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The impact of growth curves changes in assessing premature infant growth

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Abstract

Objective—Assess the impact of using the recently published WHO growth standard, based on healthy, breastfed infants in multiple countries that excluded prematurely-born infants, versus the Infant Health Development Program (IHDP) growth reference constructed from premature infants, on the interpretation of the growth of premature infants after hospital discharge.

Study Design—A retrospective cohort was constructed of infants born at gestational age 35 weeks who initially presented for care at one of 32 outpatient sites between 2006 and 2008 (N=2297). Kappa statistics measured overall agreement and agreement in ever classifying infants < 5th percentile or 95th percentile for age between the WHO and IHDP. Logistic regression models identified factors associated with growth curve disagreement in classifying infants at the extremes of growth.

Results—The WHO and IHDP growth curves showed moderate agreement for all measurements (κ 0.40-0.52). When the curves disagreed on whether an infant was < 5th percentile for weight (8.3% of cohort) or length (13.6% of cohort), the WHO curve classified the infant in this category over 90% of the time. For head circumference, the IHDP curve classified more infants below the 5th percentile. Gestational age < 30 weeks was associated with growth curve disagreement for weight and length < 5th percentile.

Conclusion—Choice of growth curve affects the assessment of growth and the classification of underweight status. Longitudinal studies are needed to determine which assessment identifies the greatest number of premature infants at risk for long-term growth issues.

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CONFLICT OF INTEREST

There are no potential conflicts of interests.

Keywords

Premature infant; growth assessment; WHO growth curve

INTRODUCTION

In 2006 the World Health Organization (WHO) published the first international growth standard,^{1,2} which replaced previously-used growth references from the Centers for Disease Control and Prevention (CDC) and other groups. Since the creation of the WHO growth standard, the CDC has recommended its use for all children between birth and 2 years of age, including prematurely born infants.^{1,3}

A growth reference is created using a population of infants that are not necessarily growing in an ideal manner, but may have characteristics similar to the children being followed clinically. One such reference is the Infant Health and Development Program (IHDP) growth chart, which included infants < 37 weeks gestational age and followed them longitudinally until 36 months corrected gestational age.⁴ This curve has been identified as the best available growth reference for very low birth weight infants because of its relatively large sample size and long follow-up period.⁵

A growth standard is created using a population of infants that are growing “ideally”. For the WHO this was defined as full-term, breast-fed infants brought up in an environment that does not constrain growth.¹ However, like many of the growth references before it,^{1,6,7} the WHO growth standard did not include premature infants in the study population.¹ Recent research from Dutch infants suggests that premature infants have lower median growth measurements across all gestational ages, even while correcting for gestational age.⁸ This raises the question of the generalizability of these growth charts to premature infants.⁵

The use of different growth curves may impact how health care professionals interpret a premature infant’s growth.^{9,10} Thus, the purpose of this study is to determine the impact of using the WHO growth standard instead of the IHDP growth reference on the interpretation of the growth of premature infants.

PATIENTS AND METHODS

Data Source and Patient Population

Eligible infants included any infant born at a gestational age between 23 and 35 weeks who presented to one of the 31 pediatric outpatient sites affiliated with Children’s Hospital of Philadelphia between January 1, 2006 and December 31, 2008. The outpatient pediatric sites include five practices located in Philadelphia and 26 private practices in urban, rural, and suburban areas throughout Pennsylvania and New Jersey. Infants’ gestational ages were determined from the best obstetric estimate taken from the infant’s discharge summary from the birth hospitalization or were estimated using multiple imputation techniques (n=120) based on birth weight and maternal complications during pregnancy. Their first visit was within 6 months adjusted gestational age and the patients remained in the CHOP practice system through 2 years adjusted gestational age or December 31, 2010, whichever occurred

first. If there were no patient visits after 12 months adjusted gestational age, the patient was considered lost to follow-up (n=235). Exclusion criteria included infants with a genetic or chromosomal diagnosis associated with a primary growth disorders as outlined in Osstrijk et al.¹¹ (n=12) and infants missing both gestational age and birth weight (n=61). After applying these exclusion criteria, there were 2297 patients in the final cohort. The Institutional Review Board at The Children's Hospital of Philadelphia approved this study.

