The INTERGROWTH-21st fetal growth standards: toward the global integration of pregnancy and pediatric care

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The purpose of the INTERGROWTH-21st project was to develop international, prescriptive standards for fetal growth assessed by ultrasound and fundal height, preterm postnatal growth, newborn size and body composition, maternal weight gain, and infant development at the age of 2 years. Hence, we have produced, based on World Health Organization recommendations, the first comprehensive set of international standards of optimal fetal and newborn growth that perfectly match the existing World Health Organization child growth standards. Uniquely, the same population was followed up longitudinally from 9 weeks of fetal life to 2 years of age, with growth, health, and nutritional status assessment at 2 years supporting the appropriateness of the population for construction of growth standards. The resulting package of clinical tools allows, for the first time, growth and development to be monitored from early pregnancy to infancy. The INTERGROWTH-21st fetal growth standards, which are based on observing >4500 healthy pregnancies, nested in a study of >59,000 pregnancies from populations with low rates of adverse perinatal outcomes, show how fetuses should grow—rather than the more limited objective of past references, which describe how they have grown at specific times and locations. Our work has confirmed the fundamental biological principle that variation in human growth across different populations is mostly dependent on environmental, nutritional, and socioeconomic factors. We found that when mothers' nutritional and health needs are met and there are few environmental constraints on growth, <3.5% of the total variability of skeletal growth was due to differences between populations. We propose that not recognizing the concept of optimal growth could deprive the most vulnerable mothers and their babies of optimal care, because local growth charts normalize those at highest risk for growth restriction and overweight, and can be valuable for policymakers to ensure rigorous evaluation and effective resource allocation. We strongly encourage colleagues to join efforts to provide integrated, evidence-based growth monitoring to pregnant women and their infants worldwide. Presently, there are 23.3 million infants born small for gestational age in low- to middle-income countries according to the INTERGROWTH-21st newborn size standards. We suggest that misclassification of these infants by using local charts could affect the delivery of optimal health care.

Key words: abdominal circumference, biparietal diameter, estimated fetal weight, femur length, fetal size, macrosomia, optimal growth, reference chart, skeletal growth, small for gestational age, socioeconomic status, standard, stunting

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Introduction

Recent publications[1-5] and ensuing editorials and correspondence,[6-9] as well as presentations and debates at national and international meetings, have activated a controversy that goes well beyond the boundaries of obstetrics and perinatal medicine. The controversies touch upon fundamental topics in biology, genetics, politics, and human rights. Sadly, some arguments have at times been reminiscent of the historical dispute about the influence of race or ethnicity or on human head size and shape.[10]

There is little disagreement about the similarity of human growth across healthy populations in early pregnancy, and the applicability of international standards to estimate gestational age,[2,11] evaluate size at birth worldwide,[12-14] and monitor the growth of term newborns up to 5 years of age.[15] However, challenges are being made to key conceptual and factual issues relating to fetal growth monitoring in the second half of pregnancy that are preventing the introduction of integrated care across the first 1000 days of life.

Some members of the obstetric community seem to hold firmly to the view that fetal growth differences among healthy populations, specifically >14 weeks' gestation, are strongly influenced by maternal factors such as self-reported ethnicity, nationality, or political borders. This position is difficult to sustain given the strong evidence, obtained from detailed monitoring of low-risk cohorts from early pregnancy to 2 years of age, that human growth, evaluated by markers of skeletal, fat-free mass (ie, fetal crown-rump length [CRL] and head circumference [HC], birth length, HC at birth, and infant length), is very similar among low-risk populations regardless of where they live, or their race/ethnicity,[16,17] as demonstrated more than a decade ago by the World Health Organization (WHO) Multicenter Growth Reference Study (MGRS).[18]

Differences observed in perinatal health among general populations across countries are principally due to the downstream effects of environmental, nutritional, and socioeconomic factors—frequently across generations—and this has important consequences. These are well recognized in medicine and public health, ie, a mother's ZIP code is a better indicator of her health status than her genetic code.[19,20] Our aim here, therefore, is to dispel these misconceptions and unsubstantiated beliefs that, if left uncorrected, could adversely affect the quality of care offered to women and their families.

Methodological issues relevant for the screening of fetal growth abnormalities in the general pregnant population

References vs standards

At present, clinicians around the world are using many different ultrasound charts of fetal size, based on a variety of populations and methodologies, to monitor growth. However, in a series of systematic reviews, we have shown that the majority of these charts were developed with important methodological flaws.[21-23]

All these charts are references rather than prescriptive standards. The distinction is critical. References describe how individuals *have grown* at a particular time and place, often decades beforehand. Prescriptive standards, on the other hand, are purposely developed using a selected, healthy population, to describe how humans *should grow* when nutritional, environmental, and health constraints on growth are minimal. They are based conceptually on the WHO 1995 recommendation that "human growth should be evaluated using international standards, describing how individuals should grow."[24] Of course, results from any screening test, so also in the case of growth monitoring using a standard, then require clinical judgement to interpret findings and determine future actions.

