ABSTRACT

Objective To develop fetal and neonatal population weight charts. The rationale was that, while reference ranges of estimated fetal weight (EFW) are representative of the whole population, the traditional approach of deriving birth-weight (BW) charts is misleading, because a large proportion of babies born preterm arise from pathological pregnancy. We propose that the reference population for BW charts, as in the case of EFW charts, should comprise all babies at a given gestational age, including those still in utero.

Methods Two sources of data were used for this study. For both, the inclusion criteria were singleton pregnancy, dating by fetal crown–rump length at 11 + 0 to 13 + 6 weeks’ gestation, availability of ultrasonographic measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) and live birth of phenotypically normal neonate. Dataset 1 comprised a sample of 5163 paired measurements of EFW and BW; ultrasound examinations were carried out at 22–43 weeks’ gestation and birth occurred within 2 days of the ultrasound examination. EFW was derived from the HC, AC and FL measurements using the formula reported by Hadlock et al. in 1985. Dataset 2 comprised a sample of 95 579 pregnancies with EFW obtained by routine ultrasonographic fetal biometry at 20 + 0 to 23 + 6 weeks’ gestation (n = 45 034), 31 + 0 to 33 + 6 weeks (n = 19 224) or 35 + 0 to 36 + 6 weeks (n = 31 321); for the purpose of this study we included data for only one of the three visits per pregnancy. In the development of reference ranges of EFW and BW according to gestational age, the following assumptions were made: first, that EFW and BW have a common median, dependent on gestational age; and second, that deviations from the median occur in both EFW and BW and these deviations are correlated with different levels of spread for EFW and BW, dependent on gestational age. We adopted a Bayesian approach to inference, combining information from the two datasets using Markov Chain Monte-Carlo sampling. The fitted model assumed that the mean log transformed measurements of EFW and BW are related to gestational age according to a cubic equation and that deviations about the mean follow a bivariate Gaussian distribution.

Results In the case of EFW in Dataset 2, there was a good distribution of values < 3rd, < 5th, < 10th, > 90th, > 95th and > 97th percentiles of the reference range of EFW according to gestational age throughout the gestational age range of 20 + 0 to 36 + 6 weeks. In the case of BW, there was a good distribution of values only for the cases delivered > 39 weeks’ gestation. For preterm births, particularly at 27–36 weeks, BW was below the 3rd, 5th and 10th percentiles in a very high proportion of cases, particularly in cases of iatrogenic birth. The incidence of small-for-gestational-age fetuses and neonates in the respective EFW and BW charts was higher in women of black than those of white racial origin.

Conclusion We established a BW chart for all babies at a given gestational age, including those still in utero, thereby overcoming the problem of underestimation of growth restriction in preterm birth. BW and EFW charts have a common median but differ in the levels of spread from the median. Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

There is an apparent contradiction in the relationship between the ultrasonographic estimation of fetal weight (EFW) and birth weight (BW). Although the EFW recorded within a few days before birth correlates strongly with BW and, for a given gestational age, these two measurements have essentially the same median1, in reported reference ranges, the median
BW according to gestational age for babies born preterm is substantially lower than the median EFW\(^2\)–\(^5\). This difference is likely to be the consequence of pathological fetal growth in a high proportion of preterm births. Reference ranges of EFW are representative of the whole population, whereas in reference ranges of BW, particularly for gestational ages < 37 weeks, there is overrepresentation of pathological pregnancies. One-third of preterm births are iatrogenic, due mainly to hypertensive disorders and/or suspected fetal growth restriction; there is also evidence of impaired placentation in a substantial proportion of spontaneous preterm births\(^6\)–\(^10\).

In this study, we propose that the reference population for BW charts, as in the case of EFW charts, should comprise all babies at a given gestational age, including those still in utero. Development of these charts was based on the assumptions that, first, for a given gestational age, the median BW is the same as the median EFW in the reference population, and, second, deviations from the median occur in both BW and EFW and these deviations follow a bivariate Gaussian distribution, with different levels of spread for BW and EFW, dependent on gestational age. These assumptions enable data on EFW derived from routine scans early in gestation to be combined with BW at term to produce reference charts for BW and EFW for gestational ages from 20 + 0 to 42 + 6 weeks.

