Customized growth charts: rationale, validation and clinical benefits

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Appropriate standards for the assessment of fetal growth and birthweight are central to good clinical care, and have become even more important with increasing evidence that growth-related adverse outcomes are potentially avoidable. Standards need to be evidence based and validated against pregnancy outcome and able to demonstrate utility and effectiveness. A review of proposals by the Intergrowth consortium to adopt their single international standard finds little support for the claim that the cases that it identifies as small are due to malnutrition or stunting, and substantial evidence that there is normal physiologic variation between different countries and ethnic groups. It is possible that the one-size-fits-all standard ends up fitting no one and could be harmful if implemented. An alternative is the concept of country-specific charts that can improve the association between abnormal growth and adverse outcome. However, such standards ignore individual physiologic variation that affects fetal growth, which exists in any heterogeneous population and exceeds intercountry differences. It is therefore more logical to adjust for the characteristics of each mother, taking her ethnic origin and her height, weight, and parity into account, and to set a growth and birthweight standard for each pregnancy against which actual growth can be assessed. A customized standard better reflects adverse pregnancy outcome at both ends of the fetal size spectrum and has increased clinicians' confidence in growth assessment, while providing reassurance when abnormal size merely represents physiologic variation. Rollout in the United Kingdom has proceeded as part of the comprehensive Growth Assessment Protocol (GAP), and has resulted in a steady increase in antenatal detection of babies who are at risk because of fetal growth restriction. This in turn has been accompanied by a year-on-year drop in stillbirth rates to their lowest ever levels in England. A global version of customized growth charts with over 100 ethnic origin categories is being launched in 2018, and will provide an individualized, yet universally applicable, standard for fetal growth.

Key words: birthweight, customized chart, fetal growth, GROW, LGA, maternal size, perinatal, SGA, stillbirth

Accurate standards for antenatal surveillance of fetal growth are essential for early recognition of the fetus who is at risk in an unfavorable intrauterine environment. Standards are also important after delivery, to assess the neonate's risk of immediate and long-term morbidity and for audit, benchmarking, and epidemiologic investigations.

One Size Does Not Fit All

A series of recent publications by the Intergrowth 21 project promote the use of a single universal standard for fetal growth and birthweight.[1-3] The data were derived from educated, affluent, clinically healthy women with adequate nutritional status in 8 countries. The authors call the standard "multiethnic" because it included different populations, with the implication that it is therefore suitable to be applied to multiple ethnic groups. The authors considered differences to be marginal and likely to be due to socioeconomic or other nonphysiologic factors and argued for the adoption of a single, prescriptive, universally applicable standard.

At the time of writing, there has still been no evidence presented to suggest that Intergrowth improves the identification of fetuses or neonates at an increased risk of adverse outcome. To the contrary, there is evidence of significant variation between different populations and individuals and mounting evidence against a one-size-fits-all approach: First, their "multiethnic" concept is challenged by studies that have shown substantial ethnic variation, even in selected low-risk populations, that support the notion that observed differences are physiologic, not pathologic. This evidence has included analyses of databases of birthweight[4-6] and prospective evaluation of growth curves in different ethnic groups in the National Institute of Child Health and Human Development fetal growth studies.[7]

Second, there is mounting evidence against the utility and safety of the Intergrowth standard by investigators who applied it to their own local population.[8-10] The concept of a universal standard has also been challenged from the perspective of developmental origins and fetal adaptive responses, because many biologic and cultural factors can influence fetal growth that should not be viewed as abnormal.[11]

The recently published World Health Organization (WHO) standard for fetal growth used similar methods to that of Intergrowth, selecting low-risk pregnancies from 10 countries.[12] They found differences in growth between countries and between individual maternal characteristics such as height, weight, and parity and concluded that

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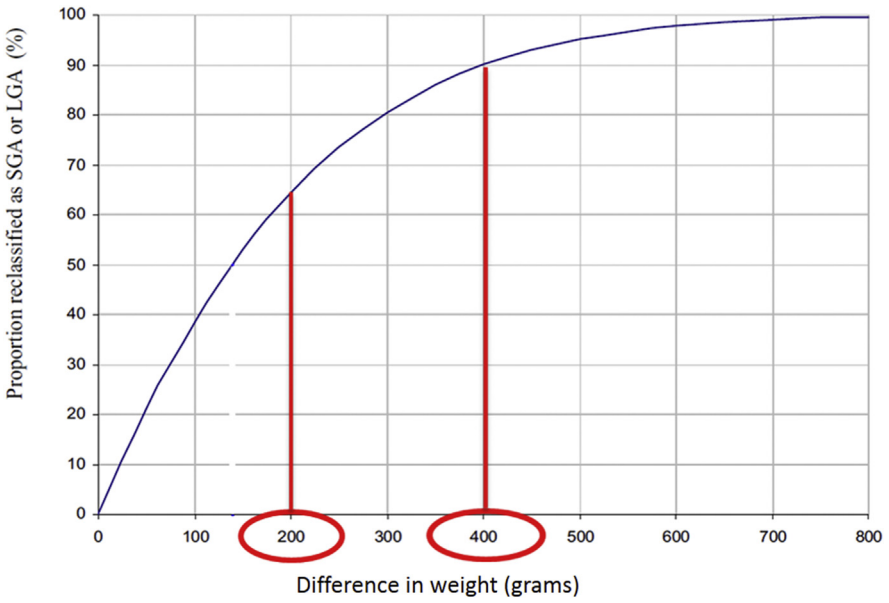
FIGURE 1
Effect of mean birthweight shift on SGA/LGA rate



