**International Estimated Fetal Weight Standards of the INTERGROWTH-21st Project**

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**ABSTRACT**

**Background:** Estimated fetal weight (EFW) and fetal biometry are complementary measures to screen for fetal growth disturbances. Our aim was to provide international EFW standards to complement the INTERGROWTH-21st Fetal Growth Standards that are available for use worldwide.

**Methods:** Women with an accurate gestational age assessment, who were enrolled in the prospective, international, multicentre, population-based, Fetal Growth Longitudinal Growth Study (FGLS) and INTERBIO-21st Fetal Study (FS), two of the components of the INTERGROWTH-21st Project, had ultrasound scans every 5 weeks from 9-14 weeks until 40 weeks’ gestation. At each visit, blinded measurements of fetal head circumference (HC), biparietal diameter, occipitofrontal diameter, abdominal circumference (AC) and femur length were obtained using standardised methods, identical ultrasound machines and dedicated research sonographers. Birthweight measurements were taken within 12 h of birth using standardised methods, identical electronic scales and dedicated research anthropometrists. We selected live babies, without any congenital abnormalities, born within 14 days of their last ultrasound scan. As most births occurred around 40 weeks’ gestation, we constructed a bootstrap model selection and estimation procedure based on resampling of the complete dataset under an approximately uniform distribution of birthweight, thus enriching the sample size at extremes of fetal sizes, to achieve consistent estimation across the full range of fetal weight. We then constructed reference centiles using second-degree fractional polynomial models.

**Findings:** Of the overall population,2,404 babies were born within 14 days of their last ultrasound scan. The mean time between the last scan and birth was 7.7 days (range 0–14) and was uniformly distributed. Birthweight was best estimated as a function of AC and HC (without FL):

log(EFW) = 5.084820 – 54.06633×(AC/100)3 – 95.80076×(AC/100)3×log(AC/100) + 3.136370 ×(HC/100),

All other measures, gestational age, symphysis-fundal height, amniotic fluid indices and interactions between biometric measures and gestational age were not retained in the selection process because they did not improve EFW prediction. Applying the formula to FGLS biometric data (n=4,231), enabled gestational age-specific EFW to be constructed.

At term, the EFW centiles match those of the INTERGROWTH-21st Newborn Size Standards but, at less than 37 weeks’ gestation, the EFW centiles were, as expected, higher than those of babies born preterm. Comparing EFW cross-sectional values to the INTERGROWTH-21st Preterm Postnatal Growth Standards confirms that preterm postnatal growth is a different biological process to intrauterine growth.

**Interpretation:** We provide an assessment of EFW as an adjunct to routine ultrasound biometry from 22 to 40 weeks’ gestation. However, we strongly encourage clinicians to evaluate fetal growth using separate biometric measures such as HC and AC, as well as EFW, so as to avoid the minimalist approach of focusing on a single value.

**INTRODUCTION**

One of the main objectives of antenatal care is screening for fetal growth disturbances 1. Although biomarkers in maternal blood have shown some potential for detecting fetal growth restriction 2,3, a recent systematic review suggested that none is sufficiently accurate to be recommended for use in clinical practice 4. This means that clinicians still rely routinely on clinical markers, including ultrasound measures, to identify fetuses at risk 5.

Ultrasound evaluation of the fetus involves measuring head circumference (HC), abdominal circumference (AC) and femur length (FL) and the values can be combined to calculate an estimated fetal weight (EFW); this estimate is often used alone in clinical practice without considering the individual measures. However, we believe that arguments about the most appropriate single measure to use are inappropriate because clinicians should use all the tools available in their armamentarium for making crucial clinical decisions that have major implications for both mothers and newborns.

The development of international EFW standards is overdue, and these should share the same conceptual basis as the published INTERGROWTH-21st standards for HC, AC and FL 6, size at birth 7, and postnatal growth in preterm infants 8,9. These standards perfectly complement the WHO Child Growth Standards 10, thereby enabling continuity of assessment of human growth from early pregnancy to childhood 11. Therefore, the objectives of this component of the INTERGROWTH-21st Project were: 1) to develop a formula to estimate fetal weight based on ultrasound biometry and birthweight and 2) to construct international EFW standards between 22 and 40 weeks’ gestation.