**METHODS**

**Study population**

Two sources of data were used for this study, based on the same inclusion criteria: singleton pregnancy, dating by fetal crown–rump length at 11 + 0 to 13 + 6 weeks' gestation, availability of ultrasonographic measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL), and live birth of phenotypically normal neonate. The pregnancies were examined at King’s College Hospital, London and Medway Maritime Hospital, Kent, UK, between January 2006 and December 2017. The ultrasound scans were carried out by sonographers who had received The Fetal Medicine Foundation (FMF) Certificate of Competence in ultrasound examination.

Dataset 1 comprised a sample of 5163 paired measurements of EFW and BW. The ultrasound examinations were carried out at 22–43 weeks’ gestation and birth occurred within 2 days of the scan\(^1\). This dataset, in which pathological pregnancies were inevitably overrepresented, was used to examine the relationship between EFW and BW; it was not used to establish the reference ranges. EFW was derived from the HC, AC and FL measurements using the formula of Hadlock \etal\(^1\). The selection of this formula was based on a previous systematic review of the literature\(^1\), in which we identified all models for EFW and found that the formula of Hadlock \etal\(^1\) was the most accurate among 70 published models for the prediction of BW, having the lowest Euclidean distance and highest proportion of pregnancies with an absolute mean error of <10.

Dataset 2, from which the reference ranges were established, comprised a sample of 95 579 pregnancies (not included in Dataset 1) with EFW obtained by routine ultrasonographic fetal biometry at 20 + 0 to 23 + 6 weeks’ gestation \((n = 45 034)\); 31 + 0 to 33 + 6 weeks \((n = 19 224)\) or 35 + 0 to 36 + 6 weeks \((n = 31 321)\). In the participating hospitals, all women with singleton pregnancy are offered routine ultrasound examinations at 11 + 0 to 13 + 6 and 20 + 0 to 23 + 6 weeks’ gestation. During the period 2011 to 2014, an additional scan was offered at 31 + 0 to 33 + 6 weeks, and subsequently (between 2014 and 2017) this was offered at 35 + 0 to 36 + 6 weeks. For the purpose of this study, we included data for only one of the second- or third-trimester visits; we used all data obtained at 31 + 0 to 33 + 6 or 35 + 0 to 36 + 6 weeks and used the data of the visit at 20 + 0 to 23 + 6 weeks only for pregnancies that did not have a third-trimester scan. In the selection of patients, care was taken to include routine scans and not follow-up scans for maternal medical conditions or a suspected problem in fetal growth. Since the objective of the study was to establish reference ranges, rather than normal ranges, we included all pregnancies undergoing these routine ultrasound examinations. In the case of BW, we restricted data to pregnancies delivering at 39 + 0 to 41 + 6 weeks because deliveries at earlier gestations constitute a fraction of the total and many of these arise from pathological pregnancies; consequently, they are not representative of the whole population, including those still in utero.

**Statistical analysis**

Measurements of EFW and BW were log transformed to make the deviations from median close to Gaussian in distribution and the variation about the median more stable across the range of gestational ages. A Bayesian approach to inference was adopted, combining information from Datasets 1 and 2 using Markov Chain Monte-Carlo sampling. The fitted model assumed that the mean log-transformed measurements of EFW and BW were related to gestational age according to a cubic equation and that deviations about the mean followed a bivariate Gaussian distribution. Gross outliers were identified from an initial model and observations with standardized residuals beyond ± 3.89 (the 0.00005\(^{th}\) percentile of the Gaussian distribution) were excluded from the final model. A range of model diagnostics was produced to assess the goodness-of-fit of the model. This included summary statistics and Gaussian probability plots of \(z\)-scores for data on EFW and BW. Non-parametric quantile regression was used for direct estimation of percentiles of the EFW and BW data for comparison with the parametric model. Details of the analysis and model diagnostics are given in Appendix S1.
Figure 1 Association between estimated fetal weight (EFW), derived from model of Hadlock et al. using measurements of head circumference, abdominal circumference and femur length, and birth weight (BW) in Dataset 1. Regression line is blue and line $EFW = BW$ is red.

Statistical software package R was used for data analyses. The R packages mvtnorm and quantreg were used for multivariate Gaussian statistics and quantile regression.

