

# Fetal Growth Curves

## Is There a Universal Reference?



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### KEYWORDS

- Fetal size • Estimated fetal weight • Fetal growth • Growth variation
- Ultrasound reference

### KEY POINTS

- There are 3 modern, prospective fetal growth standards that are similar in scope but demonstrate variation in fetal growth.
- Different fetal growth references identify different proportions of fetuses as small-for-gestational-age or large-for-gestational-age.
- A universal reference would make comparison of fetal growth simpler for clinical use and for comparison across populations but may misclassify small-for-gestational-age or large-for-gestational-age fetuses.

### INTRODUCTION

To answer the question, Does 1 fetal growth reference fit all populations? it is first necessary to know the purpose of the reference. Fetal size is important because fetal growth restriction and small-for-gestational-age (SGA) as well as macrosomia and large-for-gestational-age (LGA) fetal sizes are associated with increased risks of perinatal morbidity and mortality.<sup>1,2</sup> A range of 10th to 90th percentiles traditionally has been considered appropriate-for-gestational-age, with SGA or LGA often defined as less than 10th or greater than 90th percentiles, respectively.<sup>3</sup> Pathologic fetal growth however, follows more of a gradient, and different percentile cutoffs result in different portions of fetuses who are constitutionally small and not growth restricted, and vice versa for larger fetuses. For instance, a study of UK term singleton births found increased risks of stillbirth and infant death with birthweight up to the 25th percentile and greater than the 85th percentile, suggesting that the commonly used 10th percentile and 90th percentile cutpoints miss fetuses at risk for death.<sup>4</sup> Another study in the

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Netherlands found that although risk of perinatal mortality was highest in the less than 2.3rd percentile followed by the 2.3rd percentile to less than 5th percentile, and the 5th percentile to less than 10th percentile, perinatal mortality had a U-shaped relationship, with a nadir at the 80th to 84th percentiles for births between 28 weeks and 43 weeks.<sup>5</sup> These studies (albeit of birthweight) indicate that although risks for perinatal mortality are higher at the extremes, risk is more continual in the middle of the curve. Therefore, the choice in cutpoints for a fetal growth reference likely depends on how it is being used and on trade-offs between sensitivity and specificity. This decision may differ in clinical settings compared with use in a public health context to monitor and compare populations' health and development. Ideally the 25th percentile of a population reference is used to identify the most fetuses at risk for perinatal morbidity and mortality, but for clinical use, the cutpoint depends on the health care system capacity. Using the 25th percentile estimated fetal weight (EFW) instead of 10th percentile SGA would identify more fetuses at risk of growth restriction and associated morbidity and mortality but could have large cost and health care utilization implications due to increased antenatal surveillance and obstetric intervention. Furthermore, there is potential for increased risk of iatrogenic earlier delivery with associated harm.

Another consideration when selecting a fetal growth reference is to understand how the fetal growth reference that is chosen for clinical use performs in a local population. Three diverse, modern cohort studies with longitudinal fetal measurements recently have been undertaken: International Fetal & Newborn Growth Consortium for the 21<sup>st</sup> Century (INTERGROWTH-21<sup>st</sup>) Project,<sup>6,7</sup> the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies<sup>8–10</sup> and the World Health Organization Multicentre Growth Reference Study (WHO Fetal).<sup>11,12</sup> The objective of this review is to compare these new fetal growth references in context with references in current clinical use and discuss considerations when choosing a reference for clinical practice.