**MATERIAL AND METHODS**

INTERGROWTH-21st is an international, multicentre, population-based project consisting of a number of components, including the Fetal Growth Longitudinal Study (FGLS) and INTERBIO-21st Fetal Study (FS).

FGLS was conducted between April 27, 2009, and March 2, 2014, in eight urban areas: the cities of Pelotas (Brazil), Turin (Italy), Muscat (Oman), Oxford (UK), and Seattle (USA); Shunyi County, Beijing (China); the central area of Nagpur (India), and the Parklands suburb of Nairobi (Kenya). The primary aim was to study, longitudinally, the health and development of fetuses into infancy, by monitoring growth, health, nutrition and neurodevelopment from less than 14 weeks’ gestation to 2 years of age, so as to produce prescriptive growth standards to complement the existing WHO Child Growth Standards. This was achieved by studying a cohort of healthy, well-nourished, pregnant women who were at low risk of adverse maternal and perinatal outcomes at both population and individual levels. The study details have been described elsewhere 9,12.

In contrast, FS recruited an unselected cohort of pregnant women, between February 8, 2012, and December 24, 2015, from three FGLS sites (Pelotas, Brazil; Nairobi, Kenya; Oxford, UK), and three new sites (Aga Khan University Hospital Karachi, Pakistan; Shoklo Malaria Research Unit, Mae Sot, Thailand; and Baragwanath Hospital, Soweto, South Africa). The primary aim was to study the effects of various intrauterine exposures (e.g. malnutrition, anaemia, HIV, malaria) on growth, health, nutrition, neurodevelopment and the epigenome, similarly from less than 14 weeks’ gestation to 2 years of age.

To develop the EFW formula requires as many pregnancies as possible that have a standardised scan and birthweight. In order to achieve this we included fetuses from both FGLS and FS; only those that had an ultrasound scan within 14 days of birth were included in the calculations. To develop the international standards for EFW, the formula derived was then applied on the healthy FGLS population from which the International Fetal Growth Standards were produced 6.

The INTERGROWTH-21st Project was approved by the Oxfordshire Research Ethics Committee “C” (reference: 08/H0606/139), the research ethics committees of the individual participating institutions, and the corresponding regional health authorities where the project was implemented. Participants provided written consent to be involved in the study.

**Procedures**

In both studies, women were recruited at less than 14 weeks’ gestation. All women underwent ultrasound measurement of crown–rump length (CRL) using standardised methodology13,14. In FGLS, gestational age was based on the date of the last menstrual period (LMP) provided it was certain; the woman had a regular 24–32 day menstrual cycle; she had not been using hormonal contraception or breastfeeding in the preceding 2 months, and any discrepancy between the gestational ages based on LMP and CRL, between 9 weeks and 0 days and 13 weeks and 6 days, was 7 days or less. In FS, gestational age was determined by CRL measurement alone, using the same formula loaded onto all study ultrasound machines15; if known, the LMP was recorded.

Following the dating scan, women were scanned every 5 weeks (within 1 week either side), so that the possible ranges were 14–18, 19–23, 24–28, 29–33, 34–38, and 39–42 weeks’ gestation. At each visit, fetal HC, biparietal diameter (BPD), occipitofrontal diameter (OFD), AC and FL were measured three times from three separately obtained ultrasound images of each structure. The detailed measurement protocols, including graphical displays of measurement techniques, and the unique standardisation procedures for all measurements and sonographer training have been reported elsewhere 13,16. In addition, all documentation, protocols, quality control procedures, data collection forms, and electronic transfer strategies are freely available on the INTERGROWTH-21st website.

Briefly, head measurements were taken in an axial view at the level of the thalami, with an angle of insonation as close as possible to 90°. The head had to be oval in shape, symmetrical, centrally positioned, and filling at least 30% of the monitor. The midline echo (representing the falx cerebri) had to be broken anteriorly, at a third of its length, by the cavum septi pellucidi. The thalami had to be located symmetrically on either side of the midline. Callipers were then placed on the outer border of the parietal bones (outer to outer) at the widest or longest part of the skull for the BPD and OFD, respectively; the HC was measured using the ellipse facility on the outer border of the skull.