RESULTS

Pregnancy characteristics of the two datasets are summarized in supplementary Tables S1 and S2. The association between EFW and BW in the 5163 pregnancies of Dataset 1, in which birth occurred within 2 days of the ultrasound examination, is shown in Figure 1. For a given gestational age, the median EFW is essentially the same as the median BW. Further evidence to support the assumption of equivalence in means of EFW and BW is provided in Appendix S1.

The median, 3rd, 10th, 90th and 97th percentiles of EFW and BW according to gestational age are shown in Figure 2 and the median, 3rd, 5th, 10th, 25th, 75th, 90th, 95th and 97th percentiles of EFW and BW for each gestational week between 20 + 3 and 41 + 3 weeks are shown in Table 1. The standard deviation and percentiles of EFW and BW for each gestational day between 20 + 0 and 42 + 6 weeks are shown in Table S3.

The distribution of EFW according to gestational age in our chart is compared with those of the World Health Organization (WHO) and INTERGROWTH-21st charts in Figure 3 and Table S4. The median and 10th percentiles of the WHO chart, and more so those of...
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Both EFW and BW are given in g. It was assumed that EFW and BW have a common median, dependent on gestational age.

The proportion of cases in Dataset 2 with EFW and BW < 3rd, < 5th, < 10th, > 90th, > 95th and > 97th percentiles of the appropriate reference range according to gestational age is shown in Table S5. The distribution of EFW values was well balanced throughout the gestational-age range of 20 + 0 to 36 + 6 weeks, whereas a good distribution of BW values was observed only in cases delivered > 39 weeks' gestation. For preterm births, particularly at 27–36 weeks, BW was below the 3rd, 5th and 10th percentiles in a very high proportion of cases (Figure 4, Table S6). This was particularly marked in cases delivered preterm due to iatrogenic causes (40.3%, 45.1% and 52.5% for BW < 3rd, < 5th and < 10th percentile, respectively); this is not surprising because, in 1200 (67.0%) of the 1790 cases of iatrogenic preterm birth, the indication for delivery was hypertensive disease and/or fetal growth restriction. However, a high proportion of small-for-gestational-age (SGA) neonates was also observed among spontaneous preterm births; the proportion of spontaneous preterm births with BW below the 3rd, 5th and 10th percentiles was 8.6%, 12.4% and 19.8%, respectively (Table S6).

The proportion of pregnancies in women of white and black racial origin in Dataset 2 with EFW and BW < 3rd, < 5th and < 10th percentiles of the appropriate reference range according to gestational age is shown in the INTERGROWTH-21st chart4, are substantially lower than the respective ones in our FMF chart between 24 and 38 weeks of gestation.

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EFW and birth-weight charts

Figure 4 Percentage of cases in Dataset 2 with birth weight below 3rd ( ), 5th ( ) and 10th ( ) percentiles of reference range of birth weight according to gestational age.

Figure 5 Percentage of pregnancies of white women ( ) and black women ( ) in Dataset 2 with estimated fetal weight (EFW) (left) or birth weight (right) below 10th percentile of appropriate reference range.

Table S7 and the proportions of cases with EFW and BW < 10th percentiles are illustrated in Figure 5. The data demonstrate that the incidence of SGA fetuses and neonates in the respective EFW and BW charts was higher in women of black than in women of white racial origin.

DISCUSSION

Principal findings of the study

In this study we have established reference ranges according to gestational age for BW and EFW. These two charts have a common median but they differ in the levels of spread from the median. The BW charts rely on the principle that, at a given gestational age, especially < 37 weeks, the reference population should include not only those babies that have been born, but all also, because preterm births are inherently pathological, babies still in utero.

The study has demonstrated that a very high proportion of preterm births are SGA; this should not be surprising because, in many such cases, there is iatrogenic birth for hypertensive disease and/or fetal growth restriction. A high proportion of SGA neonates is also observed among spontaneous preterm births, providing further support to histological and uterine artery Doppler findings suggesting that in many such births there is impaired placentation. Consequently, to varying degrees, all preterm births arise from pathological pregnancy and it is misleading to use data from such pregnancies to establish reference ranges of BW according to gestational age.