## BACKGROUND

A growth chart is used as a reference against which to assess growth and calculate the percentile of size for a given gestational age. Intrauterine growth charts are based on EFW using obstetric sonogram measurements, and birthweight growth charts are based on measured birthweight. Common US birthweight charts include those by Alexander and colleagues<sup>13</sup> and a revised reference by Duryea and colleagues,<sup>14</sup> which were based on improved obstetric estimates of gestational age. Ultrasound fetal weight estimates and birthweight are highly correlated ( $r = 0.80–0.91$ ) but are not equivalent.<sup>15</sup> EFW is known to differ from birthweight by 100 g or more and can be inaccurate especially at the extremes of EFW, less than 2000 g and greater than 4000 g.<sup>15</sup> Birthweight-for-gestational age percentiles are not as clinically useful for prenatal fetal growth assessment because infants who deliver preterm are more likely to be growth restricted and, therefore, birthweight references inaccurately describe the preterm growth of fetuses who go on to deliver at term.<sup>16,17</sup> Therefore, ultrasound-derived references tend to be preferred to birthweight references for clinical antepartum monitoring. An important point is that growth references depend on accurate gestational age assessment. Unknown gestational age or an error in gestational age calculation may lead to misclassification of SGA and LGA fetuses.

## DEFINITIONS

There are 4 types of intrauterine growth charts: (1) population-based intrauterine growth references similar in concept to infant and child growth charts, where a

population is used to estimate percentiles; (2) customized growth charts, where growth percentiles are adjusted for a set of characteristics known to be associated with birthweight (eg, race/ethnicity, parity, sex, and maternal height and weight); (3) individualized growth charts where a fetal growth trajectory is calculated based on 2 previous growth measurements; and (4) conditional percentile assessment, where the fetal growth percentile is based on a previous measurement. Fetal growth references that are customized for maternal and fetal characteristics are posited to help differentiate constitutional from pathologic growth at the extremes.<sup>18</sup> There is debate, however, about whether SGA and LGA defined by customized growth charts are an improvement over population-based growth charts because customization has not been found to improve prediction of perinatal morbidity and mortality consistently.<sup>17,19,20</sup> Individualized fetal growth references identify the growth potential for an individual fetus consistent with a personalized medicine approach.<sup>21–23</sup> Although conceptually appealing, this approach has not been adopted widely in clinical practice. The conditional fetal growth percentile approach conditions individualized ranges for a subsequent fetal growth measurement on a previous fetal growth measurement, resulting in ranges that were narrower than and shifted from reference range centiles for the entire population.<sup>24,25</sup> The addition of conditional growth centiles to size centiles recently was found to improve the prediction of adverse perinatal outcomes in fetuses less than 10th percentile, which is promising.<sup>26</sup> Some of these approaches, however, require serial ultrasounds, which not always are available, and population-based references remain in wide use.

## FETAL GROWTH REFERENCES

There are many ultrasound-based fetal weight references with some of the more common ones used in clinical practice presented in **Table 1**. Studies with smaller sample sizes are limited because the percentiles at the extremes (eg, 10th and 90th) have less precision. It is difficult to estimate an appropriate sample size for developing fetal growth references, but several hundred observations have been estimated to be needed.<sup>27</sup> Growth references that use retrospective ultrasound data have the advantage of larger sample sizes but may be limited by selection bias; in other words, the reason why an ultrasound was obtained at a given gestational age may influence the fetal size measurement by an unknown amount. For growth references that use cross-sectional ultrasound data, each woman contributes data from only 1 ultrasound examination. Therefore, cross-sectional references can indicate fetal size but not fetal growth velocity. Some birthweight references are used clinically for monitoring intrauterine fetal growth with inherent limitations, as discussed previously.<sup>28,29</sup> Longitudinal references are necessary to assess fetal growth and the older, larger studies were performed outside the United States in predominantly white women (see **Table 1**). Furthermore, older fetal growth references have been found to have substantial heterogeneity in their methodology with a wide range of quality that may limit their clinical use.<sup>30</sup> Until recently, there was a lack of prospective longitudinal fetal growth studies in diverse populations.

