INTERGROWTH-21st standards for Hadlock's estimation of fetal weight

Establishing an estimated fetal weight (EFW) percentile involves two distinct steps: first, calculating the EFW based on one or more fetal biometric variables (such as head circumference (HC), abdominal circumference (AC) and femur length (FL)); and, second, plotting the EFW against the gestational age (GA) on an EFW standard, to derive a percentile.

A recently published systematic review has suggested that Hadlock's three-parameter (HC, AC and FL) formula ($EFW = 10^{(1.326 + 0.0107 \times HC + 0.0438 \times AC + 0.158 \times FL - 0.00326 \times AC \times FL)}$) is associated with the least error in estimating EFW[1,2] and may perform better in fetal weight estimation than the two-parameter (HC and AC) formula we developed recently[3]. Because our commitment is to base our recommendations on the results of systematic reviews, we present herein a newly developed prescriptive standard for EFW based upon the Hadlock formula above for estimating fetal weight. This formula was applied to fetal biometric measurements from our original study of optimally grown fetuses[4].

After calculating EFW for each fetus using this method, we applied a second-degree fractional polynomial functional form and found the best fit using a three-parameter Box–Cox Gaussian distribution (i.e. the LMS (lambda, mu, sigma) method) for the response variable, defining three distributional functions of GA (λ(GA), μ(GA) and σ(GA)). All analyses were carried out in R statistical software (https://www.r-project.org) using the generalized additive models for location, scale and shape (GAMLSS) framework[5]. The GA-specific centiles for EFW are presented in Figure 1, in comparison with the previously published centiles based on the two-parameter formula. The corresponding equations for λ(GA), μ(GA) and σ(GA) are presented in Table S1 and the main centiles are shown in Table S2.

It should be highlighted that discrepancies – and more generally the controversies about which equation or chart to use when evaluating fetal weight – illustrate the fact that the use of ultrasound to estimate fetal weight at the time of making delivery decisions and when interacting with neonatologists is a practice that needs to be challenged. Both obstetricians and neonatologists apply this information, often in conjunction with other parameters, to make important decisions about the need to deliver a baby or whether to transfer an undelivered mother to a facility with a higher-level neonatal unit. However, using an estimate for fetal weight in this context as a proxy for neonatal viability, based on a summary of ultrasound measurements of the fetal head, abdomen and femur, each with their own individual technical errors, is questionable, especially given the wide confidence intervals of such estimates, with the mean percentage error ranging from −6.9% to 22.2%[6]. There are other pathophysiological problems with using EFW to estimate neonatal risk. Indeed, each of the biometric parameters summarized

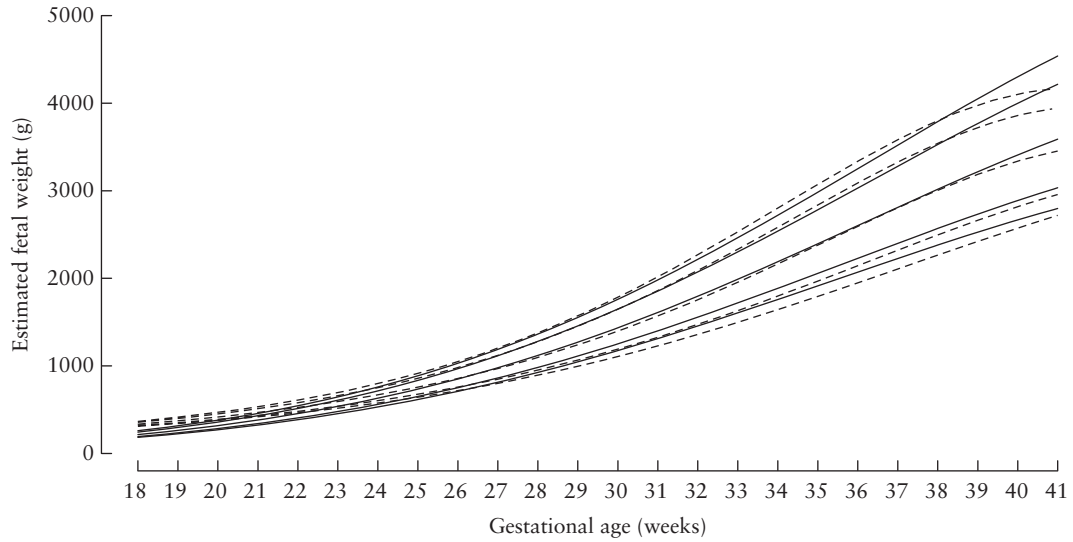

Figure 1 Gestational-age-specific standards (3rd, 5th, 50th, 95th and 97th centiles) for estimated fetal weight based on Hadlock three-parameter (——) and INTERGROWTH-21st two-parameter (– – –) formulae in INTERGROWTH-21st Fetal Growth Longitudinal Study population.