Proportion of cases at SGA/AGA or AGA/LGA limit that need to be reclassified, in a population with a birthweight distribution with standard error 382.6 g, if average birthweight varies by 200 g (64% reclassified) and 400 g (90% reclassified), respectively (see examples in text). Adapted from Gardosi J, Francis A. A customized standard to assess fetal growth in a US population. Am J Obstet Gynecol 2009;201:25.e1-7.[28] With permission.

AGA, appropriate-for-gestational age; *LGA*, large-for-gestational-age; *SGA*, small-for-gestational-age.

Gardosi. Customized growth charts. Am J Obstet Gynecol 2018.

such variation needs to be taken into account.

Intergrowth's own tables showed intercountry differences, despite their selection of low-risk, well-nourished mothers. For example, in Table 1 in the article of Villar et al,[2] the term birthweight for mothers from Italy is 3.3 kg and from the United Kingdom 3.5 kg, which is a 200-g difference that is unlikely to be explained by variation in nutritional status or socioeconomic deprivation between 2 Western European countries. In any average term birthweight distribution, a shift by 200 g results in >60% of small-for-gestational-age (SGA) or large-for-gestational-age (LGA) cases being misclassified (Figure 1). For Indian mothers, the mean Intergrowth birthweight was 2.9 kg, which is 400 g less than the average for their whole population (3.3 Kg); a shift by 400 g would reclassify 90% of SGA or LGA cases (Figure 1).

A multinational study of 1.2 million term pregnancies by Francis et al,[13] published in this issue of *AJOG*, confirmed significant differences in mean birthweights and hence SGA rates between ten country cohorts using the Intergrowth birthweight standard, and showed that these were not due to pathological factors as represented by stillbirth rates; instead, the different SGA rates merely reflected physiological variation, throwing further doubt on the utility of Intergrowth as an international standard.

The potential adverse effect of applying the wrong standard in international comparisons becomes all too apparent in a recent publication in which the Intergrowth standard was applied to low and middle income country data from the Child Health Epidemiology Reference Group (CHERG).[14] They reported that 34% of births in India were SGA (<10th Intergrowth percentile) while only 5% and 6% were SGA in their Eastern Asia and Northern Africa populations, respectively. Such high SGA rates are unlikely to be explained by malnourished, stunted, or socioeconomically disadvantaged pregnancies in India; and the low SGA rates in Northern Africa are unlikely to be explained by anything other than that the standard is misleading. Applied at local level, such findings may result in unnecessary antenatal investigations and interventions, postnatal overfeeding to compensate for presumed growth restriction, parental anxiety, and the possibility that real SGA and its associated risk is ignored; conversely, in populations that are assigned a low SGA rate, the standard will put babies at risk because real SGA may be missed.

Defining the Growth Potential

Customized charts adjust for constitutional or physiologic variation and exclude pathologic factors that affect growth, thereby defining an optimized standard that represents the growth potential of each individual fetus.[15,16] As a result, they improve the prediction of birthweight in an uncomplicated pregnancy and improve the identification of abnormal growth.

An alternative method for defining fetal growth potential is the Deter—Rossavik model of Individualized Growth Assessment to specify expected third-trimester size trajectories and birth characteristics from second-trimester measurements of several anatomic parameters.[17] This approach seeks to address the problems that are inherent with a population standard by using each fetus as its own control. Analyses recently have been extended to a larger database of 119 longitudinally scanned pregnancies with normal neonatal outcomes,[18] but the model has not been applied widely in clinical settings. One conceptual concern[19] is that the fetus could already be affected by intrauterine growth restriction in the second trimester, which is known to increase the risk of adverse outcomes early[20] or late[21] in pregnancy. Use of measurements from such a fetus could project an individual curve that does not reflect the true growth potential and, by normalizing the pathologic factors, be less likely to allow identification of abnormal growth.

In the customized model, the variables for adjustment are derived from