Data Collection and Electronic Health Record

The pediatric sites were linked by a uniform electronic medical record system provided by EpicCare® (EPIC EHR). For primary care outpatient visits, most data were captured at the point of care by clinical staff. Each type of data in the system is subject to specific validation protocols. At the broadest level, the clinical team has responsibility for the overall integrity of the clinical documentation. Other validation methods include real-time monitoring of interfaced data for errors; monthly monitoring of mandatory screening items; and monetary incentives to maintain chart accuracy. Data from this system has been validated and used in other studies.^{12, 13, 14, 15, 16, 17}

Specific data collected for this study included growth measurements such as weight, length, and head circumference, and birth information such as birth weight, gestational age and gender. Other collected information included age at first visit, and demographic information such as race, ethnicity, and insurance status. Chronic complications of premature birth including bronchopulmonary dysplasia, intraventricular hemorrhage, and retinopathy of prematurity (Table 1) were also collected from the patient's chart because of their potential influence on long-term growth of the premature infant as measures of illness severity.¹⁸

Growth Charts

At each visit, the WHO and the IHDP growth charts were used to determine the percentile for each of the three anthropomorphic measurements included in the study: weight for age (WfA), length for age (LfA), and head circumference for age (HCfA).

For the WHO growth chart, previously published, age-specific parameters were used to transform measured WfA, LfA, and HCfA at each visit into Z-scores.¹⁹ We used a normal distribution to convert these Z-scores into the same percentile groupings used in the IHDP growth reference (< 5th, 5th to 25th, 25 to 50th, 50 to 75th, 75 to 95th, and 95th).

For the IHDP growth curves, no reference data was available to calculate a z-score from raw growth data, therefore published IHDP growth charts were used to calculate a percentile range for each anthropomorphic measure. Percentile ranges were defined as < 5th, 5th to 25th, 25 to 50th, 50 to 75th, 75 to 95th, and 95th. Growth data were rounded to the nearest 100g for weight, 0.5cm for length, and 0.2cm for head circumference.

Data Analysis

For each growth parameter (WfA, LfA, HCfA), we calculated percentiles for each infant's visit based on the WHO and IHDP growth curves. These percentiles were then used to calculate agreement between the growth curves. The percentiles at all patient visits were

compared for each growth parameter using a simple kappa analysis to determine overall agreement (SAS Version 10, SAS Institute, Cary, NC). Kappa statistics range from 0 to 1 depending on the degree of agreement. Kappa statistics > 0.7 indicate excellent agreement, 0.4-0.7 moderate agreement, and < 0.4 poor agreement.

Then, for each growth parameter we compared the percentiles only for infants that were ever measured as < 5th percentile or 95th percentile on either curve. We determined the percentage of patients for whom both curves identified a child at the extremes of growth; only the WHO curve; or only the IHDP curve. We calculated a kappa to determine the agreement of the curves at the extremes of growth. Lastly, for each growth parameter, we developed separate multivariable logistic regression models to identify factors that were associated with higher odds of with growth curve disagreement in classifying infants at the extremes of growth (< 5th percentile or 95th percentile). For all analyses, we further stratified the population by gestational age as a sub-group analysis to determine how different growth curves affected the classification of infants at the extremes of growth for the extremely premature infant (gestational age < 28 weeks) and moderately premature infant (gestational age 29-35 weeks).

RESULTS

Table 1 provides the demographic information for the study cohort. Of the 2297 patients included in the study, 49% were female, 31% had a birth weight < 1500 grams, and 53.9% of the patients were born at an age greater than 33 weeks gestation.

