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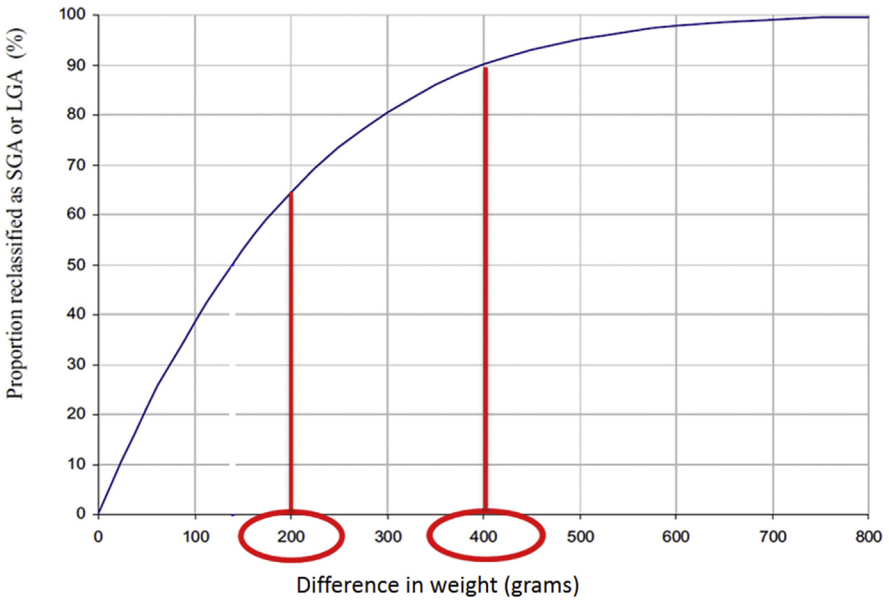
FIGURE 1
Effect of mean birthweight shift on SGA/LGA rate



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.

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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

birthweights of normally formed fetuses who were delivered at the end of uncomplicated pregnancies at term. The physiologic variables that significantly affect birthweight are consistent in many cohort studies and are quantified through multivariable analysis: fetal sex, maternal height, weight in early pregnancy, parity, and ethnic origin. Adjustment for maternal height and weight is made within normal body mass index (BMI) limits only.[16] Pathologic factors that are known at the beginning of pregnancy include hypertension, diabetes mellitus, smoking, and low and high BMI. Social deprivation may appear in the univariate analysis but does not tend to remain significant after adjustment for other factors, such as smoking and abnormal BMI.[22] The model adjusts for the physiologic but not pathologic variables, and results in a constant that represents an expected optimal birthweight at the end of an uncomplicated pregnancy.

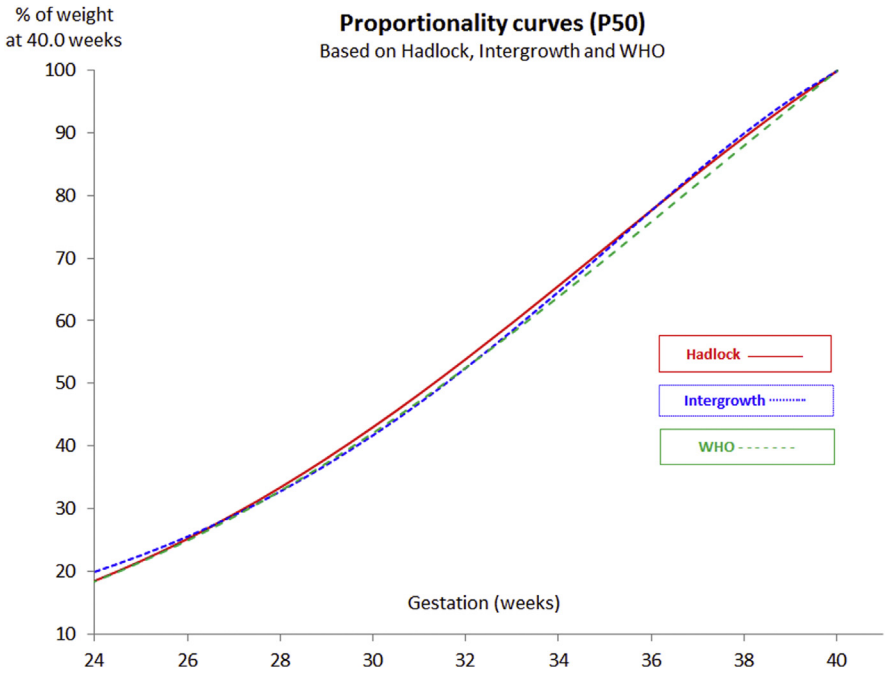
Sets of coefficients have now been derived from suitable databases from more than 25 countries and published for populations in the United Kingdom,[16] Sweden,[23] Australia,[24] New Zealand,[25] France,[26] Spain,[27] United States,[28] and Ireland,[29] with others in preparation. International comparisons have demonstrated remarkable between-country similarities in the growth potential that a baby of a standard mother can expect to reach at the end of an uncomplicated pregnancy. For example, a nulliparous mother of (Anglo-) European origin with a height of 163 cm and early pregnancy weight of 64 kg would, after an uncomplicated pregnancy, be expected to give birth to a baby who weighs 3453 g in the United States, 3456 g in the United Kingdom, 3464 g in Australia, and 3464 g in New Zealand.[28]