More recently, 3 diverse, modern cohort studies with longitudinal fetal measurements have been undertaken: INTERGROWTH,<sup>6,7</sup> NICHD,<sup>8–10</sup> and WHO Fetal.<sup>11,12</sup> INTERGROWTH was completed in 8 countries (Brazil, China, India, Italy, Kenya, Oman, United Kingdom, and United States), WHO Fetal in 10 countries (Argentina, Brazil, Democratic Republic of the Congo, Denmark, Egypt, France, Germany, India, Norway, and Thailand), and NICHD at 12 US sites (New York [2], New Jersey, Delaware, Rhode Island, Massachusetts, South Carolina, Alabama, Illinois, and California [3]). These studies were similar in that healthy women who were positioned for optimal fetal growth

**Table 1**  
Selected population-based birthweight and estimated fetal weight references

Authors, Location (y)	Inclusion Criteria and Dates <sup>a</sup> ; Data Source	Sample Size <sup>b</sup> ; Retrospective or Prospective; Cross-sectional or Longitudinal	Considerations for Use
Altman and Chitty, UK (1994) <sup>27</sup>	Pregnancies from European and Afro-Caribbean ethnic groups with accurate pregnancy dating; fetal biometric measurement from a single examination at 12–42 wk at a single hospital	663; prospective; cross-sectional	Although statistically rigorous methods used, single center may not be representative of fetal growth in local populations; cross-sectional references indicate fetal size but do not assess fetal growth.
Brenner et al, North Carolina and Ohio (1976) <sup>28</sup>	Weight of aborted fetuses 8–21 menstrual wk (1972–1975) at single hospital in North Carolina and birthweight for deliveries 21–44 menstrual wk (1962–1969) at single hospital in Ohio	430 aborted fetuses (8–21 menstrual wk) and 30,772 deliveries (21–44 wk); retrospective; cross-sectional	Birthweight references inaccurately describe the preterm growth of fetuses who go on to deliver at term.
Buck Louis et al, US (2015) <sup>8,9</sup>	Low-risk pregnancies from 4 racial/ethnic groups with accurate dating (2009–2013); randomized among 4 ultrasound schedules with fetal biometric measurements taken at 6 examinations from 10 wk to 41 wk; 12 community and perinatal centers	1737; prospective; longitudinal	NICHD; racially/ethnic diverse; rigorous credentialing of sonographers, use of standardized protocol, highly accurate and reliable measurements on quality assurance <sup>60</sup>
Di Battista et al, Italy (2000) <sup>61</sup>	Low-risk pregnancies with accurate dating and at least 5 (and up to 9) examinations (1987–1990); fetal biometric measurements taken between 12th and 40th wk at 2 obstetric units, which are major public health centers	238; unclear; longitudinal	Smaller sample size may decrease precision in the centiles; homogeneous population may not be representative of fetal growth in local populations.

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<b>Table 1</b> <b>(continued)</b>			
<b>Authors, Location (y)</b>	<b>Inclusion Criteria and Dates<sup>a</sup>; Data Source</b>	<b>Sample Size<sup>b</sup>; Retrospective or Prospective; Cross-sectional or Longitudinal</b>	<b>Considerations for Use</b>
Gallivan et al, U.K. (1993) <sup>62</sup>	Low-risk pregnancies with accurate dating (1987–1990); fetal biometric measurements taken at examinations approximately 2-wk intervals from 26 wk until delivery at 2 hospitals	67; prospective; longitudinal	Smaller sample size may decrease precision in the centiles; homogeneous population may not be representative of fetal growth in local populations.
Hadlock et al, Texas (1991) <sup>39</sup>	Low-risk pregnancies from white middle-class patients with certain menstrual history; fetal biometric measurement taken at a single examination from 10 wk to 41 wk at a single hospital	392; prospective; cross-sectional	Homogeneous population may not be representative of fetal growth in local populations; cross-sectional references indicate fetal size but do not assess fetal growth.
Jeanty et al, Belgium (1984) <sup>63</sup>	Low-risk pregnancies from white middle-class patients who were university personnel with certain menstrual history; fetal biometric measurements taken at 6–24 examinations at a single hospital	48; prospective; longitudinal	Smaller sample size may decrease precision in the centiles; homogeneous population may not be representative of fetal growth in local populations.
Johnsen et al, Norway (2006) <sup>64</sup>	Low-risk pregnancies with accurate dating; fetal biometric measurements taken at 4–5 examinations at least 3 wk apart from 20 to 42 wk at single antenatal clinic	634; prospective; longitudinal	Homogeneous population may not be representative of fetal growth in local populations.
Kiserud et al, international (2017) <sup>11,12</sup>	Low-risk pregnancies with accurate dating (2009–2014); fetal biometric measurements taken approximately every 4 wk from 14 to 40 wk, 10 countries	1,362; prospective; longitudinal	WHO; diverse; rigorous credentialing of sonographers, use of standardized protocol