The AC measurements were taken in a cross-sectional view of the fetal abdomen as close as possible to circular, with the umbilical vein in the anterior third (at the level of the portal sinus), with the stomach bubble visible. The sonographer was instructed to avoid applying too much pressure with the transducer, which can distort the circular shape of the fetal abdomen. The abdomen had to fill at least 30% of the monitor screen, preferably, and the spine had to be at either a 3 o’clock or 9 o’clock position to avoid internal shadowing; the kidneys and bladder had not to be visible. For the measurements, the contour of the ellipse was placed on the outer border of the abdomen.

Finally, the FL was measured using a longitudinal view of the fetal thigh closest to the probe and with the femur as close as possible to the horizontal plane. The angle of insonation of the ultrasound beam was about 90°, with the full length of the bone visualized, unobscured by shadowing from adjacent bony parts, and the femur had to fill at least 30% of the monitor screen. The intersection of the callipers was placed on the outer borders of the edges of the femoral diaphysis (outer to outer) ensuring clear femoral edges; ultrasound artefacts of the femoral edges such as the proximal trochanter or pointed femoral spurs were not included in the measurement (detailed methods and a graphical display of how the bone structures are localized are available on the INTERGROWTH-21st website).

The same ultrasound machine was used at all sites (Philips HD-9 [Philips Ultrasound, Bothell, WA, USA] with curvilinear abdominal transducers C5-2, C6-3, V7-3). To avoid expected value bias, the machine was adapted so that fetal measurements were not visible on the screen to the sonographer. Only after three measurements of each structure were recorded were the average values revealed for clinical purposes. All ultrasound data were submitted electronically to the study database. Data were entered locally directly onto the web-based system 17.

After each set of measurements, sonographers scored the quality of their images on the basis of standard image-scoring criteria 18,19. Images that did not score the maximum amount of points were repeated until the best possible score was achieved. The quality control methods used across all sites are described in detail elsewhere 18,20.

Birthweight was measured within 12 h of birth using identical electronic scales (Seca, Hangzhou, China) at all sites. The equipment, which was calibrated twice a week, was selected for accuracy, precision and robustness, as shown in previous studies 21. Measurement procedures were standardised on the basis of WHO recommendations to ensure maximum validity 22 and each measurement was collected independently by two study anthropometrists 23. If the difference between the two measurements exceeded the maximum allowable difference of 5 g, then both observers independently retook that measurement a second and, if necessary, a third time. The training, standardisation, monitoring processes, and quality control methods used across all sites are described in detail elsewhere 22,23.

**Statistical analysis**

*Estimation of fetal weight:*

From the FGLS and FS cohorts we identified all live babies, without any congenital abnormalities, born greater than 24 weeks’ gestation and within 14 days of the last ultrasound scan. Given the study design, we expected the births to have occurred uniformly between 0 and 14 days following the last ultrasound scan, i.e. a mean time of 7-8 days between last scan and birth. This cut-off provided allowed a greater number of births at low gestational ages to be included, where most of the existing formulae have been prone to prediction error, likely because scarce data exist for estimation 24. Potential predictors for birthweight were:

* HC, BPD, OFD, AC and FL, in cm or transformed into Z-scores using the INTERGROWTH-21st equations 6;
* Gestational age on the day of the last scan, in weeks;
* Symphysis-fundal height, in cm;
* Amniotic fluid, assessed by the deepest vertical pool and amniotic fluid index in cm;
* The cross sectional head area (HA) and abdominal area (AA) computed from their orthogonal diameters, in cm2.

We hypothesized that the contribution of any given anthropometric measurement to EFW might vary with gestational age. Therefore, we also considered interactions between HC, BPD, OFD, AC and FL and gestational age on the day of the last scan. Statistical modelling was conducted using second-degree fractional polynomials 25.