In practice, maternal characteristics are entered into a software program (GROW; Gestation Network; Birmingham, UK, www.gestation.net) to calculate an individually adjusted term optimal weight for 40.0 weeks (280 days) gestation. This predicted weight endpoint is then combined with a standard proportionality function[16] to provide a gestation-related optimal weight (GROW) curve. We used the standard Hadlock estimated fetal weight (EFW) curve[30] and converted it from a fetal weight-by-gestation curve to a percent of term weight-by-gestational age curve, with the Hadlock 40-week weight assigned 100%. This allows any term optimal weight to be substituted for 100%, thereby specifying the expected weight for gestational age trajectory (GROW curve) up to that predicted endpoint. We have since compared the proportionality curve based on Hadlock[30] with ones based on the 2 recently published EFW curves by Intergrowth[3] and WHO.[12] As Figure 2 shows, the results are remarkably similar, despite the fact that the underlying curves originate from different studies, and suggest that the proportionality method is a robust way to outline the growth trajectory to the term optimal weight.

The use of a fetal-, rather than a neonatal, weight-based standard helps to highlight the association between fetal growth restriction and preterm birth[16,31] because the standard is derived from normal term pregnancies; the prevalence of SGA in preterm babies tends to be hidden by the use of a neonatal curve that is derived from preterm birthweights that are abnormal by definition. The normal range around the GROW curve is derived from the standard error of the multiple regression model and the term optimal weight that together give a coefficient of variation (CV) of 11%; the 90th and 10th percentile limits are then reached by $\pm 1.28 \times CV$, or $\pm 14\%$ of the term optimal weight.[16]

It is worth noting that the use of term weight with a fetal weight-derived

FIGURE 2
Comparison of proportionality curves



Derived from Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology 1991;181:129-33; Stirnemann J, Villar J, Salomon LJ, et al. International estimated fetal weight standards of the INTERGROWTH-21st Project. Ultrasound Obstet Gynecol 2017;49:478-86; and Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization Fetal Growth Charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. PLOS Med 2017;14:e1002220, according to method described previously.[16]

WHO, World Health Organization.

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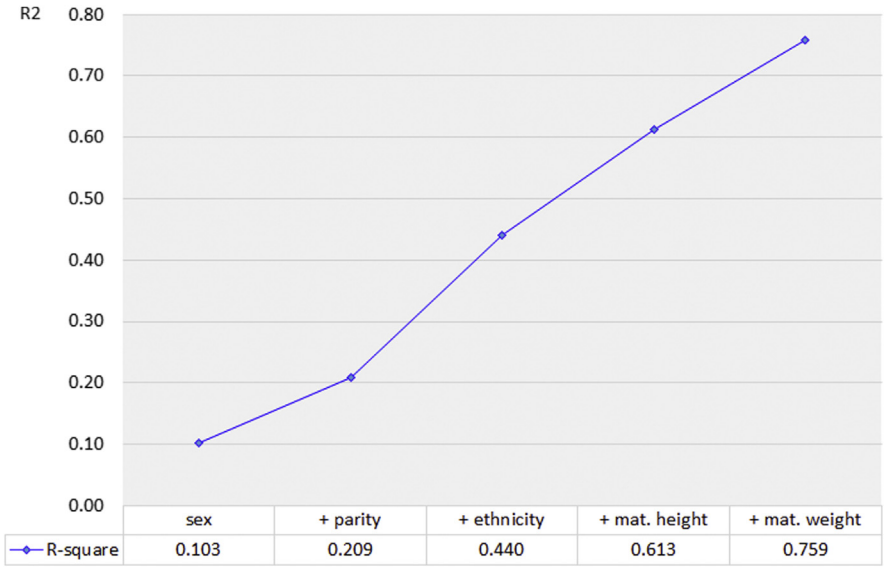
FIGURE 3
Birthweight prediction



R square of model, with gestational age-controlled residuals of birthweight within mid tertile of the distribution. Stepwise addition of variables (sex, parity, ethnicity, maternal height, maternal weight). Data source: West Midlands singleton births 2009-2013; n=131,570.

mat, maternal.