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<b>Table 1</b> <b>(continued)</b>			
<b>Authors, Location (y)</b>	<b>Inclusion Criteria and Dates<sup>a</sup>; Data Source</b>	<b>Sample Size<sup>b</sup>; Retrospective or Prospective; Cross-sectional or Longitudinal</b>	<b>Considerations for Use</b>
Marsal et al, Sweden and Denmark (1996) <sup>65</sup>	Low-risk pregnancies; fetal biometric measurements taken approximately every 3–4 wk at 4 perinatal centers	86; prospective; longitudinal	Smaller sample size may decrease precision in the centiles; homogeneous population may not be representative of fetal growth in local populations.
Mongelli and Gardosi, UK (1995) <sup>66</sup>	Low-risk pregnancies; fetal biometric measurements taken approximately every 2–3 wk starting from 24 wk to 32 wk for a maximum of 4 examinations at a single center	226; prospective; longitudinal	Homogeneous population may not be representative of fetal growth in local populations; EFW was calculated using a modified Hadlock formula.
Nasrat and Bondagii, Saudi Arabia (2005) <sup>67</sup>	Arab women with certain menstrual history and without insulin requiring diabetes (1995–2002); all examinations from a single hospital over the study period	Approximately 1150; retrospective; cross-sectional	Retrospective ultrasound data may be limited by selection bias, or the reason for why an ultrasound was obtained at a given gestational age may influence the fetal size measurement by an unknown amount; cross-sectional references indicate fetal size but do not assess fetal growth.
Salomon et al, France (2006) <sup>68</sup>	Low-risk pregnancies from examinations taken by trained operators during a 1-year period across France	19,647; unknown; cross-sectional	Single country may not be representative of fetal growth in local populations; cross-sectional references indicate fetal size but do not assess fetal growth.

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<b>Table 1 (continued)</b>			
<b>Authors, Location (y)</b>	<b>Inclusion Criteria and Dates<sup>a</sup>; Data Source</b>	<b>Sample Size<sup>b</sup>; Retrospective or Prospective; Cross- sectional or Longitudinal</b>	<b>Considerations for Use</b>
Snijders and Nicolaides, UK (1994) <sup>69</sup>	Women selected with low-risk pregnancies and known menstrual histories (1987–1993); 40 patients included for each 7-d interval from 14 wk to 40 wk; database from single hospital	1040; retrospective; cross-sectional	Retrospective ultrasound data may be limited by selection bias, or the reason for why an ultrasound was obtained at a given gestational age may influence the fetal size measurement by an unknown amount; cross-sectional references indicate fetal size but do not assess fetal growth.
Stirnemann et al, international (2017) <sup>7</sup>	Low-risk pregnancies with accurate dating (2009–2014); fetal biometric measurements taken at examinations approximately every 5 wk from 9 wk to 14 wk until 40 wk, 8 countries	4321; prospective; longitudinal	INTERGROWTH; created new EFW formula using head and abdominal circumference; diverse; rigorous credentialing of sonographers; use of standardized protocol; separate reference for fetal biometrics <sup>6</sup>
Williams et al, California (1982) <sup>29</sup>	Birthweight from matched birth, death, and fetal death certificates from the Center for Health Statistics of the California Department of Health Services (1970–1976)	2,288,806; retrospective; cross-sectional	Birthweight references inaccurately describe the preterm growth of fetuses who go on to deliver at term. Computer screening method applied to correct errors in gestational age.