Some prediction bias would be expected because of significant growth between the day of the last scan and birth 24,26,27. We addressed this issue by calculating the expected EFW on the day of ultrasound, using the following steps:

(1) In pregnancies from FGLS and FS delivering within 14 days following the last scan, we developed a model to predict birthweight from the most recent ultrasound measurements;

(2) In the complete FGLS dataset we calculated EFW from ultrasound biometry using the previous model. We then fitted a 2nd degree fractional polynomial for mean weight as a function of gestational age between 22 and 40 weeks;

(3) Returning to the dataset of births within 14 days (step (1)), we calculated, for each fetus, the expected weight at the time of the last scan by subtracting the average weight gain between the time of the last scan and birth using the model built in step (2);

(4) This calculated weight was then used for further modelling.

As expected, owing to the prospective, population-based design of FGLS, most births occurred close to 40 weeks’ gestation, meaning that the scatter of observations across the 22-40 week window was very uneven. We were aware that estimation using the complete data would yield very accurate estimates at 40 weeks’ gestation, where the greatest contribution of the data is found but with limited model validity for lower birthweights. To overcome this problem and allow accurate birthweight estimation over the whole range of observed data, we constructed a bootstrap model selection and estimation procedure based on resampling of the complete dataset under an approximately uniform distribution of birthweight 28–30, i.e. birthweight was divided into 500g strata and each sample was built by randomly selecting five observations with replacement from each stratum. In a first resampling run of 100 samples, candidate models – which include three elements: the variables, the coefficients and respective fractional polynomial powers - were elicited using the backward elimination algorithm described by Ambler and Royston 31, which provides protection against over-fitting. In a second step, the coefficients of all candidate models were estimated in B=1,000 bootstrap samples: in each sample, a single model was selected using Akaike’s Information Criterion (AIC). Candidate models were then ordered by their frequency of selection within the 1,000 samples and the five most frequent models were kept for further assessment of goodness of fit.

Assessment of goodness of fit in the complete dataset relied on inspection of residuals with quantile-quantile plots and residuals versus fitted plots. Given that we estimated fetal weight at the time of the last scan using an average model for growth, we investigated the bias of our model for EFW by calculating the mean of percent prediction errors defined by:

100 x (EFW - Birthweight)/Birthweight

for decreasing time-to-birth intervals (i.e. from 14 to 0 days). Finally, we also calculated the absolute percent prediction error defined by the mean of the absolute prediction errors.

*Construction of reference centiles:*

The construction of reference centiles was based solely on FGLS data. The sample size was based on pragmatic and statistical considerations; the latter focused on the precision and accuracy of one extreme centile, i.e., the 3rd or 97th centile, and regression-based reference limits 32,33. We have shown that a sample of 4,000 women would obtain precision of 0.03 SD at the 3rd or 97th centile. Further details on the precision obtained at the 5th or 10th centiles by sample size (ranging from 500 to 6,000) were included in a table in a previous publication 34.

The data from all the study sites were pooled to construct the Fetal Growth Standards, using the same statistical approach adopted by WHO in constructing their Child Growth Standards 6,12. The statistical methods used were based on published recommendations 35,36 complemented by recent scientific reviews 5,37,38. Our overall aim was to produce centiles that change smoothly with age and maximize simplicity without compromising model fit.

We explored the following statistical methods: mean and SD method using fractional polynomials 25; Cole’s lambda (λ), mu (μ), and sigma (σ) (LMS) method 39–41, which estimates three age-specific parameters (the median [μ], coefficient of variation [σ], and a Box-Cox power transformation at each gestational age to remove skewness [λ], thereby making the data roughly normally distributed); the LMST 42 (lambda, mu, sigma, assuming Box-Cox t distribution) method, which assumes a shifted and scaled (truncated) t distribution to take account of skewness and leptokurtosis; the LMSP 43 (i.e., lambda, mu, sigma, assuming Box-Cox power exponential distribution) method, which assumes a Box-Cox power exponential distribution to take account of skewness, platykurtosis, and leptokurtosis. Furthermore, to present the curves, we assessed three smoothing techniques: fractional polynomials 25, cubic splines 44 and penalized splines 45.

Using de-trended quantile-quantile (q-q) plots (worm plots) 46, significant evidence of deviations from normality was seen so we resorted to using the more complex LMS, LMST and LMSP methods allowing for skewness and kurtosis.