Difference between growth curves, all visits

Between 2006 and 2008, the 2297 patients made a total of 30,013 visits where a weight was measured, 15,282 visits where a length was measured, and 14,585 visits where a head circumference was measured. The agreement between the two growth curves for weight for age had a kappa of 0.46 (95% CI 0.45-0.46) or moderate agreement. The WHO growth curve identified significantly more patients in lower growth percentiles (0-75%) than IHDP and fewer in higher growth percentiles (over 75%) (Figure 1a). Agreement between the two growth curves for length for age revealed less agreement than with WfA, with a kappa of 0.40 (95% CI 0.39-0.41). As with weight for age, the WHO growth curve identified significantly more premature infants with lower length percentiles (0-50%), and fewer patients with higher length percentiles (50-100%) than the IHDP curve (Figure 1b).

HCfA showed a different pattern than WfA and LfA. The level of agreement was moderate between the two growth charts with a kappa of 0.52 (95% CI 0.51-0.53). The WHO growth chart identified significantly fewer infants in lowest percentiles for head circumference (0-75%), and more infants in the highest percentiles (Figure 1c).

Differences between growth curves in identifying infants < 5th percentile

The number of patients where weight, length, or head circumference was ever identified as under the 5th percentile by either the WHO or IHDP growth curves or both is shown in Table 2. For patients ever identified as underweight (< 5th percentile) by 24 months AGA, the two growth curves had a moderate agreement (kappa = 0.60, 95% CI 0.55-0.65). Patients

ever identified as < 5th percentile for height had a lower agreement than those identified as underweight (kappa = 0.52, 95% CI 0.48-0.56), whereas the agreement between the growth curves for HCfA < 5th percentile was higher than the other measures (kappa = 0.71, 95% CI 0.65-0.77). The WHO curve was more likely to identify a child < 5th percentile for weight (WHO only 7.4%, IHDP only 0.9%) and length (WHO only 13.5%, IHDP only 0.1%), whereas the IHDP was more likely to identify a child < 5th percentile for head circumference (WHO only 1.3%, IHDP only 4.7%). The two curves were more likely to both identify an infant < 5th percentile for length (17.2% of population) compared to weight or head circumference.

After stratifying the population by gestational age, extremely premature infants with a gestational age < 28 weeks were more likely to be identified as having a weight or length < 5th percentile than moderately premature infants (Table 2). However, unlike the moderately premature group, the WHO curve also identified more infants with a gestational age < 28 weeks with a head circumference under the 5th percentile (WHO 6.1% of population compared to 0.4% of the moderately premature group).

Multivariable analysis (Supplemental Table 3) identified factors associated with higher odds of disagreement between the two growth curves in ever classifying a patient as < 5th percentile for any growth parameter. Gestational age < 30 weeks, when compared to gestational ages 33 to 35 weeks, was associated with higher odds of differing underweight and underlength classification between the two growth curves. Other factors were not associated with differing classifications of WfA, LfA, or HCfA, both in entire population of infants and in extremely premature and moderately premature sub-groups.

Differences in identifying infants > 95th percentile

The agreement between the growth curves to identify infants with a growth parameter > 95th percentile was higher than for identifying infants with a growth parameter < 5th percentile, with kappa statistics ranging from 0.68 to 0.73. The WHO was more likely to classify an infant > 95th percentile for head circumference (WHO only 14.1%, IHDP only 0.4%), while the IHDP was more likely to classify an infant as ever being > 95th percentile for weight and length for age (Table 2). These results were similar when we examined the extremely premature and moderately premature infants separately.

Multivariable analysis found that male gender was associated with a higher odds of differing classification of infants labeled > 95th percentile for WfA (OR 2.11, 95% CI 1.61-2.75), and LfA (OR 1.87, 95% CI 1.46-2.39). Several factors were associated with differing classification of HCfA > 95th percentile, including race, insurance status, and age at first visit. Unlike the other growth parameters, younger gestational age at birth and male gender was associated with lower odds of differing classification of HCfA of > 95th percentile (Supplemental Table 3).