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proportionality function makes the GROW curve a standard that can be applied to assess fetal as well as neonatal weight.

Validation

One test of the customized method is to assess the correlation between predicted and actual birthweight in normal pregnancy, according to the number of physiologic variables entered. The multivariable regression provides an R^2 of the model; although this has been shown to increase by 50% when adjustment is made for maternal variables (from R^2=0.18 to 0.29),[32] the overall correlation is still poor. However, because the model is not designed to predict pathologic factors, but optimal weight free from pathology, it is more appropriate to assess the additional contribution of each physiologic variable within the mid tertile of the distribution, where most growth-related pathologic factors are likely to have been excluded.[33] This analysis shows that the R^2 value rises stepwise with each variable entered, to an R^2 of 0.76, which indicates that, together, these factors account for 76% of normal variation within this central part of the birthweight distribution (Figure 3).

More clinically relevant is the effect of adjustment of the standard on the cut-offs for LGA and SGA. The effect of customization at the LGA end has been examined by relatively few studies to date. Larkin et al,[34] Cha et al,[35] and Gonzalez et al,[36] who studied a cohort with diabetes mellitus, all found that the customized model identified previously unrecognized LGA populations who were at risk of intrapartum morbidity. Sjaarda et al[37] found hitherto unidentified pregnancies at risk because of LGA if the model was adjusted to exclude maternal weight. Constantine et al[38] compared fully customized with partially customized LGA that was adjusted for ethnicity and sex only and found both methods to be associated similarly with adverse outcomes; however, primary outcome cases (a composite of neonatal outcomes that are associated with fetal overgrowth and gestational diabetes mellitus) had a significantly higher average percentile and a 50% higher LGA rate (19.3% vs 13.2%) when the fully customized LGA standard was used.[38]

At the SGA end of the spectrum, a number of studies have shown that customized SGA was associated more closely with pathologic outcomes than various local or national standards.[23,39-44] Typically, customized assessment resulted in an additional group being identified as SGA, which was also associated significantly with increased perinatal mortality risk. A systematic review found that both customized and population-based SGA had higher rates of adverse outcomes, but the reported point estimates for customized SGA tended to be higher and, in the instance of fetal death, were more than double that for population-based SGA, albeit with overlapping 95% confidence intervals (95% CI): customized, 7.8 (95% CI, 4.2−12.3), vs population based, 3.3 (95% CI, 1.9−5.0).[45]

Application of the fetal weight−based proportionality curve in the optimality model, as explained earlier, results in more preterm babies being identified as SGA.[31,46,47] Hutcheon et al[48] suggested that this is the main advantage of the customized growth chart, and adjustment for individual variation had little additional effect. Using a Swedish dataset, they compared a customized model with the Hadlock curve adjusted for sex only and reported similar relative risks of SGA for stillbirth and neonatal death. However, this conclusion has been questioned on several grounds.[32,33] Although the authors claimed to use our original method for customizing percentiles, their model adjusted for maternal size only in wide categories rather than continuous variables, which would have blunted the effect. They also did not identify and exclude pathologic factors to allow customized percentiles to reflect the full growth potential. Even so, although relative risk values were similar, their comparative tables still suggest that 5−10% more deaths were identified by their modified customization method.

Carberry et al[49] looked at term birthweight in an Australian cohort and found no advantages in a customized

SGA over a locally derived population standard. The study has added interest because it assessed outcome through perinatal morbidity indices and neonatal body fat with the use of air displacement plethysmography. However, information on maternal and pregnancy characteristics for customization was based mostly on maternal recall. In a large database in Scotland, partial customization (maternal height and parity) was compared with an unspecified population standard at term,[50] and the investigators found that this model did not improve association of SGA with stillbirth and infant death. It is uncertain whether the results were affected by an absence of maternal weight and ethnicity variables or by the missing data on maternal height. Also, the analysis used the Net Reclassification Index, the statistical reliability of which has been questioned.[51]

Mikolajczyk et al[52] analyzed WHO Global Survey data from 24 low- and middle-income countries and compared the association between pregnancy outcomes and SGA defined by either the standard Hadlock fetal weight curve or the use of the proportionality fetal weight equation,[16] adjusted by country-specific average term birthweight, or stepwise increasing the adjustment up to a fully customized model including sex, maternal height and weight, and parity. The data posed challenges that included dating of pregnancies, and maternal weight was obtained mostly at the end of pregnancy or in labor. However, the investigators showed clearly that adjustment by country average weight was the main improvement over the single (Hadlock) weight standard and that additional adjustment, even for sex of the neonate, added no demonstrable advantages.

