OBSTETRICS

The satisfactory growth and development at 2 years of age of the INTERGROWTH-21st Fetal Growth Standards cohort support its appropriateness for constructing international standards

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BACKGROUND: The World Health Organization recommends that human growth should be monitored with the use of international standards. However, in obstetric practice, we continue to monitor fetal growth using numerous local charts or equations that are based on different populations for each body structure. Consistent with World Health Organization recommendations, the INTERGROWTH-21st Project has produced the first set of international standards to date pregnancies; to monitor fetal growth, estimated fetal weight, Doppler measures, and brain structures; to measure uterine growth, maternal nutrition, newborn infant size, and body composition; and to assess the postnatal growth of preterm babies. All these standards are based on the same healthy pregnancy cohort. Recognizing the importance of demonstrating that, postnatally, this cohort still adhered to the World Health Organization prescriptive approach, we followed their growth and development to the key milestone of 2 years of age.

OBJECTIVE: The purpose of this study was to determine whether the babies in the INTERGROWTH-21st Project maintained optimal growth and development in childhood.

STUDY DESIGN: In the Infant Follow-up Study of the INTERGROWTH-21st Project, we evaluated postnatal growth, nutrition, morbidity, and motor development up to 2 years of age in the children who contributed data to the construction of the international fetal growth, newborn infant size and body composition at birth, and preterm postnatal growth standards. Clinical care, feeding practices, anthropometric measures, and assessment of morbidity were standardized across study sites and documented at 1 and 2 years of age. Weight, length, and head circumference age- and sex-specific z-scores and percentiles and motor development milestones were estimated with the use of the World Health Organization Child Growth Standards and World Health Organization milestone distributions, respectively. For the preterm infants, corrected age was used. Variance components analysis was used to estimate the percentage variability among individuals within a study site compared with that among study sites.

RESULTS: There were 3711 eligible singleton live births; 3042 children (82%) were evaluated at 2 years of age. There were no substantive differences between the included group and the lost-to-follow up group. Infant mortality rate was 3 per 1000; neonatal mortality rate was 1.6 per 1000. At the 2-year visit, the children included in the INTERGROWTH-21st Fetal Growth Standards were at the 49th percentile for length, 50th percentile for head circumference, and 58th percentile for weight of the World Health Organization Child Growth Standards. Similar results were seen for the preterm subgroup that was included in the INTERGROWTH-21st Preterm Postnatal Growth Standards. The cohort overlapped between the 3rd and 97th percentiles of the World Health Organization motor development milestones. We estimated that the variance among study sites explains only 5.5% of the total variability in the length of the children between birth and 2 years of age, although the variance among individuals within a study site explains 42.9% (ie, 8 times the amount explained by the variation among sites). An increase of 8.9 cm in adult height over mean parental height is estimated to occur in the cohort from low-middle income countries, provided that children continue to have adequate health, environmental, and nutritional conditions.

CONCLUSION: The cohort enrolled in the INTERGROWTH-21st standards remained healthy with adequate growth and motor development up to 2 years of age, which supports its appropriateness for the construction of international fetal and preterm postnatal growth standards.

Key words: development, INTERGROWTH-21st fetal growth standards, postnatal growth

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Although human growth, from cell to whole body, is recognized as a universal biologic process, some entrenched views persist regarding fetal growth, in particular that it should be compared with a site-specific rather than prescriptive population. This view is not held by the World Health Organization (WHO) or by the Centers for Disease Control & Prevention,[1,2] which recommend using international neonatal standards. Likewise, such standards have now been adopted to estimate the burden and consequences of babies being born small for gestational age in low- and middle-income countries.[3]

We have summarized the key statistical, physiologic, ethnic, and genetic evidence relating to this issue.[4,5] Practically, the debate focuses on whether it is correct to monitor fetal growth using 1 of the many site-specific charts available. Typically,

such charts are based on different populations for each fetal body structure and have been developed at hospital level.[4] These multiple, site-specific charts are references, not international standards that are used commonly in most other areas of biology and medicine.

