this context, it is important to bear in mind that studies demonstrate the association between prematurity, accelerated weight gain in the first months of life and the occurrence of chronic diseases in adulthood.²⁵

Therefore, growth graphs are important tools that need to be selected with discretion, as information about the individual's nutritional status will guide health professionals to define nutritional paths to be adopted and that will impact the health of the infants.

The time factor stands outamong the limitations of the current research, since only the year 2018 was considered and this meant that NB hospitalized for a minimum period of 7 days were accepted in the research, as their exclusion would compromise the size of the sample, as the sample was mainly composed of late preterm infants who are often hospitalized for shorter periods. Another limitation was

the absence of maternal data, as the information used in thestudy was collected from an existing database.

The agreement between the curves was considered perfect, except when NB born with less than 33 gestational weeks were evaluated, in which case the agreement found was substantial. About 20% of the NB were classified as SGA by Intergrowth-21st and with PNGR according to Fenton's standards; however the weight classification changed to adequate when analyzed by Fenton and Intergrowth-21st, respectively. Approximately 90% of the percentiles from the Fenton analyses were statistically lower than those from Intergrowth-21st. These findings demonstrate the importance of choosing the growth chart to be used for the assessment of premature infants, as approaches based on its diagnoses can have an impact in the short and long term on the lives of this population.

However, studies are needed to assess whether NB classified as having growth restriction according to one of the curves are under an increased risk of presenting morbidities. The more we understand about the existing graphs, the more confident health professionals will be in their clinical practices and there will begreater assurance regarding the health of the infants.

Author's contribution

Peixoto LO: data collection, tabulation and analysis, writing and revision of the manuscript. Pinto MRC: data analysis and revision of the manuscript. Silva JQ: writing of the manuscript. Meireles AVP: supervision and revision of the manuscript. Nobre RG and Frota JT: revision of the manuscript. All authors approved the final version of the article. The authors declare no conflict of interest.

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