As most of the women had 4-6 ultrasound scans, the effect of correlated data within fetuses was investigated. First, in a sensitivity analysis, a random observation time was sampled for each fetus and the modeled centiles in this subset were visually compared to the complete dataset. The approach is justified by the experimental design of the study that ensures non-informative observation times 47. This analysis showed minimal or no change in estimated centiles (median, 3rd and 97th centiles) over the whole 22-40 weeks’ gestation range. Second, we considered mixed effect models accounting for repeated measurements within LMS, LMST and LMSP frameworks. This analysis also showed no impact on the estimated centiles. The best fit was found using a 3-parameter Box-Cox Gaussian distribution (i.e. the LMS method) for the response variable with a second-degree fractional polynomial functional form for gestational age. This method also gives estimated SD of EFW, allowing estimation of centiles.

Goodness of fit for the overall model was done by comparing empirical centiles (calculated per completed week of gestation) to the fitted centiles, using de-trended q-q plots of the residuals across gestational age 46, and plots of residuals versus fitted values.

All analyses were carried out in R statistical software 48 using the Generalised Additive Models for Location, Scale and Shape (GAMLSS) framework 49–51.

**RESULTS**

To create an EFW formula, the subsets of 2,404 babies in FGLS (N=1556) and FS (N=848), born within 14 days of their last ultrasound scan, were examined: 130 (5.4%) were born preterm (<37 weeks’ gestation) and 78 (3.2%) term low birthweight (<2,500g and ≥37 weeks’ gestation). The mean time between the last ultrasound scan and birth was 7.7 (range 0–14) days and was uniformly distributed, except for 0 days (i.e. birth on the day of the last scan), which occurred in only 34 (1.4%) cases (Table 1).

Following correction for potential growth between the last scan and birth (steps 1 – 4 in the statistical methods), the actual fetal weight at the time of the last scan was best estimated as a function of AC and HC with the following model:

log(EFW) = 5.084820 – 54.06633×(AC/100)3 – 95.80076×(AC/100)3×log(AC/100) + 3.136370 ×(HC/100)

where EFW is expressed in g, AC and HC in cm, and the log function designates the natural logarithm.

None of the other covariates including FL, BPD, OFD, gestational age, symphysis-fundal height, amniotic fluid indices or interactions between biometric measurements and gestational age were retained in the selection process. This model suggests a linear relationship between log(EFW) and HC. Despite the negative coefficients, the two terms involving AC describe an increasing sigmoid-shaped relationship between AC and birthweight (Figure A.1, Appendix) for a fixed HC value of 26 cm (the average value at 28 weeks’ gestation6). The relationship between birthweight and HC is plotted in Figure A.2 (Appendix) for a fixed AC value of 23 cm (the average at 28 weeks’ gestation 6).

The performance of the model for EFW was assessed both by mean and absolute percent prediction errors: mean percent prediction error is used as a measure of potential bias of EFW due to growth between the last scan and birth, whereas mean absolute prediction error presents the dispersion of the errors. The mean percent prediction error steadily tended towards zero as the time interval between the last scan and birth decreased: it was -10.7% (95%CI [-12.1; -9.4]) in babies born exactly 14 days after the last scan (N=196) and -0.8% (95%CI [-2.3; 0.6]) in those born within 1 day (N=198) (Figure A.3, Appendix), showing that our model was unbiased for predicting weight at the time of the last scan and that the correction we applied to compensate for time to birth was appropriate. In the group born within 1 day of the last scan, the mean absolute prediction error was 7.6%, with 80%, 90% and 95% of predicted weights falling within 11%, 14% and 18% of the true birthweight.

The creation of the international EFW standards was based on the complete FGLS dataset. The gestational age-specific observed and smoothed centiles for EFW are presented in Figure 1. Similarities between smoothed centile curves (3rd, 50th, and 97th centiles) and observed values, assessed by gestational age-specific comparisons, demonstrate excellent agreement. The overall differences between empirical and smoothed centiles were small: the mean differences were 16 (SD 28) g, 13 (SD 17) g and 5 (SD 33) g for the 3rd, 50th and 97th centiles respectively.

