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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Received Nov. 27, 2017; revised Jan. 4, 2018; accepted Jan. 5, 2018.

This study was supported by the INTERGROWTH-21st grant 49038 from the Bill and Melinda Gates Foundation to the University of Oxford. The funder played no role in the study design; collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the article for publication. Dr Papageorghiou is supported by the Oxford Partnership Comprehensive Biomedical Research Center, with funding from the Department of Health's National Institute for Health Research Biomedical Research Centers funding scheme.

The authors report no conflicts of interest. The INTERGROWTH-21st project was approved by the Oxfordshire Research Ethics Committee 'C' (reference: 08/H0606/139), the research ethics committees of the individual institutions, and the regional health authorities where the project was implemented. Participants provided written consent to be involved in the Fetal Growth Longitudinal Study.

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0002-9378/$36.00 • © 2018 Published by Elsevier Inc. • https://doi.org/10.1016/j.ajog.2018.01.011

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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