The use of references instead of standards has important implications at individual and populations levels that impact clinical care and public health policies. To understand why, it is important to realize that the distribution of size in the general population does not constitute a standard. The prevalence of stunting among children globally illustrates the point well, as the rate of stunting is inversely related to the level of socioeconomic status (SES).[25] Therefore, size charts based on the distribution of biometric measures in low and high SES populations will be very different from each other. A chart based on a low SES sample will clearly underestimate the prevalence of small for gestational age (SGA) and stunting, which are markers of social inequity.[25]

These differences can be illustrated when assessing the INTERGROWTH-21st project and the WHO-sponsored study by Kiserud et al,[4] which had completely different objectives. The former was a comprehensive evaluation of human growth and development across the first 1000 days of life, leading to the construction of fetal and preterm postnatal growth standards; it included an assessment of newborn body composition, infant feeding practices, and preterm postnatal growth, as well as postnatal growth and neurodevelopment evaluation at 2 years of age to assess the appropriateness of the complete cohort for the construction of standards (Panel 1). The INTERGROWTH-21st project[26] also adhered rigorously to the WHO recommendations for assessing human size and growth (see below).[24] In contrast, the WHO-sponsored study was hospital-based, and generated fetal growth references not standards[4]; the selection of the population to study, outcome measures, ultrasound equipment, and analytical strategy were different, as indeed was the lack of masking the ultrasound measures to avoid potential observer bias.

This need to differentiate standards from reference charts is not an obscure intellectual matter but a vitally important global issue with marked political and socioeconomic ramifications. How else can progress toward United Nations Sustainable Developmental Goal 3.1 (end preventable deaths of newborns and children <5 years of age) be measured, unless international standards are used to compare the health and nutritional status of infants, as was done in assessing progress toward Millennium Development Goal 1 (eradicate extreme

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PANEL 1
INTERGROWTH-21st project characteristics

Large prospective study of 59,137 pregnant women

Population based: all institutions providing pregnancy and delivery care in 8 geographically limited urban areas with low rates of adverse perinatal outcomes and low pollution, domestic smoke, radiation, and other toxic substances

Sampling of individual women within 8 geographic areas using predefined criteria for construction of standards

Participants followed up to age 2 y

Pregnancy, neonatal anthropometry, and perinatal conditions recorded for total population (59,137 pregnant women) in 8 geographic areas using standardized procedures, identical equipment, and centrally trained staff

Environmental conditions evaluated using special data collection form developed in collaboration with Center for Environmental Research and Children's Health, University of California, following WHO recommendations

Excluded from standards only severe maternal or fetal conditions defined a priori

A priori data analysis plan based on WHO recommendations to construct human growth standards

Use of skeletal growth measures from <14 wk' gestation to age 2 y for comparisons across populations, as recommended by WHO

Three complementary data analysis strategies to support pooling data for construction of standards

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International standards for human growth from <14 wk' gestation to age 2 y

International preterm postnatal growth standards as recommended by WHO

Preterm postnatal motor development assessment following WHO milestones

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Published real-time, online data management system

Ultrasound equipment selected based on predefined criteria after extensive public consultation according to WHO administrative requirements

Ultrasound measures in triplicate and corroborated by newborn anthropometry

Ultrasound results masked to operators to eliminate expected result bias

Standardized equipment at all sites for ultrasound; maternal, newborn, and child anthropometry

Ultrasound machines calibrated with standard phantom

Published system of:
- Training, standardization, and certification of ultrasound operators
- Quality-control strategy for all maternal and postnatal measures
- Assessment of intraobserver and interobserver variation of ultrasound fetal biometry
- Protocols for quality control of ultrasound image review, data monitoring, and random sample remeasurement

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WHO, World Health Organization.

Papageorghiou. INTERGROWTH-21st fetal growth standards. Am J Obstet Gynecol 2018.

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poverty and hunger) by showing changes in stunting rates based on the international WHO child growth standards?[27] Making late fetal growth charts country- or region-specific would not only make this task impossible, it risks confusing the interpretation of all other growth and health indicators across populations.

How were the INTERGROWTH-21st populations selected?

The first step in creating prescriptive international standards of optimal fetal growth was to select free-living populations in defined geographic areas with minimal constraints on growth, and good maternal and perinatal health outcomes. The second step was to select, from the whole population, healthy pregnant women at low risk of adverse outcomes.[26] This is very different to the policy of recruiting women from selected hospitals, which frequently introduces bias, because women who attend certain hospitals for pregnancy care may be different from the overall population of pregnant women—particularly when the population is served by private and public hospitals, and recruitment is from one but not the other.

In the INTERGROWTH-21st project (Panel 2), all institutions providing obstetric care in 8 delimited urban areas with no or low levels of major, known, nonmicrobiological contamination,[28] were selected to ensure that the study was population-based. Thus, a strategy of including delimited geographic areas where the health, educational, and nutritional needs of all the inhabitants are mostly reached is very different to that of the WHO-sponsored[4] and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)[5] fetal studies, which selected a number of convenient hospitals. This lack of population-based sampling means that the sites selected by these 2 studies would have been ineligible for the INTERGROWTH-21st project.