Analysis within Maternal Subgroups

It is possible therefore that, in fetuses who have survived to term, fetal growth deficit is more subtle and not marked enough to demonstrate differences in the cohort as a whole, even if the method is sound and all variables for customization are available. Instead, their benefits become apparent with analysis of the effect of customization on the constituent subgroups of any heterogeneous maternity population.

We undertook such analyses[32] in the same Swedish birth registry dataset as that referenced above,[23] applying customized and uncustomized standards with the same fetal weight–based proportionality curve. We first looked at parity and found customized SGA to be better aligned to perinatal mortality risk; the uncustomized standard showed an exaggerated SGA rate for nulliparous women that did not reflect a rise in mortality rate. Although first pregnancies can have more complications, such as preeclampsia and prolonged labor, increased clinical awareness and appropriate management should not have to rely on defining more babies as SGA if they are not, and can lead to unnecessary investigations and interventions.

In the same study,[32] we analyzed SGA rates in 4 BMI groups (<20, 20-25, 25-30, ≥30 kg/m^2). Perinatal mortality rates were directly proportional to BMI; SGA defined by customized percentiles also increased with BMI and was well-aligned with the perinatal mortality trend. In contrast, uncustomized SGA rates were statistically different from the mortality risk, being very high in thin mothers and low in obese mothers. This finding contradicts previously held assertions, which were based on data from the same Swedish register of births, that obesity was protective of SGA.[53] In fact, population-based percentiles obscure the fact that a baby may be relatively small compared with its growth potential. Application of the customized standard identifies that obese mothers have an increased risk of having a growth-restricted baby.[32,54]

We also looked at maternal size groups predefined according to height and weight, within a subgroup of pregnancies with normal BMI (20-25 kg/m^2; ie, symmetrically small and large mothers). Here, the perinatal mortality rate was similar for all groups, and customized SGA rates were correspondingly similar; but the population-based standard showed a high SGA rate for small mothers and a low SGA rate for large mothers and hence did not reflect the perinatal mortality trend.[32]

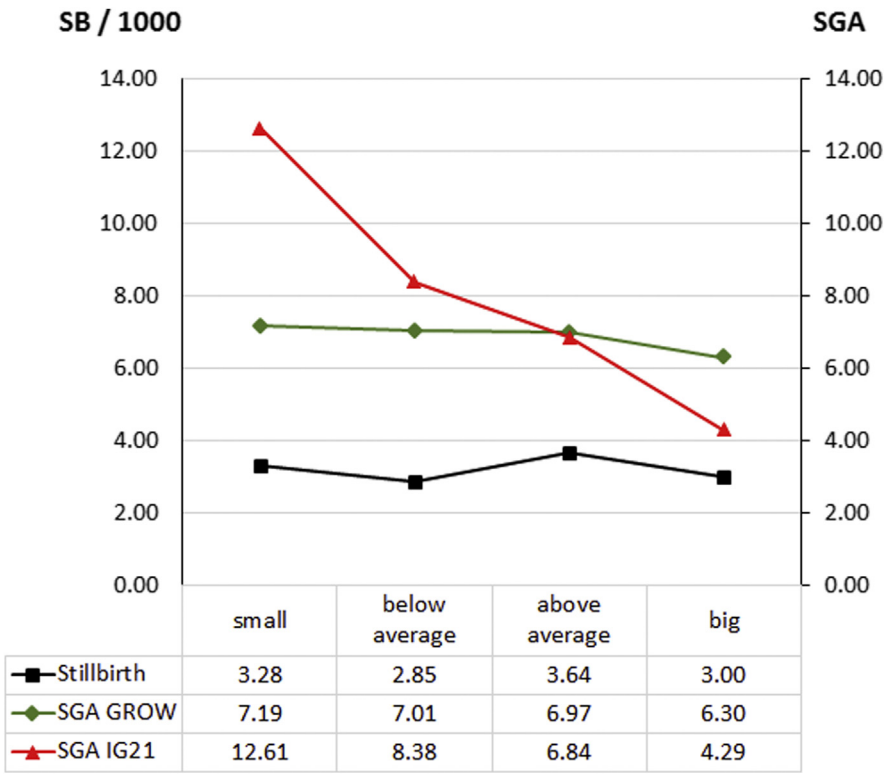
We repeated this assessment after the publication of the Intergrowth fetal weight standard,[3] applying it to a previously described English database[22] using stillbirth as the outcome. The results show again good alignment between maternal size groups and stillbirth risk when SGA was customized but not when the Intergrowth standard is applied (Figure 4). The clinical implication is that small mothers with normally small babies may be subjected to unnecessary investigations, interventions, and anxiety and that large mothers are reassured falsely when being assessed with the use of a one-size-fits-all chart that does not take individual variation into account.