<sup>a</sup> Dates not provided for some studies.

<sup>b</sup> Sample size is for number included in construction of the fetal growth reference after inclusions and exclusions from the study sample.

and had a known last menstrual period underwent serial ultrasounds across pregnancy for fetal biometric measurement, although specific inclusion and exclusion criteria varied. A minor difference was that statistical analytical approaches varied among the 3 studies.<sup>31</sup> It also is important to note that INTERGROWTH created a new EFW formula based only on head circumference (HC) and abdominal circumference (AC), whereas NICHD and WHO Fetal used the Hadlock 1985 formula based on HC, AC, and femur length (FL).<sup>7,32</sup>

The 3 studies varied in their approach as to whether to create a unified fetal growth curve for their studies. The INTERGROWTH and WHO Fetal studies followed similar procedures as the WHO Multicentre Growth Reference Study (MGRS) Child Growth Standards which derived a single international growth chart for boys and girls ages 0 to 5 years.<sup>33,34</sup> The INTERGROWTH and WHO Fetal studies differed, however, in their aims at assessing whether there were significant differences between populations. INTERGROWTH operated according to the concept that if conditions were equally optimized, human fetuses grow the same. They, therefore, did not test statistical significance as to whether there were any differences between populations but evaluated the similarities between fetal growth among the sites. A standardized site difference at different gestational ages was calculated and fetal growth was considered similar if the standardized site difference was within a somewhat arbitrary range of  $-0.5$  to  $0.5$  SD. Correspondingly, they pooled their contributors according to likeness of growth, that is, that variation was within a pragmatically set limit (a coefficient of SDs).<sup>35</sup> Thus, INTERGROWTH prescribed to the concept that 1 reference fits all. The WHO Fetal, on the other hand, aimed at assessing whether there were significant differences between populations and found that differences existed.<sup>11</sup> The WHO Fetal reached a different conclusion from both INTERGROWTH and the World Health Organization (WHO) child growth studies, which reported that it is possible to establish and use 1 reference, including multiple populations, but that the use and interpretation have to take into account that populations are significantly different.<sup>36</sup> The NICHD study was designed to assess differences in fetal growth not among countries but among racial/ethnic groups, given the well-described differences in AC and FL in children and adults of differing racial/ethnic groups.<sup>8,37,38</sup>

When comparing the results of INTERGROWTH, NICHD, and WHO Fetal studies directly, the percentiles for fetal biometrics and EFW varied among the studies.<sup>31</sup> Differences in EFW are presented in **Fig. 1** and **Table 2** (no statistical testing was performed). The 50th percentile EFW for INTERGROWTH was smaller beginning at 26 weeks of gestation than the 50th percentile EFW for WHO Fetal and all racial/ethnic groups in NICHD, with differences persisting through 40 weeks. At 32 weeks of gestation, a time when a growth ultrasound may be obtained, the 50th percentile for EFW was 1755 g in INTERGROWTH and 1901 g in WHO Fetal, a difference of 146 g; and 1960 g for non-Hispanic white, 1879 g for Hispanic, 1830 g for Asian or Pacific Islander, and 1837 g for non-Hispanic black women in the NICHD study, a difference from INTERGROWTH ranging from 75 g to 205 g. The implications of these differences are that different proportions of SGA and LGA are identified in a local population, depending on which fetal growth curve is used as a reference.