Healthy pregnant women with a naturally conceived singleton pregnancy, who met the individual inclusion criteria,[26] were identified prospectively in the INTERGROWTH-21st project. Approximately one third of the healthy women who met these criteria were enrolled in the Fetal Growth Longitudinal Study, 1 of the project's 5 studies. This is the cohort from which the fetal growth standards,[1] and the standards for: (1) symphysis-fundal height,[29] (2) gestational weight gain,[30] (3) early pregnancy dating,[2] (4) estimated fetal weight (EFW),[3] (5) newborn body composition,[31] and (6) the postnatal growth of preterm infants were derived,[32] as well as, in 2018, (7) fetal velocity growth and (8) neurodevelopment at 2 years of age. These tools are available as Supplementary Material for clinical use. Underlying these tools was a series of systematic reviews of current clinical practice and development of methodologies based on a deep understanding of the issues to arrive at optimal scientific analytical framework. It should be noted that there was wide heterogeneity in methods, tests, and definitions used in previous studies (Panel 3).

Women were recruited <14 weeks' gestation, and pregnancies were dated based on a certain last menstrual period, but corroborated by ultrasound measurement of the CRL.[33] Ultrasound scans were then performed every 5 ± 1 weeks from the initial dating scan by dedicated research staff using identical, midrange ultrasound machines at each

study site, with rigorous training and standardization procedures,[34,35] quality-control measures,[36] and blinding of measurements.

Moreover, unlike any other longitudinal study of ultrasound in pregnancy, the infants involved in the fetal growth standards were followed up for 2 years after birth, using the same standardized methods employed in the WHO child growth standards to measure growth,[18] neurodevelopment, auditory processing, and sleep-wake patterns at 2 years of age.[37] We have recently reported that the fetal growth standards cohort remained healthy up to 2 years of age, with adequate growth and motor development assessed using WHO tools,[15,38] supporting its appropriateness for the construction of the international fetal and preterm postnatal growth standards.[17]

Evaluating similarities in fetal growth among populations

Critics of the INTERGROWTH-21st project often misquote our conclusions by claiming we believe that all babies everywhere grow in the same way or birthweight is the same in general populations throughout the world. This is self-evidently not the case. Rather, we have demonstrated that measures of fetal and newborn skeletal growth are similar across diverse geographical settings when most of the mothers' socioeconomic, educational, nutritional, and health needs are met and environmental constraints on growth are low.[16]

Skeletal growth was chosen as the outcome measure to evaluate similarities in growth based on the WHO recommendation to avoid fat-based indicators, eg, abdominal circumference (AC), when comparing populations for the construction of human growth standards. This is vitally important for fetal growth screening in developed countries with an obesity epidemic, and for those developing countries in epidemiological transition.

The specific recommendation[39] is to use markers of skeletal or linear growth because they are: (1) mostly resistant to skewing in response to "excessive nutrition"[39]; (2) normally distributed (unlike fat-related indicators); (3) more precisely measurable than fat-related indicators; (4) consistent with pediatric practice worldwide as they were used by WHO to generate the WHO child growth standards; and (5) although responsive to undernutrition or infection, this is hardly relevant in our healthy populations.

The comparison to assess similarities or differences in the WHO MGRS was based on infant height.[18] The corresponding measure in fetuses is CRL (that can be measured reliably until 14 weeks' gestation) and length at birth; these showed remarkable similarities among sites using the 3 analytical approaches described below. It is difficult to see that large variation should exist between these 2 time points, but we assessed it; as length is not measurable (due to fetal curling) we used HC as a skeletal measure between 14 weeks of gestation and at birth.

Conversely, assessing similarities in fetal growth among populations by EFW, a composite calculation from 3 different fetal anthropometric measurements, contradicts these physiological concepts; it also adds considerable error to any estimation, especially at term. In addition, fetuses can reach the same EFW through several permutations of the equation's components, which are clearly not comparable. The continued use in the literature of an old equation,[40] determined using a very small sample, adds to the confusion, especially as it includes femur length measures obtained using old ultrasound equipment, which yields different results to modern ultrasound machines.[41]

Many studies have shown that the 95% confidence interval of the random error associated with EFW accuracy exceeds 14% of birthweight, which is close to 400 g for the average birthweight at term. In fact, a systematic review concluded that "the size of the random errors (of EFW) remains a major obstacle to confident use in clinical practice."[42] Accuracy is even worse for small and large fetuses for which growth estimation is clinically more important. All these are very important issues when comparing differences in EFW values among populations, which is why it is much more logical to compare populations using the individual skeletal parameters, such as length and HC separately.