Customized charts reduce false-positive diagnoses of SGA when ultrasound estimated fetal weight measurements are plotted on customized vs uncustomized fetal weight curves.[55] This becomes most apparent in our multiethnic population, a large proportion of which are of South Asian origin. It was a frequent clinical observation that scan measurements that were plotted on the prevalent Hadlock EFW chart[30] returned many SGA results. In our West Midlands database, 56% of these scans would not plot as SGA on the customized GROW chart. This group had the same risk for perinatal death as the non-SGA group (relative risk, 1.2; 95% CI, 0.5–3.0), which confirmed that an uncustomized standard applied in this subgroup results in the majority of cases identified as SGA are false positives.[56]

Clinical Application

The use of customized percentiles is recommended by the Royal College of Obstetricians and Gynaecologists Guidelines[57] for the assessment of birthweight and antenatal surveillance of fetal growth. Customized percentile calculators are freely available via the Gestation Network (www.gestation.net) that is administered by the Perinatal Institute and have been or are currently in use by over 300 clinicians and researchers in 30 countries. They can be applied in case-by-case assessment of neonatal weight or in spreadsheet format to analyze whole databases for audit or research. A global version of the GROW

FIGURE 4
Maternal size, small-for-gestational-age and stillbirth risk



	small	below average	above average	big
Stillbirth	3.28	2.85	3.64	3.00
SGA GROW	7.19	7.01	6.97	6.30
SGA IG21	12.61	8.38	6.84	4.29

Stillbirth rate and smallness for gestational age according to Intergrowth-21st and GROW standards equalized for <10th percentile cases by Intergrowth =7.7%. Data source: West Midlands database 2009-2013; singleton, normally formed, n=62,652. Maternal size groups defined in 4 weight and corresponding height ranges to remain within body mass index range of 20-25 kg/m^2: (1) *small*: weight, <57 kg; height, 148–167 cm; (2) *below average*: weight, 57.0–60.3 kg; height, 153–171 cm; (3) *above average*: weight, 60.3–65.0 kg; height, 157–174 cm; (4) *big*: weight, ≥65.0 kg; height, 161–180 cm.

BMI, body mass index; *GROW*, gestation-related optimal weight; *IG21*, Intergrowth21; *SGA*, small for gestational age.

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percentile calculator was recently released and includes coefficients for over 100 ethnic or country of origin groups.

For antenatal surveillance, customized GROW charts are produced at the beginning of pregnancy, once the expected date of delivery is confirmed by the ultrasound dating scan. The chart is either printed out at the beginning of pregnancy or can be displayed electronically, either as a stand-alone GROW application or integrated with the hospital's maternity information system. It displays the calendar dates for each week of gestation on the X axis and has 2 Y axes for plotting fundal height measurement in centimeters and for EFW in grams. Individual parameters (head circumference, abdominal circumference, femur length) are not plotted because (1) there are no validated coefficients for individual adjustment or customization, (2) EFWs are more meaningful for the mother and clinician in the assessment of small as well as large babies, and (3) accuracy of EFW and antenatal identification of SGA and LGA can be audited through birthweight as a gold standard, whereas no such standards exist for individual ultrasound measurement. Although abdominal circumference is the main component in determining EFW, the latter has been shown to be able to detect additional at-risk cases compared with abdominal circumference alone.[58] Serial EFW measurement has also been found to be as good as or better than serial abdominal circumference in the prediction of adverse outcome.[59]

GROW charts provide not only the optimal predicted birthweight endpoint for that pregnancy but also the slope of the normal growth curve that will lead to this point, together with upper and lower limits that can be set at 90th and 10th or 95th and 5th percentiles. The weight of the fetus at any point in the third trimester can be assessed within the customized limits for that pregnancy. In pregnancies with suspected SGA and normal umbilical artery Doppler, customized assessment of fetal size was a better predictor of adverse outcome than growth velocity.[60] Yet, serial measurements are also important and can be evaluated with reference to the predicted customized slope of the GROW curve. The measurements may be within normal limits; however, if the trajectory is slower than that predicted, action in terms of further investigations or expedited delivery has to be considered.[61]