The 3rd, 5th, 10th, 50th, 90th, 95th, and 97th fitted centile curves for EFW according to gestational age, which represent the international standards, are presented in Figure 2. The corresponding equations for λ(t), μ(t) and σ(t), are presented in Table 2, allowing for calculations by readers of Z-scores: by estimating the EFW and knowing gestational age desired centiles can be calculated: for example, given AC = 26 cm and HC = 29 cm, at 30 weeks and 0 days:

log(EFW) = 5.084820 – 54.06633×(26/100)3 – 95.80076×(26/100)3×log(26/100) + 3.136370 × (29/100)

= 7.312292

Therefore, EFW = exp(7.312292) = 1,499 grams.

To compute the corresponding Z-score at 30 weeks’ gestation, using Table 2, we must first calculate:

λ(30) = -4.257629 - 2162.234 × 30-2 + 0.0002301829 × 303

= -0.4451729

μ(30) = 4.956737 + 0.0005019687 × 303 – 0.0001227065 × 303 × log(30)

= 7.241468

and

σ(30) = 10-4 × (-6.997171 + 0.05755900 × 303 - 0.01493946 × 303 × log(30))

= 0.017517

Finally, Z = [0.017517×-0.4451729]-1×[(7.313229/ 7.241468)-0.4451729 − 1] = 0.5617023

Similarly, the 3rd centile (α=0.03) - i.e. Z=-1.88 - at 30 weeks and 0 days is calculated as follows using Table 2:

logC0.03(30) = 7.241468 × (-1.88 × 0.017517 × (-0.4451729) + 1)-1/0.4451729

= 7.008552

The 3rd centile for EFW at 30 weeks’ gestation is therefore:

C0.03(30) = exp(7.008552)

= 1,106 grams

The actual values for these centiles according to gestational age are presented in the appendix (Table A.1).

**DISCUSSION**

The INTERGROWTH-21st Project provides standards for early human growth based on populations that conform to the prescriptive approach recommended by WHO 21,52. By prescriptive, we mean we have observed a cohort of prospectively enrolled women whose risk of adverse maternal and perinatal outcomes (including fetal growth restriction) was low based on their individual clinical profiles and the socioeconomic and demographic characteristics of the underlying geographically diverse populations. In fact, the INTERGROWTH-21st Project is unique because it has produced, for the first time, fetal ultrasound, newborn size and preterm postnatal growth data set that have all been collected from the same underlying populations using the same rigorously applied methodologies.

We now present international EFW standards to complement the existing set, along with a formula for EFW based on HC and AC. Compared with several previous formulae 24 , we found that FL did not improve the EFW, which concurs with previous work, in particular in growth restricted fetuses 53. Furthermore, it is likely that incorporating FL in the formula would increase the prediction error, as its measurement is associated with the highest inter- and intra-observer variability compared to AC and HC 54.

Unusually, we have lowered the starting gestational age to 22 weeks, 2 weeks below the customary cut-off of 24 weeks’ gestation for viability, for two reasons: to facilitate the early recognition of fetal growth restriction around the recommended time of the second trimester anatomy scan 55 and to anticipate the possible extension of the limit of viability 56.

At the upper end of gestation, the centiles closely match those of the INTERGROWTH-21st Newborn Size Standards at 40 weeks 7. The 3rd, 50th and 97th EFW centiles are 2,554 g, 3,338 g and 4,121 g, respectively (Appendix), whereas for newborns (both sexes combined) they are 2,591 g, 3,321 g and 4,154 g, respectively (Figure A.4). These similarities between fetal and birth weight centiles suggest that our model is valid for developing a formula for EFW using ultrasound biometry.

In contrast, earlier in pregnancy there are significant discrepancies. For example, at 33 weeks’ gestation, the 3rd, 50th and 97th EFW centiles are 1,495 g, 1,954 g and 2,529 g, respectively (Appendix); for newborns (both sexes combined), they are 1,190 g, 1,903 g and 2,715 g respectively. It is possible that these differences are due to an overrepresentation of small – as well as large, to a lesser extent – babies in preterm births, even in the selected pregnant and newborn populations we have studied.