Why not to use AC alone to compare populations considering that it is associated with perinatal outcomes in late pregnancy? The response, based on the recommendation of skeletal linear growth, is that AC is a fat-/tissue-based measure equivalent to weight. Hence, if a marker of fat/tissue mass were used to

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PANEL 2	
Different studies of INTERGROWTH-21st project	
NCSS	Demographic and pregnancy characteristics, birth length, head circumference, weight and neonatal conditions of all newborn babies from 8 geographically defined populations using identical methods and instruments
FGLS	A subgroup of NCSS: women who met individual inclusion criteria from these populations were followed up from <9 wk through to end of pregnancy; this included serial fetal ultrasound scans and newborn anthropometry and body composition
Infant Follow-Up Study	All FGLS newborns were then followed up until age 2 y for growth, health, and development
Preterm Postnatal Follow-Up Study	All preterm births in FGLS cohort that underwent detailed regular anthropometry and followed up to age of 2 y
Preterm and Impaired Fetal Growth Syndromes Study	Nested case-control study including all preterm births as well as all newborns with impaired fetal growth from NCSS

FGLS, Fetal Growth Longitudinal Study; *NCSS*, Newborn Cross-Sectional Study.

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PANEL 3

INTERGROWTH-21st international standards for monitoring growth and development from early pregnancy to 2 years of age

INTERGROWTH-21st international standards for:	INTERGROWTH-21st systematic review and conceptual basis supporting international standards
First-trimester dating[2]	Systematic review of charts of pregnancy dating by fetal crown-rump length[11]
Late pregnancy dating[63]	Study design and implementation[26]
Fetal growth by ultrasound[1]	Ultrasound methodology, standardization, and quality control[33-36,64,65]
Estimated fetal weight by ultrasound[3]	Systematic review of charts of fetal size by ultrasound[21]
Symphysis-fundal height[29]	Systematic review of novel biomarkers for predicting intrauterine growth restriction and stillbirths[66,67] Systematic review and meta-analysis on predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction[68]
Phenotypic classification of SGA[69] Phenotypic classification of preterm birth[70]	Conceptual issues on preterm birth[71-73] Systematic review of novel biomarkers for prediction of spontaneous preterm birth phenotype[74]
Newborn size for gestational age and sex from 24 wk' gestation to term[55,75]	Systematic review of charts of newborn anthropometry[22]
Newborn body composition and weight for length standards[31]	Conceptual issues for preterm standards[76] Systematic review of preterm postnatal charts[23]
Preterm postnatal growth based on international feeding recommendations[32]	Preterm postnatal growth: new paradigm[77] Anthropometric protocols, standardization, and quality-control methods for international growth standards[78,79]
Maternal weight gain during pregnancy[30]	Systematic review of gestational weight gain charts[80]
Postnatal follow-up to age 2 y with neurodevelopmental assessment to evaluate appropriateness of population for creating growth standards[17]	Systematic review of differential effects of intrauterine growth restriction on childhood development[81] A simplified multidimensional set of neurodevelopment assessment tools[37]
Free e-learning training courses[82,83]	Evaluation of dissemination activities[84,85]

SGA, small for gestational age.

Papageorghiou. INTERGROWTH-21st fetal growth standards. Am J Obstet Gynecol 2018.

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compare growth across populations, it would be observed in the third trimester of pregnancy that, compared to non-overweight populations, those in the midst of the obesity epidemic have fetuses with larger AC values. This is observed in one of the NICHD publications,[43] which shows an increase in AC in overweight women compared to those of normal weight.

Importantly, in the context of the NICHD argument, fetal AC changes are mostly due to liver growth supported by a small component of abdominal subcutaneous fat. It is, therefore, very difficult to understand how the different ethnic groups they studied can have differential, genetically driven, liver growth during the second part of pregnancy.

Why outcome measures should be masked

It is a basic research principle across all biological subjects that any outcome measures being obtained, especially by medical observers, should be masked, as prior knowledge or real-time plotting by the operator can strongly influence their measurement. Prior knowledge increases the risk of bias in favor of the hypothesis under investigation, which certainly applies to ultrasound measurements, where the operator can influence the values obtained. In the INTERGROWTH-21st project, the identical ultrasound machines used at every site were adapted to enable measurements to be taken in a blinded fashion; this has not been the case in all other fetal studies despite the well-recognized potential for bias.

Which is the most appropriate analytical strategy?

Data from studies combining populations should be analyzed in 2 steps: first, by evaluating the similarities among sites (or ethnic groups in the case of the NICHD fetal study) and second by estimating the centiles. For the first step, we followed the WHO recommended strategy for the construction of growth standards based on 3 complementary methods after the literature was systematically reviewed.[44] In contrast the WHO-sponsored study on fetal growth used a *P* value-multiple testing—based strategy; while the NICHD study was designed to create separate standards for the 4 ethnic groups, so the issue of potential pooling was not assessed. In the NICHD study, judgements of differences were again based on a *P* value and although the potential clinical significance was assessed, this was done a posteriori rather than as a judgement on whether pooling should take place or not. This is another core element that differentiates these 3 publications (Panel 1).

It is obvious that statistical significance is not the same as clinical significance and that small differences, well within the measurement error of ultrasound equipment, may achieve statistical significance in a study with a large sample size. For example, in a study than included women enrolled in the NICHD study,[43] the median femur length was 0.8 mm longer and the median humerus

length 0.6 mm longer in 443 obese vs 2320 nonobese women (in context the lengths were 71.0 vs 70.2 mm; and 62.2 vs 61.6 mm, respectively). The differences are judged to be statistically significant because the *P* values are .01 and .03, respectively, but are of minimal clinical relevance and well within measurement error, which may in any case be higher in obese women.