Currently, the slope of the curve is assessed visually, but the application is moving towards digital quantification. The concept of a fetus' growth trajectory 'crossing percentile lines' is insufficient because it ignores the time element (ie, the period over which the growth deficit has extended). In a serially scanned cohort of Dutch primiparous women, fetal weight gain was significantly slower in pregnancies that required admission to the neonatal intensive care unit (20 g/d) than if the pregnancy was uncomplicated (24 g/d).[62] In time, there will be more information on antenatal growth velocity and outcome on which to base recommendations, and the next version of GROW will link growth trajectories that are adjusted for each pregnancy with action prompts and decision support.

GROW charts are provided as part of the Growth Assessment Protocol (GAP), a comprehensive program that includes hands-on and remote training supported by e-learning, competency

assessment, and evidence-based protocol templates for local adaptation. In the United Kingdom, GAP has been implemented in just under 80% of hospitals (www.perinatal.org.uk/gap-uptake.aspx), generating customized charts for >600,000 pregnancies each year. In the Netherlands, the Royal Midwifery Association has licensed a Dutch version of GROW for their membership, and New Zealand has recently commenced a Maternal Fetal Medicine Network and health ministry recommended national roll-out. Individual clinicians and institutions in a number of countries have also commenced implementation.

Antenatal Detection of SGA

Although there has been progress with biomarkers and uterine artery Doppler to screen for preeclampsia and early onset intrauterine growth restriction (IUGR), the majority of growth restriction is late in onset, with the growth of the fetus outstripping placental function and reserve, the prediction of which has been poor.[61] Therefore, the emphasis has to be on surveillance and on raising awareness of the importance of fetal risk caused by IUGR. A fetus that is SGA by customized percentiles has a 7-fold increased risk of intrauterine death.[22]

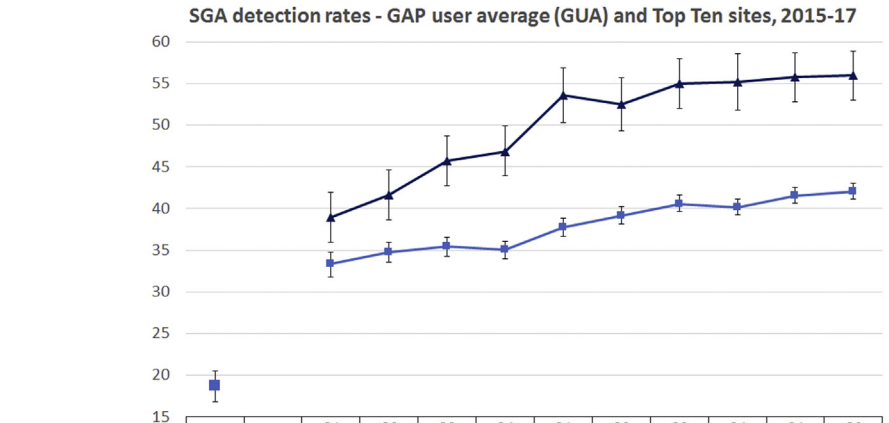
Surveillance protocols are based on early pregnancy risk assessment, with algorithms that identify 36% of our population as being at significantly increased risk of SGA and stillbirth.[63] This leads to 2 main care pathways: (1) low risk, which in health systems with well-established midwifery services is monitored with serial fundal height measurements, and (2) increased risk, which requires serial ultrasound scans throughout the third trimester. A controlled study has shown that training in standardized fundal height measurement and plotting on customized charts significantly increased antenatal detection of SGA and LGA fetuses while reducing false-positive diagnoses.[64] Detection of SGA in high-risk pregnancies is proportional to the number of third-trimester scans, which are usually performed only 2−3 times and only up to 34−36 weeks gestation, because of chronic shortages in ultrasound resources in the National Health Service (NHS).[65] In a nonresearch environment, a routine or indicated scan at 36 weeks gestation has only a 36% chance to predict SGA birthweight,[66] which is likely to be due to the fact that most customized i.e. nonconstitutional SGA at term is due to late onset IUGR.