In our heterogeneous unselected population, arising from two maternity hospitals in England, about 20% of the women were of black racial origin and in these women the incidence of SGA fetuses and neonates was higher than in white women. This finding is compatible with the results of a previous study which reported that fetal growth is affected by several maternal characteristics: BW increased with maternal weight, height and parity and, after adjustment for these variables, BW was lower in black than in white women. It could therefore be assumed that it is physiological for black women to produce smaller babies than white women and that different reference ranges for these racial groups should be provided. An alternative view is that, in black women living in England, the delivery of smaller babies is a consequence of pathological influences that would be masked by customized BW percentiles. We have reported that, in black women, after adjustment for other demographic and pregnancy characteristics, there
is increased risk for several adverse pregnancy outcomes, including miscarriage, stillbirth, pre-eclampsia, fetal growth restriction and both iatrogenic and spontaneous preterm birth; it is uncertain whether such increased risks are a consequence of genetic predisposition, socioeconomic deprivation or both. We have also shown that BW according to gestational age is reduced in antepartum stillbirths and there is no significant difference in the proportion of antepartum stillbirths that are SGA when BW is corrected for maternal characteristics.

Strengths and limitations of the study

The main strength of our study is the production of BW reference charts for all babies at a specific gestational age, including those still in utero. This avoids bias and underestimation of SGA in the assessment of BW in babies born preterm. Additional strengths include the large study population of women undergoing routine ultrasound examination in pregnancy for Database 2 and use of their data only once to avoid the potential correlation of measurements from different visits, the close proximity of the ultrasound examination to birth for Database 1, the dating of pregnancies based on fetal crown–rump length, the fact that trained sonographers carried out fetal biometry according to a standardized protocol and the utilization for calculation of EFW of a widely used model which has been shown to be the most accurate of 70 previously reported models. In the establishment of reference ranges, we included all pregnancies undergoing routine ultrasound examination and did not attempt to select only uncomplicated pregnancies in women thought to be healthy and well-nourished.

A potential limitation of this study is our assumption that, for a given gestational age, EFW and BW have the same median. This was based on the findings from Dataset 1, but was not possible to investigate further for the whole population. Another limitation is the extent of extrapolation and interpolation resulting for use of EFW and BW data. We wanted to include data on EFW arising from routine screening of the whole population and this inevitably restricted the data to the three narrow gestational age ranges of 20–36 weeks. In the case of BW, we restricted data to pregnancies delivering at term to avoid bias from inclusion of preterm births, many of which arise from pathological pregnancies. Despite the extensive extrapolation and interpolation of data, the model diagnostics demonstrated a satisfactory fit of the model.

Comparison with previous studies

Salomon et al. used the Hadlock formula to construct EFW charts from biometric data obtained during routine ultrasound examination at 20–36 weeks’ gestation in 18,959 normal fetuses. The authors compared the EFW to BW charts obtained during the same study period and in the same single health authority and noted that, for preterm births, the EFW was substantially higher than the BW; they recommended that the EFW of preterm fetuses should not be compared with the distribution of BW, because fetal growth restriction is over-represented in preterm births, but rather they should be compared with EFW charts. In our study, we have taken this observation further, highlighting that there is an inherent problem in the traditional construction of BW charts, especially for preterm births, and recommend that they should be revised based on data from all babies at a given gestational age, including those still in utero.

Marsal et al. recognized that BW charts do not represent the intrauterine population and proposed that it would be preferable to use EFW charts to assess the growth of both fetuses and neonates. They performed a longitudinal study of ultrasonographic fetal biometry at 10–41 weeks’ gestation in 86 uncomplicated pregnancies that delivered at term; they then combined the data from 759 EFWs and 86 BWs to derive an intrauterine growth chart using a fourth-degree polynomial equation. We agree with Marsal et al. on the need to revise BW charts and have demonstrated that EFW and BW charts have a common median, but they differ in the levels of spread from the median.

Two international multicenter studies have recently reported the construction of charts of EFW according to gestational age. Two international multicenter studies have recently reported the construction of charts of EFW according to gestational age. In the INTERGROWTH-21st project, data were derived from 2,404 live babies without congenital abnormality, who were born within 14 days of an ultrasound scan; women were recruited from urban areas in several countries (Brazil, China, England, India, Italy, Kenya, Oman, Pakistan, South Africa, Thailand and USA) and had serial ultrasound scans and fetal biometry throughout pregnancy. Two cohorts of women were examined; one was unselected and the other was selected to include healthy, well-nourished, pregnant women who were at low risk of adverse maternal and perinatal outcomes. The authors reported that the data from different centers were similar and they therefore pooled all data and used fractional polynomial models to construct an international optimal fetal growth chart that would be appropriate for healthy pregnancies in all countries of the world.