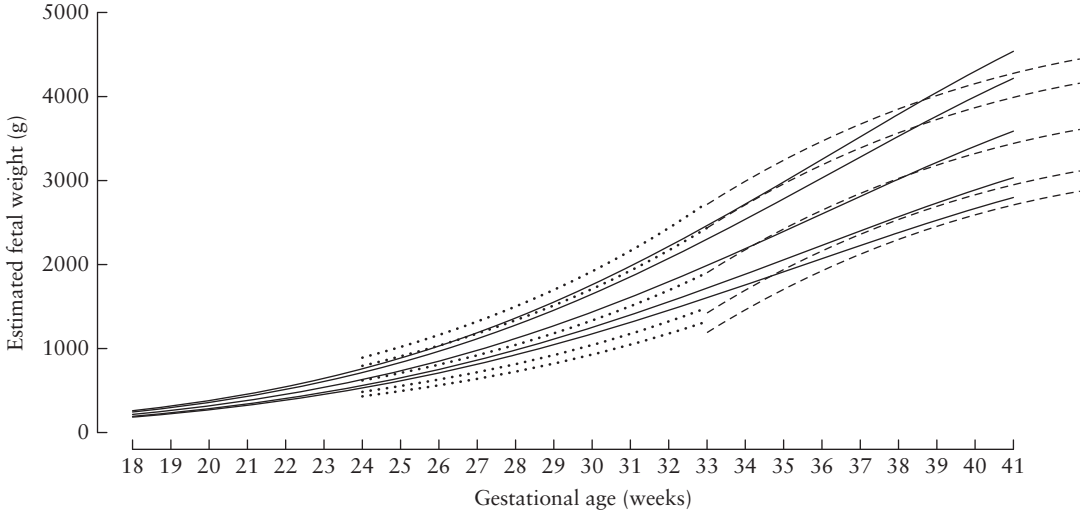

Figure 2 Gestational-age-specific standards (3rd, 5th, 50th, 95th and 97th centiles) for estimated fetal weight based on Hadlock three-parameter formula in INTERGROWTH-21st Fetal Growth Longitudinal Study population (——), and INTERGROWTH-21st newborn (33–43 weeks' gestation)[12] (– – –) and very preterm (< 33 weeks' gestation)[11] (·····) birth-weight reference charts.

in the EFW value has different risk implications. For example, in a recent systematic review and meta-analysis, third-trimester ultrasound screening for late-onset fetal growth restriction (FGR) performed better when based on AC than EFW, and there is a close association between AC in the third trimester and neonatal morbidity[7]. On the other hand, an isolated, mid-trimester, short FL is associated with an increased risk of FGR and preterm birth, in the absence of aneuploidy, congenital anomaly and skeletal dysplasia[8]. To complicate matters further, neonatal mortality, although strongly associated with GA at birth, was found in a systematic review to be best predicted by multivariable models rather than birth weight or GA alone in very preterm infants, the priority group for this clinical dilemma[9].

Finally, the neonatologist will decide which chart to use to judge the implications of the EFW provided by the obstetrician. We strongly believe that, for risk assessment of the neonate, it is logical that the same chart for assessment of weight for GA should be used by both the obstetricians and neonatologists. On the one hand, because FGR is over-represented in premature deliveries, the use of birth-weight curves to interpret EFW may miss the diagnosis of FGR[10], as preterm infants are known to be somewhat smaller than fetuses of the same GA while still *in utero*[11]. Figure 2 illustrates the difference in interpretation according to the use of EFW or birth-weight standards. On the other hand, if the ultimate objective of estimating fetal weight is for the neonatologist to assess risk, to refine the infant's clinical management and to communicate the

likelihood of death or disability to the parents, then the same chart should be used by both the obstetricians and neonatologists, as, otherwise, the same pregnancy may be evaluated on the same day using two different tools, resulting in two separate risk assessments being made. Hence, there should be no need for EFW charts in this context of immediate neonatal risk assessment.

In summary, we recommend that:

1. Fetal growth should not be evaluated using a single summary measure. Rather, it should be assessed over time based on the trajectory of individual parameters, plotted separately against the INTERGROWTH-21st fetal growth standards, to enable growth/size to be evaluated for each gestational period.
2. If an EFW value is added to complement the individual parameter during fetal growth monitoring, the most evidence-based strategy is to use the EFW standard we have presented here; this standard matches methodologically the INTERGROWTH-21st fetal growth standards.
3. When interacting with the neonatologist to decide clinical actions, the INTERGROWTH-21st newborn birth-weight standards (33–43 weeks' gestation)[12] or very preterm reference charts (< 33 weeks' gestation)[11] allow evaluation of neonatal size and risk, according to the week of gestation. This change of standards is required, even if it complicates the process, because neonatal size at birth is different from EFW, and the risk assessments therefore differ (Figure 2).
4. The responsible next step is always to provide the parents with the error range of the birth-weight estimation. If the neonate is to be delivered prematurely, postnatal growth can then be monitored in the neonatal unit and in the pediatric follow-up clinic using the INTERGROWTH-21st preterm postnatal growth standards[13] that were constructed specifically to ensure continuity of care, using the same pregnant cohort as the fetal and neonatal standards.

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SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Equations for parameters and computation of *Z*-scores and centiles for estimated fetal weight according to gestational age

Table S2 Centiles for estimated fetal weight, per gestational week