DISCUSSION

This study shows that the use of the WHO or IHDP growth curves can lead to significantly different interpretations of premature infant growth. When using the WHO growth curve, a

clinician is more likely to identify a premature infant as smaller in weight and length for age and larger in head circumference for age when compared to the IHDP growth curve. There was only moderate agreement between the two growth curves for two clinically relevant classifications of growth (< 5th and > 95th percentiles). Early gestational age, especially under 30 weeks gestation, was the primary risk factor for incongruent classification of weight and length, particularly for measurements under the 5th percentile. The decision to use one growth curve over another to evaluate longitudinal growth affects the interpretation of the growth of a premature infant, particularly among infants with a gestational age under 30 weeks. The implication of these different interpretations is large, as clinicians may pursue changes in feeding protocols or other medical management based on where a premature infant lies on the growth curve they use.

There are several potential mechanisms for the lack of agreement between the IHDP and WHO growth curves. First, the growth curves were constructed using different methods. The IHDP growth curves were created as a growth reference representing a group of preterm infants born in the mid-1980's. In 2006, the WHO growth standard was published as the first prescriptive chart by which a health care provider could compare a patient's growth with the growth of an "ideal," standard population of full-term, breast-fed infants raised in an environment that did not constrain growth.¹ After adjustment for their gestational age at birth, premature infants should be able to achieve these standards set by full-term, breast-fed infants. However, there is little data to support this claim.⁸

In addition, premature infants were excluded from the WHO study population because of chronic medical conditions such as bronchopulmonary dysplasia that interfere with growth.¹ The WHO growth curves label a relatively high percentage of the infants under the 5th percentile. This suggests the ideal set by the WHO curve may be more difficult to reach by the average set of premature infants, which is further supported by lower median weight and height of preterm infants compared to full term peers up to four years of age.⁸ Another possible explanation is that infants with these chronic conditions of premature birth may require more intervention to achieve this ideal growth than previously prescribed now that a growth standard is available for comparison. Whether this idealized growth results in improved outcomes of preterm infants is unknown.

Another mechanism for the lack of agreement between the IHDP and WHO is time frame included in the study population. The patients recruited for the IHDP were preterm infants that reached 40 weeks gestational age within a 10 month period in 1985. Since this time it has become standard practice to feed preterm infants calorie supplemented breast milk or high calorie formula to provide sufficient nutrition for adequate growth.²⁰ As such, premature infants born today, supplemented with extra calories, may weigh more those measured for the IHDP study. Alternatively, growth measurements that may have been normal in 1985 may be too small for infants born in the early 21st century, given the increased rates of obesity over the past 25 years. This data is supported by our findings that more premature infants were below the 5th percentile for weight and length on the WHO growth chart when compared to the IHDP. Head circumference has not shown such a trend over time, and these secular trends may explain why head circumference, overall, acted differently compared to other growth parameters when the WHO growth curve was used.

Although our results suggest preterm infants born at early gestational ages will have an increased risk of incongruent classification of growth depending on the curve used, they do not suggest which curve is correctly labeling the infant. This study does not have the ability to make this judgment as there is no gold standard for ideal preterm infant growth. Potential future solutions are longitudinal studies which seek to identify growth of premature infants with ideal outcomes.²¹ This study is also limited by its ability to control and standardize care providers' measurement of growth and data input into the EPIC EHR at the point of care, although our methods minimize variability and maintain validity as suggested in other studies.^{13, 14, 15, 16, 17}