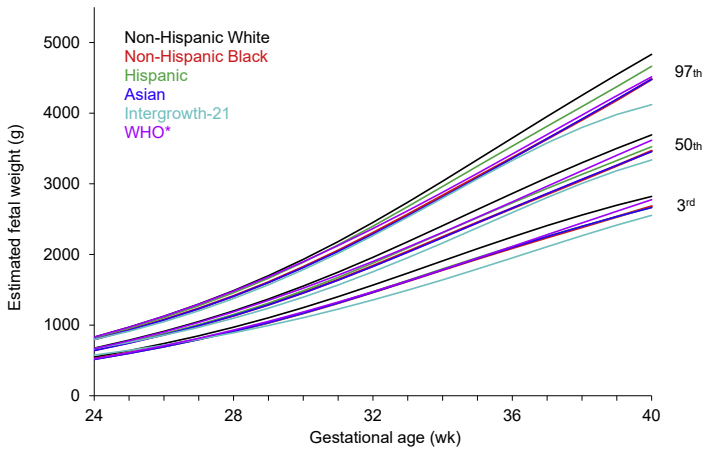
Similarly, the WHO Fetal found EFW and growth trajectory variation were significantly different among 10 countries.<sup>11</sup> **Fig. 2** demonstrates that the 90th percentile of EFW varied across the countries, indicating that again, a different proportion of LGA is identified in a local population when using a unified international growth curve. These findings are in line with the NICHD study group demonstration that different proportions of healthy nonwhite fetuses from low-risk pregnancies would be identified as SGA less than the 5th percentile using a non-Hispanic white or unified standard, which is notable because the older Hadlock and colleagues 1991 study included only white women.<sup>9,39</sup>

## CONSIDERATIONS

The findings from 3 modern, multicenter fetal growth reference studies, INTERGROWTH, NICHD, and WHO Fetal, demonstrate wide variation in fetal growth among



Standards for Estimated Fetal Weight 24-40 Wk



**Fig. 1.** Variation in EFW among 3 studies. Standards for EFW 24 weeks to 40 weeks. INTERGROWTH, NICHD, and WHO Fetal, for 24 weeks to 40 weeks of gestation. Estimated 3rd, 50th, and 97th percentiles for fetal weight by study. \*Values are the 2.5th and 97.5th for the WHO Fetal. Also, NICHD and WHO Fetal calculated EFW from HC, AC, and FL using the Hadlock 1985 formula,<sup>32</sup> whereas INTERGROWTH created a new formula,<sup>7</sup> based only on HC and AC. (From Fetal growth standards: the NICHD fetal growth study approach in context with INTERGROWTH-21st and the World Health Organization Multicentre Growth Reference Study. American Journal of Obstetrics and Gynecology, 2018, with permission.)

different countries and racial and ethnic groups. Variations in fetal growth are similar to variations observed in child growth and that also persist in adult populations.<sup>33,34,40</sup> Body proportion as measured by ratio of sitting height to height and mean stature for adult populations differ across 4 geographic areas, including Australia/New Zealand/Papua New Guinea, Africa, Europe, and Asia.<sup>41</sup> In the United States, black people have shorter sitting height and longer leg length for a similar mean height compared with white people.<sup>42</sup> The racial and ethnic differences in neonatal anthropometry in the NICHD study were not explained by differences in individual socioeconomic factors.<sup>43</sup> These findings indicate that differences among the 3 fetal growth studies may be explained in large part by differences in the international case mix and support the concept that there is natural genetic or inherent variation in fetal growth.

The determinants of fetal growth, however, are not fully understood.<sup>44,45</sup> Normal regional and ethnic variations in body size and proportion likely are due to a combination of genetic and environmental factors.<sup>41</sup> In twin and intergenerational studies, up to 40% of birth size is estimated to be heritable, with fetal genetic factors explaining 31% of variation in birthweight and length and maternal genetic factors explaining 22% and 19%, respectively.<sup>44,46</sup> Africans and East Asians have higher birthweight-lowering genetic variants than Europeans, consistent with the finding that 50th percentile EFW and birthweight were lower in these groups in the NICHD Fetal Growth Studies.<sup>8,47</sup> A genome-wide association study also found a novel genome-wide locus that was associated with reduced fetal weight, manifested by decreased HC but not AC or FL.<sup>48</sup> Genetic factors associated with fetal growth are influenced by environmental factors displaying a developmental plasticity and natural variation in fetal growth.<sup>49,50</sup> It may not be optimal size but optimal adaptation that is important.