Therefore, the clinically relevant difference should be defined a priori, and *P* values have no place in deciding whether these differences are clinically meaningful. Furthermore, the use of multiple testing for comparing individual populations against each other is an irrelevance, as it was never suggested that fetuses from one site, eg, in India, should be evaluated using charts from another site, eg, in Brazil or the United States. What is recommended is to create international standards by combining data from prescriptive populations against which all samples are compared. Standardization of tools and measures is a central practice not only in biology and medicine, but also in all fields of science and even the arts.

Hence, the INTERGROWTH-21st project set up its a priori conditions on whether to pool the data sets based on the WHO internationally accepted 3-component strategy used for the WHO child growth standards. The clinically relevant difference was also defined a priori using the appropriate, recommended outcome measure for evaluating growth across populations. We are unsure why the investigators of the WHO-sponsored study, who must have been aware of the WHO expert committee recommendations, did not follow them or use even the most practical analytical method, namely sensitivity analysis. This is relevant because they advocated pooling their data, despite calling them different, without conducting a standard sensitivity analysis.[4]

To conduct such an evaluation, we used the SD of the all sites' combined value of fat-free measures as the denominator for the standardization process,[45] following WHO previous work.[18] For fetal growth, this involved values for both CRL and HC obtained from the

mean of 3 highly standardized measures of the same individual at each visit. When this protocol was applied to the INTERGROWTH-21st fetal growth data, which constituted 128 comparisons of fetal CRL and HC from early pregnancy to term, as well as birth length, only 1 value was marginally outside (standardized study discrepancy −0.58)[16] the primary cut-off of ±0.5 SD, recommended by the WHO MGRS group.[44]

A key question is: what would the 2 recently published fetal studies' results have been had the investigators followed the same analytical strategy as the WHO MGRS group?[18,44] To explore this question, we have produced the matching

analyses, which the authors did not perform. Figure 1 shows that, when the results of the 2 studies are combined, the differences among all the study sites are well within the limits established a priori for fetal skeletal measures, in agreement with the INTERGROWTH-21st previous publications. This was to be expected because the actual 50th centile of fetal HC according to gestational age was almost identical across these populations (Figure 2).

Race/ethnicity is not a biological factor influencing fetal growth

Several groups have suggested adjusting fetal growth charts for maternal

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FIGURE 1

Fetal HC growth in the INTERGROWTH-21st, NICHD, and WHO-sponsored studies are remarkably similar
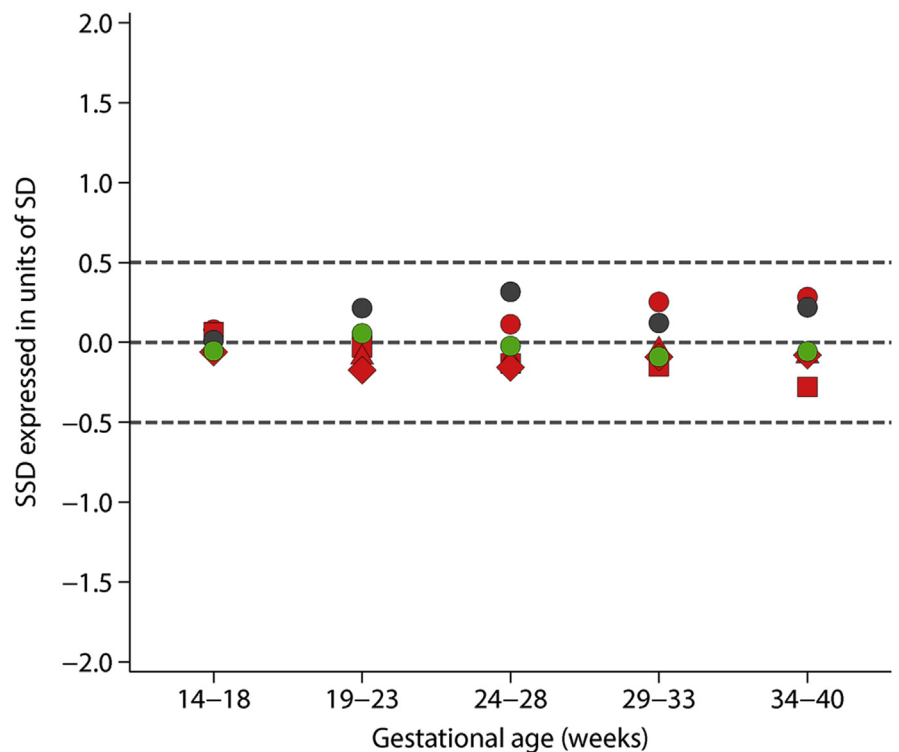
Standardized study discrepancy (SSD) of fitted fetal head circumference. Study-specific means were obtained as unweighted average of values from published charts (by gestational week) for 5 gestational age intervals. SSD was calculated as difference between individual study mean and mean of all studies combined, divided by Fetal Growth Longitudinal Study (FGLS) adjusted SD,[7] at each gestational age interval. World Health Organization—sponsored study[15] (gray circles); FGLS of INTERGROWTH-21st[20] (green circles); and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development fetal growth studies[19]: white (red circles), black (squares), Hispanic (triangles), Asian (diamonds).