Antenatal detection of SGA has been established as an auditable key performance indicator and is facilitated by the GROW application. Trained staff enter details of the outcome of pregnancy, and the software then calculates the customized birthweight percentile and referral, detection and false positive rates. The results are available through automated local reports and provide benchmarking and trend analysis. The audit is not mandated, but its uptake has increased steadily because clinicians and managers realize the advantages of monitoring service improvements.

Maternity units are required to undertake a baseline audit before implementation of GAP and are often surprised how low their detection rates are, averaging 18.7% (95% CI, 16.8−20.5), which in fact is similar to historic published reports of 15−16% in low-risk populations.[67,68] Figure 5 shows, against this baseline, the quarterly trend in detection rates for the last 2 years in units that have established routine postnatal audit. There was a gradual, overall rise to 42.0% (95% CI, 41.1−43.0), which represents a 2.5-fold increase from baseline, and a more pronounced improvement to 56.0% (95% CI, 53.0−58.9) for the top 10 performing units. These centers can be characterized as most engaged with the protocol, training, and audit program, which highlights that performance is effort related.

Software is also available to undertake missed case audit, which facilitates more focused and structured investigations into reasons that newborn SGA cases are missed, such as a lack of referral, poor scan quality, or system issues such as shortages in ultrasound services or a lack of up-to-date protocols for surveillance or management. A limitation of such routine audits is that it cannot evaluate instances of growth restriction that occur without the fetus falling below the SGA cut-off limit.

FIGURE 5
Detection of small for gestational age



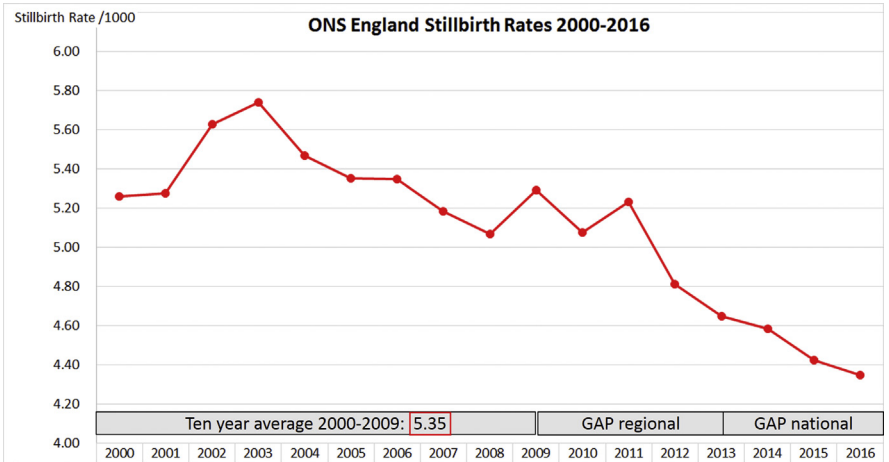
	Baseline		Q1 2015/16	Q2 2015/16	Q3 2015/16	Q4 2015/16	Q1 2016/17	Q2 2016/17	Q3 2016/17	Q4 2016/17	Q1 2017/18	Q2 2017/18
GUA Detection Rate	18.7		33.3	34.8	35.5	35.0	37.8	39.2	40.6	40.2	41.6	42.0
Top Ten Detection Rate			38.9	41.6	45.7	46.9	53.6	52.5	55.0	55.2	55.8	56.0
Cases - GAP User Average	13,844		27,414	43,406	53,233	56,393	65,455	73,360	74,774	77,507	83,388	92,112
Cases - Top Ten Average			7,535	7,876	8,806	8,927	8,174	11,200	11,424	10,844	12,884	8,388

Trend of antenatal detection rate of newborn infants with SGA birthweight (<10th customized percentile). Baseline rates, GAP user average, and average for top ten performing units are shown.

GAP, Growth Assessment Protocol; *GUA*, GAP user average; *SGA*, small for gestational age.

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

FIGURE 6
Trend in stillbirth rates in England



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
England	5.26	5.28	5.63	5.74	5.47	5.35	5.35	5.18	5.07	5.29	5.08	5.23	4.81	4.65	4.59	4.42	4.35
Upper CI	5.45	5.47	5.82	5.93	5.66	5.54	5.53	5.36	5.24	5.47	5.25	5.40	4.98	4.81	4.75	4.59	4.51
Lower CI	5.08	5.09	5.44	5.55	5.29	5.17	5.17	5.01	4.90	5.12	4.91	5.06	4.65	4.49	4.43	4.27	4.19

Stillbirth rates (per 1000) in England: ONS.[75] The rate remained similar over a 10-year period (2000, 5.26; 2009, 5.29) and averaged 5.35; the fall to 4.35 by 2016 following the implementation of the GAP program represented a 19% drop ($P<.01$).