The EFW formula and standards we present are also unique because we avoided the many common limitations identified by previous reviews 5,24: retrospective design; use of routinely obtained measurements; suboptimal pregnancy dating strategies; variable time-to-birth without controlling for bias; absence of prospective ultrasound quality control, standardisation, and calibration of equipment; hospital-based sampling; absence of sampling from a healthy, well nourished, underlying population, and no blinding of measurements.

Conversely, our standards are prescriptive, whereas reference charts describe only fetal size at a given place and time. The standards were prospectively derived, population-based and multinational. We have shown (using several analytical strategies) that the eight populations were consistently similar and could be pooled to create international standards 52. Uniform research methods, protocols, processes and measurement tools were used throughout; this was combined with standardised identical equipment, training, a centralized electronic data management system and close monitoring of staff. The analytical approach aimed to identify and correct potential biases, and followed WHO recommendations to present the observed and smoothed data and explore the best fitting model with an a-priori strategy 57.

Using ultrasound, we have separately examined HC, AC and FL providing a comprehensive evaluation of structures that have different growth patterns; these measurements are often combined to calculate EFW. There are advantages in using a summary approximation: it is the most commonly measured marker of size at birth; as birthweight is associated with morbidity and mortality it is helpful when counselling parents and enables paediatricians to make management decisions 58; it may also help to refine the management of large babies.

However, there are also disadvantages in using only a single summary measure of size: firstly, there is a loss of the most granular information available when using the individual measurements, in terms of fetal skeletal and fat-based growth. Secondly, the fact that the individual measurement errors are compounded means that estimation is prone to inaccuracy; previous studies have shown that 95% prediction intervals for random error are in the region of ± 14% of birthweight, and this is a particular problem in low and high birthweight babies 24. Finally, as for other ultrasound measures, there are numerous locally-derived EFW equations and reference charts 24 but until now no international standards existed, unlike the situation for newborn size and infant growth 7,8,10. This may be at least partly responsible for the poor efficiency of screening strategies using biometry and EFW 59.

Therefore, we strongly recommend that, for clinical use, all the individual fetal measures together with the summary measure of EFW should be used together to make clinical decisions. In perinatal medicine, there is no room for a quick, minimalist approach, which might lead to the early delivery of an at-risk fetus. Finally, implementation of the standards may raise concerns regarding the generalizability of data originating from a limited number of sites and/or a highly selected, low-risk population. As we have previously argued11, having separate standards for a given country, institution or ethnic group, has no biological basis and makes little sense in modern, multicultural societies. The international INTERGROWTH-21st standards describe optimal growth and can be used to assess both individuals and populations.

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**FIGURE LEGENDS**

Figure 1. Comparison of empirical and smoothed centiles for estimated fetal weight between 22 and 40 weeks’ gestation. Broken line: smoothed centiles; Red points: empirical centiles

Figure 2. 3rd, 10th, 50th, 90th and 97th smoothed centile curves for estimated fetal weight

Figure 3. Comparison of fitted 3rd, 50th, and 97th centiles for estimated fetal weight (red solid lines) compared with the INTERGROWTH-21st preterm postnatal weight of both sexes combined (dashed blue lines).

Figure A.1. Relationship between fetal weight and abdominal circumference in the final model, plotted for a fixed value of head circumference of 26 cm.

Figure A.2. Relationship between fetal weight and head circumference in the final model, plotted for a fixed value of abdominal circumference of 23 cm.

Figure A.3. Bias in estimation of fetal weight as a function of time to birth: mean percent prediction error and 95% confidence interval for the mean, per day between the last ultrasound scan and birth

Figure A.4. Overlaid gestational age specific centiles for estimated fetal weight and birthweight: the 3rd, 10th, 50th, 90th and 97th centiles are plotted in blue for estimated fetal weight and in red for birthweight.