**Table 2**  
Fiftieth percentiles for fetal anthropometric measurements by gestational age for the 3 studies<sup>a</sup>

Gestational Age (wk) <sup>b</sup>	Estimated Fetal Weight <sup>c</sup> (g), Fiftieth Percentiles					WHO Fetal
	NICHD White	NICHD Hispanic	NICHD Asian	NICHD Black	INTERGROWTH	
24	674	651	640	647	668	665
25	787	758	745	751	756	778
26	912	876	862	866	856	902
27	1050	1007	990	994	969	1039
28	1202	1151	1132	1134	1097	1189
29	1369	1311	1287	1289	1239	1350
30	1552	1486	1456	1459	1396	1523
31	1749	1676	1637	1642	1568	1707
32	1960	1879	1830	1837	1755	1901
33	2180	2090	2031	2040	1954	2103
34	2408	2307	2238	2247	2162	2312
35	2637	2521	2448	2452	2378	2527
36	2864	2731	2656	2654	2594	2745
37	3086	2935	2862	2854	2806	2966
38	3299	3134	3065	3054	3006	3186
39	3502	3330	3263	3256	3186	3403
40	3693	3525	3455	3466	3338	3617

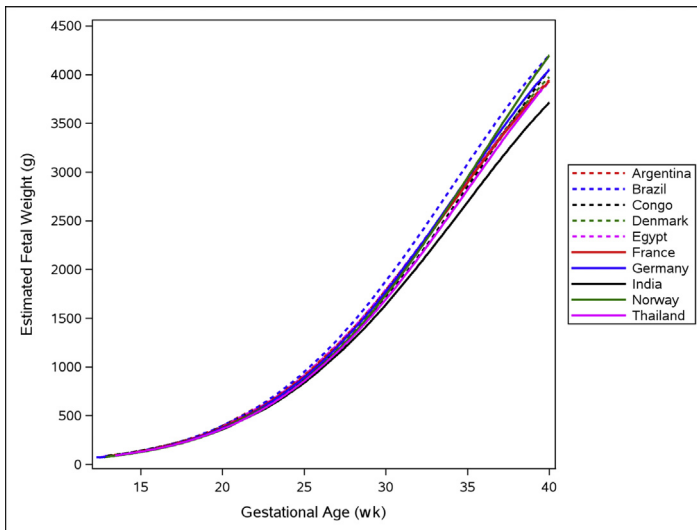
<sup>a</sup> The NICHD,<sup>8,9</sup> INTERGROWTH,<sup>6,7</sup> and WHO Fetal.<sup>11,12</sup>

<sup>b</sup> Results were reported for the exact day (eg, 16.0 wk).

<sup>c</sup> Note that NICHD and WHO Fetal calculated EFW from HC, AC, and FL using the Hadlock 1985 formula,<sup>32</sup> whereas INTERGROWTH created a new formula,<sup>7</sup> based only on HC and AC.

Data from Fetal growth standards: the NICHD fetal growth study approach in context with INTERGROWTH-21st and the World Health Organization Multicentre Growth Reference Study. *American Journal of Obstetrics and Gynecology*, 2018.<sup>31</sup>