In the WHO study, data were derived from 1,387 healthy women with low-risk pregnancies and unrestricted nutritional and social background who had serial ultrasound scans throughout pregnancy; women were recruited from 10 countries (Argentina, Brazil, Democratic Republic of the Congo, Denmark, Egypt, France, Germany, India, Norway and Thailand) and a total of 7,924 sets of ultrasound measurements were analyzed by quantile regression to establish longitudinal reference intervals for EFW. The authors reported that there were significant differences in fetal growth between countries.

In our study, in comparison with the INTERGROWTH-21st and WHO studies, the population was unselected and considerably larger, the data were derived from two centers in the same country and the scans were
carried out by sonographers with extensive training in ultrasound examination in pregnancy. Our approach, like the one of INTERGROWTH-21st, used a parametric model. This differs from the approach of the WHO study, which used non-parametric quantile regression. A benefit of the parametric models is that they can be used easily to obtain z-scores and percentiles for individual measurements. A drawback is the imposition of a specific parametric relationship. We used a cubic polynomial to represent the relationship between median level of log-transformed weight assuming the same median for both EFW and BW. Our model assumed that deviations around the median for BW and EFW followed a bivariate Gaussian distribution.

The 10th percentile of our EFW chart was considerably higher than those of the INTERGROWTH-21st and WHO charts4,5. For example, at 36 weeks’ gestation, the 10th percentile according to our chart was 2531 g, whereas the respective values in the WHO and INTERGROWTH-21st charts are 2352 g and 2144 g. Such differences are likely to be a consequence of underlying differences in the study populations and demonstrate that the desire for a single international standard for all countries is not appropriate; a single standard would underestimate growth restriction in countries with normal big babies, such as Norway, and overestimate growth restriction in countries with normal small babies, such as India.

Conclusions

This study has highlighted the necessity for construction of BW charts to be based on all babies at a particular gestational age, including those still in utero. Within a given country there are variations in BW that depend on maternal characteristics, such as racial origin, but adjustment for such characteristics may be inappropriate because such adjustments could result in underestimation of the increased perinatal risk of a disadvantaged group. The value of adjustment for maternal weight, height and parity remains controversial.

If our charts are to be used in different countries it would be necessary to ensure that the distribution of values is appropriate, otherwise adjustments would be necessary to tailor the charts for a specific setting or to change the cut-offs for defining SGA or large-for-gestational age. In the latter case, these charts could be considered as a benchmark rather than a reference chart.

ACKNOWLEDGMENT

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REFERENCES


SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Statistical analysis and justification

Table S1 Characteristics of study population of 5163 pregnancies with paired measurements of estimated fetal weight and birth weight separated by a maximum of 2 days (Dataset 1)
**Table S2** Characteristics of study population of 95 579 pregnancies in Dataset 2

**Table S3** Median, 3rd, 5th, 10th, 25th, 75th, 90th, 95th and 97th percentiles of estimated fetal weight (EFW) and birth weight (BW) (in g) for each gestational age (GA) day between 20 and 42 weeks

**Table S4** Comparison of 10th, 50th and 90th percentiles of estimated fetal weight (in g) according to gestational age (GA) between our FMF chart and WHO5 and INTERGROWTH-21st-4 charts

**Table S5** Number and percentage of cases in Dataset 2 with estimated fetal weight (EFW) < 3rd, < 5th < 10th, > 90th, > 95th and > 97th percentiles of reference range of EFW, according to gestational age (GA), and respective values for birth weight (BW)

**Table S6** Number and percentage of cases in Dataset 2 with birth weight below 3rd, 5th and 10th percentiles of reference range of birth weight according to gestational age (GA), for iatrogenic and spontaneous births

**Table S7** Number and percentage of pregnancies of white and black women in Dataset 2 with estimated fetal weight (EFW) and birth weight (BW) below 3rd, 5th and 10th percentiles of the appropriate reference range according to gestational age (GA)