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FIGURE 2

Comparison of INTERGROWTH-21st, NICHD, and WHO-sponsored studies show limited discrepancies in fetal HC
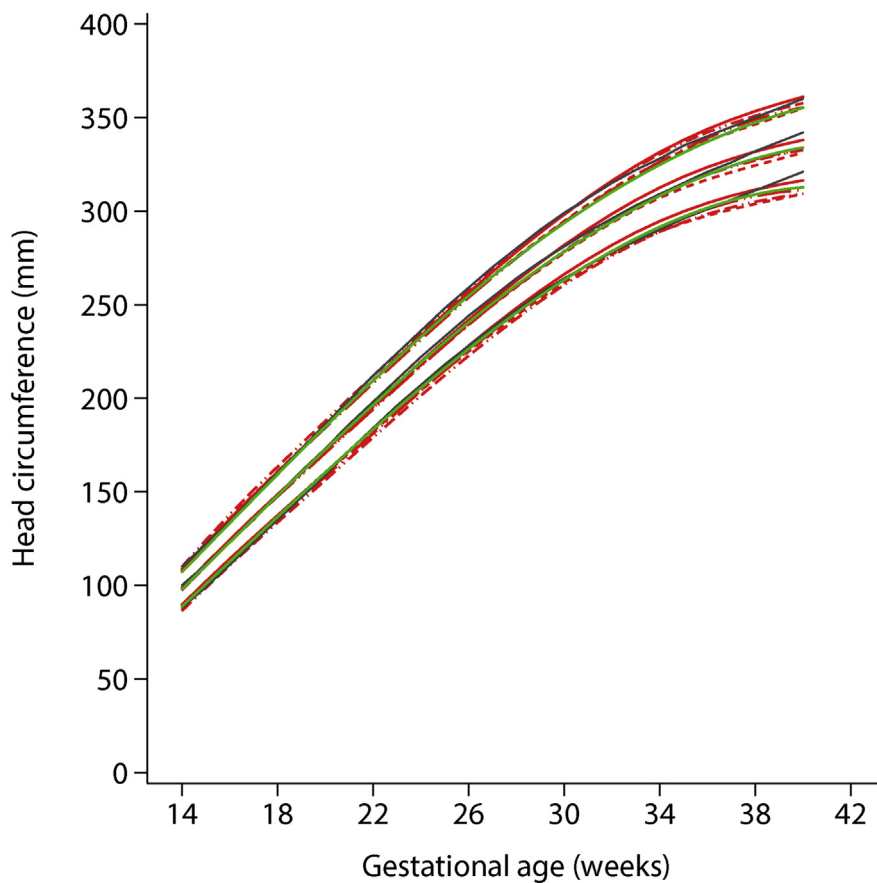
Comparison of fitted 5th, 50th, and 95th centiles of fetal head circumference. World Health Organization—sponsored study[15] (gray solid lines); Fetal Growth Longitudinal Study of INTERGROWTH-21[st20] (green solid lines); and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development fetal growth studies[19]: white (solid red lines), black (dashed red lines), Hispanic (dash-dot red lines), Asian (dot-dot-dash red lines).

Papageorghiou. INTERGROWTH-21st fetal growth standards. Am J Obstet Gynecol 2018.

characteristics, in particular self-reported race/ethnicity. However, the use of race/ethnicity is problematic in most nonisolated populations because of large ancestral admixture due to global migration, invasions, and other population movements. There are also at least 116 definitions of self-reported race/ethnicity in the biomedical literature.[46]

The alternative, more compelling view is that race/ethnicity is simply a social construct that represents a proxy for SES, education, and social class background, which is related to many poor health and social outcomes, eg, stillbirth and[47] maternal mortality.[48] In the NICHD fetal study, which proposed using different charts in the United States for "non-Hispanic whites, non-Hispanic blacks, Hispanics, and Asian/Pacific islanders," differences seen in fetal growth between these groups must be taken in the context of the enormous differences in annual family income and other SES markers such as marital status, education, and private health insurance. In addition, the fact that SES and race/ethnicity often merge is frequently ignored when making adjustments and,

in our view, presents a dangerous precedent.