This neglected aspect of obstetric practice means that clinical decisions are made based on reference charts that were derived from a wide range of different study populations. For example, a woman may have an early gestational age assessment with the use of a fetal crown-rump length chart based on a study of 80 women from Glasgow, Scotland,[6,7] followed by a clinical assessment with the use of a fundal height chart based on 313 women from Cardiff, Wales.[8] Fetal biometry values may then be compared with 1 of many local charts,[9] and, during the same ultrasound scan, estimated fetal weight may be determined from an equation based on 109 fetuses studied in Texas during the 1980s,[10,11] complemented by a recent chart from other US populations.[12]

If the woman requires further assessment, the umbilical Doppler measures are judged with the use of yet another reference population.[13] At birth, the anthropometric measures of the newborn infant could be evaluated with the use of a multiplicity of reference charts, all of which are totally unrelated to the fetal growth charts that were being used just a few weeks earlier.

The INTERGROWTH-21st Project aimed to resolve these issues by conducting studies of human growth and development that involved pregnant women who were enrolled at <14 weeks gestation specifically to monitor their fetuses, newborn infants, and children prospectively up to 2 years of age to generate a single set of international standards to make judgements on the growth of all humans.[14] The studies were based conceptually on the WHO prescriptive approach to constructing human growth standards.[15] The study populations across geographically delimited areas were selected because they had the recommended health, nutrition, and socioeconomic status that was required to construct international standards.[15]

Hence, the INTERGROWTH-21st Standards (from maternal weight gain, to pregnancy dating, fetal growth and estimated fetal weight, to brain structures, amniotic fluid volume, umbilical artery Doppler measures, and newborn body composition) are prescriptive because they are based on a cohort of "healthy" pregnancies and babies from the same geographically selected populations in which most of the health and nutritional needs of mothers were met and adequate antenatal care provided.

Nevertheless, the question always remains with studies that are focused on fetal growth as to how "healthy" were these children after birth and during childhood (ie, are they truly healthy?). We took this question seriously very early in the planning of the project and added a clinical and developmental follow-up evaluation[16-18] beyond the customary early neonatal period as a further criterion to support the assertion that INTERGROWTH-21st babies represent true standard populations.[19] The key milestone of 2 years of age was identified as a realistic and biologically relevant time point.[20]

Hence, we first compared the INTERGROWTH-21st Standards[4,21,22] with the WHO Child Growth Standards.[23] We demonstrated that, during the early neonatal period, the participants who were selected were appropriate and met the WHO prescriptive criteria for optimal growth.[15] We then extended, for the first time in this literature, the prescriptive evaluation by designing the Infant Follow-up Study of the INTERGROWTH-21st Project.

This study aimed to evaluate the growth, nutrition, morbidity, and motor development at 2 years of age of the infants who were included in the international fetal and preterm growth standards to reinforce their prescriptive nature against which fetuses and preterm infants worldwide can now be compared.

Materials and Methods

INTERGROWTH-21st was a multicenter, population-based project that was conducted between 2009 and 2016 in 8 locations: Pelotas, Brazil; Turin, Italy; Muscat, Oman; Oxford, UK; Seattle, WA; Shunyi County, Beijing, China; the central area of Nagpur, India, and the Parklands suburb of Nairobi, Kenya.[14,24]

The primary aim of the project was to study growth, health, nutrition, and neurodevelopment from <14 weeks gestation to 2 years of age.[14] In the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project,[21] we recruited women from these 8 populations who initiated antenatal care at <14 weeks gestation and who met the entry criteria of optimal health, nutrition, education, and socioeconomic status.[14]

Gestational age was estimated based on the date of the last menstrual period and corroborated by ultrasound measurement of crown-rump length at 9^{+0} to 13^{+6} weeks gestation with the use of a standard protocol. All fetuses in the Fetal Growth Longitudinal Study were eligible to contribute data to the construction of the international fetal growth standards; all infants who were born at <37 weeks gestation in the Fetal Growth Longitudinal Study were eligible to contribute data to the construction of the international Postnatal Growth Standards for Preterm Infants. At each postnatal visit, a record of any illnesses in the preceding months was noted in addition to anthropometric measurements and a developmental assessment.

Weight, length, and head circumference were obtained within 12 hours (and no >24 hours) of birth on the postnatal wards and at follow-up visits that were scheduled at 1 and 2 years of age (±1 month). Measurements were taken exclusively by the same teams who were trained and standardized at regular intervals for the INTERGROWTH-21st Project.[25]

All study sites used the same methods and equipment: electronic scales (Seca, Hangzhou, China) for weight (sensitivity of 10 g to 20 Kg); a specially designed Harpenden infantometer (Chasmors Ltd, London, UK) for recumbent length, and a metallic nonextendable tape (Chasmors Ltd) for head circumference.[26,27] Measurement procedures were standardized according to WHO recommendations.[28] During the