**TABLES**

Table 1. Gestational age at birth and birthweight in the subset of babies that were born within 14 days of their last ultrasound scan in the INTERGROWTH-21st Project.

|  |  |  |  |
| --- | --- | --- | --- |
|  | INTERBIO-21st Fetal Study  N=848 | Fetal Growth Longitudinal Study  N=1556 | Total  N=2404 |
| Gestational age at birth |  |  |  |
| <28 weeks | 2 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| ≥28 and <32 weeks | 3 (0.4%) | 6 (0.4%) | 9 (0.4%) |
| ≥32 and <37 weeks | 56 (6.6%) | 62 (4%) | 118 (4.9%) |
| ≥37 and <44 weeks | 787 (92.8%) | 1487 (95.6%) | 2274 (94.6%) |
| Birthweight |  |  |  |
| <1000 g | 1 (0.1%) | 2 (0.1%) | 3 (0.1%) |
| ≥1000 and 1499g | 5 (0.6%) | 1 (0.1%) | 6 (0.2%) |
| ≥1500 and 1999g | 9 (1.1%) | 15 (1%) | 24 (1%) |
| ≥2000 and 2499g | 79 (9.3%) | 76 (4.9%) | 155 (6.4%) |
| >2500g | 754 (88.9%) | 1462 (94%) | 2216 (92.2%) |

Table 2. Equations for parameters and computation of Z-scores and centiles for EFW in relation to gestational age in exact weeks (GA). Abbreviations: GA is for gestational age, in exact weeks; EFW: estimated fetal weight in g. The log function denotes the natural logarithm (base e).

|  |
| --- |
| **Skewness** |
| λ(GA) = –4.257629 – 2162.234 × GA-2 + 0.0002301829 × GA3 |
| **Mean** |
| μ(GA) = 4.956737 + 0.0005019687 × GA3 – 0.0001227065 × GA3 × log(GA) |
| **Coefficient of variation** |
| σ(GA) = 10-4 × (–6.997171 + 0.057559 × GA3 – 0.01493946 × GA3 × log(GA)) |
| **Z-score**  Y=log(EFW) |
| If λ(GA)=0, Z(GA) = σ(GA)-1 × log[Y/μ(GA)]  If λ(GA)≠0, Z(GA) = [σ(GA) × λ(GA)]-1 × [(Y/μ(GA))λ(GA) − 1] |
| **Centiles**  Zα defined by Pr(z ≤ Zα)=α for z ~ N(0,1), i.e. Zα = Φ-1(α)  If λ(GA)=0, log[Cα(GA)] = μ(GA) × exp[σ(GA) × Zα]  If λ(GA)≠0, log[Cα(GA)] = μ(GA) × [Zα × σ(GA) × λ(GA) +1]1/λ(GA) |

**APPENDIX**

Table A.1. Centiles for EFW per completed week of gestation

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 3rd | 10th | 50th | 90th | 97th |
| 22 | 463 | 481 | 525 | 578 | 607 |
| 23 | 516 | 538 | 592 | 658 | 694 |
| 24 | 575 | 602 | 668 | 751 | 796 |
| 25 | 642 | 675 | 756 | 857 | 913 |
| 26 | 716 | 757 | 856 | 980 | 1048 |
| 27 | 800 | 848 | 969 | 1119 | 1202 |
| 28 | 892 | 951 | 1097 | 1277 | 1376 |
| 29 | 994 | 1064 | 1239 | 1453 | 1570 |
| 30 | 1105 | 1189 | 1396 | 1648 | 1784 |
| 31 | 1226 | 1325 | 1568 | 1861 | 2017 |
| 32 | 1356 | 1472 | 1755 | 2090 | 2267 |
| 33 | 1495 | 1630 | 1954 | 2332 | 2529 |
| 34 | 1641 | 1796 | 2162 | 2582 | 2798 |
| 35 | 1794 | 1969 | 2378 | 2836 | 3069 |
| 36 | 1951 | 2146 | 2594 | 3086 | 3331 |
| 37 | 2109 | 2323 | 2806 | 3324 | 3578 |
| 38 | 2266 | 2496 | 3006 | 3540 | 3798 |
| 39 | 2416 | 2658 | 3186 | 3726 | 3982 |
| 40 | 2554 | 2805 | 3338 | 3871 | 4121 |