CI, confidence interval; *GAP*, Growth Assessment Protocol; *ONS*, Office of National Statistics.

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

Reducing Avoidable Stillbirths

The effect of any composite intervention is difficult to assess as perinatal death, and other 'hard' outcome measures are relatively rare. Randomized trials, usually the gold standard, are not very feasible, (1) because of the large numbers required to have sufficient power, (2) because the relative simplicity of a randomized, controlled trial design is challenged by the large learning component, competency assessment, and need to raise overall awareness; and (3) randomized assessment, individually or in clusters, requires clinical equipoise that cannot be guaranteed if a method is already recommended on the basis of observational evidence and clinical guidelines, such as those in place from the Royal College of Obstetricians and Gynaecologists.[57]

The relevant model therefore is "evaluation in practice," which is a rigorous before-and-after assessment of the impact of wide-ranging implementation, as was undertaken in the successful "back to sleep" campaign for sudden unexplained deaths in infancy[69] and which was never investigated by a randomized, controlled trial. Stillbirth rates are a suitable measure of the effects of such a program. Nine-tenths of fetal deaths occur antenatally, and one-half of all normally formed stillbirths (counted in the United Kingdom from 24 weeks gestation) are SGA, even after adjustment for delay between fetal death and assessment of weight at delivery,[70,71] although an additional unknown number are IUGR without being SGA. Traditionally, two-thirds of stillbirths used to be categorized as "unexplained" and, by implication, unavoidable; however, a new classification of 'relevant conditions' rather than 'causes' and inclusion of a category of SGA defined by customized percentiles found that the majority of such unexplained deaths were in fact SGA and, by implication, IUGR.[71] Confidential case reviews by independent panels have furthermore shown that, at least two-thirds of SGA deaths are associated with substandard care.[72] Such findings helped to prioritize stillbirth as a potentially avoidable outcome; they also led to better explanations given to grieving parents who were trying to come to terms with their loss and assisted clinicians in planning subsequent pregnancies and to improve antenatal services overall.

Customized charts are considered a central component of this program, because they give clinicians more confidence when assessing whether the situation is reassuring or calls for action. Fetal weights that plot as SGA or are on a slow trajectory on customized growth curves are less likely to be considered constitutionally small, and management recommendations in national guidelines[57] are further encouragement to adopt a proactive clinical approach.

According to the aforementioned observations, it is estimated that up to two-thirds of normally formed stillbirths are SGA or IUGR and that two-thirds of these are considered to have had substandard care that was likely to have caused or contributed to fetal death; this would make >40% of stillbirths potentially avoidable. Therefore, in health systems where one-half of pregnancies with SGA or IUGR are identified antenatally, a 20% reduction in stillbirth rates should be achievable with increased awareness, education, and the appropriate evidence-based protocols.

The Growth Assessment Protocol (GAP)

GAP was commenced in the West Midlands, a health region with one of the highest perinatal mortality rates in the United Kingdom. Its implementation led to the first ever drop in stillbirth rates to below the national average, and further analysis found that this reduction was confined to pregnancies with SGA/IUGR.[73] Subsequently, implementation extended to 2 additional health regions, which together demonstrated a significant reduction in stillbirth rates, while they remained the same in regions that did not take up GAP.[74] Although this was an evaluation in practice rather than a trial, examination of Bradford Hill causality criteria confirmed that the reduction in stillbirths was attributable to the implementation of GAP.[74]

Since then, there has been a national roll-out of the program and, to date, includes almost 80% of all Hospital

Trusts and Health Boards across the United Kingdom. GAP has led to a year-on-year reduction in stillbirth rates (per thousand) in England to 4.35 by 2016[75], their lowest ever level, which represents a 19% drop from the preceding 10-year average (2000−2009) of 5.35 (Figure 6). Scotland also implemented GAP in 12 (86%) of its 14 Health Boards as part of a nationally commissioned program, while also benefitting from an ongoing national maternity quality improvement program; its own 10-year (2000−2009) average stillbirth rate of 5.41 dropped similarly by 20% to 4.31 by 2016.[76]

Ongoing work includes the development and provision of electronic tools to facilitate routine audit, risk assessment, auto-plotting of measurements, and decision support, which prompt evidence-based referral protocols and management pathways. Hitherto country specific, the global version of customized antenatal GROW charts with over 100 ethnic/country of origin categories will be launched in 2018 to provide an individualized, yet universally applicable, standard for fetal growth. ■

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