There is also no scientific evidence that self-reported race/ethnicity is biologically or genetically related to fetal growth. Actually, all the genetic evidence across global populations demonstrates the opposite, ie, only a very small proportion of human linear growth is related to genetic factors. As measured in observational studies, the differences between geographic locations cannot explain >10% of the variability in human length. In addition, strong genetic evidence from a multiancestry, genomewide association study meta-analysis involving 153,781 participants identified as many as 60 genetic loci associated with birthweight (as a proxy for fetal growth) with only 15% of the variance in birthweight being captured by assays of fetal genetic variation.[49]

Furthermore, in any country, such as the United States, whose inhabitants often have mixed ancestral backgrounds, it is impossible to see how racial/ethnic classification could even be implemented during the course of routine antenatal care, especially as some of the groupings are hardly scientific. For example, based on US census practice, "Asian" includes Chinese, Japanese, South Indian, and Pacific Islander groups. Black American and African Americans are often grouped together, although health behaviors between African-born and American-born blacks are acknowledged to be different.[50] Hispanics are presumably an ethnic group of European origin with (or without) native-American mixing? In fact, the infeasibility and inaccuracy of defining race/ethnicity in contemporary multicultural settings was recently demonstrated in an Australian study,[51] using the gestation-related optimal weight customized charts.[52] In a sense, however, the impracticality is an irrelevance because racial-/ethnic-specific charts are indefensible on biological grounds.[53]

Interestingly, one of the quotations often used to justify having racial/ethnic fetal growth charts is from a paper by Bogin and Varela-Silva[54] in 2010,

although the authors themselves actually provided rather different views. They stated that "even if specific genotypes are discovered, their direct contribution to normal ethnic (so-called 'racial') variation in human body shape may be relatively small. At 40 weeks' gestation, fetuses identified as African-Americans have, on average, relatively longer legs than fetuses identified as European-Americans. But the difference, as measured by (total length/CRL) is less than 1%."[54] Such views and those of many other scientists accord with the belief that race/ethnicity is a social rather than a biological construct and a form of categorization that is ill-defined, especially in populations that have experienced high ancestral admixture rates.

The rationale for adjusting for other factors is similarly questionable. For example, parity (nulliparous women have on average smaller fetuses, but are also at higher risk of other features of placental insufficiency such as preeclampsia) or maternal weight, highly dependent on overnutrition and undernutrition, are questionable and are not unchanging characteristics. Even characteristics that do not change within an individual's life—such as maternal height—are highly changeable within just a few generations and therefore nutritionally dependent.

Implications for screening in the general pregnant population: local charts vs international standards

It is suggested that fetal growth charts for EFW and common ultrasound biometric measures >14 weeks' gestation "reveal a wide range of variation in human fetal growth across different parts of the world" with "significant differences in fetal growth between countries."[4] It is hard to understand how borders between countries, often drawn on maps by colonial powers, can possibly have a biological influence on human growth, nor how heterogeneity within populations can be negated by national boundaries.

So, what happens if "population-specific high-quality reference intervals" for each population are created?[4] Apart

FIGURE 3
Local references artificially "fix" the rate of SGA at 10%; international standards show different SGA rates as expected
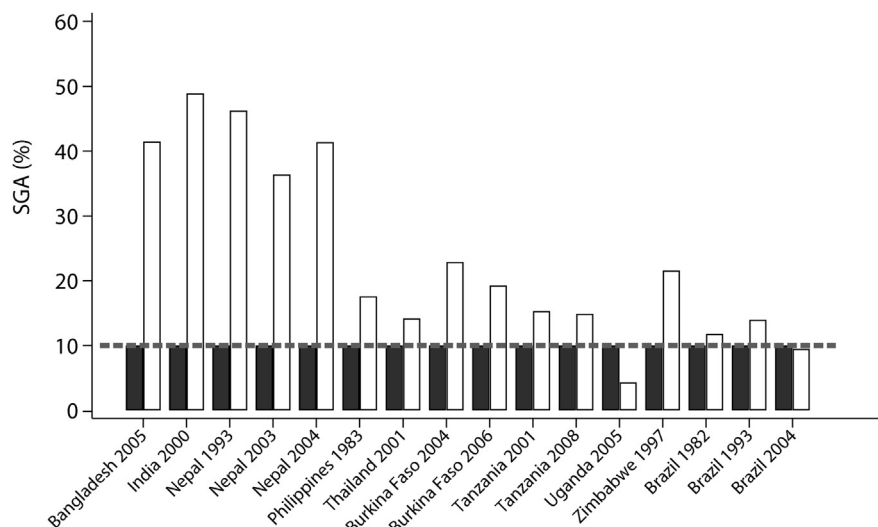
Rates of small for gestational age (SGA) from 16 prospective cohorts of newborns from 10 low- and middle-income countries. Empty columns show prevalence of SGA using INTERGROWTH-21st standards,[47] compared with effect of using fixed cut-off SGA rate of 10% that would result from using local reference charts (black columns). Data from Kozuki et al.[56]

Papageorghiou. INTERGROWTH-21st fetal growth standards. Am J Obstet Gynecol 2018.

from the obvious hindrance of having to create hundreds of high-quality reference intervals for countries, regions, cities, villages, or hospitals, this approach is entirely fallacious. If a reference range is created for each region, by definition 10% of fetuses and newborns will be <10th centile of each local chart, and 10% will be >90th centile. Pretending that a uniform proportion of the population of fetuses across the world have the same degree of growth aberration is nonsensical and entirely at odds with differences in rates of maternal obesity, diabetes, preeclampsia, malnutrition, and infectious diseases. "Fixing" charts in this way would mean that no country, region, or city would have an excess of underweight or overweight babies—a concept so far removed from common sense and biological principles as to be difficult to comprehend.