Given the natural variation in fetal growth and differences in fetal growth percentiles among references, selecting a universal reference would make comparison of fetal growth simpler for clinical use and for comparison across populations. The disadvantage of a universal reference, however, is that it may describe fetal growth in local populations inaccurately, leading to misclassification of fetuses as SGA and LGA. Fetal growth is influenced by maternal and paternal characteristics, which are known to vary by country and adapt to many external factors, including altitude, nutrition, and other environmental conditions.<sup>18,51,52</sup> For example, the INTERGROWTH and WHO Fetal references were developed in populations living at altitudes less than 1600 m and 1500 m, respectively, and may perform differently for populations living at higher altitude.<sup>7,11</sup> The WHO Fetal also demonstrated that there was more variation in fetal growth in the higher percentiles (eg, 90th) than in the lower percentiles (eg, 2.5th, 5th, and 10th), indicating that the upper percentiles may need more adjustment (ie, customization) at the population level.<sup>11</sup> Country as a proxy for local ethnic mix has been found the most important factor in predicting adverse outcomes in infants compared with customizing for additional individual characteristics.<sup>53</sup> Therefore, it is critical to test how a fetal growth reference performs in relation to clinically meaningful outcomes, including neonatal morbidity and mortality, in the local population to which it is being applied.



**Fig. 2.** Variation in EFW among countries in the WHO Fetal. The 90th percentiles for EFW for the 10 participating countries in the WHO Fetal.<sup>11</sup> These findings indicate that a different proportion of LGA are identified in a local population when using a unified international growth curve. (From The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight. PLOS Medicine, 2017.)

The process of selecting a national reference for fetal growth may be borrowed from the process of selecting a reference for child growth. The Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics recommend US health care providers use the population-based WHO standard charts for children from birth until ages 2 years, and the 2000 CDC growth reference charts for children ages 2 years to 20 years.<sup>54</sup> The INTERGROWTH and WHO Fetal growth charts were created with the intention of being used internationally. Only INTERGROWTH included a US site, whereas the NICHD study was performed only in the United States but with similar study procedures as the WHO, so the data eventually could be combined. Currently, the WHO recommends use of their fetal growth reference for clinical use in all countries with the caveat that the charts should be tested and monitored for performance in local populations. The American College of Obstetricians and Gynecologists does not refer to a specific fetal growth reference when defining fetal growth restriction or LGA whereas the Society for Maternal-Fetal Medicine recommends use of population-based fetal growth references (such as Hadlock).<sup>1,2,55</sup> The Hadlock reference included only white women from a single center, which may not represent fetal growth in other race/ethnic groups, and, given that it was a cross-sectional reference, 1-time measurement of fetal growth (ie, EFW percentile at a given gestational age) indicates only size.<sup>39</sup> In order to know how a fetus arrived at an EFW, at least 2 measurements separated in time are needed to estimate a trajectory. Consideration of other factors, such as abnormal Doppler velocimetry, amniotic fluid assessment or maternal complications, and clinical judgment, also are important determinants for clinical monitoring and intervention.<sup>56</sup> The newer prospective fetal growth curves also allow estimation of fetal growth velocity, which has potential to better distinguish pathologic from normal fetal growth.<sup>57-59</sup>

## SUMMARY

There are 3 modern, prospective fetal growth standards that are similar in scope but demonstrate variation in fetal growth. Different fetal growth charts classify different proportions of fetuses as below or above a cutoff point (eg, below the 10th percentile or greater than the 90th percentile). It is important to know how a growth reference performs in a local population in relation to important clinical outcomes, including fetal morbidity and mortality when implementing in clinical practice. Whether adjusting these population-based fetal growth references further by customization or individualization with conditional growth improves detection of perinatal morbidity and mortality requires future study.

## CLINICS CARE POINTS

- Ultrasound references tend to be preferred to birthweight references for clinical antepartum monitoring because infants who deliver preterm are more likely to be growth restricted, and, therefore, birthweight references inaccurately describe the preterm growth of fetuses who go on to deliver at term.
- Different fetal growth references classify different proportions of fetuses as below or above a cutoff point (eg, below the 10th percentile or greater than the 90th percentile).
- Fetal growth references should be tested and monitored for performance in local populations.

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## DISCLOSURE

The author has nothing to disclose.

## DISCLAIMER

K.L. Grantz is a US federal government employee. The named author alone is responsible for the views expressed in this article, which do not necessarily represent the decisions or the stated policy of the NICHD.

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