It is important for healthcare providers to recognize the differences between the growth curves presented. Although the WHO is currently recommended for use in all infants from 0-2 years of age, premature infants at lower gestational ages are at increased risk of being labeled as < 5th percentile on the WHO chart while their growth may be classified as normal compared to other preterm infants as measured by the IHDP chart. Without outcome measures to validate which assessment is "correct," and to determine appropriate intervention to minimize poor outcomes in either poorly grown or obese children, these changes could lead to unnecessary intervention in the growth and nutrition of discharged premature infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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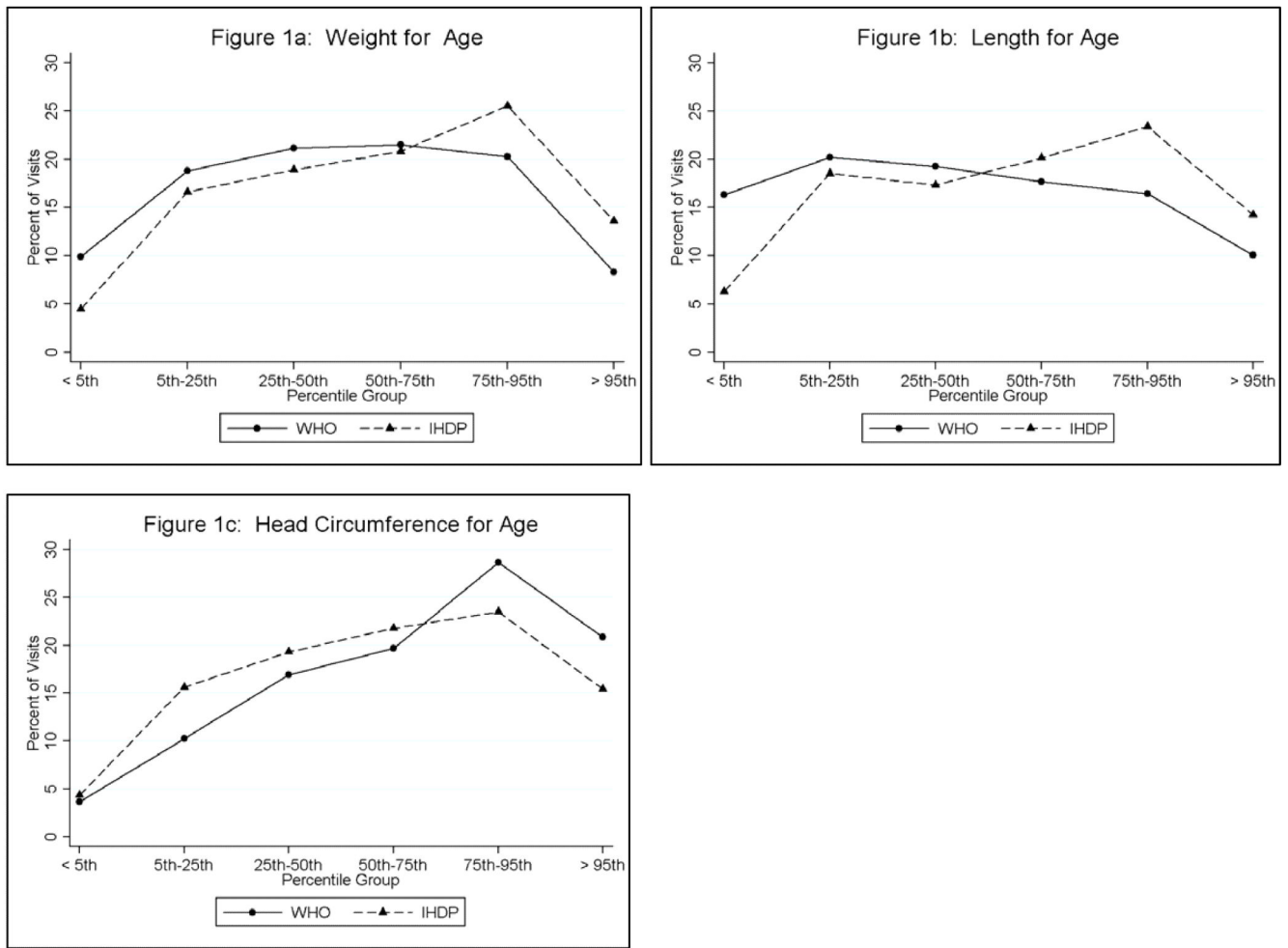


Figure 1. Comparison of weight-for-age, length-for-age, and head circumference-for-age percentiles when measured using the WHO growth standard (solid line) and IHDP growth reference (dotted line).