This has been unequivocally demonstrated in 2 recently published reanalyses of data from low- and middle-income countries, using a birthweight <10th centile of the INTERGROWTH-21st
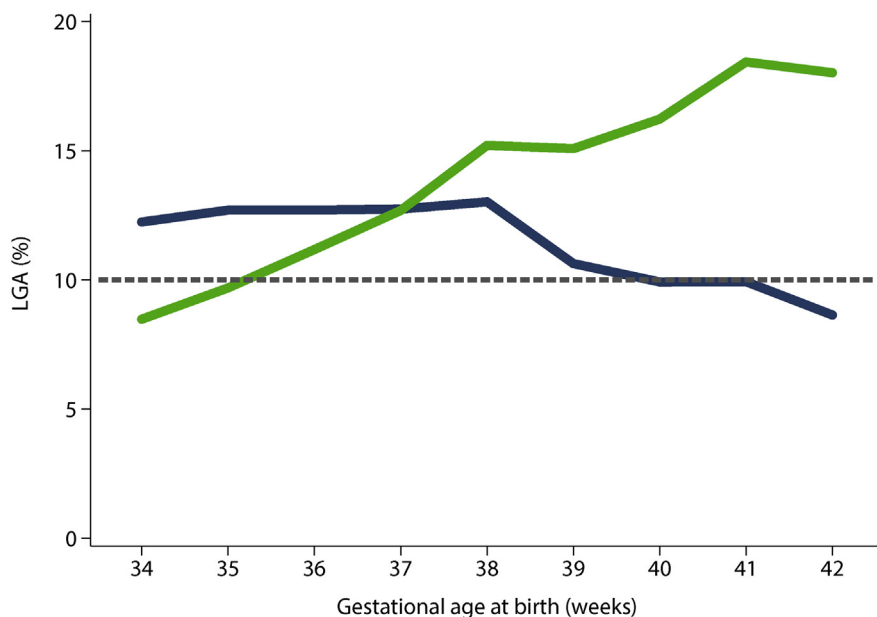
newborn size for gestational age/sex standards[55] as the definition of SGA. In the first study, the overall SGA prevalence was 24% among 16 birth cohorts[56]; in the second, the rate was 19% among 14 cohorts.[12] Of course, the prevalence would have been 10% had local charts been used (Figure 3).

At the other end of the health spectrum, we have previously shown that in England in 2011 through 2012 there were, as expected, 11% live singleton babies born >33 weeks' gestation >90th centile if local charts of birthweight for gestational age are used.[57] However, when INTERGROWTH-21st international standards are used for the cut-off point,[55] the rate of overweight newborns increased to 19% overall, which matches the high prevalence of obesity in pregnant women and children in England (Figure 4).[58,59]

An additional practical issue specific to the WHO-sponsored reference charts, in terms of their global use for screening, is that they are sex-specific and their use presupposes prenatal sex determination. Even if we assume that the

FIGURE 4
Higher rates of LGA newborns by international standards than a local reference, matching the high prevalence of overweight in the general population

Prevalence of large for gestational age (LGA) (>90th birthweight centile) newborns in England in 2011 through 2012. Estimated prevalence of LGA using British 1990 growth reference centiles[49] (blue line) or INTERGROWTH-21st newborn size at birth standards[47] (green line). The horizontal dotted line represents the expected (by definition) 10% of newborns above the 90th centile of a local reference chart.

Papageorghiou. INTERGROWTH-21st fetal growth standards. Am J Obstet Gynecol 2018.

determination is accurate and that parents want to know the fetal sex, the practice is banned in some countries.[60]

Conclusions
The WHO child growth standards[15] are now used in nearly every country in the world to measure the growth of children from 0-5 years of age.[61] The INTERGROWTH-21st project was designed using exactly the same prescriptive approach as the WHO MGRS, ie, based on WHO recommendations regarding the construction of human growth standards.[24] The charts generated by the WHO MGRS and INTERGROWTH-21st project integrate perfectly so that, for the first time in history, a uniform method exists for monitoring linear growth from the "womb to classroom."[62]

Many of the clinical tools derived from the same healthy cohort as the fetal growth standards are now being used routinely around the world, eg, the preterm postnatal growth standards, which were adopted by both WHO[13] and the Centers for Disease Control and Prevention[14] in the context of the Zika epidemic. These and other standards derived from the same cohort, eg, for measuring symphysis-fundal height[29] and maternal weight gain,[30] as well as tools for estimating gestational age in early[2] and late[63] pregnancy have had >65,000 downloads from our website (data up until Nov. 21, 2017) and close to 10,000 health care professionals have been trained using INTERGROWTH-21st e-learning modules.

There is no scientific rationale for using local references instead of standards in clinical practice, and customization based on the color of a mother's skin, the sex of her fetus, or her nationality is unacceptable in the 21st century. Furthermore, classifying any of the 23.3 million infants born SGA in low- to middle-income countries according to the INTERGROWTH-21st newborn size standards for gestational age/sex[12] as normally grown by local charts could potentially deprive them of their right to better health care given that most are SGA because of impaired fetal growth due to malnutrition and/or infectious diseases. ■

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