Table 1

Demographics of study cohort (N=2297)

	All N=2297	23-28 Weeks GA N=391	29-35 Weeks GA N=1906
	N (%)	N (%)	N (%)
Female	1129 (49.15)	189 (48.34)	940 (49.32)
Birth Weight (g)			
0-499	12 (0.52)	9 (2.3)	3 (0.16)
500-749	116 (5.05)	113 (28.9)	3 (0.16)
750-999	163 (7.1)	130 (33.25)	33 (1.73)
1000-1249	202 (8.79)	109 (27.88)	93 (4.88)
1250-1499	219 (9.53)	24 (6.14)	195 (10.23)
1500-1749	270 (11.75)	1 (0.26)	269 (14.11)
1750-1999	380 (16.54)	0 (0)	380 (19.94)
2000-2499	623 (27.12)	0 (0)	623 (32.69)
>2500	312 (13.58)	5 (1.28)	307 (16.11)
Race			
White	976 (42.49)	126 (32.23)	850 (44.6)
Black	965 (42.01)	221 (56.52)	744 (39.03)
Other	356 (15.5)	44 (11.25)	312 (16.37)
Hispanic	77 (3.35)	13 (3.32)	64 (3.36)
Adjusted age at first visit (wks)	37.7 ± 5.3	39.6 ± 7.8	37.3 ± 4.5
Insurance			
All Private	1053 (45.84)	106 (27.11)	947 (49.69)
Any Medicaid	766 (33.35)	159 (40.66)	607 (31.85)
Any Self Pay	478 (20.81)	126 (32.23)	352 (18.47)
GA at Birth			
23-26	184 (8.01)	184 (47.06)	
27-28	207 (9.01)	207 (52.94)	
29-30	248 (10.8)		248 (13.01)
31-32	421 (18.33)		421 (22.09)
33-35	1237 (53.85)		1237 (64.9)
Comorbidities			
BPD	224 (9.75)	169 (43.22)	55 (2.89)
NEC	91 (3.96)	47 (12.02)	44 (2.31)
ROP	251 (10.93)	177 (45.27)	74 (3.88)
IVH_any_grade	176 (7.66)	92 (23.53)	84 (4.41)
IVH_gr_III_IV	35 (1.52)	32 (8.18)	3 (0.16)

Table 2

Differences between WHO and IHDP growth curves in ever identifying an infant (in 24 months) below 5th or above 95th percentile

	All			<=28 Weeks			>28 Weeks		
	Both	WHO Only	IHDP Only	Both	WHO Only	IHDP Only	Both	WHO Only	IHDP Only
< 5th Percentile									
Weight	287 (12.5)	171 (7.4)	21 (0.9)	93 (23.8)	83 (21.2)		194 (10.2)	88 (4.6)	21 (1.1)
Length	394 (17.2)	310 (13.5)	1 (0)	93 (23.8)	117 (29.9)		301 (15.8)	193 (10.1)	1 (0.1)
Head Circumference	154 (6.7)	32 (1.4)	108 (4.7)	55 (14.1)	24 (6.1)		99 (5.2)	8 (0.4)	108 (5.7)
> 95th Percentile									
Weight	702 (30.6)	109 (4.7)	160 (7)	61 (15.6)	4 (1)	42 (10.7)	641 (33.6)	105 (5.5)	118 (6.2)
Length	659 (28.7)	92 (4)	222 (9.7)	49 (12.5)	1 (0.3)	33 (8.4)	610 (32)	91 (4.8)	189 (9.9)
Head Circumference	816 (35.5)	324 (14.1)	10 (0.4)	100 (25.6)	22 (5.6)	1 (0.3)	716 (37.6)	302 (15.8)	9 (0.5)

Numbers shown in each box, with percentages shown in parenthesis.